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

A. 510(k) Number:

k142994

B. Purpose for Submission:

New device

C. Measurand:

Aldosterone

D. Type of Test:

Quantitative, Chemiluminescent Immunoassay

E. Applicant:

Immunodiagnostic System Ltd

F. Proprietary and Established Names:
IDS iSYS Aldosterone
IDS iSYS Aldosterone Control Set
IDS iSYS Aldosterone Calibration Verifiers

G. Regulatory Information:

1. Regulation section:
   21 CFR 862.1045, Aldosterone Test System
   21 CFR 862.1660, Quality Control Material (assayed and unassayed)

2. Classification:
   Class II
   Class I, reserved

3. Product code:
   CJM
   JJX

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   Refer to indications for use below.

2. Indication(s) for use:

   The IDS iSYS Aldosterone assay (IS-3300) is a device intended for use in clinical laboratories for the quantitative determination of Aldosterone in human EDTA plasma on the IDS-iSYS Multi-Discipline Automated System. Aldosterone measurements are used in the diagnosis and treatment of primary aldosteronism (a disorder caused by excessive secretion of Aldosterone by the adrenal gland), hypertension caused by primary aldosteronism, selective hyperaldosteronism, selective hyperaldosteronism, edematous states and other conditions of electrolyte balance.

   The IDS-iSYS Aldosterone Control Set (IS-3330) is intended for use as assayed quality control samples to monitor the accuracy of the IDS Aldosterone assay on the IDS iSYS Multi-Discipline Automated System.

   The IDS-iSYS Aldosterone Calibration Verifiers (IS-3335) is a device intended for medical purposes for use in the quantitative verification of calibration of the IDS-iSYS Aldosterone Assay when performed on the IDS iSYS Multi-Discipline Automated System.

3. Special conditions for use statement(s):

   For prescription use only.

   For in vitro diagnostic use.

4. Special instrument requirements:

   IDS iSYS Multi-Discipline Automated Analyzer

I. Device Description:

The Aldosterone assay is an in vitro diagnostic device consisting of the following:

The reagent cartridge contains:

- Magnetic particles coated with streptavidin in a phosphate buffer containing

bovine protein with sodium azide as a preservative (<0.1%). 1 bottle, 3mL.

- Aldosterone and an acridinium ester derivative linked to sheep protein in a phosphate buffer containing bovine, sheep and mouse proteins with sodium azide as a preservative (<0.1%). 1 bottle, 8.1mL.
- Anti-aldosterone monoclonal antibody(mouse) labeled with biotin in a phosphate buffer containing bovine, sheep and mouse proteins with sodium azide as a preservative (<0.1%). 1 bottle 5.1mL.
- A phosphate buffer with sodium azide as a preservative (<0.1%). 1 bottle 4.5mL.

The kit calibrators (not sold separately) are composed of a lyophilized human serum matrix containing Aldosterone with preservatives; three vials each of 2 concentration levels, 1.0mL.

The IDS iSYS Aldosterone Control set is composed of a lyophilized human serum matrix containing Aldosterone and preservatives; three vials each of 3 concentration levels, 1.0mL.

The IDS iSYS Aldosterone Calibration Verifiers are composed of a lyophilized human serum matrix containing Aldosterone with preservatives. It is supplied in four vials of level 0 and 2 vials each of levels 1, 2 and 3.

Each human blood donor using used to produce the base pool of human serum has been tested by an FDA approved method and found to be non-reactive for HIV-1/2 Antibody, HCV Antibody, HTLV-1/2 Antibody, HBc Antibody, a Serologic Test for Syphilis (STS) and Hepatitis B Surface Antigen (HBsAg).

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Siemens Healthcare Diagnostics Ltd. Coat-A-Count® Aldosterone
   Control: IDS-iSYS 25-Hydroxy Vitamin DS Control Set
   Calibration Verifiers: IDS-iSYS 25-Hydroxy Vitamin DS Calibration Verifiers

2. Predicate 510(k) number(s):
   k831178
   k091849
   k111650

3. Comparison with predicate:

IDS iSYS Aldosterone **Similarities**		
Item	New Device IDS iSYS Aldosterone (k142994)	Predicate Device Siemens Coat-a-count aldosterone (k831178)
Intended Use	For in vitro diagnostic quantitative measurement of aldosterone in EDTA plasma.	Same

IDS iSYS Aldosterone **Similarities**		
Item	New Device IDS iSYS Aldosterone (k142994)	Predicate Device Siemens Coat-a-count aldosterone (k831178)
Sample matrix	EDTA plasma	Same
Sample size	200uL	Same
Reagent storage	2-8°C	Same

IDS iSYS Aldosterone **Differences**		
Item	New Device IDS iSYS Aldosterone (k142994)	Predicate Device Siemens Coat-a-count aldosterone (k831178)
Measuring range of assay	3.9 to 120ng/dL	2.5 to 120 ng/dL
Test Principal	Chemiluminescent using an acridinium-ester derivative	Radioactivity using ^{125}I-labelled aldosterone
Antibody	Monoclonal mouse-anti-aldosterone antibody	Antiserum against aldosterone (species origin not stated)
Analytical sensitivity	3.2ng/dL	1.1ng/dL
On-board reagent stability	35 days	n/a
Assay duration	43 minutes to first result	Minimum 18 hours (overnight incubation)
Calibration	Two point calibration and master curve	Full standard curve to be run with each assay run
Calibration interval	4 days	Per assay run
Calibrator levels	Two levels	7 levels
Calibrator matrix	Lyophilized human serum with sodium azide	Lyophilized human serum
Automation	Automated	Manual

IDS iSYS Aldosterone Control Set **Similarities**		
Item	New Device IDS iSYS Aldosterone Control Set (k130526)	Predicate Device IDS-iSYS 25-Hydroxy Vitamin DS Control Set (k091849)
Intended Use	Intended for medical purposes for quality control of the assay on the IDS-iSYS Multi-Discipline Automated System	Same
Levels	3	Same

IDS iSYS Aldosterone Control Set **Differences**		
Item	New Device IDS iSYS Aldosterone Control Set (k130526)	Predicate Device IDS-iSYS 25-Hydroxy Vitamin DS Control Set (k091849)
Format	Lyophilized	Ready to use
Analyte	Aldosterone	25-Hydroxy Vitamin D
Matrix	Human Serum	Horse Serum
Reconstituted stability	4 hours	2.5 hours
Unopened stability	12 months	6 months

Calibration Verifier Similarities		
Item	New Device IDS iSYS Aldosterone Calibration Verifiers (k130526)	Predicate Device IDS-iSYS 25-Hydroxy Vitamin DS Calibration Verifiers (k111650)
Intended Use	Used for medical purposes for use in the quantitative verification of calibration of the assay	Same
Matrix	Lyophilized human serum with sodium azide	Same
Levels	4	Same
Unopened stability	6 months	Same

Calibration Verifier Differences		
Item	New Device IDS iSYS Aldosterone Calibration Verifiers (k130526)	Predicate Device IDS-iSYS 25-Hydroxy Vitamin DS Calibration Verifiers (k111650)
Format	Lyophilized	Ready to use
Analyte	Aldosterone	25-hydroxy Vitamin D
Matrix	Human serum	Horse serum
Reconstituted stability	4 hours	2.5 hours

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

- How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - Second Edition (CLSI C28-A2)
- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition (CLSI EP05-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical

Approach; Approved Guideline (CLSI EP6-A)
- Interference Testing in Clinical Chemistry; Approved Guideline (CLSI EP 7-A)
- Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (CLSI EP9-A 1995)
- Protocols for Determination of Limits of Detection and Limits of Quantitation (CLSI EP17-A)
- Stability Testing of In Vitro Diagnostic Reagents (EN 13640:2002 guideline)

L. Test Principle:

The IDS-iSYS Aldosterone assay is based on chemiluminescence technology. There is no sample pre-treatment necessary for measurement of aldosterone in EDTA plasma samples. The samples are placed into an appropriate secondary tube and then onto the IDS-iSYS sample rack which is then loaded on the IDS-iSYS system.

The IDS-iSYS Aldosterone assay is designed in a competitive immunoassay format. A volume of the sample is pipetted into a cuvette on the instrument's carousel. Biotinylated monoclonal anti-Aldosterone antibody is then added and the reaction is incubated. Following this incubation step, an Aldosterone- acridinium-conjugate tracer is added. The acridinium tracer will bind to any sites on the antibody not already occupied by the Aldosterone present in the sample. The final incubation step is for the addition of Streptavidin-coupled magnetic particles grouped with an assay buffer to increase the reaction volume and allow better distribution of the magnetic particles within the sample. Following this third incubation step the particles are "captured" using a magnet and undergo a series of three washing cycles. The washing step will separate the bound from any un-bound analyte in the sample. Finally, the addition of NaOH and H_2O_2 will cause light to be emitted by the acridinium label. As the signal generated [shown as Relative Light Units (RLUs)] comes from the Aldosterone-acridinium-tracer, the signal will be inversely proportional to the concentration of the analyte, Aldosterone, present in the sample.

The RLUs generated from each sample are read off a two-point calibration curve which is adjusted using two Aldosterone calibrators and using the equation parameters of a stored Master Curve.

M. Performance Characteristics (if/when applicable):

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

   a. Precision/Reproducibility:

   Precision was determined in accordance with CLSI EP5-A2.

   Three lots of IDS iSYS Aldosterone assay reagents were used to assay six samples (produced from pooled K3 EDTA plasma) over a minimum of 20 assay days on two instruments. Samples were run in duplicates, twice a day, to provide 80 replicates over 40 runs. Results are summarized in the table below.

Concentration Mean (ng/dL)	N	Within Run		Between Run		Between Day		Total	
		SD	%CV	SD	%CV	SD	%CV	SD	%CV
7.5	80	0.63	8.4	0.50	6.70	0.52	7.00	0.96	12.8
21.5	80	1.03	4.8	1.03	4.80	0.29	1.40	1.49	6.9
29.3	80	0.94	3.2	0.88	3.00	0.99	3.40	1.62	5.5
49.3	80	1.62	3.3	0.84	1.70	1.81	3.70	2.57	5.2
65.7	80	1.43	2.2	3.57	5.40	1.43	2.20	4.10	6.2
98.7	80	4.00	4.1	3.00	3.00	3.19	3.20	5.94	6.0

b. Linearity/assay reportable range:

The claimed assay range for this device is 3.9 to 120ng/dL. The linear range of the assay was determined following a protocol based on CLSI EP6-A guidelines. A high plasma sample with Aldosterone concentrations at 133.6ng/dL was diluted with a low sample at 2.7ng/dL at equal proportions to create 11 intermediate samples. A total of 13 samples with different concentrations of aldosterone were tested in quadruplicate using one reagent lot . The observed concentrations were plotted against the expected concentrations and a linear regression curve was fitted.

The overall linearity analyses were: $y=1.00x-1.24$, $r^2=1.00$.

The sponsor's claimed measuring range is 3.9 to 120 ng/dL, which was supported by the linearity study.

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

Traceability: The IDS-iSYS Aldosterone calibrators, controls and calibration verifiers are traceable to in-house reference calibrators produced by dissolving Aldosterone in Dioxane. The concentration was calculated by UV quantitation using the molar extinction coefficient of $\varepsilon=15000$ at an absorbance of 240nm. Preparation was gravimetric with no adjustment.

Stability
Accelerated and Real-time stability studies were performed with the IDS-iSYS Aldosterone reagent cartridges, calibrators and calibration verifiers. The data demonstrate the reagent cartridges and calibrators are stable for 6 months, calibration verifiers are stable for 15 months and controls are stable for 12 months when stored at 4°C unopened, upright and in the dark.

After reconstitution, the calibrators and kit controls may be stored for 2 hours at room temperature and on-board the analyzer continuously for 4 hours. Calibration verifiers may be stored on-board the analyzer continuously for 4 hours.

The stability study protocol and acceptance criteria has been provided and found to be adequate.

Calibration frequency: A master calibration curve, generated against the internal reference calibrators, is supplied to the user on a CD with each IDS-iSYS Aldosterone kit. The IDS-iSYS Aldosterone kit Calibrator A and Calibrator B are assayed in triplicate to adjust the master calibration. The sponsor recommends that the kit controls be run in duplicate to verify the calibration at least once per day or according to local regulations when patient samples are being assayed. The calibration is stable for 4 days and the user will receive an automated message by the software upon expiration.

Value Assignment:
The concentration values of the kit calibrators, controls and verifiers are assigned through an internal procedure. To assign acceptable ranges to the kit assay controls and calibration verifiers, each is assayed in the IDS-iSYS Aldosterone assay with On-Board 2 point calibration. The assay controls and calibration verifiers are run in triplicate in at least 18 assays on a total of at least three analyzers. The assigned range is then calculated as the mean ±3SD for both controls and verifiers. The kit calibrators are run in duplicate for 20 assays on one analyzer and the concentration values obtained must fall within the below specified ranges.

The Kit Calibrators have the following nominal ranges:

Kit Calibrator A	5-8 ng/dL
Kit Calibrator B	85-115 ng/dL

IDS iSYS Aldosterone Control Set have the following nominal ranges:

Kit CTL1	6.5-9.5 ng/dL
Kit CTL2	12-18 ng/dL
Kit CTL3	40-65 ng/dL

IDS-iSYS Aldosterone Calibration Verifiers have the following nominal ranges:

Cal Ver 0	0.0 ng/dL
Cal Ver 1	25-35 ng/dL
Cal Ver 2	70-80 ng/dL
Cal Ver 3	125-145 ng/dL

d. Detection limit:

The Limit of blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined based on guidance from CLSI EP17-A. For one batch (MB5) LoD and LoQ calculations, 2 replicates of 7 samples were used. The samples were tested once per day over 8 days. Sample concentrations ranged from 2.1 to 8.8ng/dL. For the second batch (MB6), LoD study, 8 samples were run in 2 replicates, once per day for 5 days and for the LoQ study, 7 samples were run in 2 replicates, once per dayfor 5 days. The LoD concentrations tested were from 0 to 8.45ng/dL. The LoQ

concentrations tested were from 1.1 to 16.38ng/dL. LoB was calculated using an EDTA plasma sample with zero aldosterone tested in 5 replicates over 5 days. LoQ was defined as the lowest concentration for which an imprecision level of less than 20% CV. The highest values taken from the two lots of reagents were used to determine the detection limits values for LoB, LoD, and LoQ.

The LoB, LoD and LoQ results are summarized below:

LoB	2.0ng/dL
LoD	3.2ng/dL
LoQ	3.9ng/dL

The claimed measuring range of the device is 3.9 to 120ng/dL for EDTA plasma.

e. Analytical specificity:

The sponsor performed interference and cross-reactivity studies in accordance with CLSI guidance EP7-A2. To determine potential interference in the specific detection of Aldosterone, two base plasma samples, one in the range of approximately 10ng/dL Aldosterone ("Low") and another at approximately 40ng/dL ("High"), were spiked with the potential interferent. Control samples (blank) were spiked with a volume of relevant diluent equal to that of the spiked interferent. The mean of 26 replicates, for both spiked and control samples (Blank), were then compared. One reagent batch was used for interference testing. The differences observed between the mean spiked and control sample values were examined and assessed according to acceptance criteria of ≤10% concentration bias to the unspiked sample. Results of non-significant interference are summarized in the table below:

Substance	**Concentration tested with non-significant interference**
Triglycerides	500mg/dL
Hemoglobin	200mg/dL
Bilirubin (unconjugated)	15mg/dL
Protein (Albumin)	8g/dL
Human Anti-Mouse Antibodies (HAMA)	30ng/ml
Red Blood Cells	0.2%
Biotin	22nM
Rheumatoid Factor (RF)	1000 IU/ml

The following limitations appear in the labeling:

"Hemolyzed samples should not be used with this assay."
"If samples are turbid and/or contain visible clots they should be centrifuged""

"In patients receiving therapy with a high biotin dose (i.e. >5 mg/day), no sample should be taken until at least 8 hours after the last biotin administration."

Cross Reactivity:

A cross reactivity study was performed using other endogenous steroids and some commonly used anti-hypertensive medication according to CLSI EP 7-A2 guidelines. Stock concentrations of the substances to be checked for cross-reactivity were prepared initially in an organic solvent. A commercially available blank serum sample was used to spike the potentially cross-reacting substances. Cross reactivity was assessed using one reagent lot. Cross reactivity was defined as the point where the reduction in signal corresponds to 50% of the signal achieved in the absence of analyte, as a percentage of the analyte concentration giving the same fall in signal. Percent cross reactivity calculation is as follows:

%cross reactivity = ED50 (ng/dL) Aldosterone / ED50 (ng/dL) compound.

The results demonstrated that all substances showed <0.001% cross reactivity with the exception of 18-OH-Corticosterone and 3α, 5β-tetrahydroaldosterone.

Analyte	Concentration Tested	Cross-Reactivity
Androstenedione	0.3mg/mL	<0.001%
Androsterone	0.3mg/mL	<0.001%
Cortisol	0.3mg/mL	<0.001%
11-Deoxycortisol	0.3mg/mL	<0.001%
Cortisone	0.3mg/mL	<0.001%
Corticosterone	0.3mg/mL	<0.001%
11-Deoxycorticosterone	0.3mg/mL	<0.001%
18-Hydroxycorticosterone	0.1mg/mL	0.2%
Dexamethasone	0.3mg/mL	<0.001%
DHEA	0.3mg/mL	<0.001%
Estradiol	0.3mg/mL	<0.001%
Estrone	0.3mg/mL	<0.001%
Prednisone	0.3mg/mL	<0.001%
Prednisolone	0.3mg/mL	<0.001%
Pregnenolone	0.3mg/mL	<0.001%
Progesterone	0.3mg/mL	<0.001%
Spironolactone	0.3mg/mL	<0.001%
Testosterone	0.3mg/mL	<0.001%
Prazosin HCl	0.1mg/mL	<0.001%
Verapamil HCl	0.3mg/mL	<0.001%
Doxazosin mesylate	0.3mg/mL	<0.001%
Fludrocortisone acetate	0.3mg/mL	<0.001%
Cholesterol	0.3mg/mL	<0.001%
3α, 5β-Tetrahydoaldosterone	0.1mg/mL	3.1%

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Following CLSI EP9-A2, the sponsor performed a method comparison study of the IDS iSYS Aldosterone assay versus the LIAISON Aldosterone assay, measuring range 3.0-100ng/dL (previously cleared k130321). A total of 161 EDTA plasma samples were used in the correlation studies across both methods, following the manufacturers' instructions. 12 of the total samples were diluted in order to achieve the hard to find sample range. Sample range tested was 3.9-110.9ng/dL on the IDS iSYS Aldosterone assay and was 3.0-98.0 on the comparative device. Regression analysis is summarized below:

Passing-Bablok linear regression analysis resulted the following:

Slope (95% CI)	**Intercept (95% CI)**
1.070 (1.043 to 1.096)	-0.29 (-0.98 to 0.46)

Linear regression analysis resulted the following:

Slope (95% CI)	**Intercept (95% CI)**	**r^2**
1.053 (1.029 to 1.076)	0.09 (-0.86 to 1.05)	0.980

b. Matrix comparison:

Not applicable. Only EDTA plasma claimed as matrix type.

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:

   A reference range study was performed using healthy adults between 18 to 65 years old according to the CLSI C28-A guideline. Subjects have normal blood pressure and normal BMI. The exclusion criteria include aged below 18 or older than 65, need for prescription medications for chronic diseases, need for doctor prescribed restricted diet, pregnancy, breastfeeding or chronic diseases. Blood collection takes place between 7:00am and 10am after an overnight fasting with the same subjects in two positions: upright and supine. Upright samples were collected after walking and standing for a minimum of 30 minutes. Supine samples were collected after lying down for at least 30 minutes.

   228 samples were assessed for the reference range determination. These samples were assessed using MB1 only but on multiple machines and assessed by multiple operators. 4 subgroups (male supine, male upright, female supine and female upright) were analyzed. The observed mean and central 95% reference intervals for upright and supine positions are listed below.

Population (228)	**N**	**Mean Aldosterone (ng/dL)**	**SD (ng/dL)**	**Observed Range (Central 95%) (ng/dL)**
Supine (female)	55	9.9	9.4	<3.9 -33.6
Supine (male)	56	5.1	4.7	<3.9 -19.5
Upright (female)	56	13.8	11.9	<3.9 -50.1
Upright (male)	61	7.8	4.8	<3.9 -23.2
All supine	111	7.5	7.73	<3.9 -31.1
All upright	117	10.6	9.38	<3.9 -44.3

   The package insert recommends that "each laboratory should determine reference ranges for their local population".

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.