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

A. 510(k) Number:
k123763

B. Purpose for Submission:
New device

C. Measurand:
Renin

D. Type of Test:
Quantitative, chemiluminescent immunoassay

E. Applicant:
Immunodiagnostic Systems Ltd.

F. Proprietary and Established Names:
IDS iSYS Direct Renin Assay,
IDS-iSYS Direct Renin Control Set,
IDS-iSYS Direct Renin Calibration Verifiers

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CIB	II	21 CFR § 862.1085 Angiotensin I and renin test system	Clinical Chemistry (75)
JJX	I, reserved	21 CFR § 862.1660 Quality control material (assayed and unassayed)	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See indications for use below.

2. Indication(s) for use:

   The IDS-iSYS Direct Renin assay is intended for the quantitative determination of Direct Renin in human EDTA plasma on the IDS iSYS Multi-Discipline Automated System. Renin measurements may aid in the diagnosis and treatment of certain types of hypertension.

   The IDS-iSYS Direct Renin Control Set is used for quality control of the IDS-iSYS Direct Renin Assay on the IDS-iSYS Multi-Discipline Automated System.

   The IDS-iSYS Direct Renin Calibration Verifier is a device intended for medical

purposes for use in the quantitative verification of calibration of the IDS-iSYS Direct Renin Assay when performed on the IDS-iSYS Multi-Discipline Automated System.

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   For use with IDS-iSYS Multi-discipline Automated System

I. Device Description:

The IDS-iSYS Direct Renin assay kit comes with a Reagent Cartridge, and 2 Calibrators (Cal A & Cal B). The reagent cartridge contains 5 components: Streptavidin coated magnetic particles, two types of mouse anti-renin monoclonal antibodies– one labeled with biotin, and the other labeled with acridinium, two types of wash buffers. Two lyophilized calibrators at two concentration levels (Calibrator A 3.8-6.6 pg/mL; and Calibrator B 125-165 pg/mL) included in the kit must be reconstituted prior to use.

The IDS-iSYS Direct Renin Control Set is set is sold separately and contains three lyophilized equine serum with renin concentration at target values of 6.7-10.6 pg/mL, 47.2-69.4pg/mL, and 188.9-250 pg/ mL in lyophilized form.

The IDS-iSYS Direct Renin Calibration Verifiers contains four levels of lyophilized equine serum with renin concentrations of <0.83 pg/mL, 51.9-76.1 pg/mL, 125-165 pg/mL, and 225-280.6 pg/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   CisBio Renin III Generation

   IDS-iSYS IGFBP-3 Control Set

   IDS-iSYS IGF-I Calibration Verifiers

2. Predicate 510(k) number(s):
   k062120

   k111938

   k122141

3. Comparison with predicate:

IDS-iSYS Direct Renin Assay

Similarities		
Item	IDS-iSYS Direct Renin Assay (Candidate Device)	CisBio Renin III Generation (Predicate Device)
Intended Use	Quantitative determination of direct renin in human EDTA plasma	Same
Test Principle	Sandwich immunoassay	Same
Calibrated to a WHO Standard	First World Health Organization International Reference Preparation (68/356)	Same

Differences		
Item	IDS-iSYS Direct Renin Assay (Candidate Device)	Renin III Generation (Predicate, k062120)
Assay Method	Chemiluminescence	Radioimmunoassay
Calibration	Two-point verification of stored master curve	Perform with each assay
Reagent Storage	On-board or in refrigerator	Refrigerator only.
Measuring Range	2.0 – 256 pg/mL (multiply values with 1.8 to convert to μU/mL)	1.0 - 320 pg/mL (multiply with 1.8 to convert to μIU/mL 1.8-576 μIU/mL)
Measurement System	Photomultiplier	Gamma counter
Sample Size	190 uL	300 uL
Controls	Two controls, level 1 and level 2	One control

IDS-iSYS Direct Renin Control Set

Similarities and Differences		
Item	IDS-iSYS Direct Renin Control Set (Candidate Device)	IDS-iSYS IGFBP-3 Control Set (Predicate, k111938)
Intended use	Used for quality control of the IDS-iSYS Direct Renin assay	Used for quality control of the IDS-iSYS IGFBP-3 assay
Format	Lyophilized	Same
Number of calibrators	3	3
Storage temperature	2-8°C	Same

IDS-iSYS Renin Calibration Verifiers

Similarities and Differences		
Item	IDS-iSYS Renin Calibration Verifier Set (Candidate Device)	IDS-iSYS IGF-I Calibration Verifiers (Predicate, k122141)
Intended Use	Used for the quantitative verification of calibration of the IDS-iSYS Direct Renin assay	Used for the quantitative verification of calibration of the IDS-iSYS IGF-I assay
Format	Lyophilized	Lyophilized
Levels	4	Same
Storage temperature	2-8°C	same

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

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*

CLSI EP09-A2: *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline*

CLSI EP25-A2: *Stability Testing of In Vitro Diagnostic Reagents*

L. Test Principle:

The IDS-iSYS Direct Renin assay is based on chemiluminescence technology. EDTA plasma samples are incubated with two mouse anti-renin antibodies, one of which is labeled with biotin and the other with acridinium thus forming an immunocomplex with renin bridging the two antibodies. Streptavidin-coated magnetic particles is next introduced into the mixture and incubated, which allows capture and immobilization of renin-containing immunocomplexes. The unbound material is removed with a wash cycle. Finally, a flash chemiluminescence reaction is induced by addition of Trigger reagents (hydrogen peroxide and sodium hydroxide) that react with acridinium. The light signal is measured by a photomultiplier and expressed as relative light units (RLU). The proportion of measured RLU is directly proportional to the amount of bound renin. The measured RLU are converted to concentration of renin (expressed in pg/mL) using 2 point calibration.

M. Performance Characteristics (if/when applicable):

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

   a. Precision/Reproducibility:

   Precision of the IDS-iSYS Direct Renin assay was evaluated according to CLSI EP5-A2. Two replicates of each of the 10 pooled EDTA plasma samples (included 5 spiked samples) were tested twice a day for 20 days with two reagent lots at one site, leading to the generation of 160 data points.

Mean, within-run CV, between run CV, between day CV, and total precision CV are summarized in the table below:

Sample	Data Points	Mean pg/mL	Within run		Between run		Between day		Total precision	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
Pooled EDTA plasma 2	160	9.7	0.5	5.0	0.7	6.9	0.3	2.8	0.9	9.0
Spiked pooled EDTA plasma 3	160	10.0	0.4	3.7	0.6	6.3	0.5	4.5	0.9	8.6
Spiked pooled EDTA plasma 4	160	30.5	0.9	3.0	2.1	6.91	1.2	4.0	2.6	8.5
Spiked pooled EDTA plasma 7	160	110.6	4.3	3.9	6.7	6.1	1.6	1.5	8.1	7.4
Spiked pooled EDTA plasma 8	160	169.8	4.7	2.7	10.6	5.5	1.8	1.1	10.5	6.2
Spiked pooled EDTA plasma 9	160	231.2	7.7	3.3	16.8	7.5	5.0	2.2	19.6	8.5
Pooled EDTA plasma 10	160	249.9	13.7	5.5	12.5	3.2	6.2	2.5	17.0	6.8

Precision of the IDS-iSYS Direct Kit controls was evaluated using three lots of kit controls to generate a total of 80 replicates per level to yield similar results. Therefore, the results of one representative lot of control is shown below.

Sample	**Mean (pg/mL)**	**Within-run**		**Total**	
		SD	**%CV**	**SD**	**%CV**
Control Level 1	7.9	0.4	4.5	0.7	9.4
Control Level 2	55.0	1.4	2.5	3.8	6.9
Control Level 3	221.4	14.5	6.5	19.3	8.7

b. Linearity/assay reportable range:

The sponsor evaluated linearity according to CLSI guideline EP6-A. Samples were prepared by mixing low and high level spiked serum pools to obtain 11 concentrations across the assay range with each sample being assayed in 4 replicates. The measured Renin concentrations were plotted against the

theoretical values and an appropriate line fitted by standard linear regression resulted in the following equation: $Y= 0.98X -0.46$, $r^2= 1.00$

The results of the linearity study and LoQ study supports the sponsor's claim that the assay is linear across the measuring range of 2.0 to 256 pg/mL.

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

Traceability

IDS-iSYS Direct Renin Assay is traceable to the WHO reference material 68/356 standard. A stock of the WHO International Standard Human Renin is reconstituted in phosphate buffer containing 0.5% BSA. This stock material is then diluted into equine serum to generate a set of WHO standards and a calibration curve.

A commercially available stock of recombinant human renin is used to make the internal standards by gravimetric dilution into equine serum. The value assignment of the internal standards is made using the IDS-iSYS Direct Renin assay based on the WHO standard curve.

Value Assignment

The IDS-iSYS Direct Renin assay kit comes with 2 levels of Calibrators (Calibrator A 3.8-6.6 pg/mL; and Calibrator B 125-165 pg/mL).

The IDS-iSYS Direct Renin Control Set contains 3 levels of different concentrations of human renin in equine serum at target values of 6.7–10.6 pg/mL, 47.2–69.4 pg/mL, and 188.9–250 pg/mL.

The IDS-iSYS Direct Renin Calibration Verifier Set contains four levels of lyophilized equine serum with renin concentrations of <0.83 pg/mL, 51.9-76.1 pg/mL, 125-165 pg/mL, and 225-280.6 pg/mL.

Value assignments for the kit calibrator, controls, and calibration verifiers are made by testing on multiple lots of assay kits, multiple assays per level and the assigned values for each level is the mean of the replicates.

Stability

Stability of assay cartridges, calibrators, controls, calibration verifiers were based on accelerated stability study data. The stability study protocol and the acceptance criteria were provided and found to be acceptable. From these accelerated stability studies, the shelf-life stability of all reagents was found to be 6 months at 2-8°C. Real-time stability studies are ongoing.

Open-Vial Stability

The stability study protocol and the acceptance criteria to determine open-vial stability of the assay cartridge, control materials and the calibrators have been reviewed and found to be acceptable. After opening, the assay cartridge is stable at 2-8° C for 28 days. The reconstituted calibrators, kit controls and calibration verifiers were stable for 8 hrs when left on board the analyzer.

For the calibration frequency, the sponsor claimed that the calibration is stable

for up to 14 days.

d. Detection limit:

The analytical sensitivity was defined as the limit of detection for the IDS-iSYS Direct Renin Assay was determined as per CLSI EP17-A. The LoD was calculated from the limit of blank (LoB). LoB was determined using a blank sample assayed in 6 runs for 3 days for a total of 75 replicates. LoD was determined using 10 low renin samples assayed in 6 runs over five days for a total of 120 replicate results. LoQ was determined by testing 10 low renin EDTA plasma with three reagent lots in 10 replicates generating 100 measurements per lot. LoQ is defined as the concentration at which the inter-assay precision is < 20% CV. LoB, LoD and LoQ are summarized below:

LoB= 1.09 pg/mL

LoD= 1.63 pg/mL

LoQ= 2.0 pg/mL

The measuring range of the renin assay is 2.0 to 256 pg/mL.

e. Analytical specificity:

Cross-reactivity

The cross-reactivity of the renin antibody with pro-renin was evaluated with the IDS-iSYS Direct Renin assay by spiking pro-renin (156 to 100,000 pg/mL) into a normal EDTA plasma containing 13 pg/mL of renin. Pro-renin cross-reactivity was determined to be $\leq 2.8\%$.

Interference

The sponsor performed studies to evaluate the effects of potential interferents on the performance of the IDS-iSYS Direct Renin assay, following CLSI EP7-A2. Two levels of EDTA plasma samples containing approximately 9.2 to 32.3 pg/ml and 50.7 to 102.9 pg/mL renin were spiked with different concentrations of the listed interferents. Each level of renin was tested with each interferent in 26 replicates. The level of interference was considered not significant if there was no more than 10% difference between the result in the presence of the interferent and the unspiked control result. The table below lists the substances tested and the concentrations at which no significant interference was observed:

Interferent	Tested concentration
Triglycerides	3000 mg/dL
Haemoglobin	250 mg/dL
Bilirubin	20 mg/dL
Red Blood Cells	0.4%
Biotin	25 nM
Albumin	80 mg/mL
Beta-2-microglobulin	50 µg/mL
Cathepsin B	0.1 U/mL
Cathepsin D	0.5 U/mL
Captopril	50 µg/mL
Enalapril	50 µg/mL
Loxen (Nicardipine HCl)	50 µg/mL
Lasilix (Furosemide)	50 µg/mL
Trypsin	1.5 µg/mL
Plasmin	100 µg/mL
Human anti-Mouse Antibody (HAMA)	30 ng/mL

The sponsor has the following limitations in their labeling:

- Hemolyzed samples: "Do not use hemolyzed sample. Hemolyzed sample will give erroneous results."
- HAMA/Heterophile antibodies: "No interference was observed with samples containing HAMA up to 30ng/mL when tested with IDS-iSYS renin assay. For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce antibodies, e.g. HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples. Such interfering antibodies may cause erroneous results. Carefully evaluate the results of patients suspected of having these antibodies."

A hook effect study was performed using three high renin concentration samples, out of the range samples (up to 3056 pg/mL). Spiked samples were assayed once using one reagent lot. The IDS-iSYS Direct Renin assay stated that no hook effect was at 3056 pg/mL.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

   a. *Method comparison with predicate device:*

      A method comparison study was performed to compare the results of IDS-iSYS Renin test to Renin III Generations (predicate) using 139 EDTA plasma samples (all natural) based on CLSI EP-9A guidelines. The range of results observed with the IDS-iSYS Renin test ranged from 2.0 to 256.2 pg/mL.

      Results of regression analysis are presented in the table below:

	Linear Regression	Deming Regression	Passing Bablok
Slope (95% CI)	1.071 (1.054 to 1.088)	1.07 (1.049 to 1.103)	1.10 (1.07 to 1.15)
Intercept (95% CI)	-0.170 (-1.00 to 0.66)	-0.310 (-0.93 to 0.33)	-0.42 (-1.16 to -0.13)
Correlation Coefficient	0.992	0.992	1.00

   b. *Matrix comparison:*

      Not applicable.

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:

   In order to determine the normal range of the IDS-iSYS Direct Renin Assay, EDTA samples were collected from apparently subjects ranging from 18 to 60 years, with 124 donors (63 male, 61 female) in upright position and 121 donors (60 male, 61 female) in supine position. EDTA plasma samples were purchased from suppliers. The results are shown in table below:

Results	Gender	N	Median pg/mL	95% Range pg/mL
Upright	Male	63	22.5	3.5-52.1
	Female	61	18.5	3.6-47.4
Supine	Male	60	14.3	2.6-32.0
	Female	61	12.4	2.9-29.9

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.