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

A. 510(k) Number:

k090844

B. Purpose for Submission:

Modification to previously cleared assay

C. Measurand:

Norbuprenorphine (buprenorphine metabolite)

D. Type of Test:

Homogeneous enzyme immunoassay – qualitative and semi- quantitative

E. Applicant:

Lin-Zhi International, Inc.

F. Proprietary and Established Names:

Buprenorphine Enzyme Immunoassay, Norpbuprenorphine Drugs of Abuse Controls, Norbuprenorphine Drugs of Abuse Calibrators.

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, reserved	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 is intended for the qualitative and semiquantitative determination of norbuprenorphine (buprenorphine metabolite) in human urine, at cutoff values of 5 ng/mL and 10 ng/mL. The assay is designed for prescription use with a number of automated clinical chemistry analyzers.

   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.

   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.

   The assay provides only 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) or LCMS are the preferred confirmatory methods. 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:

   Automated clinical chemistry analyzers. (Performance in the studies submitted in the 510(k) are based on the Hitachi 717.)

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-

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phosphate dehydrogenase (G6PDH) in buffer. The calibrators and controls are ready to use human urine-based liquid and are sold separately.

J. Substantial Equivalence Information:

1. Predicate device name(s): LZI Buprenorphine Enzyme Immunoassay

2. Predicate 510(k) number(s): k081008

3. Comparison with predicate: The cutoffs for the new device are 5 and 10 ng/mL; the predicate device has one cutoff at 10 ng/mL. Related to this additional lower cutoff, there is an extra level of control material, and a change in one of the calibrator concentrations levels. Specifically, the new device has a high calibrator concentration of 75 ng/mL; the predicate device had a high calibrator concentration of 100 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 is 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:

Performance was evaluated on the Hitachi 717 Instrument.

   a. *Precision/Reproducibility:*

   Spiked samples of norbuprenorphine were prepared in a urine matrix at the concentrations shown in the table below, and were measured, 2 runs per day, with 2 replicates per run, for 22 days. Results are tabulated below.

Total Precision for qualitative mode

Sample concentration (ng/mL)	N	Results for 5 ng/mL cutoff	Results for 10 ng/mL cutoff
0 (negative)	88	88 negative	88 negative
2.5 (-75% c/o)	88	88 negative	88 negative
5.0 (-50% c/o)	88	43 positive, 45 negative	88 negative
7.5 (-25% c/o)	88	88 positive	88 negative
10 (cutoff)	88	88 positive	59 positive, 29 negative
12.5 (+25% c/o)	88	88 positive	88 positive
15.0 (+50% c/o)	88	88 positive	88 positive
17.5 (+50% c/o)	88	88 positive	88 positive
20 (+100% c/o)	88	88 positive	88 positive

Total Precision for semi-quantitative mode

Sample concentration (ng/mL)	Mean (ng/mL)	SD (ng/mL)	Percent CV	Results for 5 ng/mL cutoff	Results for 10 ng/mL cutoff
0 (negative)	0.54	0.6	121%	88 negative	88 negative
2.5 (-75% c/o)	3.05	0.4	14.4%	88 negative	88 negative
5.0 (-50% c/o)	5.21	0.5	9.4%	62 positive, 28 negative	88 negative
7.5 (-25% c/o)	7.69	0.5	6.0%	88 positive	88 negative
10 (cutoff)	10.03	0.5	5.3%	88 positive	47 positive, 41 negative
12.5 (+25% c/o)	12.07	0.5	4.4%	88 positive	88 positive
15.0 (+50% c/o)	14.49	0.8	5.5%	88 positive	88 positive
17.5 (+50% c/o)	17.02	0.6	3.7%	88 positive	88 positive
20 (+100% c/o)	19.85	0.8	4.0%	88 positive	88 positive

b. Linearity/assay reportable range:

To demonstrate linearity in the semiquantitative mode, which is used for purposes of sample dilution and quality control procedures, a drug-free urine pool spiked with 100 ng/mL pure norbuprenorphine was serially diluted in increments of 10% and results were obtained. For each sample the average of ten replicates was calculated. Percent recovery ranged from 94 to 115%.

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

Calibrators are the same as those reviewed in k081008, except for changes in calibrator levels. Stability and value assignment also followed the same protocols reviewed in k081008. The value assignment procedures and results for the additional calibrator levels in this submission were reviewed and found to be acceptable.

d. Detection limit:

Replicates of the zero calibrator and two low-concentration spiked samples (with concentrations between the zero-calibrator and the 5 ng/mL cutoff) were measured to determine the lowest value that can be differentiated from the zero calibrator with 95% confidence. In qualitative mode, the detection limit calculated was 415 mA/min. The results from testing in semi-quantitative mode, were reviewed to confirm that the detection limit is less than the claimed lower cutoff of 5 ng/mL buprenorphine.

e. Analytical specificity:

Various potentially interfering substances were evaluated for positive and negative interference with the assay. Test compounds were spiked into a buprenorphine-free sample, as well as samples containing buprenorphine at 3, 7, and 13 ng/mL (i.e., +/-2 ng/mL, or +/- 30% surrounding the assay cutoff concentrations). These compounds did not affect positivity or negativity of the samples tested. Similar results were obtained in both qualitative and semi-quantitative modes. The potential interferents and the concentrations at which they were tested are shown below.

Substance tested	Concentration (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

In addition, variations in specific gravity between 1.001 and 1.027 had no effect on results.

Cross-reactivity was evaluated by spiking concentrations up to 100,000 ng/mL of buprenorphine metabolites into drug-free urine. Results are shown below.

Compound	% Cross-reactivity
Buprenorphine	101%
Buprenorphine-Glucuronide	0.13%
Norbuprenorphine-glucuronide	0.9%

The package insert includes the complete list of all structurally related and commonly co-administered drugs tested. Very small amounts of cross-reactivity (<0.1%) were observed for heroin, levorphanol and EMDP (2-ethyl-5-methyl-3,3-diphenylpyrroline). Cross-reactivity for other compounds tested was not detected (<.002%). The package insert notes that there is a possibility that metabolites of structurally-related drugs may interfere with the test and cause false results.

f. Assay cut-off:

See Detection Limit Section, above.

2. Comparison studies:

a. Method comparison with predicate device:

A total of ninety unaltered clinical samples were tested with the LZI Buprenorphine Assay. Fifteen of the samples were from drug-free donors. Based on GC/MS, six samples ranged from 0.1 to 2.4 ng/mL; fourteen samples ranged from 2.5 to 4.9 ng/mL; seven samples ranged from 5 to 7.5 ng/mL and forty seven samples were above 7.5 ng/mL. Results are shown in the tables below for both the 5 ng/mL cutoff mode and the 10 ng/mL cutoff mode.

GCMS → 5 ng/mL cutoff BUP Assay ↓	Low Negative by GC/MS (concentration < 50% below the cutoff concentration)	Near Cutoff Negative (concentration between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (concentration between 50% above the cutoff and the cutoff concentration)	High Positive (concentration > 50% above the cutoff concentration))	Percent Agreement with GCMS
Positive	0	2	7	47	96.40%
Negative	22	12	0	0	100%

GCMS → 10 ng/mL cutoff BUP Assay ↓	Low Negative by GC/MS (concentration < 50% below the cutoff concentration)	Near Cutoff Negative (concentration between 50% below the cutoff and the cutoff concentration)	Near Cutoff Positive (concentration between 50% above the cutoff and the cutoff concentration)	High Positive (concentration > 50% above the cutoff concentration))	Percent Agreement with GCMS
Positive	0	2	8	31	95.1%
Negative	36	12	1	0	98.0%

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

     b. *Matrix comparison:* Not applicable. The test is only for urine specimens.

3. Clinical studies:

     a. *Clinical Sensitivity:* Not reviewed for this device type.

     b. *Clinical specificity:* Not reviewed for this device type.

     c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off**:**

Not applicable; the device is for determining presumptive positive or negative based on the analytical cutoffs of 5 ng/mL and 10 ng/mL.

5. Expected values/Reference range:

Not applicable. The test is not intended for quantifying buprenorphine or norbuprenorphine; 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 and (2) permitting laboratories to establish quality control procedures.

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.