510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:
k083867

B. Purpose for Submission:
New device

C. Measurand:
Sex Hormone Binding Globulin (SHBG)

D. Type of Test:
Quantitative immunoassay

E. Applicant:
Beckman Coulter, Inc.

F. Proprietary and Established Names:
Access Sex Hormone Binding Globulin Reagent
Access Sex Hormone Binding Globulin Calibrators
Access Sex Hormone Binding Globulin Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
JIT	Class II	21 CFR § 862.1150	Clinical Chemistry (75)
CDZ	Class I, reserved	21 CFR § 862.1680	Clinical Chemistry (75)
JJX	Class I, reserved	21 CFR § 862.1660	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   The Access SHBG assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of Sex Hormone Binding Globulin levels in human serum and plasma using the Access Immunoassay Systems. The Access Sex Hormone Binding Globulin assay is indicated for use in the assessment of androgen disorders.

   The Access SHBG Calibrators are intended to calibrate the Access SHBG assay for the quantitative determination of Sex Hormone Binding Globulin levels in human serum and plasma using the Access Immunoassay Systems.

   The Access SHBG QC is intended for monitoring system performance of the Access SHBG assay.

2. Indication(s) for use:
   See intended use(s) above.

3. Special conditions for use statement(s):
   For prescription use only; For *in vitro* diagnostic use

4. Special instrument requirements:
   Performance characteristics were provided for the Access UniCel Dxl 800 Immunoassay System

I. Device Description:

The kit contains the following components:

R1a	Paramagnetic particles coated with mouse monoclonal anti-SHBG in a buffered protein (bovine and mouse) matrix with < 0.1% sodium azide and 0.1% ProClin 300.
R1b	Mouse monoclonal anti-SHBG alkaline phosphatase (bovine) conjugate in a buffered protein (bovine) matrix with < 0.1% sodium azide and 0.1% ProClin 300.
R1c	TRIS buffer with < 0.1% sodium azide and 0.1% ProClin 300.

SHBG calibrators (0, 3, 9, 27, 80 and 200 nmol/L) and SHBG quality controls (10 and 100 nmol/L) are sold separately. All calibrators (except the 0) and controls are prepared from purified human SHBG in a protein (bovine) buffered matrix with < 0.1% sodium azide and 0.1% ProClin 300. All human source materials used in the preparation of the calibrators and controls were tested using FDA-approved methods and found to be non-reactive for the presence of hepatitis B, hepatitis C, HIV-1 and HIV-2.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   DPC Immulite® SHBG

2. Predicate K number(s):
   k941797

3. Comparison with predicate:

Item	Device	Predicate
Similarities		
Intended use	The Access SHBG Assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of SHBG levels in human serum and plasma using the Access Immunoassay Systems. The Access	Immulite SHBG is a solid-phase, two-site chemiluminescent enzyme immunometric assay designed for the quantitative measurement of sex hormone binding globulin (SHBG) in serum. It is intended strictly for in vitro diagnostic use as an aid in the

	SHBG assay is indicated for use in the assessment of androgen disorders.	differential diagnosis of hirsutism.
Product type	Immunoassay	same
Assay format	Chemiluminescent, two-site sandwich immunoassay	same
Differences		
Specimens	Serum or plasma (heparin)	serum
Components	Mouse monoclonal antibody against SHBG in the capture phase and a mouse monoclonal anti-SHBG antibody conjugated to alkaline phosphatase (bovine) in the signal phase.	Mouse monoclonal antibody against SHBG in the capture phase and a polyclonal rabbit anti SHBG antibody conjugated to alkaline phosphatase (bovine) in the signal phase.
Assay range	0.33 to 200 nmol/L	0.5 to 180 nmol/L
Interference	No interference with acetaminophen (200 mg/L), acetylsalicylic acid (652 mg/L), alpha-fetoprotein (492 µg/L), conjugated bilirubin (300 mg/L), unconjugated bilirubin (200 mg/L), cortisol (100 mg/L), 11-deoxycortisol (4 mg/L), 5α-dihydroxytestosterone (20 mg/L), hemoglobin (4 g/L), heparin (72000 U/L), human serum albumin (60 g/L), ibuprofen (0.5 g/L), estradiol (3.6 µg/L), GAS6 (235 µg/L), laminin (6064 µg/L), multivitamin supplement (0.9% v/v), protein S (26 mg/L), testosterone (20 mg/L), thyroglobulin (300 µg/L), thyroxine-binding globulin (193 mg/L), transferring (4 g/L) and triglycerides/Intralipid (50 g/L)	No interference observed with hemolysis or bilirubin.
Cross-reactivity	No cross-reactivity with alpha-fetoprotein (492 µg/L), cortisol (100 mg/L), 5α- dihydroxytestosterone (20 mg/L), 11-deoxycortisol (4 mg/L), estradiol (3.6 µg/L), GAS6 (235 µg/L), laminin (6064 µg/L), protein S (26 mg/L), testosterone (20 mg/L) thyroglobulin (300 µg/L), thyroxine-binding globulin (193 mg/L) and transferring (4 g/L)	No cross-reactivity with alpha-fetoprotein (400 IU/mL), cortisol (100 mg/L), 11-deoxycortisol (4 mg/L), 5α-dihydroxytestosterone (20 mg/L), estradiol (3,600 µg/L), human serum albumin (50 g/L), testosterone (20 mg/L), thyroglobulin (300 µg/L), thyroxine-binding globulin (193 mg/L) and transferring (4 g/L)
LoB, LoD (nmol/L)	Limit of Blank (LoB): 0.017 Limit of Detection (LoD): 0.33	LoD: 0.08
Precision	6.3 nmol/L, total CV% 5.4 38 nmol/L, total CV% 5.3 80 nmol/L, total CV% 5.5 171 nmol/L, total CV% 5.2	Within run precision is 8% at > 4.5 nmol/L; between run precision is 10% at > 12 nmol/L.
Calibrators and controls	Calibrators (0, 3, 9, 27, 80 and 200 nmol/L) and controls (10 and 100	Two SHBG Adjustors designated LOW and HIGH, containing different

	nmol/L) are sold separately. All calibrators (except the 0) and controls are prepared from purified human SHBG and are traceable to WHO 95/560	concentrations of SHBG, are provided with the kit. Traceability is not listed.
Expected values	Males, n=151, median 38.2 nmol/L; 95 percentile, 13.3 - 89.5 nmol/L. Females (nonpregnant) n=141, median 47.2 nmol/L; 95 percentile 18.2-135.5 nmol/L. Female (postmenopausal), n = 131, median 49.6 nmol/L; 95 percentile, 16.8-125.2 nmol/L.	Males, n=122, mean 32 nmol/L; 95 percentile, 13 - 71 nmol/L. Females (nonpregnant), n=111, mean 51 nmol/L; 95 percentile, 18 - 114 nmol/L.

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

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline (EP5-A2)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP7-A2)
- Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (EP17-A)

L. Test Principle:

The Access SHBG assay is a sequential two-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel along with paramagnetic particles coated with anti-SHBG antibody. During incubation, the SHBG antigen in the sample binds to the immobilized anti-SHBG antibody on the solid phase. Alkaline phosphatase conjugated anti-SHBG antibody is then added and reacts with a different antigenic site on the SHBG molecule. After incubation, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added and the light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of SHBG in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   All performance characteristics were performed on the UniCel DxI 800 analyzer.

   a. Precision/Reproducibility:

   The precision of the proposed device was evaluated using a method based on the guideline CLSI EP5-A2 using 4 patient samples. Sample 1 was a serum pool, partly depleted with anti-SHBG paramagnetic particles. Sample 2 and 3 were unaltered serum pools. Sample 4 was pooled serum spiked with human SHBG. The samples were assayed in duplicate, twice

a day (2 runs per day) for 20 days over a 28 day period for a total of 480 measurements per sample. Three separate pack lots and 2 Access UniCel Dxl 800 instrument were used for the study. The results are summarized below:

Sample	n	Mean (nmol/L)	Within run		Between-run		Total	
			SD	CV%	SD	CV%	SD	CV%
1	480	6.3	0.3	4.7	0.2	2.7	0.3	5.4
2	480	38	1.8	4.6	1.1	2.8	2.0	5.3
3	480	80	3.6	4.5	2.5	3.2	4.4	5.5
4	480	171	8.1	4.8	3.7	2.2	9.0	5.2

b. Linearity/assay reportable range:

Linearity studies were performed using 3 serum samples. Sample 1 was spiked with human SHBG to approximately 200nM. Sample 2 was an unaltered sample with approximately 35nM SHBG. Sample 3 was partly depleted with anti-SHBG paramagnetic particles to approximately 3nM SHBG. At least 6 serial dilutions were prepared from each sample using Access Wash Buffer II. Each dilution was tested in 4 replicates; neat sample concentrations were determined as the mean of 8 replicates. The data was analyzed using linear and quadratic models. The quadratic fit was found to be significant. Therefore, the degree of non linearity was assessed by calculating the % difference between the linear and non-linear model at each concentration. The results are summarized below:

Linear fit	Non-Linear fit	Nonlinearity	Nonlinearity %	Expected
0.0000	0.0004	0.0004	+ ∞	0.000
0.1068	0.1190	0.0121	11.4%	0.087
0.3350	0.3310	-0.0041	-1.2%	0.290
1.0669	0.9952	-0.0717	-6.7%	0.968
1.1798	1.0981	-0.0817	-6.9%	1.074
1.5802	1.4645	-0.1157	-7.3%	1.452
2.0896	1.9344	-0.1552	-7.4%	1.936
2.5953	2.4050	-0.1903	-7.3%	2.419
3.1010	2.8793	-0.2218	-7.2%	2.904
3.8037	3.5438	-0.2599	-6.8%	3.581
6.5037	6.1464	-0.3573	-5.5%	6.197
12.3677	11.9778	-0.3899	-3.2%	11.935
18.4248	18.1541	-0.2708	-1.5%	17.903
21.2128	21.0296	-0.1833	-0.9%	20.658
24.4570	24.3937	-0.0633	-0.3%	23.870
30.4600	30.6556	0.1956	0.6%	29.826
36.4742	36.9592	0.4850	1.3%	35.805
69.5758	71.6816	2.1058	3.0%	68.861
103.9005	107.0587	3.1583	3.0%	103.291
138.1333	141.3100	3.1767	2.3%	137.721

172.2347	174.2660	2.0314	1.2%	172.083
206.4251	206.0959	-0.3292	-0.2%	206.582

Based upon the linearity study and the limits of detection, the claimed measuring range is 0.33 to 200 nmol/L.
The package insert states:

- Samples can be accurately measured within the analytical range of the lower limit of detection (0.33 nmol/L) and the highest calibrator value (approximately 200 nmol/L).
  - If a sample contains less than the lower limit of detection for the assay, report the results as less than that value (i.e., < 0.33 nmol/L).
  - If a sample contains more than the stated value of the highest Access SHBG Calibrator (S5), report the result as greater than the value of the highest calibrator. Alternatively, dilute one volume of sample with 9 volumes of Wash Buffer II.

High-dose hook effect: The potential for a high-dose hook effect was evaluated using one patient sample spiked to approximately 49,500 nmol/L SHBG and a second sample obtained by dilution an SHBG stock solution in serum to create a sample with approximately 1000 nmol/L SHBG. The relative light units at 49,500 nmol/L and at 863 nmol/L did not fall below the relative light units generated by the highest SHGB calibrator (S5).

The product insert states:

- The access SHBG assay does not demonstrate any "hook" effect up to 49,500 nmol/L.

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The Access SHBG calibrators (0, 3, 9, 27, 80 and 200 nmol/L) and controls (10 and 100 nmol/L) are traceable to WHO 95/560 reference material. They are sold separately.

Real-time stability including shelf-life and open vial stability studies were performed for the controls and calibrators. The study protocols and statistically calculated acceptance limits were reviewed and found to be acceptable. At the time of submission, the sponsor has demonstrated acceptable unopened shelf life of 12 months for the controls and calibrators when stored at 2 to 8 °C. The sponsor has demonstrated acceptable open vial stability of 28 days for the calibrators and controls when stored at 2 to 8 °C.

Calibration Frequency: The calibration curve is stable for 28 days.

d. Detection limit:
The Limit of Blank (LoB) and the Limit of Detection (LoD) studies were performed in accordance to CLSI EP17-A. For LoB, 156 replicates of the S0 calibrator were measured. The 95th percentile of the replicates was estimated using a non-parametric approach and the 97.5% upper confidence limit of this estimate was used to estimate the LoB. For LoD, 180 replicates of 5 low level samples were measured.

The LoB was estimated to be 0.017 nmol/L
The LoD was estimated to be 0.33 nmol/L

e. Analytical specificity:
Interference from various compounds was evaluated on serum samples containing approximately 13 nmol/L and 140 nmol/L SHBG. The sponsor defined noninterference as <10% deviation from the un-spiked samples. Based on data, the sponsor claims no interference for the substances and concentrations listed in the table below:

Compound	**Concentration added to samples**	
	Low	**High**
Acetaminophen	30 mg/L	200 mg/L
Acetylsalicylic acid	390 mg/L	652 mg/L
Alpha-Fetoprotein (AFP)	74.9 µg/L	492 µg/L
Bilirubin (conjugated)	2.98 mg/L	300 mg/L
Bilirubin (unconjugated)	12.2 mg/dL	200 mg/L
Cortisol	16 µg/L	100 mg/L
11-deoxycortisol	1.58 mg/L	4 mg/L
5α-dihydroxytestosterone	0.85 µg/L	20 mg/L
Hemoglobin	2 g/L	4 g/L
Heparin	1000 U/L	72000 U/L
Human serum albumin (HAS)	51 g/L	60 g/L
Ibuprofen	0.07 g/L	0.5 g/L
Estradiol	750 ng/L	3.6 µg/L
GAS6	63 µg/L	235 µg/L
Laminin	520 µg/L	6064 µg/L
Multivitamin Supplement	0.3 % (v/v)	0.9 % (v/v)
Protein S	3.6 mg/L	26 mg/L
Testosterone	210 ng/L	20 mg/L
Thyroglobulin (Tg)	40 µg/L	300 µg/L
Thyroxine-binding Globulin (TBG)	55 mg/L	193 mg/L
Transferrin	1.3 g/L	4 g/L
Triglycerides (Intralipid)	3.29 g/L	50 g/L

To evaluate the potential cross-reactivity of various compounds whose structure is similar to SHBG the substances were spiked in the Access SHBG calibrator S0. % cross reactivity was calculated as follows:

[(mean test value-mean control value) x 100]/concentration of compound tested.

The following compounds at the listed concentrations were tested:

Substance	Concentration added to samples	
	Low	High
Alpha-fetoprotein (AFP)	74.9 µg/L	492 µg/L
Cortisol	16 µg/L	100 mg/L
5α-dihydroxytestosterone	0.85 µg/L	20 mg/L
11-Deoxycortisol	1.58 mg/L	4 mg/L
Estradiol	750 ng/L	3.6 µg/L
GAS6	63 µg/L	235 µg/L
Laminin	520 µg/L	6064 µg/L
Protein S	3.6 mg/L	26 mg/L
Testosterone	210 ng/L	20 mg/L
Thyroglobulin (Tg)	40 µg/L	300 µg/L
TBG	55 mg/L	193 mg/L
Transferrin	1.3 g/L	4 g/L

The sponsor provided data to support the claim that no significant cross-reactivity (defined as ≤ 1.3%) was observed when the calibrator S0 was spiked with the compounds listed above.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:
To compare the performance of the Access SHBG assay to the predicate device, a total of 158 unaltered serum samples ranging from 5.7 to 184.5 nmol/L SHBG were assayed on both devices. The slope, intercept and confidence interval (CI) were determined using Deming regression; the correlation coefficient (r^2) was determined by linear regression. The results are summarized in the table below:

n	Slope (95% CI)	Intercept (nmol/L) (95% CI)	r^2
158	1.09 (1.06 to 1.12)	1.84 (0.54 to 3.00)	0.94

b. Matrix comparison:
A comparison study was performed following the recommendations in CLSI EP14-A2 with a total of 61 matched serum and plasma (heparin)

samples. All samples were unaltered and ranged from approximately 10 to 200 nmol/L SHBG. Serum samples were collected in plain and gel (SST) tubes. Samples were assayed in 3 replicates on one Access UniCel Dxl 800 instrument. The slope, bias, y-intercept and confidence intervals (CI) were determined using a Deming regression and the correlation coefficient (r^2) was determined by linear regression. The results are summarized in the tables below:

	Slope (95% CI)	**Intercept (nmol/L) (95% CI)**	r^2
Serum gel vs. serum	1.00 (0.97 to 1.063)	-0.84 (-3.04 to -1.36)	0.994
Plasma (heparin) vs. serum	0.99 (0.97 to 1.01)	-0.48 (-2.17 to 1.21)	0.996

3. Clinical studies:
   a. Clinical Sensitivity:
   Not applicable.

   b. Clinical specificity:
   Not applicable.

   c. Other clinical supportive data (when a. and b. are not applicable):
   Not applicable.

4. Clinical cut-off:
   Not applicable.

5. Expected values/Reference range:
   Samples from males, females, and postmenopausal females from the United States were assayed using the proposed device. The inclusion/exclusion criteria are summarized below:

Males	**Females**	**Postmenopausal women**
• "Apparently healthy" • No known endocrine disorder • Access testosterone >1.75 ng/mL • Access human thyroid stimulating hormone (hTSH) 0.34 – 6.60 μIU/mL	• "Apparently healthy" • No known endocrine or reproductive disorder • Not pregnant with regular menstrual cycle • Access beta human chorionic gonadotropin < 2.9 IU/mL • Access estradiol values >20 pg/mL • No steroid based contraceptives • Access hTSH 0.34 –	• "Apparently healthy" • No known endocrine or reproductive disorder • No menstrual period for at least 12 months • For women < 55 years; Access human luteinizing hormone, Access human follicle stimulating hormone levels consistent with postmenopausal status, and Access estradiol levels < 88 pg/mL.

	6.60 μIU/mL	• No hormone replacement therapy • No osteoporosis medication with estrogen analog (e.g. Evista). • Access hTSH between 0.34 – 6.60 μIU/mL

Analysis was performed including a non-parametric determination of the 95% reference range and a bootstrap estimation of the 95% confidence interval (CI) of each of the range estimates. The Access SHBG reference range is summarized below:

	n	Median age	Median	95% CI
Males (20 – 50 yrs)	151	37	38.2 nmol/L	13.3 – 89.5 nmol/L
Females (20 – 46 yrs)	141	34	47.2 nmol/L	18.2 – 135.5 nmol/L
Post-menopausal females (47 – 91 yrs)	131	59	49.6 nmol/L	16.8 – 125.2 nmol/L

The product insert states:

- Each laboratory should establish its own reference ranges to assure proper representation of specific populations.

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.