510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K190088

B. Purpose for Submission:

New devices

C. Measurand:

Rheumatoid Factor (IgM)

Rheumatoid Factor (IgA)

D. Type of Test:

Quantitative and semi-quantitative chemiluminescent immunoassay

(CIA)

E. Applicant:

INOVA Diagnostics, Inc.

F. Proprietary and Established Names:
QUANTA Flash RF IgM Reagents
QUANTA Flash RF IgA Reagents

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.5775, Rheumatoid Factor Immunological Test System

2. Classification:

   Class II

3. Product code:

   DHR, System, Test, Rheumatoid Factor

4. Panel:

   Immunology (82)

H. Intended Use:

1. Intended uses:

   QUANTA Flash RF IgM is a chemiluminescent immunoassay for the quantitative determination of IgM rheumatoid factor (RF) antibodies in human serum. The presence of IgM RF antibodies, in conjunction with clinical findings and other laboratory tests, is an aid in the diagnosis of rheumatoid arthritis (RA).

   QUANTA Flash RF IgA is a chemiluminescent immunoassay for the semi-quantitative determination of IgA rheumatoid factor (RF) antibodies in human serum. The presence of IgA RF antibodies, in conjunction with clinical findings and other laboratory tests, is an aid in the diagnosis of rheumatoid arthritis (RA).

2. Indications for use:

   See above

3. Special conditions for use statement:

   For prescription use only

4. Special instrument requirements:

   BIO-FLASH chemiluminescent analyzer (K083518)

I. Device Description:

The QUANTA Flash RF IgM reagent cartridge contains the following reagents for 100 determinations:

a. Rabbit polyclonal antibody coated paramagnetic beads, ready to use
b. Assay buffer – colored pink, containing protein stabilizers and preservatives
c. Tracer IgM – Isoluminol labeled monoclonal anti-human IgM antibody, containing buffer, protein stabilizers and preservative

The QUANTA Flash RF IgA reagent cartridge contains the following reagents for 100 determinations:

a. Rabbit polyclonal antibody coated paramagnetic beads, ready to use
b. Assay buffer – colored pink, containing protein stabilizers and preservatives
c. Tracer IgA – Isoluminol labeled monoclonal anti-human IgA antibody, containing buffer, protein stabilizers and preservative

The QUANTA Flash RF IgM and RF IgA Calibrators and the QUANTA Flash RF IgM and RF IgA Controls are sold separately.

J. Substantial Equivalence Information:

1. Predicate device names:
   QUANTA Lite RF IgM and QUANTA Lite RF IgA

2. Predicate 510(k) numbers:
   K971614 and K983084

3. Comparison with predicate:

Similarities		
Item	Device QUANTA Flash RF IgM Reagents	Predicate QUANTA Lite RF IgM ELISA
Antigen	Rabbit polyclonal antibody	Same
Sample type	Serum	Same

Differences		
Item	Device QUANTA Flash RF IgM Reagents	Predicate QUANTA Lite RF IgM ELISA
Intended Use	QUANTA Flash RF IgM is a chemiluminescent immunoassay for the quantitative determination of IgM rheumatoid factor (RF) in human serum. The presence of IgM RF antibodies, in conjunction with clinical findings and other laboratory tests, is an aid in the diagnosis of rheumatoid arthritis (RA).	QUANTA Lite RF IgM is an enzyme-linked immunosorbent assay (ELISA) for the semiquantitative detection of IgM rheumatoid factor (RF) antibodies in patient sera. The presence of these antibodies, when considered in conjunction with other laboratory and clinical findings, is an aid in the diagnosis of rheumatoid arthritis (RA).
Analytical Measuring Range	0.3 – 490.0 IU/mL	0.0 – 100 Units
Solid phase	Paramagnetic microparticles (beads)	96-well polystyrene plate
Detection/Operating principle	Chemiluminescent immunoassay	Enzyme-linked immunosorbent assay
Conjugate	Isoluminol conjugated monoclonal anti-human IgM antibody	HRP conjugated monoclonal anti-human IgM antibody
Cut-Off	5.0 IU/mL	6.0 Units
Calibration	Lot specific Master Curve with	Five lot-specific calibrators

Differences		
Item	Device QUANTA Flash RF IgM Reagents	Predicate QUANTA Lite RF IgM ELISA
	two calibrators (sold separately)	(part of kit)
Units	Chemiluminescent units (CU)	Same
Traceability	WHO Reference Reagent – Rheumatoid Arthritis Serum (NIBSC code: W1066)	WHO international reference preparation (64/2)

Similarities		
Item	Device QUANTA Flash RF IgA Reagents	Predicate QUANTA Lite RF IgA ELISA
Antigen	Rabbit polyclonal antibody	Same
Sample type	Serum	Same

Differences		
Item	Device QUANTA Flash RF IgA Reagents	Predicate QUANTA Lite RF IgA ELISA
Intended Use	QUANTA Flash RF IgA is a chemiluminescent immunoassay for the quantitative determination of IgA rheumatoid factor (RF) in human serum. The presence of IgA RF antibodies, in conjunction with clinical findings and other laboratory tests, is an aid in the diagnosis of rheumatoid arthritis (RA).	QUANTA Lite RF IgA is an enzyme-linked immunosorbent assay (ELISA) for the semiquantitative detection of IgA rheumatoid factor (RF) antibodies in patient sera. The presence of these antibodies, when considered in conjunction with other laboratory and clinical findings, is an aid in the diagnosis of rheumatoid arthritis (RA).
Analytical Measuring Range	1.3 – 900.0 CU	0.0 – 100 Units
Solid phase	Paramagnetic microparticles (beads)	96-well polystyrene plate
Detection/Operating principle	Chemiluminescent immunoassay	Enzyme-linked immunosorbent assay
Conjugate	Isoluminol conjugated monoclonal anti-human IgM antibody	HRP conjugated monoclonal anti-human IgM antibody
Cut-Off	20.0 CU	6.0 Units

Differences		
Item	Device QUANTA Flash RF IgA Reagents	Predicate QUANTA Lite RF IgA ELISA
Calibration	Lot specific Master Curve with two calibrators (sold separately)	Five lot-specific calibrators (part of kit)
Units	Chemiluminescent units (CU)	Same

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

EP05-A3, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline, Third Edition
EP6-A, Evaluation of Linearity of Quantitative Measurement, Approved Guideline, Second Edition
EP07-A2, Interference Testing in Clinical Chemistry, Approved Guideline, Second Edition
EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline, Second Edition
EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline, Third Addition

L. Test Principle:

The QUANTA Flash RF IgM and RF IgA assays are microparticle chemiluminescent immunoassay designed for use on the BIO-FLASH instrument. The instrument 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 RF IgM and RF IgA assays utilize a reagent cartridge format, which is compatible with the BIO-FLASH instrument.

Purified rabbit polyclonal antibodies are coated onto paramagnetic beads which are stored in the reagent cartridge. The ready-to-use reagent cartridge is loaded onto the BIO-FLASH instrument. Samples are also loaded onto the instrument in sample racks. A patient serum sample is prediluted 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 IgM or anti-human IgA 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" reagents 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 IgM or IgA which is in turn proportional to the amount of RF antibodies bound to the rabbit antibodies on the beads.

The QUANTA Flash RF IgM and RF IgA assays utilize a predefined lot-specific Master Curve that is uploaded into the instrument through the reagent cartridge barcode. Based on the results obtained by running two calibrators, an instrument-specific Working Curve is created, which is used by the software to calculate chemiluminescent units (CU) from the RLU value obtained for each sample.

M. Performance Characteristics:

1. Analytical performance:

All the results presented below met the manufacturer's pre-specified acceptance criteria.

a. Precision/Reproducibility:

Precision: The imprecision of the QUANTA Flash RF (IgM) and RF (IgA) assays was evaluated according to CLSI EP05-A03 by running patient samples across the assay ranges, ten for the IgM assay and nine for the IgA assay. Samples were run in duplicates, twice a day, for 20 days using one reagent lot (total of 80 replicates per sample). Controls were run as quality controls during each run. The results are summarized in the tables below:

QuantaFlash RF IgM		Repeatability		Between-Run		Between-Day		Within-Lab Imprecision	
Sample ID	Mean (IU/mL)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD)	CV (%)
1	1.2	0.1	5.4	0.0	3.1	0.0	3.3	0.1	7.0
2	2.3	0.1	4.1	0.1	5.2	0.0	1.6	0.2	6.8
3	2.7	0.1	3.8	0.1	3.6	0.1	3.5	0.2	6.3
4	3.7	0.2	4.6	0.1	3.2	0.1	2.2	0.2	6.0
5	5.4	0.2	3.2	0.2	3.2	0.2	2.9	0.3	5.4
6	20.6	0.8	4.0	0.4	1.8	0.6	2.8	1.1	5.2
7	83.9	2.9	3.4	2.7	3.2	2.1	2.5	4.5	5.3
8	181.3	9.0	4.9	8.6	4.8	0.0	0.0	12.4	6.9
9	379.3	16.3	4.5	22.5	5.	4.2	1.1	28.4	7.5
10	408.8	19.2	4.7	21.6	5.3	10.8	2.6	30.9	7.6

QuantaFlash RF IgA		Repeatability		Between-Run		Between-Day		Within-Lab Imprecision	
Sample ID	Mean (CU)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	10.6	0.4	3.5	0.3	2.8	0.4	3.7	0.6	5.8
2	11.2	0.6	5.3	0.0	0.4	0.2	1.9	0.6	5.6
3	20.9	0.8	4.0	0.0	0.0	0.7	3.2	1.1	5.2
4	21.6	0.7	3.3	0.3	1.2	0.5	2.5	0.94	4.3

QuantaFlash RF IgA		Repeatability		Between-Run		Between-Day		Within-Lab Imprecision	
Sample ID	Mean (CU)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
5	48.7	2.1	4.3	0.7	1.4	0.6	1.1	2.3	4.6
6	107.0	2.5	2.4	2.8	2.7	2.2	2.1	4.4	4.1
7	415.8	11.2	2.7	5.8	1.4	8.8	2.1	15.4	3.7
8	721.1	31.7	4.4	16.0	2.2	30.8	4.3	47.0	6.5
9	749.3	25.3	3.4	20.2	2.7	21.9	2.9	39.1	5.2

Site-to-Site Reproducibility: Eight samples were tested according to CLSI EP05-A03 at three different sites with one reagent lot to evaluate the site-to-site reproducibility for both the IgM and IgA assays. Each sample was run in replicates of five, once a day for five days, to generate 25 data points per sample at each site (N=75 per sample for all sites combined). Data were analyzed for within-run, between-day, between-site, and total imprecision. The results are summarized in the tables below.

QuantaFlash RF IgM		Repeatability		Between-Day		Between-Site		Total	
Sample	Mean (CU)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	1.7	0.1	6.4	0.1	4.4	0.1	2.7	0.1	8.2
2	3.0	0.1	4.0	0.1	1.7	0.2	7.5	0.3	8.7
3	4.6	0.2	3.3	0.2	4.0	0.1	2.2	0.3	5.6
4	6.3	0.2	2.9	0.3	4.1	0.5	7.8	0.6	9.3
5	23.2	0.9	3.9	0.7	2.9	0.2	1.1	1.2	5.0
6	92.8	2.4	2.6	2.9	3.1	5.1	5.5	6.3	6.8
7	200.3	9.4	4.7	10.7	5.4	4.9	2.4	15.1	7.5
8	412.9	15.5	3.8	17.3	4.2	36.2	8.8	43.0	10.4

QuantaFlash RF IgA		Repeatability		Between-Day		Between-Site		Total	
Sample	Mean (CU)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
1	11.2	0.5	4.2	0.4	3.3	0.4	3.1	0.7	6.2
2	11.3	0.5	4.0	0.2	2.1	0.3	2.5	0.6	5.2
3	21.9	0.7	3.4	0.1	0.4	0.6	2.9	1.0	4.5
4	23.2	0.9	3.9	0.2	1.0	0.8	3.6	1.3	5.4
5	51.7	1.3	2.5	0.7	1.2	0.5	0.9	1.5	2.9
6	112.6	3.2	2.9	2.3	2.1	0.0	0.0	4.0	3.5
7	462.4	13.2	2.9	10.9	2.4	19.8	4.3	26.1	5.6
8	738.4	27.3	3.7	2.5	3.0	45.3	6.1	57.4	7.8

Lot-to-lot Imprecision:

For both the IgM and IgA assays, a lot-to-lot imprecision study was performed according to CLSI EP05-A03 by testing eight samples with three different lots of reagents in five replicates for five days, to generate 25 data points per lot (total 75 replicates). The results are summarized in the tables below:

QuantaFlash RF IgM		Repeatability		Between-Day		Within-Lot		Between-Lot		Within Lab Imprecision	
Sample	**Mean (CU)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
1	2.9	0.1	3.8	0.0	1.6	0.1	4.1	0.0	1.0	0.1	4.2
2	3.3	0.1	3.1	0.1	2.2	0.1	3.8	0.1	3.4	0.2	5.1
3	4.6	0.2	3.6	0.1	3.0	0.2	4.7	0.0	0.0	0.2	4.7
4	23.2	0.8	3.4	0.7	3.1	1.1	4.6	0.4	1.6	1.1	4.8
5	209.8	9.8	4.7	14.0	6.7	17.1	8.2	9.8	4.7	19.7	9.4
6	1.6	0.1	5.2	0.1	5.5	0.1	7.6	0.1	4.1	0.1	8.7
7	92.9	3.8	4.1	2.4	2.6	4.5	4.9	4.8	5.2	6.6	7.1
8	6.0	0.2	3.8	0.2	2.9	0.3	4.8	0.1	1.4	0.3	5.0

QuantaFlash RF IgA		Repeatability		Between-Day		Within-Lot		Between-Lot		Within Lab Imprecision	
Sample	**Mean (CU)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**	**SD**	**CV (%)**
1	11.7	0.5	4.3	0.4	3.8	0.7	5.7	0.0	0.0	0.7	5.7
2	22.6	0.7	3.0	0.6	2.7	0.9	4.0	0.2	0.9	0.9	4.1
3	22.5	0.6	2.9	0.4	1.8	0.8	3.4	0.6	2.6	1.0	4.3
4	52.9	1.3	2.5	0.8	1.6	1.6	3.0	0.4	0.8	1.6	3.1
5	487.0	13.6	2.8	11.5	2.4	17.8	3.7	7.2	1.5	19.2	3.9
6	11.4	0.4	3.4	0.2	2.0	0.5	4.0	0.0	0.3	0.5	4.0
7	113.2	3.3	2.9	2.3	2.0	4.0	3.5	0.0	0.0	4.0	3.5
8	722.7	21.9	3.0	23.7	3.3	32.3	4.5	18.7	2.6	37.3	5.2

b. Linearity/assay reportable range:

The linearity of QUANTA Flash RF IgM and QUANTA Flash RF IgA was evaluated by a study performed according to CLSI EP6-A. The linearity was evaluated using four human serum samples for the QUANTA Flash RF IgM and three human serum samples for the QUANTA Flash RF IgA with various RF antibody concentrations which were combined with another human serum sample containing low levels of RF antibodies in 10% increments (from 0% to 90% of low sample) to obtain a set of samples with values that cover the entire analytical measuring range (AMR) of the assays. The dilutions were assayed in duplicates. Results were

analyzed according to the guideline performing regression analysis and identifying the best fitting polynomial.

For the QUANTA Flash RF IgM, the results of the analysis of sample sets 1, 2, and 4 demonstrate that that the best fitting polynomial is a linear one. For sample set 3, the best fitting polynomial found was a second order polynomial. The deviation from linearity between the linear regression and the second order polynomial met the acceptance criteria. All four sample sets showed dilution linearity individually and in combination:

RF IgM Sample Set	Test Range (CU)	Slope (95% CI)	Y-intercept (95% CI)	R^2	Avg % Recovery
1	60.5 – 544.1	0.92 (0.88 – 0.96)	25.9 (11.9 – 39.9)	0.99	104.0%
2	10.8 – 108.3	1.04 (0.99 – 1.10)	0.6 (-2.8 – 4.0)	0.99	105.6%
3	1.5 – 15.3	1.00 (0.95 – 1.05)	-0.6 (1.1 – -0.1)	0.99	91.2%
4	0.2 – 1.5	1.07 (0.99 – 1.14)	-0.1 (-0.1 – 0.0)	0.98	96.7%
Combined	0.2 – 544.1	0.98 (0.97 – 0.99)	2.7 (0.5 – 4.9)	1.00	99.3%

For the QUANTA Flash RF IgA, sample sets 2 and 3 were found linear For sample set 1, the best fitting polynomial found was a third order polynomial. The deviation from linearity between the linear regression and the second order polynomial met the acceptance criteria.

RF IgA Sample Set	Test Range (CU)	Slope (95% CI)	Y-intercept (95% CI)	R^2	Avg % Recovery
1	104.5 – 1045.0	1.00 (0.96 – 1.04)	12.8 (-12.4 – 38.1)	0.99	102.9%
2	10.8 – 107.7	0.94 (0.90 – 0.98)	5.1 (2.7 – 7.6)	0.99	106.6%
3	1.1 – 11.1	0.97 (0.92 – 1.02)	0.3 (-0.1 – 0.6)	0.99	104.9%
Combined	1.1 – 1045.0	1.01 (1.00 – 1.02)	1.7 (-2.8 – 6.2)	1.00	104.8%

Auto-rerun: For both assays, the auto-rerun function was validated by testing samples greater than the highest value that can be directly measured (three samples > 490 IU/mL for the RF IgM assay and two samples > 900 CU for the RF IgA assay) with the auto-rerun feature enabled. The same samples were also run after being manually diluted 20-fold. The results of the manually-diluted samples were multiplied by 20,

and compared with the results obtained by the instrument with the auto-rerun feature. Obtained results were divided by expected results (those obtained after manual dilution) to calculate percent recovery. Recovery values were 93.5%, 99.6% and 104.9%, with an average of 99.3% recovery for the RF IgM assay. Recovery values were 104.0% and 104.9%, with an average of 104.4% recovery for the RF IgA assay.

Hook effect: Two high positive samples with RF IgM concentrations above the assay measuring range (1755.2 IU/mL and 1830.6 IU/mL) were tested to evaluate a potential hook effect. No hook effect was observed up to 1830.6 IU/mL. Two high positive samples with RF IgA concentrations above the assay measuring range (3151.8 CU and 42710.4 CU) were tested to evaluate a potential hook effect. No hook effect was observed up to 42710.4 CU.

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

Traceability: For the QUANTA Flash RF IgM, Master Curve Standards are traceable to the WHO Reference Reagent – Rheumatoid Arthritis Serum (NIBSC code: W1066). Based upon this standardization, results are reported in International Units (IU)/mL. For the QUANTA Flash RF IgA, no international standard serum for RF IgA antibodies is available that allows for the standardization of RF IgA antibody assays.

Stability:
Kit stability (unopened): The real-time and accelerated stability of each kit was tested using three lots of kits (with three different lots of RF IgM or RF IgA paramagnetic beads), calibrators, and controls. Both the real-time and accelerated stability testing supports a claim of one year at stability for unopened kits, calibrators and controls stored at 2–8°C.

Opened Reagent Cartridges: To establish the in-use stability of each assay, two lots of cartridges were tested with eight RF IgM and six RF IgA specimens (with different reactivity levels) along with the Negative and Positive Controls. The specimens were tested periodically for 91 days and the results were compared to internal criteria. The onboard stability of both assays was set at 80 days.

Sample stability: For the QUANTA Flash RF IgM, five human serum samples, (one negative, one around the cut-off , and three positive samples) and for the QUANTA Flash RF IgA four human serum samples, (one negative, one around the cut-off, and two positive samples) were tested in duplicates for up to 21 days while stored at 2–8°C; up to 48 hours while stored at room temperature; and after repeated freeze/thaw cycles up to three cycles. Results were compared to those obtained on control samples at time zero. Based on the results, the sponsor recommends that the samples can be stored up to 48 hours at room temperature; up to 14 days at 2–8°C; and can be subjected to up to three freeze/thaw cycles (when samples are stored at or below −20°C).

d. Detection limit:

Limit of Blank (LoB): The LoB of each assay was determined by assaying four system rinse (blank) samples in five replicates per sample over three days with two reagent lots. A total of 60 data points per lot were generated. The LoB for each lot was calculated separately. The LoB of both two RF IgM lots was below the measuring range and was determined to be 0.0 IU/mL (415 RLU) and 0.0 IU/mL (450 RLU). The claimed LoB value for the QUANTA Flash RF IgM assay is 0.0 IU/mL. The LoB of both two QUANTA Flash RF IgA lots was determined to be 0.3 CU and 0.1 CU/mL. The claimed LoB value for the RF IgA assay is 0.3 CU.

Limit of Detection (LoD): The LoD of each assay was determined by assaying four low-level samples with RF IgM or RF IgA tested in five replicates over three days on two reagent lots (60 replicates per lot). The LoD value was determined consistent with CLSI EP17-A2 guideline with proportions of false positives (alpha) less than 5% and false negatives (beta) less than 5%. The determined LoD of the QUANTA Flash RF IgM assay for the two lots were below the measuring range of one lot (0.0 IU/mL) and 0.1 IU/mL for the other; the claimed LoD is 0.1 IU/mL. The determined LoD of both lots of the QUANTA Flash RF IgA assay was 0.5 CU; the claimed LoD is 0.5 CU.

Limit of Quantitation (LoQ): The LoQ of both assays was determined by testing four low level samples run in replicates of five for three days on two reagent lots (30 replicates per sample). The LoQ was determined with a total within-laboratory imprecision of 20%. The claimed QUANTA Flash RF IgM LoQ is 0.3 IU/mL while the claimed QUANTA Flash RF IgA is 1.2 CU.

e. Analytical specificity:

The interference studies were performed according to CLSI EP07-A2. Four serum specimens were tested (negative: near the cut-off, low positive, and high positive) for each assay. Interfering substances were spiked into every specimen in 10% of total specimen volume, and the resulting samples were assessed in triplicate. Recovery of the unit values was calculated compared to control samples spiked with the same volume of diluent (10% of total). No interference was identified in either assays by the following substances at the stated concentrations:

Endogenous Interferent	Concentration		Exogenous Interferent	Concentration
Bilirubin (Conjugated)	1 mg/mL		Ascorbic Acid	60.1 mg/L
Cholesterol	332.5 mg/dL		Methotrexate	9.1 mg/mL
Hemoglobin	2 mg/mL		Prednisone	0.3 mg/L
Human IgG	70 mg/mL			
Triglyceride	1000 mg/dL			

f. Assay cut-off:

The cut-offs of the QUANTA Flash RF assays was determined by testing a set of samples from a reference population of 191 samples [117 apparently healthy donors; 27 infectious disease controls; 13 false positive samples; 12 antiphospholipid syndrome; 9 systemic lupus erythematosus; 8 celiac diseas;, and 5 vasculitis]. The cut-off was established based on the 95th percentile of the results obtained on the reference subjects, along with the results of 42 samples from patients with rheumatoid arthritis, to provide optimal differentiation between positive and negative samples. From these studies, the RF IgM cut-off was assigned at 5 IU/mL and the RF IgA cut-off was assigned at 6 CU.

2. Comparison studies:

a. Method comparison with predicate device:

Samples from the clinical validation studies (see below) were tested with QUANTA Flash RF assays and the predicate QUANTA Lite RF assays. Samples within the assays' measuring ranges were included in the method comparison analysis (577 for the RF IgM assay and 612 samples for the RF IgA assay).

		Quanta Lite RF IgM		
		Negative	Positive	Total
Quanta Flash RF IgM	Negative	291	52	343
	Positive	11	223	234
	Total	302	275	577

Positive percent agreement: 81.1% (223/275) 95% CI: 76.0%–85.3%
Negative percent agreement: 96.4% (291/302) 95% CI: 93.6%–98.0%

		Quanta Lite RF IgA		
		Negative	Positive	Total
Quanta Flash RF IgA	Negative	385	27	412
	Positive	10	190	200
	Total	395	217	612

Positive percent agreement: 87.6% (190/217) 95% CI: 82.5%–91.3%
Negative percent agreement: 97.5% (385/395) 95% CI: 95.4%–98.6%

b. Matrix comparison:

Not applicable; these assays indicate serum only.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:

A total of 706 samples were included in the clinical evaluation for the QUANTA Flash RF IgM and IgA assays. This validation set of samples included 296 samples from patients with Rheumatoid Arthritis (RA); samples from patients with other autoimmune diseases (e.g., systemic lupus erythematous (SLE), Sjögren's syndrome, Crohn's disease, autoimmune hepatitis); and samples from patients with other diseases (e.g., osteoarthritis, and infectious diseases). Clinical sensitivity and specificity for RA is summarized in the following tables:

		Clinical Diagnosis of RA		
		Positive	Negative	Total
QUANTA Flash RF IgM	Positive	206	48	254
	Negative	90	362	452
	Total	296	410	706

Sensitivity: 69.6% (95% CI: 64.1–74.6%)
Specificity: 88.3% (95% CI: 84.8–91.1%)

		Clinical Diagnosis of RA		
		Positive	Negative	Total
QUANTA Flash RF IgA	Positive	168	39	207
	Negative	128	371	499
	Total	296	410	669

Sensitivity: 56.8% (95% CI: 51.1 – 62.3%)
Specificity: 90.5% (95% CI: 87.3 – 93.0%)

The distribution of the cohort and the RF IgM and RF IgA positivity rate for each clinical subgroup are summarized below:

Diagnosis Group	N	RF IgM N Positive	RF IgM % Positive	RF IgA N Positive	RF IgA % Positive
Rheumatoid Arthritis	296	206	69.6%	168	56.8%
Other autoimmune diseases					
Systemic lupus erythematosus	28	4	14.3%	4	14.3%
Mixed Connective Tissue Disease	8	1	12.5%	1	12.5%
Sjögren's Syndrome	30	7	23.3%	6	20.0%
Polymyositis	10	3	30.0%	2	20.0%
Dermatomyositis	5	2	40.0%	0	0
Autoimmune Hepatitis	30	0	0	1	3.3%
Hashimoto's Disease	8	0	0	0	0
Grave's Disease	6	1	16.7%	0	0
Ulcerative Colitis	50	8	16.0%	10	20.0%
Crohn's Disease	30	3	10.0%	2	6.7%
Celiac Disease	29	0	0	0	0
Other diseases					
Osteoarthritis	30	3	10.0%	0	0
Psoriatic Arthritis	12	0	0	0	0
Polymyalgia Rheumatica	15	2	13.3%	0	0
Fibromyalgia	10	1	10.0%	0	0
Ankylosing Spondylitis	8	0	0	0	0
Infectious diseases					
Hepatitis B	20	1	5.0%	0	0
Hepatitis C	19	0	0	1	5.3%
Syphilis	12	1	8.3%	0	0
Parvovirus	10	2	20.0%	2	20.0%
Lyme Disease	10	0	0	0	0
Total Controls	410	48	11.7%	39	9.5%
Total	706				

4. Clinical cut-off**:**

   Not applicable.

5. Expected values/Reference range:

The expected value in the normal population is negative.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.