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

INOVA DIAGNOSTICS, INC.
DR. GABRIELLA LAKOS
DIRECTOR OF RESEARCH AND DEVELOPMENT
9900 OLD GROVE ROAD,
SAN DIEGO, CA, 92131

Re: K152875
Trade/Device Name: QUANTA Flash® ß2GP1-Domain1
QUANTA Flash® ß2GP1-Domain1 Controls
HemosIL® Acustar Anti-ß2GPI-Domain 1
HemosIL® Acustar Anti-ß2GPI-Domain 1 Controls
Regulation Number: 21 CFR § 866.5660
21 CFR § 862.1660
Regulation Name: Multiple autoantibodies immunological test system
Quality control material (assayed and unassayed)
Regulatory Class: II
Product Code: MSV, JJX
Dated: September 29, 2015
Received: October 5, 2015

Dear Dr. Lakos:

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)*
K152875

Device Name
QUANTA Flash® ß2GP1-Domain1

Indications for Use *(Describe)*
The QUANTA Flash® ß2GP1-Domain1 is an in vitro chemiluminescent immunoassay (CIA) for the semi-quantitative determination of IgG autoantibodies to ß2GP1-Domain1 in human serum or citrated plasma. The presence of anti-ß2GP1-Domain1 autoantibodies is used in conjunction with clinical and other laboratory findings as an aid in the diagnosis of antiphospholipid syndrome. The QUANTA Flash® ß2GP1-Domain1 is not intended to replace assays for antibodies against the whole ß2GP1 molecule. Testing for antibodies to the whole ß2GP1 molecule is required according to the classification criteria for antiphospholipid syndrome.

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.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

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The burden time for this collection of information is estimated to average 79 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
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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)*
K152875

Device Name
QUANTA Flash® ß2GP1-Domain1 Controls

Indications for Use *(Describe)*
The QUANTA Flash ß2GP1-Domain1 Controls are intended for quality control purposes of the QUANTA Flash ß2GP1-Domain1 chemiluminescent immunoassay (CIA) kit.

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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Indications for Use

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

510(k) Number *(if known)*
K152875

Device Name
HemosIL® AcuStar Anti-ß2GPI Domain 1

Indications for Use *(Describe)*
The HemosIL® AcuStar Anti-ß2GPI Domain 1 is an in vitro chemiluminescent immunoassay (CIA) for the semi-quantitative determination of IgG autoantibodies to ß2GPI Domain 1 in human serum or citrated plasma. The presence of anti-ß2GPI Domain 1 autoantibodies is used in conjunction with clinical and other laboratory findings as an aid in the diagnosis of antiphospholipid syndrome. The HemosIL® AcuStar Anti-ß2GPI Domain 1 is not intended to replace assays for antibodies against the whole ß2GPI molecule. Testing for antibodies to the whole ß2GPI molecule is required according to the classification criteria for antiphospholipid syndrome.

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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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)*
K152875

Device Name
HemosIL® AcuStar Anti-ß2GPI Domain 1 Controls

Indications for Use *(Describe)*
The HemosIL AcuStar Anti-ß2GPI Domain 1 Controls are intended for quality control purposes of the HemosIL AcuStar Anti-ß2GPI Domain 1 chemiluminescent immunoassay (CIA) kit.

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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Table of Contents

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

Administrative data

Submitter: Inova Diagnostics, Inc
9900 Old Grove Road,
San Diego, CA, 92131

Purpose of submission: New device(s)

Devices in the submission: QUANTA Flash® ß2GP1-Domain1
QUANTA Flash® ß2GP1-Domain1 Controls
HemosIL® AcuStar Anti-ß2GPI Domain 1
HemosIL® AcuStar Anti-ß2GPI Domain 1 Controls

Scientific contact: Gabriella Lakos, Director of Research, Rheumatology
Inova Diagnostics, Inc.
9900 Old Grove Road, San Diego, CA, 92131
Phone: 858-586-9900/1393
Fax: 858-863-0025
email: glakos@inovadx.com

Quality Systems contact: Ronda Elliott, VP, Quality Systems and RA
Inova Diagnostics, Inc
9900 Old Grove Road, San Diego, CA, 92131
Phone: 858-586-9900/1381
Fax: 858-863-0025
email: relliot@inovadx.com

Device name (assay kit):

Proprietary name:	QUANTA Flash® ß2GP1-Domain1 HemosIL® AcuStar Anti-ß$_2$GPI Domain 1
Common name:	Anti-β2GPI Domain 1 Chemiluminescent immunoassay
Classification name:	Anti-β2GPI Domain 1 antibody, antigen and control

Regulation Description Multiple autoantibodies immunological test system

Regulation Medical Specialty Immunology

Review Panel Immunology

Product Code	System, Test, Antibodies,B2-Glycoprotein I (B2-GPI) (MSV)	
Regulation Number	866.5660	
Device Class	2	
Device name (Controls):	Proprietary name:	QUANTA Flash® ß2GP1-Domain1 Controls HemosIL® AcuStar Anti-ß$_2$GPI Domain 1 Controls
	Common name:	Domain1 Controls
	Classification name:	single (specified) analyte controls (assayed and unassayed)
Regulation Description	Quality control material (assayed and unassayed)	
Regulation Medical Specialty	Clinical Chemistry	
Product Code	JJX	
Regulation Number	862.1660	
Device Class	1 (reserved)	

Predicate device

QUANTA Lite® β2GPI IgG ELISA, 510(k) number: K970551

Device description

The QUANTA Flash® ß2GP1-Domain1 assay is designed to run on the BIO-FLASH® instrument. This platform is a fully automated closed system with continuous load and random access capabilities that automatically processes the samples, runs the assay and reports the results. It includes liquid handling hardware, luminometer and computer with software-user interface. The QUANTA Flash® ß2GP1-Domain1 assay utilizes a reagent cartridge format, which is compatible with the BIO-FLASH instrument.

The assays included in this submission, the QUANTA Flash® ß2GP1-Domain1 marketed by Inova Diagnostics Inc. (9900 Old Grove Road, San Diego, CA 92131) and HemosIL® AcuStar Anti-ß$_2$GPI Domain 1 marketed by Instrumentation Laboratory (180 Hartwell Road Bedford, MA 01730), are equivalent assays. Therefore all data stated hereafter and referred to as: QUANTA Flash® ß2GP1-Domain1 data is equivalently also valid for HemosIL® AcuStar Anti-ß$_2$GPI Domain 1.

Recombinant ß2GP1-Domain1 protein is coated onto paramagnetic beads, which are stored lyophilized in the reagent cartridge. The reagent pack is prepared for use in the BIO-FLASH® system by pressing down on the grey lid of the reagent pack to pierce the induction seals on the reagent tubes. Once the seals are broken, the beads are rehydrated by adding the entire contents of the vial of resuspension buffer to the bead reagent tube using the transfer pipette supplied with the kit. Only the hole above the bead reagent

tube is accessible at this point. The beads are then mixed with the resuspension buffer by pipetting up and down 30 times. This amount of mixing ensures complete resuspension of the beads. The label covering the remaining three reagent holes is now removed, and the reagent cartridge is then loaded onto the BIO-FLASH instrument. Samples are also loaded onto the instrument in sample racks. A patient serum sample is prediluted 1:10 by the BIO-FLASH with system rinse in a small disposable plastic cuvette. Small amounts of the diluted patient serum, the beads, and assay buffer are all combined into a second cuvette, and mixed. This cuvette is then incubated at 37°C. The beads are magnetized and washed several times. Isoluminol conjugated anti-human IgG antibodies are then added to the cuvette, and again incubated at 37°C. The beads are magnetized and washed repeatedly. The isoluminol conjugate is oxidized when Trigger 1 (Fe(III) coproporphyrin in sodium hydroxide solution) and Trigger 2 (urea-hydrogen peroxide in sodium chloride solution) are added to the cuvette, and the flash of light produced from this reaction is measured as Relative Light Units (RLU) by the BIO-FLASH optical system. The RLU are proportional to the amount of isoluminol conjugate that is bound to the human IgG, which is in turn proportional to the amount of anti- ß2GP1-Domain1 antibodies bound to the corresponding ß2GP1-Domain1 on the beads.

The QUANTA Flash® ß2GP1-Domain1 assay utilizes a predefined lot specific Master Curve that is uploaded onto the instrument through the reagent cartridge barcode. Every new lot number of reagent cartridge must be calibrated before first use, with the QUANTA Flash® ß2GP1-Domain1 Calibrators. Based on the results obtained with the two Calibrators included in the reagent kit, an instrument specific Working Curve is created, which is used to calculate chemiluminescent units (CU) from the instrument signal (RLU) obtained for each sample.

The QUANTA Flash® ß2GP1-Domain1 kit contains the following materials:

One (1) QUANTA Flash ß2GP1-Domain1 Reagent Cartridge, containing the following reagents for 50 determinations:

a. ß2GP1-Domain1 antigen coated paramagnetic beads in a suspension.
b. Assay Buffer – buffer containing protein stabilizers and preservatives.
c. Tracer IgG – Isoluminol labeled anti-human IgG antibodies in buffer, containing protein stabilizers and preservative.
d. Sample Diluent – buffer containing protein stabilizers and preservatives.
d. Resuspension Buffer – buffer containing protein stabilizers and preservatives.
e. QUANTA Flash ß2GP1-Domain1 Calibrator 1: One (1) barcode labeled tube containing 1.0 mL prediluted, ready to use reagent. Calibrators contain human antibodies to ß2GP1-Domain1 in stabilizers and preservatives.
f. QUANTA Flash ß2GP1-Domain1 Calibrator 2: One (1) barcode labeled tube containing 1.0 mL prediluted, ready to use reagent. Calibrators contain human antibodies to ß2GP1-Domain1 in stabilizers and preservatives

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The QUANTA Flash® ß2GP1-Domain1 Controls kit contains three vials of Low Control and three vials of High Control.

- QUANTA Flash ß2GP1-Domain1 Low Control: Three (3) barcode labeled tubes containing 1.0 mL, ready to use reagent. Controls contain human antibodies to ß2GP1-Domain1 in stabilizers and preservatives.
- QUANTA Flash ß2GP1-Domain1 High Control: Three (3) barcode labeled tubes containing 1.0 mL, ready to use reagent. Controls contain human antibodies to ß2GP1-Domain1 in stabilizers and preservatives.

Intended use(s)

QUANTA Flash® ß2GP1-Domain1

The QUANTA Flash® ß2GP1-Domain1 is an *in vitro* chemiluminescent immunoassay (CIA) for the semi-quantitative determination of IgG autoantibodies to ß2GP1-Domain1 in human serum or citrated plasma. The presence of anti-ß2GP1-Domain1 autoantibodies is used in conjunction with clinical and other laboratory findings as an aid in the diagnosis of antiphospholipid syndrome. The QUANTA Flash® ß2GP1-Domain1 is not intended to replace assays for antibodies against the whole ß2GP1 molecule. Testing for antibodies to the whole ß2GP1 molecule is required according to the classification criteria for antiphospholipid syndrome.

QUANTA Flash® ß2GP1-Domain1 Controls

The QUANTA Flash ß2GP1-Domain1 Controls are intended for quality control purposes of the QUANTA Flash ß2GP1-Domain1 chemiluminescent immunoassay (CIA) kit.

HemosIL AcuStar Anti-ß$_2$GPI Domain 1

The HemosIL® AcuStar Anti-ß$_2$GPI Domain 1 is an *in vitro* chemiluminescent immunoassay (CIA) for the semi-quantitative determination of IgG autoantibodies to ß$_2$GPI Domain 1 in human serum or citrated plasma. The presence of anti-ß$_2$GPI Domain 1 autoantibodies is used in conjunction with clinical and other laboratory findings as an aid in the diagnosis of antiphospholipid syndrome. The HemosIL® AcuStar Anti-ß$_2$GPI Domain 1 is not intended to replace assays for antibodies against the whole ß$_2$GPI molecule. Testing for antibodies to the whole ß$_2$GPI molecule is required according to the classification criteria for antiphospholipid syndrome.

HemosIL AcuStar Anti-ß$_2$GPI Domain 1 Controls

The HemosIL AcuStar Anti-ß2GPI Domain 1 Controls are intended for quality control purposes of the HemosIL Anti-ß2GPI Domain 1 chemiluminescent immunoassay (CIA) kit.

Indications for use

Same as Intended use.

Substantial equivalence

The QUANTA Flash ß2GP1-Domain1 and the QUANTA Flash ß2GP1-Domain1 Controls have a similar intended use and assay principle as the predicate device.

Comparison to predicate device

QUANTA Flash® ß2GP1-Domain1 reagent kit

Similarities		
Item	**Applicant**	**Predicate Device**
	QUANTA Flash® ß2GP1-Domain1	QUANTA Lite® $ß_2$ GPI IgG ELISA
Intended use	The QUANTA Flash® ß2GP1-Domain1 is an *in vitro* chemiluminescent immunoassay (CIA) for the semi-quantitative determination of IgG autoantibodies to ß2GP1-Domain1 in human serum or citrated plasma. The presence of anti-ß2GP1-Domain1 autoantibodies is used in conjunction with clinical and other laboratory findings as an aid in the diagnosis of antiphospholipid syndrome. The QUANTA Flash® ß2GP1-Domain1 is not intended to replace assays for antibodies against the whole ß2GP1 molecule. Testing for antibodies to the whole ß2GP1 molecule is required according to the classification criteria for antiphospholipid syndrome.	QUANTA Lite® ß2 GPI IgG is an enzyme linked immunoassay (ELISA) for the semi-quantitative detection of $ß_2$ GPI IgG antibodies in human serum. The presence of $ß_2$ GPI IgG antibodies can be used in conjunction with clinical findings and other laboratory tests to aid in the diagnosis of certain autoimmune disease thrombotic disorders such as those secondary to systemic lupus erythematosus (SLE) or other lupus-like thrombotic diseases.
Assay methodology	Solid phase (heterogeneous) immunoassay	Solid phase (heterogeneous) immunoassay
Shelf life	One year	One year

Differences		
Item	**QUANTA Flash ß2GP1-Domain1**	**Predicate Device**
Detection/ Operating principle	Chemiluminescent immunoassay	Enzyme-linked immunosorbent assay
Solid phase	Paramagnetic microparticles (beads)	96-well plate
Antigen	Recombinant domain1 of ß2-Glycoprotein1	purified ß2-Glycoprotein1
Conjugate	Isoluminol conjugated anti-human IgG	HRP conjugated anti-human IgG
Calibration	Lot specific Master Curve + two Calibrators (included in kit)	Five lot specific calibrators (Included in the kit)
Units	< 20 CU Negative result ≥ 20 CU Positive result	< 20 SGU Negative result ≥ 20 SGU Positive result
Analytical Measuring Range	3.6 – 1380.4 CU Reportable range = up to 13804.0 CU	9.4 – 150.0 SGU
Sample type	Serum or citrated plasma	Serum

QUANTA Flash ß2GP1-Domain1 Calibrators

Item	**QUANTA Flash ß2GP1-Domain1 Calibrators**	**Predicate Device**
Intended use	No separate intended use; calibrators are part of the kit.	No separate intended use; calibrators are part of the kit.
Analyte	Anti-ß2GP1-Domain 1 antibodies	Anti-ß2GP1 antibodies
Method	QUANTA Flash® ß2GP1-Domain1	QUANTA Lite® $ß_2$ GPI IgG ELISA
Unit	Chemiluminescent Units (CU) QUANTA Flash Arbitrary Units (U/ml) HemosIL AcuStar	SGU
Matrix	Human serum, stabilizers, and preservative	Human serum, stabilizers, and preservative
Physico-chemical characteristics	Liquid, prediluted, ready to use	Liquid, prediluted, ready to use
Storage	2-8 ^{o}C	2-8 ^{o}C
Shelf life	One year	One year

QUANTA Flash ß2GP1-Domain1 Controls

Item	**QUANTA Flash ß2GP1-Domain1 Controls**	**Predicate Device**
Intended use	The QUANTA Flash ß2GP1-Domain1 Controls are intended for quality control purposes of the QUANTA Flash ß2GP1-Domain1 chemiluminescent immunoassay (CIA) kit.	No separate intended use; controls are part of the kit.
Analyte	Anti-ß2GP1-Domain1 antibodies	Anti- ß2GP1- antibodies
Method	QUANTA Flash ß2GP1-Domain1 chemiluminescent immunoassay	QUANTA Lite® $ß_2$ GPI IgG ELISA
Unit	QUANTA Flash (CU) HemosIL AcuStar (U/ml)	SGU
Matrix	Human serum, stabilizers, and preservative	Human serum, stabilizers, and preservative
Physico-chemical characteristics	Liquid, ready to use	Liquid, prediluted, ready to use
Levels	2 (low and high)	2 (negative and positive)
Storage	2-8^{o}C	2-8^{o}C
Shelf life	One year	One year

Analytical performance characteristics

Value assignment and traceability of Calibrators and Controls

The QUANTA Flash ß2GP1-Domain1 Calibrators and Controls are manufactured by diluting human serum that contains high titer of anti-ß2GP1-Domain1 antibodies with antibody stabilizer buffer, containing preservative. The human serum is obtained from commercial sources and it is tested for markers of infectious substances.

The target CU is achieved through trial dilutions on small scale. Once a dilution is selected, the Calibrators and Control are bulked, tested, and adjusted. Upon completion of the manufacturing process, the Calibrators and Controls are tested on at least two instruments, on at least two lots of reagent cartridge, in replicates of 10 to determine final value assignment.

There are no international reference standards for anti- ß2GP1 IgG. Calibrators and controls are assigned values based on a 20 CU cut-off between positive (high) and negative (low) during assay development. Calibrators are specified in the labeling and supplied with the assay. Control materials are sold separately. The table below summarizes the control and calibrators target values.

List of ß2GP1-Domain1 Standards, Calibrators and Controls:

Points on master curve	Assigned Value (CU)
Point 1	3.6
Point 2	18.5
Point 3	43.7
Point 4	90.0
Point 5	316.0
Point 6	1380.4

Material	Manufacturing Target Value (CU)	Manufacturing Target Range (CU)
Calibrator 1	19.0	17 – 21
Calibrator 2	316.0	276 – 356
Control Low	10.0	8 – 12
Control High	50.0	40 – 60

Sample Matrix Comparison

Seventy-nine matched serum and citrated plasma samples (with different reactivity levels, 13.9% of samples around the cut-off) were tested side-by-side in singleton on QUANTA Flash® ß2GP1-Domain1 and analyzed according to CLSI Guideline EP09/A3.

The user can select the type of sample matrix at the time of loading the samples onto the BIO-FLASH instrument. The choices on matrices are serum or plasma, and each of them is associated to a specific protocol that uses different sample dilution factors (1/10 for serum and 1/8.4 for plasma) to compensate for the addition of the anticoagulant (sodium citrate) in the citrated plasma sample collection. The BIO-FLASH assay protocol for serum and plasma is the same after the initial dilution step. The plasma dilution factor was chosen to be consistent with the rest of the APS assay family (QUANTA Flash aCL IgG and ß2GP1 IgG), where the dilution factor ratio between the serum protocol and the plasma protocol is 1.19 (in the Domain1, 10 / 8.4 = 1.19).

Percent difference and unit difference were calculated for each paired sample. Paired samples are considered equivalent if the percent difference between them is ≤15% or if the difference in units (CU) is ±3 CU (which is ≤15% of the cut-off). In addition, a linear regression comparison was performed and its acceptance criteria and results are summarized in the table below.

Acceptance Criteria		Serum vs. Plasma
Weighted R	≥0.975	0.997
Intercept of the regression line (Constant bias)	±3CU	0.1
Slope of the regression line (Proportional bias)	0.9-1.1	1.01
Weighted S y/x (Standard error of estimate)	≤0.5	0.064
Predicted bias (difference) at cut-off	±3CU	0.3
95% CI of the bias	<20% ±4CU	0.00 to 1.03

All paired samples fulfill the acceptance criteria, where 53/60 positive samples showed ≤10% difference, being 12.8% the maximum difference obtained. Therefore, the assay is claimed to be used with serum and citrated plasma.

Precision

The precision of the QUANTA Flash ß2GP1-Domain1 assay was evaluated on 8 serum samples containing various concentrations of anti-Domain1 antibodies in accordance with CLSI EP05-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline. Samples were run in duplicates, twice a day, for 20 days.

Data were analyzed with the Analyse-it for Excel method evaluation software, and within run, between run, between day and total precision were calculated.

Acceptance criteria: Total %CV: < 15%

Results are summarized in the Table below.

QUANTA Flash ß2GP1-Domain1 Precision Study Decision Summary										
			Within Run		Between-Run		Between-Day		Total	
Sample	**N**	**Mean (CU)**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Precision 1	80	10.4	0.9	8.3%	0.0	0.0%	0.5	4.3%	1.0	9.4%
Precision 2	80	18.4	0.9	4.6%	0.5	2.9%	0.5	2.6%	1.1	6.0%
Precision 3	80	22.8	1.4	6.1%	0.9	3.8%	0.0	0.0%	1.6	7.2%
Precision 4	80	54.3	2.5	4.6%	1.4	2.5%	1.2	2.2%	3.1	5.6%
Precision 5	80	99.6	6.4	6.5%	0.0	0.0%	0.0	0.0%	6.4	6.5%
Precision 6	80	318.3	18.6	5.9%	0.0	0.0%	4.9	1.6%	19.3	6.1%
Precision 7	80	538.1	30.3	5.6%	7.9	1.5%	28.7	5.3%	42.5	7.9%
Precision 8	80	947.8	82.8	8.7%	57.3	6.0%	0.0	0.0%	100.7	10.6%

Summary of Precision study QUANTA Flash® ß2GP1-Domain1, according to the CLSI EP5-A2 guideline

	No. of samples	**Within Run**	**Between-Run**	**Between-Day**	**Total**
ß2GP1-Domain1	8	4.6-8.7%	0.0-6.0%	0.0-5.3%	5.6-10.6%

Plasma Precision Verification

The precision of the QUANTA Flash B2GP1-Domain1 assay using plasma samples was verified using 3 plasma samples containing various concentrations of anti-Domain1 antibodies in accordance with CLSI EP15-A3, User Verification of Precision and Estimation of Bias; Approved Guideline - Third Edition. Samples were run in replicates of 5, once a day, for 5 days.

Data were analyzed with the Analyse-it for Excel method evaluation software, and within run, between day and total precision were calculated.

Acceptance criteria: Total %CV: < 15%

Results are summarized in the Table below.

QUANTA Flash ß2GP1-Domain1 Plasma Precision Verification Summary								
			Within Run		Between-Day		Total	
Sample	**N**	**Mean**	**SD**	**%CV**	**SD**	**%CV**	**SD**	**%CV**
Plasma Precision 1	25	444.6	15.0	3.4%	7.9	1.8%	16.9	3.8%
Plasma Precision 2	25	92.0	2.3	2.5%	0.3	0.3%	2.3	2.5%
Plasma Precision 3	25	18.7	0.9	4.6%	1.2	6.2%	1.5	7.8%

Limit of Blank (LoB) and Limit of Detection (LoD)

The LoD of the QUANTA Flash® ß2GP1-Domain1 assay is 1296 RLU, which is below the analytical measuring range of the assay. It was determined consistent with CLSI EP17-A2 guideline with proportions of false positives (alpha) less than 5% and false negatives (beta) less than 5%; based on 140 determinations, with 60 measurements on blank samples and 80 measurements of low level samples. The LoB is 425.7 RLU.

These values are below the value of the lowest QUANTA Flash ß2GP1-Domain1 Master Curve standard, i.e. below the Analytical Measuring Range.

Analytical Measuring Range (AMR)

QUANTA Flash ß2GP1-Domain1: 3.6 CU – 1380.4 CU

The AMR is defined by the values of the lowest and highest Master Curve Standards.

Auto-rerun function and reportable results

The BIO-FLASH software has an Auto-rerun option available. If this option is selected, the instrument will automatically rerun any sample that has a result of result >1380.4 CU by further diluting it by a factor specified in the assay definition file (10 fold), thereby bringing the measured value within the AMR. The final result will be calculated by the software by taking into account the additional dilution factor. As the highest value that can be measured is 1380.4 CU, the highest value that can be reported is 13804 CU.

To validate the Auto-rerun function, three high positive specimens with results above the analytical measuring range were selected. The samples were run with the Auto-rerun function enabled on the BIO-FLASH. Then the specimens were manually diluted the same way as it happens in the Auto-rerun function (10 fold), and tested on the BIO-FLASH. The results were within the analytical measuring range after auto-rerun or manual dilution for all specimens. The % recovery values for results obtained with the auto-rerun results compared to the results obtained by manual dilution were between 91.9% and 99% (average 94.9%).

High concentration hook effect

To assess hook effect, measurement signal (RLU) was examined by performing serial dilutions of two high positive samples (with results above the AMR when tested as neat samples). RLU values showed increase with increasing antibody concentrations above the AMR, thereby confirming that high positive specimens above the analytical measuring range do not show hook effect up to 16,060.8 CU (theoretical value calculated using the highest value in the AMR and its dilution factor) in the ß2GP1-Domain1 assay.

Linearity

The linearity of the AMR was evaluated by a study according to CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline. Five serum samples and three plasma samples with various ß2GP1-Domain1 antibody concentrations were diluted with negative serum or plasma in 10% increments (from 0% to 90% negative serum) to obtain values that cover the AMR. The dilutions were assayed in duplicates. Percent recovery of obtained mean results was

calculated compared to the expected mean results (based on the dilution factor). Moreover, obtained values of individual replicates were plotted against expected values, and linear regression analysis was performed.

Acceptance criteria: - Recovery is between 80-120%, or ± 4 CU, whichever is greater.
- For linear regression analysis, slope is between 0.9-1.1, and R2 is ≥ 0.95.

All five serum specimens showed dilution linearity individually and combined.

Sample	Test Range (CU)	Slope (95% CI)	R^2	% Recovery Range
1	1640.7 to 164.1	1.04 (0.98 - 1.09)	0.99	95.1%-106.2%
2	454.7 to 45.5	0.99 (0.96 - 1.03)	0.99	95.5%-104.1%
3	124.9 to 12.5	1.03 (1.00 - 1.05)	1.00	94.3%-103.3%
4	81.1 to 8.1	1.01 (0.95 - 1.08)	0.98	83.9%-106.7%
5	10.3 to 1.0	0.96 (0.91 - 1.01)	0.99	90.9%-113.9%
Combined	1640.7 to 1.0	1.01 (0.99 to 1.02)	1.00	83.9%-113.9%

All three plasma specimens showed dilution linearity individually and combined.

Plasma	Test Range (CU)	Slope (95% CI)	R^2	% Recovery Range
1	1,357.6 to 135.8	1.02 (0.96 - 1.07)	0.99	86.6%- 102.6%
2	182.2 to 18.2	0.97 (0.93 - 1.01)	0.99	90.1%- 100.0%
3	17.7 to 3.5	0.96 (0.93 - 0.99)	1.00	98.2%- 111.9%
Combined	1,357.6 to 3.5	0.96 (0.94 - 0.98)	0.99	86.6%- 111.9%

These data demonstrate the linearity of the analytical measuring range (3.6 CU – 1380.4 CU) of the QUANTA Flash ß2GP1-Domain1 assay using serum or plasma samples.

Interference

The interference study was performed according to CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition. Five specimens were tested, three serum samples (negative: 10.7 CU; low positive: 55.9 CU; high positive: 456.6 CU) and two plasma samples (negative: 6.6 CU; high positive: 132.4 CU). Interfering substances (bilirubin, hemoglobin, triglycerides and cholesterol) were spiked into every specimen at three different concentrations in 10% of total specimen volume, and the resulting samples were assessed in triplicates with the ß2GP1-Domain1 assay. For Rheumatoid Factor IgM, the samples are diluted to varying extent depending on the desired concentrations of RF as an interferent, and the resulting samples were assessed in triplicates with the ß2GP1-Domain1 assay. Recovery of the unit values was calculated compared to control samples. Acceptance criteria for the interference studies were 85%-115% recovery, or ±4 CU difference, whichever is greater.

No interference was detected with bilirubin up to 100 mg/dL (recovery: 92.9% to 109.4%), hemoglobin up to 200 mg/dL (recovery: 95.6% to 106.3% or 1.7 CU), triglycerides up to 1000 mg/dL (recovery: 92.5% to 107.7%), cholesterol up to 224.3 mg/dL (recovery: 92.5% to 107.7%), and RF IgM up to 500 IU/mL (recovery: 86.2% to 109.9% or 0.9 CU).

Cross-reactivity

A potential cross-reactivity of the QUANTA Flash® ß2GP1 Domain1 CIA with other autoantibodies was evaluated with 613 control samples that were included in the clinical validation study. These samples were from patients with autoimmune diseases that are characterized with disease specific autoantibodies, or from patients with infection. The composition of the cohort and the anti-ß2GP1 Domain1 positivity rate is shown in the Table below:

Diagnosis	**Number of samples**	**# pos**	**% pos**
Crohn's Disease	104	1	1.0%
Ulcerative Colitis	94	0	0.0%
Rheumatoid Arthritis	168	0	0.0%
Osteoarthritis	49	0	0.0%
Scleroderma	127	2	1.6%
Hepatitis B virus	21	0	0.0%
Hepatitis C virus	10	0	0.0%
Syphilis	40	0	0.0%
Total controls	**613**	**3**	**0.5%**

Based on the results, the QUANTA Flash ß2GP1 Domain1 assay does not show cross-reactivity with autoantibodies that are present in various autoimmune diseases or with antibodies against infectious agents.

Lot to lot comparison

Twenty-six samples with various reactivity levels were tested with three different reagent lots: RP0003 (RP3), RP0011 (RP11) and 131001P1 (PP1). The samples covered the total analytical measuring range of the assay. Results were processed by linear regression analysis and bias calculation according to CLSI EP09-A3, Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline. Pair-wise comparisons were performed between lot RP3 vs RP11 and lot RP11 vs PP1.

Acceptance criteria and results are in the Table below. All results were within the acceptance limits.

Acceptance criteria		**RP3 vs RP11**	**RP11 vs PP1**	**PP1 vs RP3**
Weighted R for linear regression	≥ 0.975	0.996	0.998	0.986
Intercept of the regression line (constant bias)	± 3 CU	1.9	0.06	-1.3
Slope of the regression line (proportional bias)	0.9 - 1.1	1.03	1.04	1.00
Weighted S y/x (Standard error estimate)	≤ 0.5	0.07	0.05	0.13
Predicted bias (difference) at cut-off	± 3 CU	2.5	0.8	-1.2
95% CI of the bias	≤ 20% or ± 4 CU	1.1 to 3.8	-0.3 to 1.8	-3.9 to 1.6

Stability

Shelf life

To establish the initial claim for shelf life, accelerated stability studies were performed for 4 weeks at 37 °C, where one week is equal to six months at 5 ± 3°C.

Accelerated stability testing was performed on each of the following sealed components of the QUANTA Flash® ß2GP1-Domain1 to establish initial stability claim:

- QUANTA Flash® ß2GP1-Domain1 Reagent Kit (1 Lot)
- ß2GP1-Domain1 beads (3 Lots)
- Resuspension Buffer (3 Lots)
- Calibrators 1 and 2 (3 Lots)
- Low and High controls (3 Lots)

Each week a new sealed component was placed in the incubator, and all components were tested at the end of the experiment together with the one that was stored at 5 ± 3°C. The recovery of the measured values was calculated for each time point (compared to those obtained with 5 ± 3°C stored reagent). All calculations were performed by comparing results of sealed components stored at 5 ± 3°C (control) to those stored at 37 ± 3°C (test) for 1, 2, 3, and 4 weeks, where one week is equal to six months at 5 ± 3°C. Linear regression analysis was performed between recovery values and the number of days.

Acceptance criteria for one year preliminary expiration dating:

- Beads, Resuspension Buffer, and Reagent Kit:

With regression analysis, the lower and upper 95% CI interval of the regression line is between 85% and 115% recovery at day 14, and no individual data point has ≤75% or ≥125% recovery at day 14.

- Controls and Calibrators:

With regression analysis, the lower and upper 95% CI interval of the regression line is between 90% and 110% recovery at day 14, and no individual data point has ≤80% or ≥120% recovery at day 14.

All components tested fulfilled the acceptance criteria above, so one year expiration dating was assigned to each component

In-use (onboard) stability

Calibrators

Onboard stability claim: 4 calibrations, or 8 hours onboard

During assessment of on-board stability, Calibrators were placed uncapped, onboard the instrument, and calibration was performed altogether five times over 8.5 hours. Controls and a panel of characterized patient specimens were run on each calibration curve.

Calibrators are considered stable if all five calibrations performed in the 8.5 hour period are successful, and average Calibrator RLU recovery values are between 90% and 110% compared to the first use.

A total of 5 successful calibrations were performed over a 8.5 hour period. Calibrator RLU values remained within the 90-110% range. Moreover, all Controls and patient panel samples ran within their expected range. This supports the claim that calibrators can be used for up to 4 calibrations over an 8 hour period.

Controls

Onboard stability claim: up to 15 uses, at 10 minutes onboard per use

During assessing on-board stability, 2 vials of each Control were assayed twice a day for a total of 20 runs. The first run was used to establish baseline value, by running each vial in duplicate, and then additional 19 runs were performed, by running each vial in singleton. During runs, the Controls were left uncapped, onboard the instrument for 15 minutes per run. When not in use, the controls were capped, and stored at 5 ± 3°C. Percent recovery of each value was calculated compared to the baseline value. Controls are considered stable when all values run within their established range, and the linear regression line obtained by plotting %recovery values against the number of runs stays between 85% and 115% at run 15. All controls ran within their respective acceptable ranges for all runs. Moreover, the regression line remained between 85% and 115% at run 15 for both Controls. These results support the claim that controls can be used for up to 15 times, at 10 minutes per use.

Reagent Cartridge

To establish the in-use (onboard) stability of the QUANTA Flash ß2GP1-Domain1 reagent cartridge, three lots of reagent cartridge were tested with up to 4 serum specimens (with different reactivity levels) along with the Low and High Controls. The specimens were tested periodically up to 64 days. Percent recoveries were calculated compared to the day zero average values, and linear regression analysis was performed by plotting %recovery against the number of days. The claim was established using the following criteria (using the one that is fulfilled first):

- The stability claim is established at the actual measurement day preceding the day when the 95% confidence interval of the regression line reaches 85% or 115% recovery, or
- At the actual measurement day preceding the day when 2 data points or ≥2% of the recovery data (whichever is greater) is ≤ 75% or ≥ 125% recovery.

As none of these endpoints were reached during the duration of the study, the in-use (onboard) stability of Domain1 reagent cartridge was set at 60 days.

Real time stability

Real time stability testing has been scheduled to be performed approximately every three months on the reagent cartridge, Calibrators and Controls, to verify the one year expiration that was assigned based on accelerated stability studies. At the time of the submission, results were available up to 12 months for reagent cartridge, up to 15 months on Calibrators and Controls.

For reagent cartridge, QC panel samples were tested in singleton at each time point. The QC panel is a group of characterized patient samples with target values, used by the QC Department for reagent release and QC.

- Acceptance criteria: results should fall within their respective QC ranges.

Calibrators were used to calibrate a cartridge at each time point. After calibration, the QC panel samples were tested in singleton at each time point.
- Acceptance criteria: results should fall within their respective QC ranges.

Controls were tested in singleton on a calibrated cartridge at each time point. Individual values were compared to the values that were assigned to the Controls at release.
- Acceptance criteria: results should fall within their acceptable ranges as were established at the release of the Controls.

All results to date were within the acceptance limit, therefore one year expiration dating has been verified through real-time studies.

Sample stability

Sample stability claim: -Samples can be stored at room temperature for up to 48 hours.
-Samples can be stored at 2-8°C for up to 14 days.
-Samples can be frozen and thawed up to 3 times.

During the sample stability study, eight (four serum and four plasma samples) samples with varying anti-Domain1 levels have been tested along with Low and High Controls at different time points after being stored at each temperature condition. For the room temperature claim, samples were tested at 0, 8, 24 and 48 hours. For the 2-8°C claim, samples were tested at 0, 1, 2, 3, 7 and 14 days. For the freeze and thaw claim, samples were tested after 0, 1, 2 and 3 cycles. Samples were tested in duplicates at each time point. Percent recoveries were calculated at each time point compared to the time zero average values. Samples are considered stable if the recovery is between 85%-115% for positive samples. Samples are considered stable if the recovery is between 80-120%, or 20% of the cutoff in units (4 CU) for negative samples.

This study has been performed using serum and citrated plasma samples and all results fulfilled the acceptance criteria above, so the following claims have been established for both serum and citrated plasma:

-Samples can be stored at room temperature for up to 48 hours.
-Samples can be stored at 2-8°C for up to 14 days.
-Samples can be frozen and thawed up to 3 times.

Cut-off, reference range

QUANTA Flash ß2GP1-Domain1: Negative <20 CU
Positive ≥20 CU

The reference population for establishing cut-off for the ß2GP1-Domain1 assay consisted of 30 subjects:

Sample Type	Number of Samples
Apparently healthy blood donors	5
Viral hepatitis	4

Sample Type	Number of Samples
Systemic Lupus erythematosus (without history of thrombotic events)	10
Syphilis	10
HIV	1

All specimens were the same matrix (Serum). All specimens were unaltered. The cut-off was established in accordance to CLSI EP28-A3c: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition. The Analyse-it for Excel software was used to make the calculations. The 99th percentile of the obtained values was calculated as 7866 RLU.
The cutoff was set to 7880 RLU, which was set to equal 20 CU. One Systemic Lupus erythematosus (without history of thrombotic events) patient tested positive at this cutoff level.

Clinical performance characteristics

Clinical sensitivity, specificity

A cohort of 1090 characterized samples, none of which were used for establishing the reference range, was used to validate the clinical performance of the QUANTA Flash ß2GP1-Domain1 CIA. All samples were run on the QUANTA Flash ß2GP1-Domain1. The distribution of the cohort and the ß2GP1-Domain1 positivity rate is in the Table below:

Cohort	**N=1090**	**No (%) positive**
APS combined	**270**	**138 (51.1%)**
pAPS	180	102 (56.6%)
sAPS	90	36 (40.0%)
Infectious diseases	**71**	**0 (0.0%)**
Hepatitis B virus (HBV)	21	0 (0.0%)
Hepatitis C virus (HCV)	10	0 (0.0%)
Syphilis	40	0 (0.0%)
Other diseases	**566**	**3 (0.5%)**
Crohn's Disease (CD)	104	1 (1.0%)
Ulcerative Colitis (UC)	94	0 (0.0%)
Rheumatoid Arthritis (RA)	168	0 (0.0%)
Osteoarthritis (OA)	49	0 (0.0%)
Scleroderma	127	2 (1.6%)
Others	24	0 (0.0%)
Conditions "without APS"	**183**	**0 (0.0%)**
Pre-eclampsia/eclampsia	34	0 (0.0%)
Fetal loss no APS	45	0 (0.0%)
SLE no APS	37	0 (0.0%)
Thrombosis no APS	41	0 (0.0%)
Atopic Dermatitis	26	0 (0.0%)

Clinical sensitivity and specificity for APS (n=270) using the control population (n=820) is calculated in the table below.

Cohort 1 (n=1090)		**Diagnosis**			**Percent Agreement (95% confidence)**
		APS	Controls	Total	
QUANTA Flash® Domain 1 CIA	Positive	138	3	141	Sensitivity = 51.1% (45.0-57.2%)
	Negative	132	817	949	Specificity = 99.6% (98.9-99.9%)
	Total	270	820	1090	

To assess diagnostic efficiency, ROC analysis was performed on the validation sample pool for APS. The results are below:

Test	Area	95% CI	SE	Z	p
QUANTA Flash B2GP1-Domain1 (CU)	0.84	0.81 to 0.86	0.015	22.24	<0.0001

Expected values

The expected value in the normal population is "negative". Anti-ß2GP1-Domain1 antibody levels were analyzed in a cohort of 400 apparently healthy blood donors (191 females, ages 17 to 60 years, average age 32.3 years, and 209 males ages 17 to 60 years, average age 34.7 years) using the QUANTA Flash® ß2GP1-Domain1. This patient population was different from the one that was used to establish or validate the cutoff, and was only used to assess expected values. With a cut-off of 20 CU, one sample (0.25%) was positive (34.2 CU) on the QUANTA Flash ß2GP1-Domain1. The mean concentration was 3.8 CU, and the values ranged from <3.6 to 34.2 CU.

Comparison with predicate device

Samples for method comparison analysis included all samples that fell within the reportable range from the clinical validation study, along with 8 additional samples, for a total of 238 samples. These additional samples were contrived by diluting ß2GP1-Domain1 positive samples with negative serum in order to increase the number of samples around the cut-off. All samples were tested on the QUANTA Flash® ß2GP1-Domain1 CIA and the QUANTA Lite® β_2GPI IgG ELISA, which is used as a predicate device. Out of the 238 total samples, 22 samples (9.24%) were around the cut-off (15.1 to 25.2 CU).

Method Comparison, samples within reportable range:

All (n=238)		**QUANTA Lite® β_2GPI IgG ELISA**			**Percent Agreement (95% confidence)**
		Positive	Negative	Total	
QUANTA Flash® ß2GP1-Domain1 CIA	Positive	101	28	129	Pos. Agree = 91.0% (84.1-95.6%)
	Negative	10	99	109	Neg. Agree = 78.0% (69.7-84.8%)
	Total	111	127	238	Total Agree = 84.0% (78.7-88.4%)

There are 28 samples that reported a positive result in the new device but negative in the predicate device, 26/28 (92.9%) are from samples with an APS diagnosis and 2/28 (7.1%) are controls. There are 10 samples reported a negative result in the new device but positive in the predicate device, 5/10 (50.0%) are from control samples and 5/10 (50.0%) from APS samples.

Method Comparison, samples around the cut-off:

All (n=22)		**QUANTA Lite® β_2GPI IgG ELISA**			**Percent Agreement (95% confidence)**
		Positive	Negative	Total	
QUANTA Flash® ß2GP1-Domain1 CIA	Positive	4	3	7	Pos. Agree = 80.0% (28.4-99.5%)
	Negative	1	14	15	Neg. Agree = 82.4% (56.6-96.2%)
	Total	5	17	22	Total Agree = 81.8% (59.7-94.8%)