

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

A. 510(k) Number:

k110298

B. Purpose for Submission:

New Device

C. Measurand:

Opiates

D. Type of Test:

Competitive enzyme immunoassay; qualitative and semi-quantitative

E. Applicant:

Lin-Zhi International, Inc.

F. Proprietary and Established Names:

Opiate Enzyme Immunoassay

G. Regulatory Information:

1. Regulation section:
21 CFR § 862.3650 Opiate Test System
2. Classification:
Class II
3. Product code:
DJG, Enzyme Immunoassay, Opiate
4. Panel:
91 (Toxicology)

H. Intended Use:

1. Intended use(s):
See Indications for use, below.

2. Indication(s) for use:

The Opiate Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of opiates in human urine, at a cutoff value of 300 ng/mL when calibrated against morphine. The assay is designed for prescription use with a number of automated clinical chemistry analyzers.

The semi-quantitative mode is for purposes of (1) enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as GCMS or (2) permitting laboratories to establish quality control procedures.

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 chromatography (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):

The assay is for prescription use

4. Special instrument requirements:

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting sample, mixing reagent, measuring enzymatic rates at 340 nm and timing the reaction accurately can be used to perform this homogeneous immunoassay.

Performance studies in this submission were performed on the Hitachi 717.

I. Device Description:

The Opiate Enzyme Immunoassay is a homogeneous enzyme immunoassay ready-to-use liquid reagent. The assay is comprised of two ready-to-use liquid reagents, R1 (1 x 100 mL or 1 x 1000 mL) and R2 (1 x 37.5 or 1 x 375 mL). R1 solution contains a mouse monoclonal anti-morphine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD), stabilizers, and sodium azide (0.09%) as a preservative. R2 solution contains glucose-6-phosphate dehydrogenase (G6PDH) labeled with morphine in buffer, with sodium azide (0.09%) as a preservative. The kits will be provided in two configurations, with R1 x 100 mL; R2 x 37.5 mL and with R1 x 1000 mL; R2 x 375 mL.

Previously cleared (k020769) Calibrators and Controls are sold separately and contain negative human urine with sodium azide as preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Opiate Enzyme Immunoassay
2. Predicate 510(k) number(s):
k020368
3. Comparison with predicate:

Similarities and Differences		
Item	Candidate device (Opiate Enzyme Immunoassay)	Predicate device (k020368)
Intended Use	<p>The Opiate Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of opiates in human urine, at a cut off value of 300 mg/mL. The assay is designed for professional use with a number of automated clinical chemistry analyzers.</p> <p>The semi-quantitative mode is for purposes of: 1) enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as GCMS or 2) permitting laboratories to establish quality control procedures.</p> <p>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 chromatography (GC/MS or LC/MS) is the preferred</p>	Same

Similarities and Differences		
	confirmatory method. Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary result is positive.	
Sample Types	Urine	Same
Test Principle	Competitive enzyme immunoassay	Same
Cutoff	300 ng/mL	Same

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

No Standards/Guidance Referenced

L. Test Principle:

The Opiate Enzyme Immunoassay is a competitive enzyme immunoassay 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. Enzyme activity decreases upon binding to the antibody, and the drug concentration in the sample is measured in terms of enzyme activity. In the absence of drug in the sample, morphine-labeled G6PDH conjugate is bound to antibody and enzyme activity is inhibited. When free drug is present in the sample antibody binds to the free drug, the unbound morphine-labeled G6PDH then exhibits its maximum enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH resulting in an absorbance change measured spectrophotometrically at 340 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

Performance was evaluated on the Hitachi 717

a. Precision/Reproducibility:

Precision was determined by spiking morphine standards into drug free urine pool at various concentrations surrounding the cutoff: -100%, -75%, -50%, -25%, cutoff, +100%, +75%, +50%, +25% +100%. Concentrations were confirmed by GC/MS. Testing for both the with-in run and between-run studies were performed by testing each sample in replicate, with two runs per day, for 22 days. The qualitative and semi-quantitative results are presented below:

Qualitative Precision Data:

300 ng/mL Cutoff Result		Within Run		Total Precision	
Sample Concentration (ng/mL)	% of Cutoff	Number of Determinations	Immunoassay Results	Number of Determinations	Immunoassay Results
0	-100%	22	22 Negative	88	88 Negative
75	-75%	22	22 Negative	88	88 Negative
150	-50%	22	22 Negative	88	88 Negative
225	-25%	22	22 Negative	88	88 Negative
300	Cut off	22	16 Pos/6 Neg	88	51 Pos/37 Neg
375	+25%	22	22 Positive	88	88 Positive
450	+50%	22	22 Positive	88	88 Positive
525	+75%	22	22 Positive	88	88 Positive
600	+100%	22	22 Positive	88	88 Positive

Semi-Quantitative Precision Data:

300 ng/mL Cutoff Result		Within Run		Total Precision	
Sample Concentration (ng/mL)	% of Cutoff	Number of Determinations	Immunoassay Results	Number of Determinations	Immunoassay Results
0	-100%	22	22 Negative	88	88 Negative
75	-75%	22	22 Negative	88	88 Negative
150	-50%	22	22 Negative	88	88 Negative
225	-25%	22	22 Negative	88	88 Negative
300	Cut off	22	6 Pos/16 Neg	88	27 Pos/61 Neg
375	+25%	22	22 Positive	88	88 Positive
450	+50%	22	22 Positive	88	88 Positive
525	+75%	22	22 Positive	88	88 Positive
600	+100%	22	22 Positive	88	88 Positive

b. Linearity/assay reportable range:

Linearity across the range was confirmed by serially diluting a spiked urine pool containing 1000 ng/mL of morphine to obtain the concentrations listed in the table below. Each sample was assayed in replicates of 10 on the Hitachi 717 analyzer in the semi-quantitative mode. The results were averaged and compared to the expected result and the percent recovery was calculated.

Results are presented in the table below:

Expected Value (ng/mL)	Mean Observed Value (ng/mL)	Recovery (%)
1000	1099.09	109.9
900	957.84	106.4

800	832.13	104.0
700	710.24	101.5
600	619.26	103.2
500	523.29	104.7
400	425.71	106.4
300	303.31	101.1
200	225.04	112.5
100	116.31	116.3
20	20.81	104.1
0	0	Not Applicable

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

Traceability:

Five levels of calibrators (0, 150, 300, 600, 1000 ng/mL) and two levels of control material (225 and 375 ng/mL) are available for use with the Opiate Enzyme Immunoassay. These calibrator and control solutions are human urine based and were previously cleared under k020769

Stability and Value assignment:

Stability and value assignment of the calibrators and controls was evaluated in k020769.

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:*

The cross-reactivity of various potential interfering drugs was tested by spiking a final concentration of up to 3,000,000 ng/mL of each substance into drug-free urine. The structurally un-related compounds were spiked into samples containing morphine at concentrations $\pm 25\%$ of the cutoff. Compounds that interfered with the performance of the device were further tested at $\pm 50\%$ of the cutoff concentration. Samples evaluated in both semi-quantitative and qualitative mode. Results summarize the approximate quantity of each compound that is equivalent in assay reactivity to the 300 ng/mL morphine cutoff and are presented below:

Structurally Related Compounds

Compound	Compound Concentration	Cross-reactivity (%)
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	(ng/mL)	
6-Monoacetyl Morphine	400	85.85
Codeine	200	169.00
Dihydrocodeine	700	43.44
Heroin	300	107.88
Hydrocodone	2300	13.74
Hydromorphone	1900	17.23
Levorphanol	8000	4.01
Morphine	300	101.15
Morphine-3-Glucuronide	800	39.12
Morphine-6-Glucuronide	300	109.03
Nalbuphine	3,000,000	0.006
Naloxone	2,700,000	0.046
Naltrexone	800,000	0.011
Normorphine	30,000	0.316
Norcodeine	130,000	0.24
Oxycodone	60,000	0.51
Oxymorphone	140,000	0.23
Thebaine	2,000	16.12
Codeine-6-β-Glucuronide	250	124.38

Structurally Unrelated Compounds

Compound	Concentration (ng/mL)	-25% Cutoff		+25% Cutoff	
		Semi-quant	Qualitative	Semi-quant	Qualitative
Acetaminophen	500,000	NEG	NEG	POS	POS
Acetylsalicylic Acid	3,000,000	NEG	NEG	POS	POS
Albuterol	3,000,000	NEG	NEG	POS	POS
Amitriptyline	50,000	NEG	NEG	POS	POS
Amobarbital	3,000,000	NEG	NEG	POS	POS
d-Amphetamine	3,000,000	NEG	NEG	POS	POS
Benzoylcegonine	3,000,000	NEG	NEG	POS	POS
Bupropion	1,000,000	NEG	NEG	POS	POS
Caffeine	3,000,000	NEG	NEG	POS	POS
Carbamazepine	500,000	NEG	NEG	POS	POS
Chlorpromazine	80,000	NEG	NEG	POS	POS
Clomipramine	30,000	NEG	NEG	POS	POS

Desipramine	130,000	NEG	NEG	POS	POS
Dextromethorphan	40,000	NEG	NEG	POS	POS
Doxepine	175,000	NEG	NEG	POS	POS
Ecgonine	3,000,000	NEG	NEG	POS	POS
Ephedrine	1,400,000	NEG	NEG	POS	POS
Fentanyl	300,000	NEG	NEG	POS	POS
Fluoxetine	800,000	NEG	NEG	POS	POS
Fluphenazine	3,000,000	NEG	NEG	POS	POS
Ibuprofen	500,000	NEG	NEG	POS	POS
Imipramine	20,000	POS	POS	POS	POS
Lidocaine	3,000,000	NEG	NEG	POS	POS
Maprotiline	600,000	NEG	NEG	POS	POS
Meperidine	25,000	NEG	NEG	POS	POS
Methadone	700,000	NEG	NEG	POS	POS
Methapyrilene	300,000	POS	POS	POS	POS
Methaqualone	3,000,000	NEG	NEG	POS	POS
Metronidazole	700,000	NEG	NEG	POS	POS
Nicotine	800,000	NEG	NEG	POS	POS
Nortriptyline	110,000	NEG	NEG	POS	POS
Oxazepam	3,000,000	NEG	NEG	POS	POS
Phencyclidine	900,000	NEG	NEG	POS	POS
Phenobarbital	3,000,000	NEG	NEG	POS	POS
Propoxyphene	260,000	NEG	NEG	POS	POS
Ranitidine	3,000,000	POS	NEG	POS	POS
Secobarbital	3,000,000	NEG	NEG	POS	POS
Talwin	100,000	NEG	NEG	POS	POS
Thioridazine	70,000	NEG	NEG	POS	POS
Tramadol	500,000	POS	NEG	POS	POS
Valproic Acid	3,000,000	NEG	NEG	POS	POS

The following compounds interfered with the performance of the assay at +/- 25% of the cutoff concentration of morphine: Imipramine, Methapyrilene, Ranitidine, Tramadol. These compounds were further tested at +/-50% of the cutoff and were shown to have no detectable interference with the assay.

Endogenous Compounds:

The following endogenous compounds were spiked into urine spiked with morphine to $\pm 25\%$ of cutoff (225 or 375 ng/mL). The spiked solutions were evaluated on the Hitachi 717. The substances listed in the following table were determined not to interfere at the concentrations tested:

Compound	Concentration (ng/mL)	-25% Cutoff		+25% Cutoff	
		Qual.	Semi-	Qual.	Semi-

			quant		quant
Acetone	1000	NEG	NEG	POS	POS
Ascorbic Acid	1500	NEG	NEG	POS	POS
Creatinine	500	NEG	NEG	POS	POS
Ethanol	1000	NEG	NEG	POS	POS
Galactose	10	NEG	NEG	POS	POS
β -Globulin	500	NEG	NEG	POS	POS
Glucose	3000	NEG	NEG	POS	POS
Hemoglobin	300	NEG	NEG	POS	POS
Human Serum Albumin	500	NEG	NEG	POS	POS
Oxalic Acid	100	NEG	NEG	POS	POS
Riboflavin	0.3	NEG	NEG	POS	POS
Sodium Chloride	6000	NEG	NEG	POS	POS
Urea	6000	NEG	NEG	POS	POS

The package insert includes a complete list of all structurally related, structurally un-related and endogenous compounds tested.

Specific gravity:

Eight drug-free urine samples with specific gravity ranging from of 1.002 to 1.027 (1.002, 1.005, 1.008, 1.010, 1.012, 1.018, 1.02, 1.027 were spiked with morphine to achieve concentrations of $\pm 25\%$ of the cut-off (225 ng/mL or 375 mg/mL).

The original and the spiked samples were tested with Opiate Enzyme Immunoassay on the Hitachi 717 in the qualitative and semi-quantitative modes. The results indicate that there is no positive or negative interference due to specific gravity.

pH:

The effect of pH was tested across the range of 3 to 11 (pH 3, 4, 5, 6, 7, 8, 9, 10, and 11). Drug free urine sample pools were pH adjusted then divided into two aliquots and then spiked with morphine to achieve $\pm 25\%$ of the cutoff. No positive or negative interference due to pH was observed.

f. Assay cut-off:

See Detection Limit Section, above.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 88 unaltered clinical samples (44 positive and 44 negative) were tested with the Opiate Enzyme Immunoassay on the Hitachi 717 analyzer. The opiate concentrations for each sample were confirmed by GC/MS or LC/MS. Results are shown in the tables below:

Qualitative:

Candidate Device Results	Negative	Low Negative (<50% of the cutoff by GC/MS)	Near Cutoff Negative (50% below the cutoff to the cutoff by GC/MS)	Near Cutoff Positive (50% above the cutoff to the cutoff by GC/MS)	High Positive (>50 above the cutoff by GC/MS)	Percent Agreement with GCMS
Positive	0	1	3	9	34	90.9%
Negative	3	25	12	1	0	97.7%

Summary of Discordant Results (Qualitative)

Opiate Assay (POS/NEG)	Drug/Metabolite GC/MS or LC/MS value based on cross reactivity profile
Positive	40.6 ng/mL (Morphine)
Positive	244.62 ng/mL (Morphine)
Positive	252.7 ng/mL (Morphine)
Positive	241.9 ng/mL (Morphine)
Negative	320.7 ng/mL (Morphine)

Semi-Quantitative:

Candidate Device Results	Negative	Low Negative (<50% of the cutoff by GC/MS)	Near Cutoff Negative (50% below the cutoff to the cutoff by GC/MS)	Near Cutoff Positive (50% above the cutoff to the cutoff by GC/MS)	High Positive (>50 above the cutoff by GC/MS)	Percent Agreement with GCMS
Positive	0	0	3	9	34	93.18%
Negative	3	26	12	1	0	97.6%

Summary of Discordant Results (Semi-Quantitative)

Opiate Assay (POS/NEG)	Drug/Metabolite GC/MS or LC/MS value based on cross reactivity profile
Positive	244.62 ng/mL (Morphine)
Positive	252.7 ng/mL (Morphine)
Positive	241.9 ng/mL (Morphine)
Negative	320.74 ng/mL (Morphine)

The tables above demonstrate that in this study qualitatively discrepant results were observed only for near-cutoff samples (+/- 50% of the cutoff concentration),

with the exception of 1 low negative sample that resulted in a positive result in the qualitative mode. A supplementary study, with an additional 42 unaltered patient samples was performed by the sponsor to support method comparison. Results from the additional study are presented below:

Qualitative:

Candidate Device Results	Negative	Low Negative (<50% of the cutoff by GC/MS)	Near Cutoff Negative (50% below the cutoff to the cutoff by GC/MS)	Near Cutoff Positive (50% above the cutoff to the cutoff by GC/MS)	High Positive (>50 above the cutoff by GC/MS)	Percent Agreement with GCMS
Positive	0	0	0	7	6	100%
Negative	20	4	5	0	0	100%

Semi-Quantitative:

Candidate Device Results	Negative	Low Negative (<50% of the cutoff by GC/MS)	Near Cutoff Negative (50% below the cutoff to the cutoff by GC/MS)	Near Cutoff Positive (50% above the cutoff to the cutoff by GC/MS)	High Positive (>50 above the cutoff by GC/MS)	Percent Agreement with GCMS
Positive	0	0	0	7	6	100%
Negative	20	4	5	0	0	100%

No additional discrepant results were observed in the supplementary study.

b. Matrix comparison:

Not Applicable, urine is the only indicated matrix.

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.