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

A. 510(k) Number:

k081008

B. Purpose for Submission:

New device

C. Measurand:

Norbuprenorphine

D. Type of Test:

Qualitative and semi-quantitative Homogenous Enzyme Immunoassay

E. Applicant:

Lin-Zhi International, Inc.

F. Proprietary and Established Names:

Buprenorphine Enzyme Immunoassay
Norbuprenorphine Drugs of Abuse (DAU) Calibrators
Norbuprenorphine Drugs of Abuse (DAU) Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DJG	Class II	21 CFR 862.3650- Opiate Test System	91-Toxicology
DLJ	Class II	21 CFR 862.3200 – Clinical Toxicology Calibrators	91-Toxicology
LAS	Class I	21 CFR 862.3280 – Clinical Toxicology control material	91- Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use below

2. Indication(s) for use:

   The Lin-Zhi International (LZI) Buprenorphine Enzyme Immunoassay when used in conjunction with Beckman Coulter Synchron LX, CX and UniCel DxC automated clinical chemistry analyzers, is intended for the qualitative and semi-quantitative determination of norbuprenorphine (buprenorphine metabolite) in human urine, at a cutoff value of 10 ng/mL.

   The Norbuprenorphine Drugs of Abuse (DAU) Calibrators are for use as calibrators in qualitative and semi-quantitative calibration of the Lin-Zhi International (LZI) Buprenorphine Enzyme Immunoassay with Beckman Coulter Synchron LX, CX and UniCel DxC automated clinical chemistry analyzers.

   The Norbuprenorphine Drugs of Abuse (DAU) Controls are for use as assayed quality control materials to monitor the precision of the Lin-Zhi International (LZI) Buprenorphine Enzyme Immunoassay with Beckman Coulter Synchron LX, CX and UniCel DxC automated clinical chemistry analyzers.

   The assay provides a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/mass spectrometry (GC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when the preliminary result is positive.

3. Special conditions for use statement(s):

   The assay is for prescription use.

4. Special instrument requirements:

   Beckman Coulter Synchron CX, LX and UniCel DxC automated clinical chemistry analyzers.

I. Device Description:

The assay consists of ready-to-use liquid reagents. Reagent 1 contains mouse monoclonal anti-buprenorphine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD) and stabilizers. Reagent 2 contains buprenorphine-labeled glucose-6-phosphate dehydrogenase (G6PDH) in buffer. The calibrators controls are ready to use human urine-based liquid and are sold separately.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   CEDIA Buprenorphine Assay, Microgenics Corporation

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

   k040316

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	The assay is intended for the qualitative and semi-quantitative determination of norbuprenorphine (buprenorphine metabolite) in human urine.	The assay is for detecting the presence of Buprenorphine in human urine.
Ready to use	Yes	Yes
Determination mode	Qualitative and semi-quantitative	Qualitative and semi-quantitative
Matrix	Urine	Urine
Storage	2-8°C until expiration date	2-8°C until expiration date

Differences		
Item	Device	Predicate
Metabolite cross-reactants	Norbuprenorphine	Buprenorphine-3-β-D glucuronide
Calibrators level	6 levels (0, 5, 10, 20, 40 and 100 ng/ml)	5 levels (0, 5, 20, 50 and 75 ng/ml)
Cutoff	10 ng/ml	5 ng/ml
Stability	12 months at 2-8°C	60 days at 2-8°C
Control Levels	2 levels (7 and 13 ng/mL)	2 levels (3 and 7 ng/mL)

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

None referenced

L. Test Principle:

The Lin-Zhi Buprenorphine assay is a homogeneous enzyme immunoassay with ready-to-use liquid reagent. The assay is based on competition between drug in the

sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for a fixed amount of antibody in the reagent. In the absence of drug in the sample, the antibody binds the conjugated buprenorphine-labeled G6PDH thus the enzyme activity id inhibited. When free drug is present on the sample, the antibody will bind to the free drug and the unbound buprenorphine-labeled G6PDH exhibits its maximal enzyme activity. The G6PDH activity is measured spectrophotometrically at 340 nm because of conversion of NAD to NADH.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Intra-assay and between run precision was determined by spiking a standard norbuprenorphine solution into drug free urine at various concentrations (-75%, -50%, -25%, at the cutoff, +25% and 50%, 75% and 100% of the cutoff). Concentrations were confirmed by LC/MS. Testing for intra-assay imprecision was performed with 21 replicates in one day on the CX4CE, LX20 Pro and DxC 600 analyzers. The between run testing was performed twice a day for 10 days on all three analyzers. The qualitative and semi-quantitative results are presented below:

Qualitaitve:

Within Run		CX4CE	LX20 Pro	DxC 600
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	# Neg/#Pos	# Neg/#Pos
0 (negative)	21	21/0	21/0	21/0
2.5 (-75% c/o)	21	21/0	21/0	21/0
5.0 (-50% c/o)	21	21/0	21/0	21/0
7.5 (-25% c/o)	21	21/0	21/0	21/0
10 (cutoff)	21	8/13	0/21	3/18
12.5 (+25% c/o)	21	0/21	0/21	0/21
15.0 (+50% c/o)	21	0/21	0/21	0/21
17.5 (+50% c/o)	21	0/21	0/21	0/21
20 (+100% c/o)	21	0/21	0/21	0/21

Between Run		CX	LX	DxC
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	# Neg/#Pos	# Neg/#Pos
0 (negative)	20	20/0	20/0	20/0
2.5 (-75% c/o)	20	20/0	20/0	20/0
5.0 (-50% c/o)	20	20/0	20/0	20/0

Between Run		CX	LX	DxC
7.5 (-25% c/o)	20	20/0	20/0	20/0
10 (cutoff)	20	8/12	0/20	7/13
12.5 (+25% c/o)	20	0/20	0/20	0/20
15.0 (+50% c/o)	20	0/20	0/20	0/20
17.5 (+50% c/o)	20	0/20	0/20	0/20
20 (+100% c/o)	20	0/20	0/20	0/20

Semi-Quantitative

Within Run		CX4CE	LX20 Pro	DxC 600
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	# Neg/#Pos	# Neg/#Pos
0 (negative)	21	21/0	21/0	21/0
2.5 (-75% c/o)	21	21/0	21/0	21/0
5.0 (-50% c/o)	21	21/0	21/0	21/0
7.5 (-25% c/o)	21	21/0	21/0	21/0
10 (cutoff)	21	4/17	0/21	3/18
12.5 (+25% c/o)	21	0/21	0/21	0/21
15.0 (+50% c/o)	21	0/21	0/21	0/21
17.5 (+50% c/o)	21	0/21	0/21	0/21
20 (+100% c/o)	21	0/21	0/21	0/21

Between Run		CX	LX	DxC
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	# Neg/#Pos	# Neg/#Pos
0 (negative)	20	20/0	20/0	20/0
2.5 (-75% c/o)	20	20/0	20/0	20/0
5.0 (-50% c/o)	20	20/0	20/0	20/0
7.5 (-25% c/o)	20	20/0	20/0	20/0
10 (cutoff)	20	4/16	4/16	10/10
12.5 (+25% c/o)	20	0/20	0/20	0/20
15.0 (+50% c/o)	20	0/20	0/20	0/20
17.5 (+50% c/o)	20	0/20	0/20	0/20
20 (+100% c/o)	20	0/20	0/20	0/20

b. Linearity/assay reportable range:

Linearity across the range was confirmed by serially diluting a spiked urine pool containing 100 ng/mL of Norbuprenorphine in 10% increments. Each sample was assayed in replicates of 10 on each analyzer in the semi-quantitative mode. The results were averaged and compared to the expected result and the percent recovery was calculated. Sponsor calculated the %

recovery by dividing the recovered result by the target concentration and then multiplying by 100. All samples except for the 40 ng/mL sample performed on the DxC 600 recovered within ± 15% of the expected value. Results are presented below:

Sample ng/ml	CX4CE			LX20 Pro			DxC 600		
Expected	Observed Mean	SD	% Recovery	Mean	SD	% Recovery	Mean	SD	% Recovery
5	5.4	0.1	108.2	5.4	0.5	107.4	5.5	0.3	109.2
10	10.2	0.3	102.1	11.0	0.2	109.8	10.2	0.4	102
20	19.6	0.3	98.0	20.2	0.5	101.2	19.9	0.5	99.6
30	30	0.6	99.9	31.6	0.6	105.5	31.3	0.9	104.32
40	42.1	0.9	105.2	44.5	2.0	111.2	46.6	0.8	116.5
50	53.9	2.6	107.7	55.7	2.8	111.3	56.1	3.4	112.2
60	67.8	2.7	113	64.3	3.0	107.2	66.5	4.0	110.9
70	77.5	2.1	110.7	79	8.8	112.8	73.3	4.4	104.7
80	83.9	3.7	104.9	y = 1.1203x -0.9484 r^2 =0.9978			y = 1.0936x -0.2831 r^2 =0.9941		
90	91.1	4.4	101.2						
	y = 1.0605x -0.1027 r^2 =0.9938								

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

Calibrators and Controls:

A commercially available norbuprenorphine standard solution from Cerolliant Analytical Reference Standards is used and traceable to NIST standard. This standard solution is made into a secondary (lower concentration) stock solution. The secondary stock solution is then spiked into the calibrators and controls to the desired concentration. The concentrations are confirmed by GC/MS.

Stability Studies:

Real time and accelerated studies have been conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following expiration date:

When stored at 2-8 ºC unopened product is good until expiration date which is 18 months.

On board stability is good for 14 days when stored at 2-8 ºC.

d. *Detection limit:*
Not applicable. This assay is qualitative and semi-quantitative only. Semi-quantitative values should be used to estimate concentration for dilution purposes only.

e. *Analytical specificity:*

Various potentially interfering substances were evaluated for *potential positive/and or negative interference* with the assay. Test compounds were spiked into a negative and a positive sample to various concentrations. The substances listed in the table below were determined not to interfere at the concentrations shown:

Interfering Substance	Concentration Tested mg/dL
Acetone	1000
Ascorbic Acid	400
Creatinine	500
Galactose	10
r-Globulin	500
Glucose	1500
Hemoglobin	300
NaCl	6000
Oxalic Acid	100
Human Serum Albumin (HSA)	500
Urea	2000
Ethanol	1000
pH 3	n/a
pH 11	n/a

Interference testing over the specific gravity was performed on the Cx4CE analyzer and the results are presented below:

Specific Gravity value	Sample contains 0 ng/mL of norbuprenorphine		Sample contains 13 ng/mL of norbuprenorphine	
Sample	ng/mL	Result	ng/mL	Result
1.001	0.0	Negative	12.2	Positive

1.004	0.0	Negative	13.1	Positive
1.006	0.0	Negative	13.0	Positive
1.010	0.0	Negative	12.1	Positive
1.012	0.0	Negative	13.0	Positive
1.015	0.3	Negative	12.2	Positive
1.017	0.0	Negative	13.1	Positive
1.027	0.0	Negative	12.3	Positive

There is the possibility that other substances and/or factors not listed above may interfere with the test and cause false results, e.g., technical or procedural errors

Cross-reactivity was evaluated by spiking various concentrations of similarly structured drug compounds into drug-free urine. By analyzing various concentrations of each compound the sponsor determined the concentration of the drug that produced a response approximately equivalent to the 10 ng/mL cutoff concentration of the assay. The percentage cross reactivities of those compounds are presented below:

Compound	**Quantity equivalent to 10 ng/mL**	**% Cross-reactivity**
Buprenorphine	10.6	94.5%
Buprenorphine-Glucuronide	33.333	<0.1%
Norbuprenorphine-Glucuronide	1,036	<0.1%

f. Assay cut-off:
Analytical performance of the device around the claimed cutoff is described in precision section (1 a.) above

2. Comparison studies:

a. Method comparison with predicate device:

CX4CE BUP Assay	Negative	Low Negative by GC/MS (less than -50%) or negative by Predicate	Near Cutoff Negative (between –50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement with GC/MS
Positive	0	0	3*	8	32	93%
Negative	10	18	11	1**	0	97.5%

*****one sample contained 8.5 ng/mL Norbuprenorphine and 3.2 ng/mL buprenorphine by GC/MS, the other two samples contained 8.9 ng/mL and 9.5 ng/mL of Norbuprenorphine by GC/MS.
** sample contained 10.2 ng/mL Norbuprenorphine by GC/MS.

LX20 Pro BUP Assay	Negative	Low Negative by GC/MS (less than -50%) or negative by Predicate	Near Cutoff Negative (between –50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)	High Positive (greater than +50%)	Percent Agreement with GC/MS
Positive	0	0	1*	6	32	97.3%
Negative	10	18	13	2**	0	95.3%

*****the sample contained 8.5 ng/mL Norbuprenorphine and 3.2 ng/mL buprenorphine by GC/MS.
** the samples contained 10.2 ng/mL and 10.7 norbuprenorphine by GC/MS.

DxC 600 BUP Assay	Negative	Low Negative by GC/MS (less than -50%) or negative by Predicate	Near Cutoff Negative (between –50% and cutoff)	Near Cutoff Positive (between cutoff and +50%)30	High Positive (greater than +50%)	Percent Agreement with GC/MS
Positive	0	0	1*	6	32	97.3%
Negative	10	18	13	2**	0	95.3%

*****the sample contained 8.5 ng/mL Norbuprenorphine and 3.2 ng/mL buprenorphine.
** the samples contained 10.2 ng/mL and 10.7 norbuprenorphine by GC/MS

b. Matrix comparison:

Not applicable test is for urine samples only

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:

   Not applicable

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.