

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

A. 510(k) Number:

k062120

B. Purpose for Submission:

Clearance of a new device

C. Measurand:

Renin

D. Type of Test:

Quantitative

E. Applicant:

CIS Bio International

F. Proprietary and Established Names:

Renin III Generation

G. Regulatory Information:

1. Regulation section:
21 CFR § 862.1085
2. Classification:
Class II
3. Product code:
CIB, Angiotensin I and renin test system
4. Panel:
Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):
See indications for use below.
2. Indication(s) for use:
A radioimmunoassay for the quantitative *in vitro* diagnostic measurement of the level of renin in plasma. Renin measurements are used in the diagnosis and treatment of certain types of hypertension.
3. Special conditions for use statement(s):
For professional use only.
4. Special instrument requirements:
Gamma radiation counter

I. Device Description:

The Renin III Generation is an immunoradiometric (sandwich technique) assay. The assay comes with mouse anti-human renin monoclonal antibody coated tubes, ¹²⁵I labeled mouse anti-human renin monoclonal antibody, a standard (a zero level and 5 concentrations spanning the measuring range), a control, and wash buffer for performing the assay.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Nichols Active Renin Immunoradiometric Assay
2. Predicate 510(k) number(s):
k925998
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Analyte	Active Renin	Active Renin
Matrix	Plasma	Plasma
Test Principle	Sandwich immunoassay	Sandwich immunoassay
Detection	Gamma counter (¹²⁵ I)	Gamma counter (¹²⁵ I)
Assay Methodology	Radioimmunoassay	Radioimmunoassay

Differences		
Item	Device	Predicate
Capture	Coated tube	Coated beads
Quality Control	Positive control	Positive and negative control
Detection Limit	2.0 µU/mL (1.0 pg/mL)	1.4 µU/mL

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

None identified.

L. Test Principle:

The Renin III Generation is an immunoradiometric (sandwich technique) that uses two anti-renin monoclonal antibodies. The first antibody is coated on polystyrene tubes and recognizes both inactive and active renin. The second antibody is labeled with ¹²⁵iodine and recognizes the active form of renin. After the sample is mixed with the first antibody and washed, the second radio-labeled anti-body is added. The amount of radioactivity detected is directly proportional to the amount of renin in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
 - a. *Precision/Reproducibility:*

An Intra-Assay precision study was performed to demonstrate the precision of the assay using seven (7) plasma samples that were measured 20 times in the same assay. The results are as follows.

Determination of Intra-Assay variation

Sample	Mean value (pg / ml)	Standard deviation	CV (%)
A	3.85	0.14	3.6
B	13.8	0.34	2.5
C	31.1	0.45	1.4
G	65.4	0.96	1.5
E	145	2.6	1.8
H	224	2.3	1.0
F	262	2.3	0.9

Inter-Assay measurements were performed using six (6) plasma samples that were tested monthly during a 3 year period (more than 137 experiments) using multiple lots of reagents and 6 technicians. The sample aliquots (6 patient samples) were frozen at -70°C . Each lot was tested 3 – 4 times each month to yield a total of 136 – 140 individual results. The following table summarizes the results of these assays during that time period. Results are from the total collected number of results (N values).

Determination of Inter-Assay variation

	Plasma 1	Plasma 2	Plasma 3	Plasma 4	Plasma 5	Plasma 6
N values	137	142	137	139	139	138
Mean (pg/ml)	4	14	32	72	146	263
SD (pg/ml)	0.2	0.6	1.2	2.6	5.4	10.5
C V (%)	5.0	4.3	3.7	3.6	3.7	4.0

To determine recovery, increasing amounts of Renin were added to serum samples with various initial Renin concentrations. Each sample (non-spiked and spiked) was assayed in duplicate in one run. Renin concentrations were measured and the percentage recovery was calculated.

Serum No.	Endogenous Renin ($\mu\text{U}/\text{mL}$)	Added Renin ($\mu\text{U}/\text{mL}$)	Expected Renin ($\mu\text{U}/\text{mL}$)	Measured Renin ($\mu\text{U}/\text{mL}$)	Recovery (%)
1	29.5	5	34.5	34.2	99
2	53.4	10	63.4	63.9	101
3	108	20	128	131	102

Since the sponsor is claiming a 7 week (49 day) shelf life for this assay and the half-life for the isotope used is approximately 60 days, a study was done using the assay at the end of the claimed shelf life and at 60 days as the isotope may already be decayed enough to cause false results. The study was performed using 6 plasma samples spanning the measuring range that were tested at the end of the shelf life (“end of run”) and again at 60 days in three experiments, each with 100 tubes. The results indicate that isotope decay does not seriously impact the assay at the end of the shelflife.

b. Linearity/assay reportable range:

The claimed measuring range of the assay is 1-320 pg/mL. This was supported by the linearity study and the method comparison study (for higher values).

Studies were performed to evaluate the recovery of the assay using EDTA plasma samples of different concentrations. The samples were assayed as neat and serially diluted with zero calibrator to a ratio of 1:32 to evaluate the range of the assay. The following results were obtained.

DILUTION	Sample	MEASURED CONC.	Calculated CONC. *DF	RECOVERY / NEAT
NEAT	PL2	66.7		
1/2		30.2	60	91%
1/4		15.5	62	93%
1/8		7.9	63	94%
1/16		4.0	63	95%
1/32		2.0	65	97%

NEAT	PL5	41.0		
1/2		20.0	40	98%
1/4		10.6	42	103%
1/8		5.0	40	98%
1/16		2.6	41	101%
1/32		1.2	39	96%

NEAT	PL7	287.9		
1/2		141.3	283	98%
1/4		70.1	280	97%
1/8		35.3	282	98%
1/16		17.3	277	96%
1/32		8.8	281	97%
1/64		4.8	304	106%
1/132		2.3	298	104%

NEAT	B2	21.0		
3/4		14.6	19.5	93%
1/2		9.6	19.3	92%
1/4		5.0	19.9	95%
1/8		2.4	19.1	91%
1/16		1.2	19.8	94%

NEAT	C	34.5		
3/4		24.7	32.9	95%
1/2		16.6	33.2	96%
1/4		8.3	33.3	97%
1/8		4.2	33.2	96%
1/16		2.1	33.4	97%

- c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
 Calibrator set points are traceable to WHO 68/356. The shelf-life of the calibrator (all six levels 0, 2.5, 5, 20, 80, and 320 pg/mL) and the control were determined using real time stability testing. Shelf life of the calibrator and control was found to be 7 weeks at 2-8°C.

- d. *Detection limit:*
 Analytical sensitivity was calculated from the mean of the cpm (counts per minute) of the zero calibrator plus 2 SD of 15 replicate analyses. The value was found to be < 1 pg/mL.

Functional Sensitivity was determined by performing 11 experiments with varying operators, labs, and reagents; and was calculated using curve is drawn by plotting the %CV against 6 serum concentrations. The functional sensitivity was defined as the minimum concentration corresponding to a %CV of 20%. Though the lowest value tested was 4 pg/mL, the sponsor will claim a functional sensitivity of 5 pg/mL to allow for in-field variations.

- e. *Analytical specificity:*
 No interference was observed when samples were spiked with any of the following substances: pro-renin, Cathepsin D (another enzyme of the aspartyl protease family), or various treatments for hypertension: Captopril, Renitec, Loxen, or Lasilix. Interference was seen with Hemoglobin and Cathepsin B. Non-interference was defined as difference from control within ±15%.

Substance	[renin], pg/mL without substance	[renin], pg/mL with substance	Change In [renin] pg/mL	% Change
Lasilix, 50 µg/mL	5.1	4.8	0.3	5.9
	10.7	10.1	0.6	5.6
Cathepsin D, 0.5 U/mL	5.1	5.6	0.5	9.8
	10.7	11.1	0.4	3.7
Captopril, 50 µg / mL	5.1	4.5	0.6	11.8
	10.7	10.5	0.2	1.9
Renitec, 50 µg / mL	5.1	4.9	0.2	3.9
	10.7	10.4	0.3	2.8
Loxen, 50 µg/mL	5.1	4.8	0.3	5.9
	10.7	10.8	0.1	0.9
Hemoglobin, 3 µg/mL	5.1	4.3	0.8	16.0
	10.7	10.2	0.5	5.0
Cathepsin B, 0.1 U/mL	5.1	9.4	4.3	84.0
	10.7	14.5	3.8	35.0

A study was performed to evaluate the cross-reactivity of Pro-Renin with the Renin assay. Pro-renin cross-reactivity was < 0.4 %.

A hook effect study was performed using a solution of recombinant antigen at a concentration of 3.8 mg/L. Dilutions in the zero standard were performed from 3.8 mg/L to 0.0038 mg/L. No hook effect was observed up to 1.4 mg/L.

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A study was performed to compare the results of the CisBio Renin test to the DSL RIA Renin Assay using patient plasma samples collected from a hospital laboratory. The samples were from 50 presumed healthy male and female patients and 49 patients identified as having hypertension (abnormal renin

levels) or potentially having hypertension with values ranging from 0 to 340 pg/mL.

Linear regression analysis gave the following relationship:

$$\text{Device} = 1.052(\text{Predicate}) - 0.338; r = 0.983; r^2 = 0.966$$

- 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 Renin RIA, 125 samples from fasting adult males and females, without estrogen-progesterone treatment, apparently healthy subjects' ages 20 to 60 years were analyzed using the Renin RIA kit. The subjects were asked to perform 1 hour of activity in an upright position and then remain seated in a supine for 1 hour. At the end of each 1 hour cycle a blood sample was drawn and tested in the Renin Assay. The results are shown in the Table below.

RESULTS	AGE	N	MEAN (pg/ml)	S.D.	Range
Upright	20-40	50	13.10	6.84	5.1 - 38.7
	40-60	75	14.02	8.34	1.8 - 59.4
Supine	20-40	50	8.11	3.66	3.6 - 20.1
	40-60	75	6.18	3.42	1.1 - 20.2

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.