510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K182747

B. Purpose for Submission:

Addition of previously cleared assays on new instrument platform (Phadia 2500/5000)

C. Measurand:

Rheumatoid Factor (RF) IgM

D. Type of Test:

Automated quantitative solid-phase fluoroimmunoassays

E. Applicant:

Phadia AB

F. Proprietary and Established Names:

EliA RF IgM Immunoassay

G. Regulatory Information:

1. Regulatory 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 use:

   EliA RF IgM is intended for the in vitro quantitative measurement of IgM class rheumatoid factor antibodies in human serum and plasma (Li-heparin, EDTA) to aid in the diagnosis of rheumatoid arthritis in conjunction with other laboratory and clinical findings. EliA RF IgM uses the EliA IgM method on the instrument Phadia 2500/5000.

2. Indication for use:

   Same as Intended Use

3. Special conditions for use statement:

   Prescription use only

4. Special instrument requirements:

   For use on the Phadia 2500 and Phadia 5000 instruments

I. Device Description:

EliA uses a modular reagent system. The assay-specific, method-specific and general reagents are packaged and purchased as separate units. The reagents on Phadia 2500 and Phadia 5000 are identical; they are only filled in different containers.

(1) EliA Assay-specific reagent:

- EliA RF IgM Wells are coated with aggregated rabbit IgG – four carriers (12 wells each), ready to use;

(2) EliA Method-specific reagents:

- EliA IgM Conjugate 50 or 200: β-Galactosidase labeled anti-IgM (mouse monoclonal antibodies) in PBS containing BSA and 0.06% (w/v) sodium azide in six wedge-shaped bottles, 5 mL each, ready to use; or six wedge shaped bottles, 19 mL each, ready to use
- EliA IgM Calibrator Strips: Human IgM (0, 10, 35, 80, 500, 1000 µg/L) in PBS

containing BSA, detergent and 0.095% (w/v) sodium azide – five strips, six single- use vials per strip, 0.3 mL each, ready to use;

- EliA IgM Curve Control Strips: Human IgM (80 µg/L) in PBS containing BSA, detergent and 0.095% (w/v) sodium azide – five strips, six single-use vials per strip, 0.3 mL each, ready to use;
- EliA IgM Calibrator Well: Coated with mouse monoclonal antibodies – four carriers (12 wells each), ready to use.
- EliA Sample Diluent: PBS containing BSA, detergent and 0.095% (w/v) sodium azide – six bottles, 48 mL each, ready to use; or six bottles, 400 mL each, ready to use;

(3) EliA General reagents:

- Development Solution (0.01 %4-Methylumbelliferyl-β-D-galacto-side, <0.0010% preservative), ready for use;
- Stop Solution (4% Sodium Carbonate), ready for use;
- Dilution Wells (high density polyethylene wells), 50 carriers, ready to use;
- Pipette Tips in Racks (polyethylene tips), 24 racks × 160 tips, ready for use;
- Washing Solution (information in separate Washing Solution package insert)

Phadia 2500 and Phadia 5000 are identical instruments except for sample throughput. Phadia 2500 consists of one process module (two process lines), whereas Phadia 5000 consists of two process modules (2 x 2 process lines). Instrument operation is handled by onboard Instrument Software (ISW). Data output is administered by Information Data Manager (IDM). All steps of an assay are performed within a single process line. Thus, study protocols used for Phadia 2500 are also valid for Phadia 5000.

J. Substantial Equivalence Information:

1. Predicate device name:

   EliA RF IgM on Phadia 250 instrument

2. Predicate 510(k) number:

   K102673

3. Comparison with predicate:

Similarities		
Item	**Predicate Device Phadia 250**	**Test Device Phadia 2500/5000**
Intended Use/Indications for Use	EliA RF IgM is intended for the in vitro quantitative measurement of IgM class rheumatoid factor antibodies in serum and plasma (Li-heparin, EDTA, citrate) to aid in the diagnosis of rheumatoid arthritis in conjunction with other laboratory and clinical findings. EliA RF IgM uses the EliA IgM method on the instrument Phadia 250.	EliA RF IgM is intended for the in vitro quantitative measurement of IgM class rheumatoid factor antibodies in human serum and plasma (Li-heparin, EDTA) to aid in the diagnosis of rheumatoid arthritis in conjunction with other laboratory and clinical findings. EliA RF IgM uses the EliA IgM method on the instrument Phadia 2500/5000.
Analytical technology	Immunofluorescence measurement	Same
Reagents	Common Phadia EliA assay components	Same
Result calculation software	Phadia Information Data Manager (IDM)	Same
Assay Cutoff	Negative: < 3.5 EliA U/mL Equivocal: 3.5–5.0 EliA U/mL Positive: > 5.0 EliA U/mL	Same
Traceability	IRP 67/86 of Human Serum IgA, G, M from World Health Organization	Same
Sample volume	90 µL (20 µL of non-diluted sample)	Same
Incubation temperature	37°C	Same
Conjugate volume	90 µL	Same
Development Solution Volume	90 µL	Same
Stop Solution Volume	200 µL	Same
Assay set-up	Random access	Same

Similarities		
Item	**Predicate Device Phadia 250**	**Test Device Phadia 2500/5000**
Reagent packaging size	Various/Common	Same
Onboard storage of reagents	Yes	Same
Time to 1st result	~2 hours	Same

Differences		
Item	**Predicate Device Phadia 250**	**Test Device Phadia 2500/5000**
Sample matrix	Human serum or plasma (heparin, EDTA, citrate)	Human serum or plasma (Li-heparin, EDTA); i.e. citrate plasma is omitted for all tests
Instrument Platform	Phadia 250 (ImmunoCAP 250)	Phadia 2500 / 5000
Measuring Range	0.5 – 200 U/mL	1.0 – 200 U/mL
Daily throughput	~250 tests	Phadia 2500: ~2500 tests Phadia 5000: ~5000 tests
Sample Dilution	Phadia 250 uses a steel pipette to dilute the samples in Dilution Plates	Phadia 2500/5000 uses disposable Pipette Tips in Racks for pipetting samples in Dilution Well
Risk for carry-over	The warning "DO NOT REUSE" in the Phadia 250 DFU for EliA Conjugates is due to the fact that a low risk of conjugate contamination by carry-over from samples was identified. In order to reduce the risk, the single use statement for the conjugate was included in the Phadia 250 DFU.	When running EliA tests on the Phadia 2500/5000 instruments, there is no need for this warning statement because these instruments use disposable tips for pipetting samples and a separate pipette for the conjugate, and carry-over from samples to conjugate is impossible.

Differences		
Item	**Predicate Device Phadia 250**	**Test Device Phadia 2500/5000**
Loading of EliA Carriers	EliA carriers are loaded manually on the Loading Tray from where they can be processed directly or transferred to the cooled storage compartment.	The Phadia 2500/5000 instruments do not have such a Loading Tray. The EliA carriers are loaded into racks which are directly transferred to the cooled storage compartment.
Barcode reader	The Phadia 250 instrument has a built-in barcode reader at the front of the instrument, but the operator needs to scan the barcodes manually by showing the reagents to the barcode reader. Alternatively, the operator can also enter the characters below the barcode manually.	The Phadia 2500/5000 instruments dispose of a built-in barcode reader, and the reagents are on a moving belt which conveys them past the barcode reader. The lot-specific information will be read automatically by the instrument during loading.
Process time / Time to patient result	Phadia 250 needs one minute to process one well and provides the results at a 1-minute interval.	Phadia 2500/5000 processes two wells in parallel in 48 seconds and provides the results at a 24-second interval.

K. Standard/Guidance Documents Referenced:

- CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; September 2014
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; April 2003
- CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

EliA tests are fluorescence immunoassays for the detection and measurement of human antibodies based on EliA solid-phase components, which contain specific antigens for the antibodies to be measured.

The EliA wells are coated with aggregated rabbit IgG antigen. If present in the patient's specimen, antibodies (RF) to these proteins bind to the specific antigen. After washing away non-bound antibodies, enzyme-labeled antibodies against human IgM antibodies (EliA IgM Conjugate) are added to form an antibody-conjugate complex. After incubation, non-bound conjugate is washed away, and the bound complex is incubated with a Development Solution. After stopping the reaction, the fluorescence in the reaction mixture is measured. The assay directly measures the amount of antibody of interest bound to the antigen coating the EliA well, therefore the higher the value of fluorescent signal detected by the instrument, the higher the amount of antibody bound and detected in the sample tested. To evaluate test results, the response for patient samples is compared directly to the response for calibrators.

M. Performance Characteristics:

1. Analytical performance:

All results presented below met the manufacturer's pre-determined acceptance criteria for all analytical performance studies.

a. Precision/Reproducibility:

To determine the precision of the assay, the variability was assessed in a study with a total of 21 runs (three instruments total and seven runs per instrument). The study was performed with a single run/day over a period of seven days. Each sample was tested in four replicates/run giving in total 84 replicates per sample (3 instruments × 7 runs x 4 replicates = 84). The data were calculated against the calibration curve from Day 1. Five native patient serum samples were tested: one negative, one in the equivocal range, and three positive specimens. All samples were tested on all instruments. The results are summarized in the tables below:

Sample	Mean (EliA U/mL)	Within-Run		Between-Run		Between-instrument		Total Imprecision	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	1.6	0.2	12.7	0.1	7.1	0.1	4.2	0.2	15.2
2	3.9	0.2	5.0	0.2	4.5	0.2	6.0	0.3	9.0
3	7.0	0.3	4.8	0.2	3.1	0.4	5.3	0.5	7.8
4	73.7	1.8	2.5	3.1	4.2	5.3	7.2	6.4	8.7
5	169.6	7.3	4.3	7.9	4.6	10.8	6.4	15.2	9.0

b. Linearity/assay reportable range:

Four patient serum samples were diluted in EliA Sample Diluent and tested in triplicate with one lot of EliA RF IgM and one set of system reagents on Phadia 2500/5000. The results of the dilutions were compared with their expected values. The ratio observed/expected (O/E) was calculated. Mean observed value was used in the calculation. The results of the regression analysis are summarized in the tables below:

Sample	Dilution Range (EliA U/mL)	Slope (95% CI)	Intercept (95% CI)	R^2	%CV Range
1	0.9–41.0	1.02 (0.97–1.07)	0.37 (−0.42–1.16)	1.00	0.6–7.1
2	0.9–29.2	1.02 (0.97–1.07)	0.18 (−0.43–0.79)	1.00	1.0–8.0
3	2.2–195.5	0.96 (0.91–1.01)	−1.11 (−5.02–2.80)	0.99	0.3–4.3
4	0.8–71.5	1.01 (0.99–1.03)	0.24 (−0.27–0.75)	1.00	0.5–11.3

The reportable range (Limit of Detection, upper limit) for EliA RF IgM is from 0.6 to 200 EliA U/mL. The measuring range (Limit of Quantitation, upper limit) is from 1.0 to 200 EliA U/mL.

The following statements are included in the package inserts: "*Please note that concentration values between LoD and LoQ may show a higher uncertainty."* and "*Please note that due to differing binding characteristics of the antibodies in patient samples, not all sera can be diluted linearly within the measuring range*."

The hook effect was previously reviewed in K102673

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

Same as in the predicate devices. Refer to K102673.

d. Detection limit:

The limit of blank (LoB) and limit of detection (LoD) studies were performed on a Phadia 2500 instrument. LoB was measured in two assay runs with each run including a blank sample in 33 replicates, giving a total of 66 replicates. LoD was measured in

two assay runs by testing three low level serum samples in 11 replicates per sample in a run, giving a total of 66 replicates. The limit of quantitation (LoQ) was based on 66 determinations and a precision target of 20%. The results are summarized in the table below:

EliA RF IgM (EliA U/mL)	LoB	LoD	LoQ
Phadia 2500/5000	0.2	0.6	1.0

e. Analytical specificity:

i) Interference:
Interference by endogenous substances was previously reviewed in K102673.

ii) Carry-over:
The Phadia 2500/5000 instruments use disposable tips for pipetting samples and a separate pipette for the conjugate, therefore carry-over from samples to conjugate was not evaluated.

f. Assay cut-off:

The assay cut-offs are the same as in the predicate devices and are summarized in the tables below:

< 3.5 EliA U/mL	Negative
3.5–5.0 EliA U/mL	Equivocal
> 5.0 EliA U/mL	Positive

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2. Comparison studies:

a. Method comparison with predicate device:

See 2c. Instrument Comparison below.

b. Matrix comparison:

Matrix comparison between serum and plasma was reviewed in K102673.

c. Instrument comparison:

The purpose of this study was to evaluate conformance and show comparability of EliA RF IgM on the Phadia 250 instrument versus the Phadia 2500/5000 instrument.

A total of 105 samples (77 positive, 18 negative, and 10 equivocal samples) were run in singlicate on one Phadia 250 and three Phadia 2500/5000 instruments for

comparison. Only samples inside the measuring range were included in the calculations. Results were analyzed by Passing-Bablok regression. The results are summarized below:

Instrument	Range Tested (EliA U/mL)	Intercept (95% CI)	Slope (95% CI)	*R
PH2500/5000 A	0.9–196.8	0.068 (−0.097 to 0.447)	0.996 (0.969–1.012)	0.998
PH2500/5000 B	0.9–195.9	0.421 (0.188–0.755)	0.983 (0.953–1.017)	0.995
PH2500/5000 C	0.8–196.8	−0.023 (−0.264 to 0.210)	1.061 (1.044–1.078)	0.997
*Pearson correlation coefficient				

Positive percent agreement (PPA), negative percent agreement (NPA), and total percent agreement (TPA) were evaluated for each instrument pair comparison with equivocal results considered positive in the table below:

	PH2500/5000 A	PH2500/5000 B	PH2500/5000 C
PPA (95% CI)	100.0% (95.9%–100.0%)	100.0% (95.9%–100.0%)	100.0% (95.7%–100.0%)
NPA (95% CI)	82.4% (56.6%–96.2%)	88.9% (65.3%–98.6%)	77.8% (52.4%–93.6%)
TPA (95% CI)	97.1% (91.8%–99.4%)	98.1% (93.3%–99.8%)	96.0% (90.2%–98.9%)

Results when equivocal results are considered negative are presented in the table below:

	PH2500/5000 A	PH2500/5000 B	PH2500/5000 C
PPA (95% CI)	98.7% (93.0%–100.0%)	100.0% (95.3%–100.0%)	100.0% (95.1%–100.0%)
NPA (95% CI)	96.3% (81.0%–99.9%)	100.0% (87.7%–100.0%)	96.4% (81.7%–99.9%)
TPA (95% CI)	98.1% (93.2%–99.8%)	100.0% (96.6%–100.0%)	99.0% (94.6%–100.0%)

No sample switched from negative to positive or vice versa. Five samples in the negative range were tested equivocal. Two samples in the equivocal range were tested positive and one sample in the positive range were tested equivocal.

3. Clinical studies:

a. Clinical Sensitivity and specificity:

Clinical performance values were reviewed in K102673.

b. Other clinical supportive data (when. a is not applicable):

Not Applicable.

4. Clinical cut-off:

Same as assay cut-off

5. Expected values/Reference range:

The frequency distribution for RF IgM antibodies was investigated in a group of apparently healthy subjects (N=400) equally distributed by age and gender, using sera from a Caucasian population obtained from a blood bank. Five samples were within the equivocal and nine samples were within the positive range. The results are given in the table below all measurements are shown in EliA U/mL:

Test	N	Mean	Median	Range	95th Percentile	99th Percentile
EliA RF IgM on Phadia 2500/5000	400	0.9	<1.0*	0.0–47.0	2.9	19.2

*Any test result lower than LoQ was indicated <1.0 EliA U/mL.

N. Proposed Labelling:

The labelling is sufficient, and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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