

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

A. 510(k) Number:

K033885

B. Purpose for Submission:

New Device

C. Analyte:

Barbiturates, methadone, benzodiazepines, and propoxyphene

D. Type of Test:

Qualitative enzyme immunoassay

E. Applicant:

Lin-Zhi International, Inc.

F. Proprietary and Established Names:

Simultaneous Barbiturate-Methadone-Benzodiazepine-Propoxyphene (BMBP)

Multiple Analyte Enzyme Immunoassay

G. Regulatory Information:

1. Regulation section:

21 CFR § 862.3150 (Barbiturate test system)

21 CFR § 862.3620 (Methadone test system)

21 CFR § 862.3170 (Benzodiazepine test system)

21 CFR § 862.3700 (Propoxyphene test system)

2. Classification:

All Class II

3. Product Code:

DIS (Barbiturate test system)

DJR (Methadone test system)

JXM (Benzodiazepine test system)

JXN (Propoxyphene test system)

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

Refer to Indications for use.

2. Indication(s) for use:

The Simultaneous Barbiturate-Methadone-Benzodiazepine-Propoxyphene (BMBP) Multiple Analyte Enzyme Immunoassay is a homogeneous enzyme immunoassay with a 200 ng/mL cutoff for barbiturates (as secobarbital), 300 ng/mL cutoff for methadone, 200 ng/mL cutoff for benzodiazepines (as oxazepam), and 300 ng/mL cutoff for propoxyphene in human urine. The assay will produce a positive result if any of the four analytes are present at a concentration at or above their respective cutoffs but will not identify which drug is present. The assay is solely intended for the qualitative screening of human urine for these analytes. Measurements obtained by this device are used in the diagnosis and treatment of individuals who have used barbiturates, methadone, benzodiazepines, or propoxyphene. The assay is designed for professional use with a number of automated clinical chemistry analyzers.

The Simultaneous Barbiturate-Methadone-Benzodiazepine-Propoxyphene (BMBP) Multiple Analyte Enzyme Immunoassay provides only a preliminary analytical test result. A more specific alternative chemical method for the individual drugs must be used to obtain a confirmed analytical result. Gas chromatography/mass spectrometry (GC/MS) is the preferred confirmatory method. Clinical consideration and professional judgement should be applied to any drug-of-abuse test result, particularly when preliminary positive results are used.

The device is for in vitro diagnostic use. It is intended for prescription use only.

3. Special condition for use statement(s)

The LZI BMBP Assay provides only a preliminary analytical test result. A positive result indicates that one or more of the four analytes may be present in the sample. In addition, since the assay is designed to detect multiple analytes, it is possible that if two or more analytes are present at concentrations *below* their respective cutoffs, a positive result will be produced. The performance of this assay has been validated using the LZI methadone calibrators only. The sponsor recommends that when the BMBP assay produces a positive result, the sample be retested with individual assays for barbiturates, methadone, benzodiazepines, or propoxyphene. Following this testing, a more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/Mass spectrometry is the preferred confirmatory method. Other chemical confirmation methods are available.

The assay is not designated for use in point-of-care settings.

4. Special instrument Requirements:

The device is for use on automated clinical chemistry analyzers. Instruments should be capable of maintaining a constant temperature, pipetting samples and reagents, mixing reagents, timing reactions, measuring at 340 nm, and performing standard curve calculations.

Performance was demonstrated in this submission on the Hitachi 717 analyzer.

I. Device Description:

The device consists of two wet reagents which contain the key components of the immunoassay; a mixture of monoclonal and polyclonal antibodies against the drugs, substrate, and enzyme-labeled drug (conjugate).

J. Substantial Equivalence Information:

1. Predicate device name(s):

LZI Barbiturate Enzyme Immunoassay
LZI Methadone Enzyme Immunoassay
LZI Benzodiazepine Enzyme Immunoassay
LZI Propoxyphene Enzyme Immunoassay

2. Predicate K number(s):

K032764
K023317
K032365
K023795

3. Comparison with predicate

The BMBP assay is designed to detect all four analytes listed above with a single reagent. The four predicate devices and the BMBP assay are for use on automated analyzers.

The reagent formulations vary between the new device and the predicate devices.

Similarities		
Item	Device	Predicate
Methodology	Qualitative	Qualitative and semi-quantitative
Barbiturates cutoff	200 ng/mL	200 or 300 ng/mL
Methadone cutoff	Same	300 ng/mL
Benzodiazepines cutoff	200 ng/mL	200 or 300 ng/mL
Propoxyphene cutoff	Same	300 ng/mL

Differences		
Item	Device	Predicate
Assay Type	Qualitative	Qualitative and semi-quantitative
Reagent	Antibodies to secobarbital, methadone, oxazepam, AND propoxyphene	Antibodies to secobarbital, methadone, oxazepam, OR propoxyphene
Controls	8 per run: negative and positive for each of the four analytes	2 per run: negative and positive for the specific analyte
Calibrators	3 per run: negative, cutoff, and high	5 per run: negative, low, cutoff, intermediate, and high for the specific analyte
Sensitivity	Barbiturates: 50 ng/mL Methadone: 75 ng/mL Benzodiazepines: 25 ng/mL Propoxyphene: 50 ng/mL	Barbiturates: 25 ng/mL Methadone: 15 ng/mL Benzodiazepines: 15 ng/mL Propoxyphene: 7.5 ng/mL

K. Standard/Guidance Document Referenced (if applicable)

The sponsor referenced the following guidance document(s) in their submission:

Premarket Submission and Labeling Recommendations for Drugs of Abuse Screening Tests - Draft Guidance for Industry and FDA Staff, published December 2003.

The sponsor indicated deviation from this guidance in regards to interference testing.

L. Test Principle:

The test is an enzyme immunoassay for use on automated clinical chemistry analyzers. The BMBP assay is calibrated with the LZI Methadone Calibrators, at concentrations of 0, 300, and 1000 ng/mL. Enzyme-labeled drug and drug present in the sample compete for limited antibody binding sites. Binding of the enzyme-labeled drug inhibits its reaction with the substrate, thereby influencing the rate of absorbance change measured by the instrument. The rate of absorbance change is

proportional to the concentration of drug in the sample. Concentrations of controls and unknowns are calculated from the standard curve.

Results are read at 340 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

(All performance was established on the Hitachi 717 analyzer.)

Samples used for the precision study were the zero calibrator, cutoff calibrator, high calibrator, low control, and high control for barbiturates, methadone, benzodiazepines, or propoxyphene. For within-run precision, the study was conducted by one operator and was completed in one day. Each analyte and concentration was run 21 times and the assay was calibrated with each analytical run.

For between-run precision, the study lasted three weeks and involved two operators. Each analyte was run once per day for four consecutive working days for the first week, and repeated for the next two weeks. The assay was calibrated with each analytical run. Results of the studies are presented below.

Qualitative Precision - Barbiturates

Sample concentration, ng/mL	Mean mA/min	SD	CV%		Mean mA/min	SD	CV%
Within-Run				Between-Run			
0	598.8	3.52	0.59	0	600.0	5.31	0.88
100	625.2	5.53	0.88	100	624.4	2.63	0.42
200	659.9	5.52	0.84	200	653.3	4.18	0.64
300	679.2	5.47	0.81	300	681.2	5.70	0.84
1000	722.9	3.79	0.52	1000	726.5	6.53	0.90

Qualitative Precision - Methadone

Sample concentration, ng/mL	Mean mA/min	SD	CV%		Mean mA/min	SD	CV%
Within-Run				Between-Run			
0	596.3	4.27	0.72	0	600.3	5.94	0.99
225	638.5	5.77	0.90	225	640.0	5.45	0.85
300	657.3	3.80	0.58	300	658.7	4.29	0.65
375	673.2	4.06	0.60	375	673.3	5.30	0.79
1000	715.6	5.30	0.74	1000	707.3	5.00	0.71

Qualitative Precision - Benzodiazepines

Sample concentration, ng/mL	Mean mA/min	SD	CV%		Mean mA/min	SD	CV%
Within-Run				Between-Run			
0	602.1	3.83	0.64	0	600.8	4.96	0.83
100	635.7	3.55	0.56	100	637.6	4.21	0.66
200	655.9	4.45	0.68	200	655.6	4.53	0.69
300	683.7	4.65	0.68	300	683.0	5.31	0.78
1000	736.1	5.52	0.75	1000	739.0	7.04	0.95

Qualitative Precision - Propoxyphene

Sample concentration, ng/mL	Mean mA/min	SD	CV%		Mean mA/min	SD	CV%
Within-Run				Between-Run			
0	600.5	5.19	0.86	0	599.5	4.2	0.70
225	642.5	5.48	0.85	225	642.1	4.3	0.67
300	656.8	5.54	0.84	300	657.7	4.8	0.73
375	671.8	4.84	0.72	375	671.4	6.3	0.94
3000	702.5	5.30	0.75	3000	707.5	2.5	0.35

Precision Study Results Around the Cutoff

		Barbiturates		Methadone	
Cutoff Rate (mA/min)		632.7		656.3	
Cutoff Concentration		200 ng/mL		300 ng/mL	
Concentration of sample, ng/mL	Replicate	Rate (mA/min)	Result	Rate (mA/min)	Result
Spiked near cutoff – 25%	1	615.6	Neg	628.8	Neg
	2	624.3	Neg	628.4	Neg
	3	622.5	Neg	636.4	Neg
	4	621.6	Neg	623.2	Neg
	5	626.6	Neg	625.2	Neg
Spiked near cutoff + 25%	1	641.2	Pos	660.7	Pos
	2	646.8	Pos	664.1	Pos
	3	639.6	Pos	668.9	Pos
	4	644.8	Pos	667.9	Pos
	5	640.8	Pos	658.9	Pos

		Benzodiazepines		Propoxyphene	
Cutoff Rate (mA/min)		634.5		657.9	
Cutoff Concentration		200 ng/mL		300 ng/mL	
Concentration of sample, ng/mL	Replicate	Rate (mA/min)	Result	Rate (mA/min)	Result
Spiked near cutoff – 25%	1	620.9	Neg	628.0	Neg
	2	616.4	Neg	612.7	Neg
	3	622.5	Neg	622.1	Neg
	4	621.8	Neg	615.9	Neg
	5	622.3	Neg	632.2	Neg
Spiked near cutoff + 25%	1	644.0	Pos	675.0	Pos
	2	645.5	Pos	676.1	Pos
	3	644.5	Pos	687.6	Pos
	4	647.0	Pos	680.9	Pos
	5	650.6	Pos	682.0	Pos

b. Linearity/assay reportable range

Not applicable. The assay is intended for qualitative use.

c. Traceability (controls, calibrators, or method):

Calibrators and commercial control materials are specified in the labeling but are not supplied in the kit. Calibrators were cleared under 510K K023317 and controls were cleared under 510Ks K032764, K023317, K032365, and K023795

d. Detection limit:

Sensitivity of the assay is reported as follows:

Barbiturates:	50 ng/mL
Methadone:	75 ng/mL
Benzodiazepines:	25 ng/mL
Propoxyphene:	50 ng/mL

To determine analytical sensitivity, the sponsor assayed the negative calibrator 10 times within the same run and extrapolated the value of each measurement from the standard curve. The average and standard deviation of those readings was calculated. The analytical sensitivity was estimated by adding 2 standard deviations to the average of the readings.

e. Analytical specificity:

Cross-reactivity was established by spiking various concentrations of similarly structured drug compounds into drug-free urine calibrator matrix. By analyzing various concentration of each compound the

sponsor determined the concentration of the drug that produced a response approximately equivalent to the cutoff concentration of the assay. Results of those studies appear in the table(s) below with the targeted compound listed first:

Barbiturates

Compound	Response equivalent to cutoff in ng/mL
Secobarbital	200
Phenobarbital	400
Butalbital	470
Pentobarbital	650
Allobarbital	1000
Amobarbital	2000
Aprobarbital	450
Barbital	7000
Butabarbital	800
Cyclopentobarbital	250
Thiopental	1300

Benzodiazepines

Compound	Response equivalent to cutoff in ng/mL
Oxazepam	200
Alprazolam	75
Bromazepam	2100
Chlordiazepoxide	65
Clobazam	750
Clonazepam	65
Diazepam	80
Flunitrazepam	50
Flurazepam	90
Lormetazepam	50
Lorazepam	90
Medazepam	23
Nitrazepam	150
Norfludiazepam	15
Prazepam	75
Temazepam	80
Triazolam	45
Oxazepam-glucuronide	>10,000
Lorazepam-glucuronide	>10, 000
Temazepam-glucuronide	>10, 000

Methadone

Compound	Response equivalent to cutoff in ng/mL
Methadone	300
6-Dimethylamino-4,4-diphenyl-3-heptanol acetate hydrochloride (LAAM.HCl)	10,000
(-) a-Methadol.HCl	8,000

Propoxyphene

Compound	Response equivalent to cutoff in ng/mL
Propoxyphene	300
Norpropoxyphene	620

The following compounds were evaluated for potential positive interference with the assay. To evaluate for interference test compounds were spiked into the drug-free calibrator at various concentrations listed below. None of the compounds on the list caused a positive result with the BMBP assay.

Potential Cross-reactant	Concentration (µg/mL)
Acetaminophen	1000
Acetylsalicylic Acid	1000
Amitriptyline	50
Amphetamine	1000
Benzoyllecgonine	1000
Bupropion	1000
Caffeine	1000
Chlorpheniramine	15
Chlorpromazine	20
Cocaine	400
Codeine	1000
Dextromethorphan	50
Ecgonine	1000
Ephedrine	1000
Imipramine	20
Lidocaine	1000
Meperidine	600
Methamphetamine	1000
Methaqualone	1000
Morphine	1000

Potential Cross-reactant	Concentration (µg/mL)
Nortriptyline	50
Phencyclidine	1000
Promethazine	1000
Ranitidine	1000
Secobarbital	1000
Valproic Acid	1000

The sponsor did not evaluate the effects of pH, specific gravity, or albumin on the assay.

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.

f. Assay cut-off:

The Substance Abuse and Mental Health Services Administration (SAMHSA) has not recommended cutoff concentrations for the analytes in this assay.

Characterization of how the device performs analytically around the claimed cutoff concentration appears in the precision section, above.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 180 samples (100 negative and 80 positive) were evaluated by the candidate device and by GC/MS and/or the predicate device.

Sample description: Unaltered clinical urine samples were evaluated. 110 additional diluted samples were also included in the study. The samples were prepared by diluting clinical samples with high drug concentrations with drug-free urine. This was done in order to obtain samples near the cutoff concentration of the assay, because the sponsor was not able to obtain unaltered samples near the cutoff.

Sample selection: Twenty of the negative samples were analyzed by the candidate device and the predicate devices only. The positive samples and the remaining negative samples were analyzed by the candidate device and the predicate devices and are traceable to a GC-MS concentration.

The study included an adequate number of samples that contained drugs near to the cutoff concentration of the assay. Greater than 10% of the study samples are evenly distributed between plus and minus 50% of the claimed cutoff concentration.

Number of study sites: one

Description of the site(s): Manufacturer's facility

Type of study site: Manufacturer's staff

Operator description: Manufacturer's staff

Number of instruments used: One

Candidate Device Results vs. Predicate Device Results (four analytes)

	Positive by Predicate Devices	Negative by Predicate Devices
Positive by Candidate Device	80	7*
Negative by Candidate Device	0	93

% Agreement among positives is 92%

% Agreement among negatives is 100%

* Samples were grouped based on their concentration of barbiturates, methadone, benzodiazepines, or propoxyphene. Within each group, analytes other than the targeted drug were found:

Benzodiazepine group – one negative sample was found to contain methadone

Methadone group – two negative samples were found to contain benzodiazepines

Barbiturate group – one negative sample was found to contain benzodiazepines and two negative samples were found to contain both methadone and benzodiazepines

Propoxyphene group – one negative sample was found to contain benzodiazepines.

Candidate Device Results vs. stratified GC/MS Values - Barbiturates

Candidate Device Results	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	1 [*]	2 [†]	12	8
Negative	2	15	0	0

GC/MS values used to categorize samples in this table are determined by analyzing concentrations for secobarbital, butabarbital, and phenobarbital and calculating a final concentration based on their relative cross-reactivities to the BMBP assay.

^{*} sample was found to contain benzodiazepines

[†] samples were found to contain methadone and benzodiazepines

% Agreement among positives is 100%

% Agreement among negatives is 85%

Candidate Device Results vs. stratified GC/MS Values - Methadone

Candidate Device Results	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	2 [*]	13	7
Negative	3	15	0	0

GC/MS values used to categorize samples in this table are based on the concentration of methadone found in the sample.

^{*} samples were found to contain benzodiazepines

% Agreement among positives is 100%

% Agreement among negatives is 90%

Candidate Device Results vs. stratified GC/MS Values - Benzodiazepines

Candidate Device Results	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	1*	13	6
Negative	1	19	0	0

GC/MS values used to categorize samples in this table are determined by analyzing concentrations for clonazepam, alprazolam, oxazepam, lorazepam, and temazepam and calculating a final concentration based on their relative cross-reactivities to the BMBP assay.

* sample was found to contain methadone

% Agreement among positives is 100%

% Agreement among negatives is 95%

Candidate Device Results vs. stratified GC/MS Values - Propoxyphene

Candidate Device Results	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	1*	15	5
Negative	5	14	0	0

GC/MS values used to categorize samples in this table are determined by analyzing concentrations for propoxyphene and norpropoxyphene and calculating a final concentration based on their relative cross-reactivities to the BMBP assay.

* sample was found to contain benzodiazepines

% Agreement among positives is 100%

% Agreement among negatives is 95%

b. Matrix comparison:

Not applicable. The assay is intended for only one sample matrix.

3. Clinical studies:
 - a. *Clinical sensitivity*
Not applicable. Clinical studies are not typically submitted for this device type.
 - b. *Clinical specificity:*
Not applicable. Clinical studies are not typically submitted for this device type.
 - c. *Other clinical supportive data (when a and b are not applicable):*
4. Clinical cut-off:
Not applicable.
5. Expected values/Reference range:
Barbiturates, methadone, benzodiazepines, and propoxyphene should not be present in the urine of persons who have not taken these drugs.

N. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.