

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY**

A. 510(k) Number:

K183007

B. Purpose for Submission:

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

C. Measurand:

IgG autoantibodies specific to Sm protein (Sm) D component

D. Type of Test:

Automated semi-quantitative solid-phase fluoroimmunoassay

E. Applicant:

Phadia AB

F. Proprietary and Established Name:

EliA SmD^P Immunoassay

G. Regulatory Information:

1. Regulatory Section:

21 CFR 866.5100, Antinuclear antibody immunological test system

2. Classification:

Class II

3. Product Codes:

LKP: Anti-Sm Antibody, Antigen and Control

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use:

EliA SmD^P is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to Sm in human serum and EDTA-plasma to aid in the clinical diagnosis of systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings. EliA SmD^P uses the EliA IgG 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 SmD^P Wells are coated with a synthetic SmD3 peptide – four carriers (12 wells each), ready to use;

(2) EliA Method-specific reagent:

- EliA IgG Calibrator Strips: Human IgG (0, 4, 10, 20, 100, 600 µg/L) in PBS containing BSA, detergent and 0.095% (w/v) sodium azide in five strips, six single-use vials per strip, 0.3 mL each, ready to use;
- EliA IgG Curve Control Strips: Human IgG (20 µg/L) in PBS containing BSA, detergent and 0.095% (w/v) sodium azide in five strips, six single-use vials per strip, 0.3 mL each, ready to use;
- EliA Sample Diluent: PBS containing BSA, detergent and 0.095% (w/v) sodium azide in six bottles, 48 mL each, ready to use; or six bottles, 400 mL each, ready to use;

- EliA IgG Conjugate 50 or 200: β -Galactosidase labeled anti-IgG (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 IgG Calibrator Well: Coated with mouse monoclonal antibodies in four carriers (12 wells 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 $\times$ 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. The 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 SmD^P on Phadia 250 instrument

2. Predicate 510(k) number:

K132631

3. Comparison with predicate:

Similarities		
Item	Predicate Device Phadia 250	Test Device Phadia 2500/5000
Intended Use/Indications for Use	EliA SmD ^P is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to Sm in human serum and plasma (EDTA, citrate) as an aid in the clinical diagnosis of systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings. EliA SmD ^P uses the EliA IgG method on the instrument Phadia 250.	EliA SmD ^P is intended for the in vitro semi-quantitative measurement of IgG antibodies directed to Sm in human serum and EDTA-plasma to aid in the clinical diagnosis of systemic lupus erythematosus (SLE) in conjunction with other laboratory and clinical findings. EliA SmD ^P uses the EliA IgG method on the instrument Phadia 2500/5000.
Analytical technology	Immuno-fluorescence measurement	Same
Reagents	Common Phadia EliA assay components	Same
Result calculation software	Phadia Information Data Manager (IDM)	Same
Assay cutoff / results interpretation	Negative: < 7 EliA U/mL Equivocal: 7–10 EliA U/mL Positive: > 10 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
Reagent packaging size	Various/Common	Same

Similarities		
Item	Predicate Device Phadia 250	Test Device Phadia 2500/5000
Onboard storage of reagents	Yes	Same
Time to 1 st 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)
Instrument Platform	Phadia 250 (ImmunoCAP 250)	Phadia 2500 / 5000
Measuring Range	0.8 – 480 U/mL	1.6 – 480 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.
Loading of EliA carriers	The 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.

Differences		
Item	Predicate Device Phadia 250	Test Device Phadia 2500/5000
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 a synthetic SmD₃ peptide. If present in the patient's specimen, antibodies to SmD₃ peptide bind to the specific antigen. After washing away non-bound antibodies, enzyme-labeled antibodies against human IgG antibodies (EliA IgG 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 higher the response value, 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 $\times$ 7 runs $\times$ 4 replicates = 84). The data were calculated against the calibration curve from Day 1. Five native patient serum samples were tested: one negative, two in the equivocal range, and two 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	2.2	0.2	8.7	0.2	11.0	0.4	20.5	0.5	24.8
2	7.1	0.3	3.6	0.2	2.8	0.3	4.7	0.5	6.5
3	10.0	0.4	3.7	0.2	1.9	0.8	7.7	0.9	8.8
4	146.6	5.1	3.5	3.7	2.5	7.2	4.9	9.5	6.5
5	408.1	15.5	3.8	9.8	2.4	31.1	7.6	36.1	8.8

b. Linearity/assay reportable range:

Four patient serum samples were diluted in EliA Sample Diluent and tested in triplicate with one lot of EliA SmDP immunoassay 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	6.5–285.5	1.04 (0.95–1.12)	4.21 (–5.70–4.21)	0.99	2.7–15.4
2	8.7–392.8	0.98 (0.94–1.02)	–0.56 (–7.29 to –0.56)	1.00	0.8–10.3
3	27.1–537.4	1.01 (0.97–1.05)	–10.58 (–21.14 to –0.03)	1.00	2.9–8.6
4	0.9–11.4	1.01 (0.99–1.02)	–0.09 (–0.19–0.01)	1.00	1.6–7.2

The reportable range (Limit of Detection to upper limit) for EliA SmD^P is from 0.8 to 480 EliA U/mL. The measuring range (Limit of Quantitation to upper limit) is from 1.6 to 480 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 K132631.

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

Same as in the predicate devices. Refer to K132631.

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 six assay runs with each run including a blank sample in 12 replicates, giving a total of 72 replicates. LoD was measured in six assay runs by testing five low level serum samples in 12 replicates per sample in a run, giving a total of 360 replicates. The limit of quantitation (LoQ) was based on 360 determinations and a precision target of 20%. The results are summarized in the table below:

EliA SmD^P Assau (EliA U/mL)	LoB	LoD	LoQ
Phadia 2500/5000	0.3	0.8	1.6

e. Analytical specificity:

i) Interference:

Interference by endogenous substances was previously reviewed in K132631.

ii) Cross-reactivity:

Cross-reactivity was previously reviewed in K132631.

iii) 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 device and are summarized in the tables below:

< 7 EliA U/mL	Negative
7–10 EliA U/mL	Equivocal
> 10 EliA U/mL	Positive

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 K132631.

c. Instrument comparison:

The purpose of this study was to evaluate conformance and show comparability of EliA SmD^P on the Phadia 250 instrument versus the Phadia 2500/5000 instrument. A total of 105 samples (75 positive, 15 negative and 15 equivocal) were run in singlicate on one Phadia 250 instrument 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 and summarized below:

Instrument	Range Tested (EliA U/mL)	Intercept (95% CI)	Slope (95% CI)	*R
PH2500/5000 A	1.3–473.7	0.07 (–0.38–0.53)	1.00 (0.98–1.04)	0.995
PH2500/5000 B	1.0–467.6	0.06 (–0.39–0.24)	1.03 (1.01–1.05)	0.995
PH2500/5000 C	0.9–479.9	–0.34 (–0.70 to –0.08)	1.06 (1.03–1.09)	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)	98.9% (94.0%–100.0%)	98.9% (94.0%–100.0%)	100.0% (96.0%–100.0%)
NPA (95% CI)	93.3% (68.1%–99.8%)	100.0% (73.5%–100.0%)	100.0% (78.2%–100.0%)
TPA (95% CI)	98.1% (93.3%–99.8%)	99.0% (94.7%–100.0%)	100.0% (96.5%–100.0%)

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% (92.8%–100.0%)	100.0% (95.2%–100.0%)	100.0% (95.2%–100.0%)
NPA (95% CI)	86.7% (69.3%–96.2%)	88.9% (70.8%–97.6%)	93.3% (77.9%–99.2%)
TPA (95% CI)	95.2% (89.2%–98.4%)	97.1% (91.6%–99.4%)	98.1% (93.3%–99.8%)

No sample switched from negative to positive. One sample in the negative range was tested equivocal. One sample in the equivocal range was tested negative and four samples in the equivocal range were tested positive. One sample in the positive range was tested equivocal.

3. Clinical studies:

a. Clinical Sensitivity and Specificity:

Clinical performance values were reviewed in K132631.

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 SmD^P 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. None of test samples was within the equivocal or the positive range in the three EliA assays. The test results are given in the table below and all measurements are shown in EliA U/mL:

Test	N	Mean	Median	Range	95 th Percentile	99 th Percentile
EliA SmD ^P on Phadia 2500/5000	400	1.2	1.1	0.0–5.4	2.2	4.2

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.