

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

A. 510(k) Number:

K153560

B. Purpose for Submission:

New Device

C. Measurand:

Albumin

D. Type of Test:

Quantitative Immunoturbidimetric

E. Applicant:

The Binding Site, Ltd.

F. Proprietary and Established Names:

Optilite[®] Low Level Albumin Kit

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5040, Albumin immunological test system

2. Classification:

Class II

3. Product code:

DCF–Albumin antigen, antiserum, control

4. Panel:

Immunology (82)

H. Intended Use:

1. Intended use(s):

The Optilite Low Level Albumin Kit is intended for the quantitative in vitro measurement of albumin in CSF, urine and serum using the Binding Site Optilite analyser to aid in the diagnosis of kidney and intestinal diseases. This test should be used in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:

See Intended use(s)

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

The Binding Site Optilite

I. Device Description:

The Optilite[®] Kit contains a polyclonal sheep anti-human albumin antiserum; a calibrator; two controls (low, high), an antigen excess reagent, and a reaction buffer. All are supplied in a stabilized liquid form.

The antiserum contains 0.099% sodium azide, 0.1% E-amino-n-caproic acid (EACA), 1mM ethylenediamine-tetraacetic acid (EDTA) and 0.01% benzamidine as preservatives. The calibrator and controls contain 0.099% sodium azide, 0.1% EACA and 0.01% benzamidine as preservatives, and the reaction buffer contains 0.099% sodium azide as a preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

N Antiserum to Human Albumin
N Protein Standard SL
NT Protein Control SL

2. Predicate 510(k) number(s):

K972929
K964062
K964065

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Indications for Use/ Intended Use	The Optilite Low Level Albumin Kit is intended for the quantitative in vitro measurement of albumin in CSF, urine and serum using the Binding Site Optilite analyser to aid in the diagnosis of kidney and intestinal diseases. This test should be used in conjunction with other laboratory and clinical findings.	In-vitro diagnostic reagent for the quantitative determination of albumin in human serum, heparinized and EDTA plasma, as well as in human urine and cerebrospinal fluid (CSF) by means of immunonephelometry on the BN Systems.
Sample Matrix	Serum, urine, and CSF	Same (also heparinized and EDTA plasma)
Controls	Low, High	Low, High
Assay Traceability	ERM DA470k/IFCC	Same
Adult Reference Interval	Serum: 35,000–52,000 mg/L Urine: < 30 mg/L CSF: < 350 mg/L	Same

Differences		
Item	Device	Predicate
Test method	Turbidimetry	Nephelometry
Instrument	Binding Site Optilite	Siemens BNII
Detection antibody	Sheep anti-human albumin	Rabbit anti-human albumin
Open Vial Stability	3 months	4 weeks at 2–8°C
On-board stability	30 days	5 days at 8 hours/day for 5mL vials, 3 days at 8 hours/day for 2mL vials
Measuring range, Urine and CSF (Instrument Dilution)	11–333 (1 + 0) 110–3,325 (1 + 9)	2.2–68 (1/1) 11–340 (1/5) 44–1,360 (1/20) 220–6,800 (1/100) 440–27,200 (1/400)
Measuring range, Serum (Instrument Dilution)	2,200–66,500 (1 + 199)	350–5,500 (1/20) 6,900–110,000 (1/100)

K. Standard/Guidance Document Referenced:

- CLSI C28-A3: "Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory"
- CLSI EP05-A2 Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline–Second Edition
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach
- CLSI EP7-A2 Interference Testing in Clinical Chemistry, Approved Guideline–Second Edition
- CLSI EP17-A Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline

L. Test Principle:

The determination of soluble antigen concentration by turbidimetric methods involves the reaction with specific antiserum to form insoluble complexes. When light is passed through the suspension formed a portion of the light is transmitted and focused onto a photodiode by an optical lens system. The amount of transmitted light is indirectly proportional to the specific protein concentration in the test sample. At the end of the reaction, the Antigen Excess Control is added to detect potential antigen excess. Concentrations are automatically calculated by reference to a calibration curve stored within the instrument.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

All manufacturer’s acceptance criteria were met for all studies.

a. *Precision/Reproducibility:*

The precision and reproducibility of the new assay was evaluated by studies based on CLSI EP05-A2, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline–Second Edition*; five sample preparations for each matrix were tested in duplicate in two runs per day over 21 days using three analyzers for a total of 84 replicates per sample. A summary of the results for each sample matrix is shown below:

Serum:

LLAlb Sample	Mean mg/L	Within-Run		Between-Run		Between-Day	
		SD	%CV	SD	%CV	SD	%CV
1	4,012.8	73.3	1.8	96.2	2.4	132.1	3.3
2	14,007.3	179.2	1.3	289.3	2.1	526.5	3.8
3	28,501.1	340.9	1.2	261.4	0.9	714.0	2.5
4	36,976.7	478.1	1.3	314.4	0.9	791.3	2.1

LLAlb Sample	Mean mg/L	Within-Run		Between-Run		Between-Day	
		SD	%CV	SD	%CV	SD	%CV
5	54,447.2	866.6	1.6	843.3	1.5	1357.9	2.5

LLAlb Sample	Mean mg/L	Between-Instrument		Between-Lot		Total Precision	
		SD	%CV	SD	%CV	SD	%CV
1	4,012.8	102.1	2.5	-*	-*	179.1	4.5
2	14,007.3	526.6	3.8	-*	-*	626.8	4.5
3	28,501.1	153.0	0.5	281.8	1.0	833.2	2.9
4	36,976.7	195.7	0.5	235.3	0.6	976.5	2.6
5	54,447.2	767.9	1.4	324.2	0.6	1818.3	3.3

* Samples 1 and 2 in the serum study used four instruments and one reagent lot. It is therefore not possible to calculate between-lot CV or SD.

Urine:

LLAlb Sample	Mean mg/L	Within-Run		Between-Run		Between-Day	
		SD	%CV	SD	%CV	SD	%CV
1	22.98	0.15	0.5	0.57	1.9	0.67	2.2
2	39.04	0.22	0.6	0.68	1.7	1.04	2.7
3	153.4	1.54	1.0	1.29	0.8	2.5	1.6
4	275.05	2.12	0.8	3.7	1.3	7.78	2.8
5	1,490.2	13.3	0.9	22.3	1.5	29.35	2.0

LLAlb Sample	Mean mg/L	Between-Instrument		Between-Lot		Total Precision	
		SD	%CV	SD	%CV	SD	%CV
1	22.98	0.29	1.2	0.22	0.97	0.89	3.0
2	39.04	0.19	0.5	0.1	0.26	1.26	3.2
3	153.4	0.48	0.3	1.34	0.87	3.21	2.1
4	275.05	3.39	1.2	3.32	1.21	8.87	3.2
5	1,490.2	12.53	0.8	14.02	0.94	39.2	2.6

CSF:

LLAlb Sample	Mean mg/L	Within-Run		Between-Run		Between-Day	
		SD	%CV	SD	%CV	SD	%CV
1	145.5	0.98	0.7	1.44	1.0	8.59	5.9
2	281.5	3.55	1.3	2.19	0.8	14.79	5.3
3	439.9	3.72	0.8	6.85	1.6	14.18	3.2

LLAlb Sample	Mean mg/L	Within-Run		Between-Run		Between-Day	
		SD	%CV	SD	%CV	SD	%CV
4	593.1	5.81	1.0	7.08	1.2	19.13	3.2
5	975.2	13.81	1.4	25.08	2.6	74.82	7.7

LLAlb Sample	Mean mg/L	Between-Instrument		Between-Lot		Total Precision	
		SD	%CV	SD	%CV	SD	%CV
1	145.5	1.13	0.8	1.67	1.15	8.77	6.0
2	281.5	4.48	1.6	8.15	2.9	15.37	5.5
3	439.9	10.14	2.3	5.96	1.36	16.18	3.7
4	593.1	7.75	1.3	11.15	1.88	21.21	3.6
5	975.2	13.76	1.4	18.2	1.87	80.11	8.2

b. *Linearity/assay reportable range:*

A linearity study evaluating the analytical measuring range of the standard sample dilution (1 + 0 for CSF and urine and 1 + 199 for serum) was performed following CLSI EP6-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*. A dilution series composed of proportional dilutions of a high pool with a low pool for each sample matrix was tested in three replicates.

The linearity of this assay using the serum matrix has been confirmed using a serially diluted serum sample over the range of 1,960–74,251 mg/L. The linear regression analysis was determined as $y = 1.00x + 9.17$.

The linearity of this assay using the urine matrix has been confirmed using a serially diluted urine sample over the range of 8.1–398 mg/L. The linear regression analysis was determined as $y = 1.00x + 0.12$.

The linearity of this assay using the CSF matrix has been confirmed using a serially diluted CSF sample over the range of 9.2–373 mg/L. The linear regression analysis was determined as $y = 1.00x + 0.22$.

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

Traceability:

The master calibrator is prepared from pooled human sera and is used to control calibration between lots. The master calibrator is used to assign albumin values to assay calibrators and controls during production of each batch of kits; it is traceable to ERM-DA470k/IFCC.

Kit Stability:

Real-time stability—Studies to establish shelf-life stability (from the date of

manufacture when stored at recommended temperature 2–8°C) were previously performed on the 510(k)-cleared kit Human Albumin CSF Kit for use on SPAPLUS (K121045) demonstrating stability up to at least 18 months. This kit contains components manufactured using the same raw materials as the test device, with the exception of the high and low control materials, which are manufactured using a different buffer. Additional real time stability was therefore assessed using three manufacturing lots of control materials. Data supports an 18-month stability claim.

Open-vial stability–Testing established that the Optilite Low Level Albumin Kit Reagent, Calibrator and Controls can be stored, opened at 2–8°C for up to 3 months.

On-board stability–Testing established that the Optilite Low Level Albumin Kit Reagent can be stored on-board the Optilite Analyzer for 30 days at 8–12°C, provided that the power is left switched on as stated in the product insert.

d. *Detection limit:*

The detection limits of the assay were determined for all sample matrices. The evaluations were based on CLSI EP17-A, *Protocols for Determination of Limits of Detection and Limits of Quantitation*. Study results follow the explanation below:

Limit of Blank (LoB): The LoB is defined as the highest result expected in a sample that contains no analyte based on the 95th percentile distribution of blank results. The LoB serum sample was sample diluent, the LoB urine sample was normal donor urine, and the LoB CSF sample was a synthetic CSF fluid that mimics natural CSF without the presence of albumin. The LoB sample was tested 60 times and the mean and standard deviation (SD) were calculated.

Limit of Detection (LoD): The LoD is defined as the lowest amount of analyte in a sample that can be reliably detected. The LoD was calculated from the LoB and the combined SDs of the five LoQ samples: $LoD = LoB + [(1.645 \times SDs)]$.

Limit of Quantitation (LoQ): The LoQ study was performed by analyzing five different samples with a concentration within $\pm 10\%$ of the lowest calibrator value used at the standard dilution. These samples were tested over five days with one batch of reagent to give 60 replicate results. This data demonstrated that the total error (TE) is $< 10\%$ at the bottom of the reference range. Samples were diluted with sample diluent so that the concentrations were close to the bottom of the measuring range at the standard sample dilution (2200 mg/L). Urine samples were spiked with purified human albumin powder so that the concentrations were close to the bottom of the measuring range at the standard sample dilution (11 mg/L). CSF samples were diluted with synthetic CSF so that the concentrations were close to the bottom of the measuring range at the standard sample dilution (11 mg/L).

The claimed analytical sensitivity for each kit is summarized below:

Matrix	LoB	LoD	LoQ
Serum	0 mg/L	67.46 mg/L	2200 mg/L
Urine	1.45 mg/L	1.91 mg/L	11 mg/L
CSF	0.08 mg/L	0.47 mg/L	11 mg/L

e. *Analytical specificity:*

A study was performed following CLSI EP07-A2, *Interference Testing in Clinical Chemistry, Approved Guideline*. Samples were prepared for each interferent test from two sample pools. Minimal assay interference effects were observed when tested with the following substances:

CSF:

Two samples for each interferent, one within the normal range and well below the medical decision point (116.5–159.5 mg/L) and one with a concentration within 25% of the medical decision point (361.4–371.3 mg/L) were tested.

Substance	Concentration	Substance	Concentration
Bilirubin	200 mg/L	Acetaminophen	1324 µmol/L
Hemoglobin	5 g/L	Acetylsalicylic acid	3.63 mmol/L

Urine:

Two samples for each interferent, one with a concentration within 25% of the medical decision point (24.4–36.4 mg/L) and sample with a concentration above the reference range (50.8–230.3 mg/L or 495.8.0 mg/L) were tested.

Substance	Concentration	Substance	Concentration
Ascorbic Acid	200 mg/L	Hemoglobin	250 mg/L
Acetaminophen	1324 µmol/L	Ibuprofen	2425 µmol/L
Furosemide	90 µmol/L	Glybenclamide (glyburide)	3.9 µmol/L
Trichloromethiazide	50 mg/mL	Metformin HCl	8 mg/L
Enalapril maleate	496.7 ng/mL	Losartan	2932 ng/mL
Simvastatin	12.9 ng/mL	Acetone	7000 mg/L
Acetylsalicylic Acid	1500 mg/L	Calcium chloride	780 mg/L
Creatinine	6000 mg/L	Glucose	30,000 mg/L
Magnesium chloride	8000 mg/L	Sodium citrate	1000 mg/L
Sodium oxalate	600 mg/L	Urea	25,000 mg/L
Uric acid	200 mg/L	Urobilinogen	45 mg/L

Serum:

Two samples for each interferent, one with a concentration within 25% of the medical decision point (35,000 mg/L) and the other within the reference range were tested

(45,096–51,187 mg/L).

Substance	Concentration	Substance	Concentration
Bilirubin	200 mg/L	Acetylsalicylic acid	3.6 mmol/L
Hemoglobin	5 g/L	Intralipid	2000 mg/dL
Acetaminophen	1324 µmol/L	Triglycerides	1000 mg/dL

Metronidazole absorbs light at 340nm, the same wavelength used as the assay, thus interfering with the assay. The labelling insert includes a caution that this assay is not suitable for use with patients taking metronidazole.

Antigen Excess: No antigen excess was observed up to a level of 202 times the top of the calibration curve at the standard 1+0 sample dilution. This is equivalent to 67,384 mg/L.

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

For each sample matrix, the results obtained by the Low Level Albumin Kit assay were compared with the results obtained by the predicate assay. Care was taken to include samples that had admission diagnoses relevant to the Intended Use of the assay (e.g., samples from patients with kidney disease were included in the urine matrix study and samples from patients with central nervous system disorders were included in the CSF matrix study) although many of the final diagnoses were not known. Less than 10% of the samples in any of the matrices were contived to cover the measuring range. Only samples within both assays' measuring range were included in the analysis of the results:

Matrix	N	Passing-Bablok Analysis	95 th CI Slope	95 th CI Intercept	Pearsons r value	Sample Range
Serum	142	$y = 1.01x + 932.8$	0.97 – 1.05	-391 – 2,305	0.996	2460–61,000
Urine	122	$y = 1.06x - 0.44$	1.04 – 1.07	-1.28 – 0.31	0.994	12.1–3,225
CSF	164	$y = 1.00x + 11.76$	0.97 – 1.03	6.16 – 16.83	0.988	34.2–3,301

b. *Matrix comparison:*

Not applicable

3. Clinical studies:

a. *Clinical Sensitivity and Specificity:*

Not applicable

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

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The predicate reference ranges for albumin in serum and urine were tested and verified in accordance with CLSI C28-A3, *Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory* using samples from 50 apparently healthy subjects for each analyte. The reference range for albumin in CSF is taken a published literature reference range for albumin in CSF¹.

Normal adult albumin	Range
Serum	35,000–52,000 mg/L
Urine	< 30 mg/L
CSF	< 350 mg/L

N. Proposed Labeling:

The labeling 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.

¹ Reiber H. Reference Ranges of Analytes in CSF and Serum. In: *Laboratory Diagnosis in Neurology*. English 1st Edition Eds. Wildemann B., Oschmann P., Reiber H. THIEME; 2010; 21: 256.