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

A. 510(k) Number:

k101195

B. Purpose for Submission:

New device

C. Measurand:

6-Acetylmorphine

D. Type of Test:

Qualitative and semi-quantitative enzyme immunoassay

E. Applicant:

Lin-Zhi International, Inc.

F. Proprietary and Established Names:

6-Acetylmorphine Enzyme Immunoassay
6-Acetylmorphine Calibrators
6-Acetylmorphine Controls

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DJG- Opiate test system	II	862.3650	91-Toxicology
DLJ -Clinical toxicology calibrator	II	862.3200	91- Toxicology
LAS -Clinical toxicology control material	I, reserved	862.3280	91- Toxicology

H. Intended Use:

1. Intended use(s):

   See indications for use below

2. Indication(s) for use:

   The 6-Acetylmorphine Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of 6-Acetylmorphine in human urine, at a cutoff value of 10 ng/mL. The assay is designed for professional use with a number of automated clinical chemistry analyzers.

   The 6-Acetylmorphine Drugs of Abuse (DAU) Calibrators are for use as calibrators in the qualitative and semi-quantitative calibration of the 6-Acetylmorphine Enzyme Immunoassay.

   The 6-Acetylmorphine Drugs of Abuse (DAU) Controls are for use as assayed quality control materials to monitor the precision of the 6-Acetylmorphine Enzyme Immunoassay.

   This assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used in order to obtain a confirmed analytical result. Gas or Liquid Chromatograph/Mass Spectrometry (GC/MS or LC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary result is positive.

3. Special conditions for use statement(s):

   For professional use only

4. Special instrument requirements:

   Analyzers capable of maintaining a constant temperature, pipetting samples, mixing reagents, measuring enzymatic rates at 340 nm and timing the reaction accurately can be used to perform this assay.

I. Device Description:

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

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Microgenics CEDIA DAU 6-Acetylmorphine Assay, Microgenics Corporation
   Microgenics DAU 6-Acetylmorphine Calibrators, Microgenics Corporation
   Microgenics DAU 6-Acetylmorphine Controls, Microgenics Corporation

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

   K001178

3. Comparison with predicate:

Similarities/Differences		
Item	Device	Predicate
Intended Use	Intended for the qualitative and semi-quantitative determination of 6-acetylmorphine in human urine, at a cutoff value of 10 ng/mL. The assay is designed for professional use with a number of automated clinical chemistry analyzers.	Same
Analyte	6-Acetylmorphine	Same
Cutoff	10 ng/mL	Same
Matrix	Human Urine	Same
Calibrators	5 levels (0, 5, 10, 20, 40 ng/mL)	3 levels (0, 10, 20 ng/mL)
Controls	2 levels (7.5 ng/mL, 12.5 ng/mL)	2 levels (7.5 ng/mL, 12.5 ng/mL)
Storage	2-8 ºC until expiration date	2-8 ºC until expiration date

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods

L. Test Principle:

The 6-Acetylmorphine assay is a homogenous enzyme immunoassay with ready-to-use liquid reagent. The assay is based on competition between drug in the sample and dug labeled with enzyme glucose-6-phodphate dehydrogenase (G6PDH) for a fixed amount of antibody in the reagent. Enzyme activity decreases upon binding to the antibody, and the drug concentration in the sample is measures in terms of enzyme activity. In the absence of drug in the sample, 6-Acetylmorphine-labeled G6PDH conjugate is bound to antibody, and the enzyme activity is inhibited. On the other hand, when free drug is present in the sample, antibody would bind to free drug, the unbound 6-Acetylmorphine-labeled G6PDH then exhibits its maximal enzyme activity. Active enzyme converts nictinamide adenine dinucleotide (NAD) to NADH resulting in an absorbance change that can be measured spectrophotometrically at 340 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

Performance testing was conducted on the Hitachi 717

a. Precision/Reproducibility:

Precision was determined by spiking 6-Acetylmorphine into drug free urine at various concentrations (-75%, -50%, -25%, at the cutoff, 125% and 150%, 175% and 200% of the cutoff). Concentrations were confirmed by LC/MS. Testing for the intra-assay was performed once a day for 22 days. The between run testing was performed in replicate twice a day for 22 day. The qualitative and semi-quantitative results are presented below:

Qualitative:

		Within Run		Between Run
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	No. Observations	# Neg/#Pos
0 (negative)	22	22/0	88	88/0
2.5 (-75% c/o)	22	22/0	88	88/0
5.0 (-50% c/o)	22	22/0	88	88/0
7.5 (-25% c/o)	22	22/0	88	88/0
10 (cutoff)	22	12/10	88	47/41
12.5 (+25% c/o)	22	0/22	88	0/88
15.0 (+50% c/o)	22	0/22	88	0/88
17.5 (+50% c/o)	22	0/22	88	0/88
20 (+100% c/o)	22	0/22	88	0/88

Semi-Quantitative:

		Within Run		Between Run
Sample concentration (ng/mL)	No. Observations	# Neg/#Pos	No. Observations	# Neg/#Pos
0 (negative)	22	22/0	88	88/0
2.5 (-75% c/o)	22	22/0	88	88/0
5.0 (-50% c/o)	22	22/0	88	88/0
7.5 (-25% c/o)	22	22/0	88	88/0
10 (cutoff)	22	16/6	88	66/22
12.5 (+25% c/o)	22	0/22	88	0/88
15.0 (+50% c/o)	22	0/22	88	0/88
17.5 (+50% c/o)	22	0/22	88	0/88
20 (+100% c/o)	22	0/22	88	0/88

b. Linearity/assay reportable range:

Linearity across the range was confirmed by serially diluting a spiked urine pool containing 100 ng/mL of 6-Acetylmorphine in to concentration levels listed in the table below. Each sample was assayed in the semi-quantitative mode. The results were averaged and compared to the expected result and the percent recovery was calculated. The claimed range is 2-40 ng/mL. Results are presented in the table below:

Expected Concentration	Mean Observed Concentration	Recovery (%)
Negative	0.36	not applicable
2	2.47	123.5
5	5.48	109.6
10	9.77	97.7
15	14.22	94.8
20	19.18	95.9
30	29.14	97.1
35	32.34	92.4
40	40.51	101.3

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

A commercially available 6-Acetylmorphine 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 for both controls and calibrators have been conducted. Protocols and acceptance criteria were described and found to be acceptable. The manufacturer claims the following expiration date for both controls and calibrators:

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

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

d. Detection limit:

Performance at low drug concentrations in the semi-quantitative assay was characterized by determination of recovery (see section b above).

e. Analytical specificity:

Cross-reactivity was established by spiking various concentrations of structurally related and unrelated into drug-free urine. Results are expressed as a minimum concentration of metabolite or compound required to produce a response approximately equivalent to the cutoff concentration of the assay. The percent cross-reactivity of those compounds are presented below:

Structurally related

Compound	Equivalent to 10 ng/mL	% Cross reactivity
Codeine	500,000	0
Dextromethorphan	100,000	0
Dihydrocodine	500,000	0
Heroin	10	67.5
Hudrocodone	300,000	0
Hydromorphone	100,000	0
Imipramine	200,000	0
Levorphanol	100,000	0
Meperidine	800,000	0
Morphine	100,000	0
M3G	600,000	0
M6G	600,000	0
Nalorphine	100,000	0
Naloxone	500,000	0
Naltrexone	300,000	0
Norcodeine	600,000	0
Normorphine	100,000	0
Oxycodone	500,000	0

Compound	Equivalent to 10 ng/mL	% Cross reactivity
Oxymorphone	100,000	0

Structurally unrelated

Compound	Equivalent to 10 ng/mL	% Cross reactivity
11-nor—THC-COOH	100,000	0
Acetaminophen	500,000	0
Acetylsalicylic	500,000	0
Amitriptyline	500,000	0
Benzoylecgonine	500,000	0
Brompheniramine	100,000	0
Caffeine	500,000	0
Chlorpomazine	250,000	0
Desipramine	500,000	0
Diazepam	100,000	0
Digoxin	100,000	0
Diphenhydramine	100,000	0
Doxepin	100,000	0
Fluoxetine	500,000	0
Hydroxyzine	500,000	0
Ibuprofen	500,000	0
Methadone	500,000	0
Methamphetamine	500,000	0
Oxazepam	500,000	0
Phencyclidine	100,000	0
Phenobarbital	500,000	0
Propoxyphene	100,000	0
Ranitidine	500,000	0
Secobarbital	500,000	0
Triprolidine	100,000	0.001

Endogenous Compounds

The following endogenous compounds were added into drug-free urine, urine sample spiked to 7.5 ng/mL of 6-Acetylmorphine and one urine spiked to 12.5 ng/mL of 6-Acetylmorphine at various concentrations. The substances listed in the table below were determined not to interfere at the concentration shown:

Interfering Substance	Concentration Tested mg/dL	Interfering Substance	Concentration Tested mg/dL
Acetone	1000	Glucose	1500
Ascorbic Acid	400	Hemoglobin	300
Creatinine	500	Human Serum Albumin (HSA)	500
Ethanol	100	Oxalic Acid	100
Galactose	10	NaCl	3000
r-Globulin	500	Urea	2000

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.

pH and Specific Gravity

To test for possible positive and/or negative interference from pH urine samples having pH from 4, 5, 7, 8, 9 and 10 were used. Each of these samples were divided into two aliquots for each drug and spiked to -25% of the cutoff and 125% of the cutoff. No positive or negative interference due to pH was observed.

To test for possible positive and/or negative interference from specific gravity urine samples having specific gravity from 1.0025, 1.005, 1.0075, 1.010, 1.015, 1.017, 1.025 and 1.030 were used. Each of these samples were divided into two aliquots for each drug and spiked to -25% of the cutoff and 125% of the cutoff. No positive or negative interference due to specific gravity was observed.

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:

Eighty unaltered clinical urine samples (40 negative and 40 positive) were evaluated by the LZI 6-Acetylmorphine assay and compared to a LC/MS. Results from the study are presented below:

Qualitative

Candidate Device Results	Negative	Less than half the cutoff concentration by GC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Positive	0	0	0	6	31
Negative	10	14	16	3	0

Semi-quantitative

Candidate Device Results	Negative	Less than half the cutoff concentration by GC/MS analysis	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration)	High Positive (greater than 50% above the cutoff concentration)
Positive	0	0	0	6	31
Negative	10	14	16	3	0

% Agreement among positives is 93% (37/40)
% Agreement among negatives is 100% (40/40)

Discordant

Cutoff Value (ng/mL)	LZI 6-Acetylmorphine Assay (POS/NEG)	Drug/Metabolite LC/MS value (ng/mL)
10	Negative	10.0
10	Negative	11.0
10	Negative	13.0

b. Matrix comparison:

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.