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

A. 510(k) Number:
K040181

B. Analyte:
Dehydroepiandrosterone sulfate (DHEA-S)

C. Type of Test:
Quantitative Immunoassay and Calibrator

D. Applicant:
Beckman Coulter Inc.

E. Proprietary and Established Names:
Access® DHEA-S Reagent and Access® DHEA-S Calibrators

F. Regulatory Information:

1. Regulation section:
   21 CFR§862.1245 and 21 CFR §862.1150
2. Classification:
   Class I and Class II
3. Product Code:
   JKC and JIT
4. Panel:
   75 (Clinical Chemistry)

G. Intended Use:

1. Intended use(s):

"The Access DHEA-S assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of DHEA-S levels in human serum and plasma using the Access Immunoassay Systems."

"Access DHEA-S Calibrators are intended to calibrate the Access DHEA-S assay for the quantitative determination of DHEA-S levels in human serum and plasma using the Access Immunoassay System."

2. Indication(s) for use:
   Measurement of dehydroepiandrosterone sulfate is a convenient marker for the assessment of adrenal function. It may be used in the differential diagnosis of Cushing's syndrome, as well as in the evaluation of adrenocortical diseases, such as congenital adrenal hyperplasia and DHEA-S secreting adrenal carcinomas. In hirsute female patients, increased DHEA-S levels have been

associated with virilizing adrenal tumors. Patients with polycystic ovary syndrome have often demonstrated elevated levels of DHEA-S, suggesting an adrenal androgen contribution to the defect in this disorder.

3. Special condition for use statement(s):
   None noted.

4. Special instrument Requirements:
   Access Immunoassay Systems™ (Access, Access 2, UniCel Dxl800, and Synchron LXi725)

H. Device Descriptions:

The Access DHEA-S assay consists of a plastic cartridge that contains the assay ingredients in separate wells (paramagnetic particles coated with antibodies and DHEA-S alkaline phosphatase conjugate). The instrument system samples the reagent cartridge, and mixes the solutions with the patient sample in a separate reaction vessel. Other assay components (such as the chemiluminescent substrate) are onboard the instrument. The Access DHEA-S Calibrator kit contains six two-mL bottles, one for each of six calibrator levels.

I. Substantial Equivalence Information:

1. Predicate device name(s):
   Immulite DHEA-SO4 Reagent and Beckman Coulter Access Ultrasensitive hGH Calibrators

2. Predicate K number(s):
   K935806 and K003098

3. Comparison with predicate:
   Reagent: Both products have the same intended use, methodology, antibody source (rabbit anti-human), and chemiluminescent substrate. Both are liquid reagents. The Access DHEA-S assay uses plasma and serum (10 uL each) while the predicate uses serum (5 uL). The Access DHEA-S assay and the predicate have different reportable ranges (2 -1000 ug/dL versus 15-1000 ug/dL) and a slightly different analytical sensitivity (2 ug/dL versus 3 ug/dL).

   Calibrators: Both products are based on a bovine serum/ buffer base with surfactant and preservatives and intended for the same instrument platforms. The six Access DHEA-S Calibrators are liquid and ready to use whereas the predicate's two calibration levels are lyophilized and require reconstitution.

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

Substantial Equivalence and Performance Assessment Protocols

Area of Study	Reference Procedure	Procedure Title
Method Comparison/ Anticoagulant Studies	NCCLS EP9-A	User Comparison of Quantitative Clinical Laboratory Methods Using Patient Samples
Precision	NCCLS EP5-A	User Evaluation of Precision Performance of Clinical Chemistry Devices
Linearity	NCCLS EP6-A	Evaluation of the Linearity of Quantitative Methods
Interferences/ Cross-Reactivity	NCCLS EP7-A	Interference Testing in Clinical Chemistry
Reference Interval	NCCLS C28-A	How to Define and Determine Reference Intervals in the Clinical Laboratory
Traceability	prEN ISO 17511	Metrological Traceability of Values Assigned to Calibrator and Control Methods

K. Test Principle:

The Access DHEA-S assay is a competitive immunoenzymatic assay that utilizes anti-DHEA-S antibody-coated paramagnetic particles and DHEA-S labeled with alkaline phosphatase. In the reaction vessel, the enzyme conjugate competes with DHEA-S in the patient sample for antibody binding sites on the paramagnetic particles. Bound materials are held in a magnetic field while unbound materials are washed away. A chemiluminescent substrate is added. The light production is inversely proportional to the concentration of DHEA-S in the sample. Calculation of the amount of sample is based on a stored, multi-point calibration curve.

Access DHEA-S Calibrators are designed for use with the Access DHEA-S Reagent for generation of the DHEA-S assay calibration curve on Beckman Coulter's Access Immunoassay Systems. The Access Immunoassay Systems utilize a competitive binding immunoenzymatic method for quantitative analyte measurement.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

Data were collected using the Access and Access2 Immunoassay Analyzers. Risk assessments were performed for all analyzers, and equivalency within the Access analyzer family was validated.

a. Precision/Reproducibility:

Imprecision studies were based on NCCLS Guideline EP5-A. Commercially available human serum based control material was

used in a total of two assays per day, two replicates per assay, over 20 days, and analyzed via ANOVA.

Precision Estimates, DHEA-S Reagent Assay

		Within Run		Total Imprecision	
Human Serum Control	**Grand Mean (n=80)** (ug/dL)	**SD** (ug/dL)	**%CV**	**SD** (ug/dL)	**%CV**
Level 1	10.3	0.86	8.3	1.16	11.3
Level 2	34.4	1.10	3.2	1.76	5.1
Level 3	124.0	5.9	4.8	7.99	6.4
Level 4	347.3	8.92	2.6	15.38	4.4
Level 5	736.1	12.12	1.6	27.19	3.7

This assay exhibits a total imprecision of ≤20% at 2-20 ug/dL and ≤10% at ≥ 20 ug/dL.

Recovery of multiple replicates of spiked samples over the reportable range was within ± 10% of the expected value.

b. Linearity/assay reportable range:
Dilution of samples fortified with purified DHEA-S to within 80% of the high analytic claim yielded linear results throughout the performance range of the assay.

c. Traceability (controls, calibrators, or method):
Stability of the DHEA-S reagent assay was assessed using internal protocols that test materials at time zero and in various time and temperature combinations. The stability data supports the claimed shelf-life of 12 months.

The analyte in this assay is traceable to the manufacturer's working calibrators. Traceability process is based on prEN ISO 17511 in lieu of an internationally recognized reference standard or method for DHEA-S analysis.

The manufacturing process uses a secondary standard set to assign values to individual test lots of Access DHEA-S Calibrators. A secondary standard set is used to establish a reference curve. The test lot, as well as commercial controls and patient pool materials, are then assayed and compared to the reference curve to determine the assigned value for each calibrator level. Duplicate analysis of six individual vials (two each from the beginning, the middle, and the end of the lot filling process) are run on one instrument. The assigned value is the average of the twelve activity estimates. Assigned values must fall within established ranges for each calibrator level.

Stability testing compares the recoveries of control materials and patient pool materials run on an instrument calibrated with calibrators stored at an elevated temperature with controls and patient pool materials run on an instrument calibrated with calibrator materials that were stored at -20 ºC since time zero. The difference between the values must be ≤16%. The sponsor states that the accelerated stability data supports a shelf-life claim of 18 months and that real-time stability studies are ongoing.

d. Detection limit:

The detection limit of the assay was determined by testing ten replicates of the zero calibrator, along with a six-point calibration curve and controls, in three assays. The mean result plus two standard deviations (found to be 0.4 ug/dL) supports the limit of detection claim of <2 ug/dL which is consistent with the system software reporting of results. The sponsor claims a useable range of 2-1000 ug/dL.

e. Analytical specificity:

Interference studies were designed from NCCLS Guideline EP7-A; potentially interfering compounds were spiked individually into normal human serum. Each spiked sample was compared to the unadulterated sample. Samples containing up to 30 mg/dL bilirubin, lipemic samples containing up to 1750 mg/dL triglyceride, and hemolyzed samples containing up to 1000 mg/dL hemoglobin do not significantly affect the concentration of DHEA-S recovered. In addition, 6.0 g/dL human albumin added to endogenous albumin did not affect the concentration of DHEA-S recovered.

Substances with a structure similar to DHEA-S were evaluated for cross-reactivity by spiking them into separate aliquots of a serum pool containing ~420 ug/dL DHEA-S. The results, shown below, demonstrate minimal cross-reactivity at the concentrations tested:

Cross-Reactivity Summary

Substance	Analyte Added (µg/dL)	Neat Recovery (µg/dL)	Spiked Recovery (µg/dL)	%Cross Reactivity
DHEA	4000	427.2	440.1	0.32
DHEA Glucuronide	5000	430.5	439.1	0.17
Aldosterone	5000	426.4	406.7	-0.39
Androstenedione	1000	419.2	421.1	0.19
Androsterone	2000	410.2	416.1	0.30
Androsterone Glucuronide	5000	390.3	415.0	0.49
Cortisol	10000	437.6	429.5	-0.08
5-dihydrotestosterone	5000	390.3	394.1	0.08

Estradiol	5000	414.7	410.4	-0.09
β-Estradiol-3-SO4-17-glucuronide	5000	430.3	435.1	0.10
Estriol	5000	430.5	439.4	0.18
Estrone	5000	430.5	445.1	0.29
Estrone-3-SO4	5000	407.5	414.6	0.14
19 Hydroxyandrostenedione	5000	407.5	406.4	-0.02
Progesterone	5000	414.7	425.4	0.21
Testosterone	2000	410.2	416.7	0.33

f. Assay cut-off:
Not applicable.

2. Comparison studies:
   a. Method comparison with predicate device:
   Method comparison studies were designed using NCCLS Procedure EP9-A and were analyzed using Deming regression analysis with the following results:

   Slope = 1.028± 0.015
   Intercept = 6.6 ±5.0
   R = 0.993
   n = 263

   Sample values ranged from 15.3 to 966 ug/dL. Patient data was stripped from the samples so it was not possible to tell how many samples were from males and females or their age or health status.

   b. Matrix comparison:
   The sponsor performed serum versus plasma studies to evaluate the effect of EDTA and heparin anticoagulants on the DHEA-S method. Fifty samples from ranged from 4.5 to 625 ug/dL. There was excellent agreement (r=0.999) between serum and lithium heparin, sodium heparin, and EDTA.

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

The sponsor designed the reference interval study using the guidelines in NCCLS C28-A. The study used stored samples drawn from apparently healthy male and female subjects. Some samples in the highest age group were purchased from a commercial vendor.

Reference Interval Summary

Age (years)	Males			Females		
	N	Median* (µg/dL)	95% Reference Interval** (µg/dL)	N	Median* (µg/dL)	95% Reference Interval** (µg/dL)
<21	10	302	25-540	10	177	51-321
21-30	43	245	101-630	40	184	17-389
31-40	44	229	110-476	40	143	29-264
41-50	43	186	71-470	42	121	19-231
51-60	39	120	35-344	39	60	2-170
61-70	29	78	24-244	31	60	2-120
>71	34	45	5-253	33	35	7-177

Lot calibrator values are assigned as described above. Exact concentrations for each level are on the vial label and are embedded in a bar-coded calibration card provided with each calibration kit.

Representative Assigned Values of One Lot (Pilot Calibrator Lot)

Calibrator Level	Target Value	Assigned Value	Specification Range (ug/dL)	Pass/Fail
S0	0	0	n/a	n/a
S1	20	19	17 - 23	PASS
S2	50	50	42 - 57	PASS
S3	200	192	190 – 210	PASS
S4	500	487	480 – 520	PASS
S5	1000	992	950 – 1050	PASS

M. Conclusion:

I recommend that the Access® DHEA-S Reagent and Access® DHEA-S Calibrators be found substantially equivalent to the predicates.