LZI Opiate Enzyme Immunoassay

IVD For In Vitro Diagnostic Use Only

REF 0020b (100/37.5 mL R_1/R_2 Kit)
0021b (1000/375 mL R_1/R_2 Kit) 2°C 8°C

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International, Inc. (LZI) 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. This assay is for prescription use only.

The assay provides only a preliminary analytical result. A more specific alternative analytical chemistry method must be used in order to obtain a confirmed analytical result. Gas or Liquid Chromatography/Mass Spectrometry (GC/MS or LC/MS) are the preferred confirmatory methods (1, 2). Clinical consideration and professional judgment should be exercised with any drug of abuse test result, particularly when the preliminary test result is positive.

Summary and Explanation of Test

Opiates are naturally occurring alkaloids derived from the opium poppy, *Papaver somniferum* (3). Common opiates include morphine, codeine and heroin, which is a semi-synthetic derivative of morphine. Morphine and codeine are potent analgesics. They are among the most effective and common medications for treatment of mild to severe pain. However, these prescription drugs are frequently abused for their central nervous system (CNS) effects. Heroin is the most commonly abused opiate (4). It may be snorted, smoked, or dissolved and injected subcutaneously or intravenously. Opiates are absorbed rapidly and primarily metabolized in liver (4-6). Heroin is converted quickly to 6-acetylmorphine or morphine, which is excreted in urine both unchanged and as glucuronide conjugates. Excretion takes place over two to three days. Codeine is excreted in urine as glucuronides, norcodeine, or as morphine. The presence of opiates in urine indicates the use of heroin, morphine, codeine, and/or other synthetic opiates structurally related to morphine, such as hydromorphone and hydrocodone.

Assay Principle

The LZI Opiate assay is a homogeneous enzyme immunoassay 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 (7). 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, opiate-labeled G6PDH conjugate is bound to antibody, and the enzyme activity is inhibited. On the other hand, when drug is present in the sample, antibody binds to free drug; the unbound opiate-labeled G6PDH then exhibits its maximal enzyme activity. Active enzyme converts nicotinamide adenine dinucleotide (NAD) to NADH, resulting in an absorbance change that can be measured spectrophotometrically at a 340 nm primary wavelength.

Reagents Provided

Antibody/Substrate Reagent (R_1): Contains mouse monoclonal anti-morphine antibody, glucose-6-phosphate (G6P), nicotinamide adenine dinucleotide (NAD), stabilizers, and sodium azide (0.09 %) as a preservative.
Enzyme-drug Conjugate Reagent (R_2): Contains glucose-6-phosphate dehydrogenase (G6PDH) labeled with morphine in buffer with sodium azide (0.09 %) as a preservative.

Calibrators and Controls*

**Calibrators and controls are sold separately and contain negative human urine with sodium azide as a preservative.*

OPIATE Calibrators	REF
Negative Calibrator	0001
Low Calibrator: Contains 150 ng/mL morphine	0022
Cutoff Calibrator: Contains 300 ng/mL morphine	0023
Intermediate Calibrator: Contains 600 ng/mL morphine	0024
High Calibrator: Contains 1000 ng/mL morphine	0025

OPIATE Controls	REF
Level 1 Control: Contains 225 ng/mL morphine	0027
Level 2 Control: Contains 375 ng/mL morphine	0028

Precautions and Warning

- *This test is for in vitro diagnostic use only. Harmful if swallowed.*
- *Reagent contains sodium azide as a preservative, which may form explosive compounds in metal drain lines. When disposing such reagents or wastes always flush with a large volume of water to prevent azide build-up. See National Institute for Occupational Safety and Health Bulletin: Explosive Azide Hazards (8).*
- *Do not use the reagents beyond their expiration dates.*
- Rx only *For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.*

Reagent Preparation and Storage

The reagents are ready-to-use. No reagent preparation is required. All assay components should be refrigerated at 2-8ºC when not in use.

Specimen Collection and Handling

Urine sample may be collected in plastic or glass containers. Some plastics may absorb drugs. Use of plastics such as polyethylene is recommended (9). Use fresh urine specimens for the test. If the sample cannot be analyzed immediately, it may be refrigerated at 2-8ºC for up to seven days (10). For longer storage, keep sample frozen at -20ºC and then thaw before use. Studies have shown opiate analytes in urine are stable at -20ºC up to 12 months (11, 12). Samples should be at room temperature (18-25ºC) for testing. Samples with high turbidity should be centrifuged before analysis. Adulteration may cause erroneous results. If sample adulteration is suspected, obtain a new sample and both samples should be forwarded to the laboratory for testing. *Handle all urine specimens as if they are potentially infectious.*

Instrument

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting samples, mixing reagents, measuring enzyme rates at 340 nm and timing the reaction accurately can be used to perform this homogeneous immunoassay.
Performance characteristics presented in this package insert have been validated on the Hitachi 717 and the Beckman Coulter® AU480. If other instruments are used, performance will need to be validated by the laboratory (13, 14).

Assay Procedure

Analyzers with the specifications indicated above are suitable for performing this homogeneous enzyme immunoassay. Refer to the specific parameters used for each analyzer before performing the assay. Typical assay parameters used for the Hitachi 717 analyzer include a 20 µL sample, 200 µL of antibody reagent (R_1), and 75 µL of enzyme conjugate reagent (R_2) in 37ºC incubation temperature, 30-35 reading frames, and a 340 nm primary wavelength. For qualitative analysis use the 300 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all five calibrators. Recalibration should be performed after reagent bottle change or there is a change in calibrators or reagent lot. Two levels of controls are also available for monitoring the cutoff level: use the 225 ng/mL and 375 ng/mL controls for the 300 ng/mL cutoff.

Calibration and Quality Control

Good laboratory practices recommend the use of at least two levels of control specimens (one positive and one negative control near the cutoff) to ensure proper assay performance. Controls should be run with each new calibration and after specific maintenance or troubleshooting procedures as detailed in the instrument system manual. Each laboratory should establish its own control frequency. If any trends or sudden change in control value are observed, review all operating parameters or contact LZI technical support for further assistance. Laboratories should comply with all federal, state, and local laws, guidelines and regulations.

Results

Note: A preliminary positive test result does not necessarily mean a person took illegal drugs and a negative test result does not necessarily mean a person did not take illegal drugs. There are a number of factors that influence the reliability of drug tests.

Qualitative: The cutoff calibrator which contains 300 ng/mL of morphine is used as a reference for distinguishing a preliminary positive from negative samples. A sample with a change in absorbance (ΔmA/min) equal to or greater than that obtained with the cutoff calibrator is considered a preliminary positive. A sample with a change in absorbance (ΔmA/min) lower than that obtained with the cutoff calibrator is considered negative.

Semi-Quantitative: The semi-quantitative mode is for purposes of
(1) enabling laboratories to determine an appropriate dilution of the specimen for verification by a confirmatory method such as GC/MS, LC/MS or
(2) permitting laboratories to establish quality control procedures.
When an approximation of concentration is required, a calibration curve can be established with five calibrators. The concentration of opiates in the sample may then be estimated from the calibration curve.

Limitations

1. *A preliminary positive result from the assay indicates only the presence of opiates. The test is not intended for quantifying these single analytes in samples.*
2. *A preliminary positive result does not necessarily indicate drug abuse.*
3. *A negative result does not necessarily mean a person did not take illegal drugs.*
4. *Care should be taken when reporting results as numerous factors (e.g., fluid intake, endogenous or exogenous interferents) may influence the urine test result.*
5. *Preliminary positive results should be confirmed by other affirmative, analytical chemistry methods (e.g., chromatography), preferably GC/MS or LC/MS.*
6. *The test is designed for use with human urine only.*
7. *The test is not for therapeutic drug monitoring.*

Typical Performance Characteristics

The results shown below were performed with a single Hitachi 717 automated clinical chemistry analyzer.

Precision:

Qualitative analysis: The three calibrators and two levels of controls were evaluated. Typical results, listed as either positive (+) or negative (-), are as follows:

Concentration	Within Run (N=21)	Run-to-Run (N=12)
Negative	-	-
75 ng/mL	-	-
150 ng/mL	-	-
225 ng/mL	-	-
300 ng/mL	+	+
375 ng/mL	+	+
450 ng/mL	+	+
525 ng/mL	+	+
600 ng/mL	+	+

300 ng/mL Cutoff		Within Run (N=22)		Total Precision (N=88)	
Concentration	% of Cutoff	#Samples	EIA Result	#Samples	EIA Result
Negative	0 %	22	22 Neg	88	88 Neg
75 ng/mL	25 %	22	22 Neg	88	88 Neg
150 ng/mL	50 %	22	22 Neg	88	88 Neg
225 ng/mL	75 %	22	22 Neg	88	88 Neg
300 ng/mL	100 %	22	6 Neg/ 16 Pos	88	37 Neg/ 51 Pos
375 ng/mL	125 %	22	22 Pos	88	88 Pos
450 ng/mL	150 %	22	22 Pos	88	88 Pos
525 ng/mL	175 %	22	22 Pos	88	88 Pos
600 ng/mL	200 %	22	22 Pos	88	88 Pos

Semi-quantitative analysis: The concentrations of the cutoff level and the two levels of controls were determined with reference curves from five calibrators. Typical results (ng/mL) are as follows:

Concentration	Within Run (N=21)	Pos/Neg Result	Run-to-Run (N=12)	Pos/Neg Result
Negative	0.0	-	0.0	-
75 ng/mL	84.0	-	84.0	-
150 ng/mL	148.4	-	148.4	-
225 ng/mL	228.2	-	228.2	-
300 ng/mL	297.5	-	297.5	-
375 ng/mL	370.4	+	370.4	+
450 ng/mL	453.3	+	453.3	+
525 ng/mL	529.0	+	529.0	+
600 ng/mL	600.8	+	600.8	+

300 ng/mL Cutoff		Within Run (N=22)		Total Precision (N=88)	
Concentration	% of Cutoff	#Samples	EIA Result	#Samples	EIA Result
Negative	0 %	22	22 Neg	88	88 Neg
75 ng/mL	25 %	22	22 Neg	88	88 Neg
150 ng/mL	50 %	22	22 Neg	88	88 Neg
225 ng/mL	75 %	22	22 Neg	88	88 Neg
300 ng/mL	100 %	22	16 Neg/ 6 Pos	88	61 Neg/ 27 Pos
375 ng/mL	125 %	22	22 Pos	88	88 Pos
450 ng/mL	150 %	22	22 Pos	88	88 Pos
525 ng/mL	175 %	22	22 Pos	88	88 Pos
600 ng/mL	200 %	22	22 Pos	88	88 Pos

Limit of Detection: Sensitivity, defined as the lowest concentration that can be differentiated from negative urine with 95 % confidence, was determined to be 20 ng/mL.

Accuracy: One-hundred-thirty (130) unaltered clinical urine specimens were tested with the LZI Opiates Enzyme Immunoassay and confirmed by either GC/MS or LC/MS. Specimens having an opiate concentration greater than 300 ng/mL by GC/MS or LC/MS are defined as positive, and specimens with concentrations below 300 ng/mL by GC/MS or LC/MS were defined as negative in the table below. Adjusted GC/MS or LC/MS values have been corrected for cross-reactivity (15, 16). The correlation results are summarized as follows (near cutoff samples are defined as ± 50 % of the cutoff value):

Semi-Quantitative Accuracy Study:

300 ng/mL Cutoff	Neg	< 50 % below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	% Agreement
Positive	0	0	3*	16	40	98.3 %
Negative	23	30	17	1**	0	95.9 %

Summary of Discordant Results in Semi-Quantitative Mode:

Discrepant Sample #	Total GCMS or LCMS Result (ng/mL)	Pos/ Neg Result	Adjusted GCMS or LCMS Result (ng/mL)	Pos/ Neg Result	EIA Result (ng/mL)	Pos/ Neg Result
66*	241	-	244.6	-	320.8	+
68*	249	-	252.7	-	282.2	+
72*	277	-	242.4	-	377	+
77**	316	+	320.7	+	269.3	-

Qualitative Accuracy Study:

300 ng/mL Cutoff	Neg	< 50 % below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	% Agreement
Positive	0	1*	3**	16	40	98.3 %
Negative	23	29	17	1***	0	94.5 %

Summary of Discordant Results in Qualitative Mode:

Discrepant Sample #	Total GCMS or LCMS Result (ng/mL)	Pos/ Neg Result	Adjusted GCMS or LCMS Result (ng/mL)	Pos/ Neg Result	EIA Result (ng/mL)	Pos/ Neg Result
26*	40	-	40.6	-	406.9	+
66**	241	-	244.6	-	408	+
68**	249	-	252.7	-	410.9	+
72**	277	-	242.4	-	432.1	+
77***	316	+	320.7	+	394.4	-

Discrepant samples are based on a 300 ng/mL cutoff concentration with a 403.8 mA/min absorbance value.

Analytical Recovery: To demonstrate linearity for purposes of sample dilution and quality control (see semi-quantitative results section), a drug-free urine pool spiked with morphine was serially diluted. Each sample was run in 10 replicates and the average was used to determine the functional linearity range of the assay. When comparing the result (y) and target (x) value, using the least squares regression technique, the regression equation and correlation are as follows:

$y = 1.0619x - 2.3861$, $r^2 = 0.9976$

Expected Value (ng/mL)	Observed Value (ng/mL)	% Recovery
1000	1099.1	109.9 %
900	957.8	106.4 %
800	832.1	104.0 %
700	710.2	101.5 %
600	619.3	103.2 %
500	523.3	104.7 %
400	425.7	106.4 %
300	303.3	101.1 %
200	225.0	112.5 %
100	116.3	116.3 %

Specificity: Various potentially interfering substances were tested for cross-reactivity with the assay. Test compounds were spiked into the drug-free urine calibrator matrix to various concentrations and evaluated against the cutoff calibrator. The table listed the concentration of each test compound that gave a response approximately equivalent to that of the cutoff calibrator or the maximal concentration of the compound tested that gave a response below the response of the cutoff calibrator.

Morphine and Metabolite Opiate Compounds:

Compound	Target [ ] (ng/mL)	Semi-Quantitative	
		Result (ng/mL)	% Cross-Reactivity
6-Monoacetyl Morphine	400	343.4	85.9 %
Morphine	300	303.5	101.2 %
Morphine-3-Glucuronide	800	313.0	39.1 %
Morphine-6-Glucuronide	300	327.1	109.0 %
Normorphine	30,000	94.8	0.3 %

Structurally Related Opiate Compounds:

Compound	Target [ ] (ng/mL)	Semi-Quantitative	
		Result (ng/mL)	% Cross-reactivity
Codeine	200	338.0	169.00 %
Dextromethorphan	40,000	33.9	0.085 %
Dihydrocodeine	700	304.1	43.44 %
Heroin	300	323.7	107.88 %
Hydrocodone	2300	316.1	13.74 %
Hydromorphone	1900	327.4	17.23 %
Levorphanol	8000	320.5	4.01 %
Nalbuphine	3,000,000	193.9	0.006 %
Naloxone	85,000	39.0	0.046 %
Naltrexone	2,700,000	289.2	0.011 %
Norcodeine	130,000	306.1	0.24 %
Oxycodone	60,000	306.8	0.51 %
Oxymorphone	140,000	321.5	0.23 %
Thebaine	2000	322.3	16.12 %
Codeine-6-β-Glucuronide	250	311.0	124.38 %

Structurally Unrelated Pharmacological Compounds:

Compound	Target [ ] (ng/mL)	0 ng/mL Morphine				-25 % Cutoff Morphine		+25 % Cutoff Morphine	
		Semi-Quantitative			Qualitative	Semi-Quantitative	Qualitative	Semi-Quantitative	Qualitative
		Result (ng/mL)	Pos/Neg Result	% Cross-Reactivity	Pos/Neg Result	Pos/Neg Result	Pos/Neg Result	Pos/Neg Result	Pos/Neg Result
Acetaminophen	500,000	5.7	-	0.001 %	-	-	-	+	+
Acetylsalicylic Acid	3,000,000	6.1	-	0.000 %	-	-	-	+	+
Albuterol	3,000,000	4.9	-	0.000 %	-	-	-	+	+
Amitriptyline	50,000	42.0	-	0.084 %	-	-	-	+	+
Amobarbital	3,000,000	16.7	-	0.001 %	-	-	-	+	+
d-Amphetamine	3,000,000	41.7	-	0.001 %	-	-	-	+	+
Benzoylecgonine	3,000,000	19.2	-	0.001 %	-	-	-	+	+
Bupropion	1,000,000	19.4	-	0.002 %	-	-	-	+	+
Caffeine	3,000,000	21.1	-	0.001 %	-	-	-	+	+
Carbamazepine	500,000	3.1	-	0.001 %	-	-	-	+	+
Chlorpromazine	80,000	74.3	-	0.093 %	-	-	-	+	+
Clomipramine	30,000	37.4	-	0.125 %	-	-	-	+	+
Desipramine	130,000	24.5	-	0.019 %	-	-	-	+	+
Doxepine	175,000	80.2	-	0.046 %	-	-	-	+	+
Ecgonine	3,000,000	12.7	-	0.000 %	-	-	-	+	+
Ephedrine	1,400,000	37.8	-	0.003 %	-	-	-	+	+
Fentanyl	25,000	78.4	-	0.314 %	-	-	-	+	+
Fluoxetine	400,000	21.0	-	0.005 %	-	-	-	+	+
Fluphenazine	200,000	66.5	-	0.033 %	-	-	-	+	+
Ibuprofen	500,000	10.9	-	0.002 %	-	-	-	+	+
Imipramine	20,000	33.9	-	0.169 %	-	+	+	+	+
Lidocaine	1,000,000	87.0	-	0.009 %	-	-	-	+	+
Maprotiline	600,000	19.4	-	0.003 %	-	-	-	+	+
Meperidine	10,000	60.1	-	0.601 %	-	-	-	+	+
Methadone	25,000	41.2	-	0.165 %	-	-	-	+	+
Methapyrilene	300,000	134.0	-	0.045 %	-	+	+	+	+
Methaqualone	3,000,000	31.4	-	0.001 %	-	-	-	+	+
Metronidazole	700,000	7.5	-	0.001 %	-	-	-	+	+
Nicotine	800,000	48.0	-	0.006 %	-	-	-	+	+
Nortriptyline	110,000	18.0	-	0.016 %	-	-	-	+	+
Oxazepam	3,000,000	24.2	-	0.001 %	-	-	-	+	+
Phencyclidine	900,000	56.4	-	0.006 %	-	-	-	+	+
Phenobarbital	3,000,000	43.1	-	0.001 %	-	-	-	+	+
Propoxyphene	100,000	4.4	-	0.004 %	-	-	-	+	+
Ranitidine	1,000,000	108.1	-	0.011 %	-	+	-	+	+
Secobarbital	3,000,000	50.4	-	0.002 %	-	-	-	+	+
Talwin	100,000	21.2	-	0.021 %	-	-	-	+	+
Thioridazine	70,000	70.3	-	0.100 %	-	-	-	+	+
Tramadol	150,000	144.7	-	0.096 %	-	+	+	+	+
Valproic Acid	3,000,000	45.3	-	0.002 %	-	-	-	+	+

**It is possible that other substances and/or factors not listed above may interfere with the test and cause false positive results.*

**Potential interference from structurally unrelated and endogenous compounds were tested by spiking the potentially interfering compound into processed pooled negative urine having a drug concentration at ± 25 % of the cutoff. All were tested at a concentration of ≥ 10,000 ng/mL. If a false result was observed, the testing was repeated at the ± 50 % of the cutoff for drug.*

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

Endogenous Compound Interference Study:
The following endogenous compounds were spiked into pooled processed urine to the concentrations as listed in the table below. These solutions were then spiked with morphine to ± 25 % of cutoff (225 or 375 ng/mL) and evaluated in both semi-quantitative and qualitative modes. The substances listed did not interfere at the concentrations tested.

Compound	Target [ ] (mg/dL)	0 ng/mL Morphine			-25 % Cutoff Morphine			+25 % Cutoff Morphine		
		Semi-Quantitative		Qualitative	Semi-Quantitative		Qualitative	Semi-Quantitative		Qualitative
		Result (ng/mL)	Pos/Neg Result	Pos/Neg Result	Result (ng/mL)	Pos/Neg Result	Pos/Neg Result	Result (ng/mL)	Pos/Neg Result	Pos/Neg Result
Acetone	1000	0.0	-	-	251.6	-	-	396.2	+	+
Ascorbic Acid	1500	0.0	-	-	245.5	-	-	401.4	+	+
Creatinine	500	0.0	-	-	247.9	-	-	397.4	+	+
Ethanol	1000	0.0	-	-	244.6	-	-	395.2	+	+
Galactose	10	0.0	-	-	248.5	-	-	402.7	+	+
γ-Globulin	500	0.0	-	-	249.8	-	-	397.8	+	+
Glucose	3000	0.0	-	-	248.1	-	-	392.8	+	+
Hemoglobin	300	12.6	-	-	264.7	-	-	402.4	+	+
Human Serum Albumin	500	0.0	-	-	250.6	-	-	385.4	+	+
Oxalic Acid	100	0.0	-	-	244.4	-	-	383.9	+	+
Riboflavin	0.3	0.0	-	-	238.4	-	-	368.3	+	+
Sodium Chloride	6000	0.0	-	-	221.9	-	-	374.9	+	+
Urea	6000	0.0	-	-	188.3	-	-	315.1	+	+

pH Study:
Pooled processed urine was brought to the following pH levels (pH 3 to pH 11) as listed in the table below. These solutions were then spiked with morphine to ± 25 % of cutoff (225 ng/mL or 375 ng/mL) and evaluated in both semi-quantitative and qualitative modes. No interference was observed.

pH	0 ng/mL Morphine			-25 % Cutoff Morphine			+25 % Cutoff Morphine		
	Semi-Quantitative		Qualitative	Semi-Quantitative		Qualitative	Semi-Quantitative		Qualitative
	Result (ng/mL)	Pos/Neg Result	Pos/Neg Result	Result (ng/mL)	Pos/Neg Result	Pos/Neg Result	Result (ng/mL)	Pos/Neg Result	Pos/Neg Result
pH 3	0.0	-	-	248.1	-	-	381.9	+	+
pH 4	0.0	-	-	232.2	-	-	353.0	+	+
pH 5	2.0	-	-	231.3	-	-	353.6	+	+
pH 6	13.2	-	-	228.6	-	-	352.5	+	+
pH 7	5.4	-	-	226.7	-	-	346.9	+	+
pH 8	0.0	-	-	234.3	-	-	362.2	+	+
pH 9	2.9	-	-	230.3	-	-	356.6	+	+
pH 10	5.4	-	-	229.3	-	-	371.6	+	+
pH 11	0.0	-	-	247.5	-	-	388.6	+	+

Specific Gravity: Samples ranging in specific gravity from 1.002 to 1.027 were tested in qualitative mode against pooled processed urine samples at 0 ng/mL, 225 ng/mL, and 375 ng/mL (zero morphine concentration, negative, and positive controls for the 300 ng/mL cutoff). No interference was observed.

Bibliography:

1. Urine Testing for Drug of Abuse, National Institute on Drug Abuse (NIDA) Research Monograph 73, (1986).
2. Mandatory Guidelines for Federal Workplace Drug Testing Program, National Institute on Drug Abuse, Federal Register, **53**(69): 11970 (1988).
3. Balant L.P., and Balant-Gorgia, A.E., Opium and its derivatives, *Clin Ther*, **14**:846 (1992).
4. Glare, P.A., and Walsh, T.D., Clinical Pharmacokinetics of morphine, *Ther. Drug Monit*. **13**:1 (1991).
5. Cone, E.J., Welch, P., Mitchell, J.M., and B.D., Paul, Forensic drug testing for opiates, I. Detection of 6-acetylmorphine in urine as an indicator of recent heroin exposure; drug and assay considerations and detection times, *J. Anal. Toxicol*. **15**:17 (1991).
6. Hasselstrom, J., and Sawe, J., Morphine pharmacokinetics and metabolism in humans: Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations, *Clin Pharmacokinet*., **24**:344 (1993).
7. Rubenstein, K.E., Schneider, R.S., and Ullman, E.F., Homogeneous Enzyme Immunoassay: A New Immunochemical Technique, *Biochem Biophys Res Commun*, **47**:846 (1972).
8. Sodium Azide. National Institute for Occupational Safety (NIOSH). Pocket Guide to Chemical Hazards. Third Printing, September 2007. Available online at: https://www.cdc.gov/niosh/npg/default.html
9. Yahya, A.M., McElnay, J.C., and P.F. D'Arcy. Drug absorption to glass and plastics. *Drug Metabol Drug Interact*. **6**(1):1-45 (1988).
10. Gonzales, E., et al., Stability of pain-related medications, metabolites, and illicit substances in urine, Clinica Chimica Acta, 416:80-85 (2013).
11. Chang, B.L., Huang, M.K., and Tsai, Y.Y., Total morphine stability in urine specimens stored under different conditions. *J. Anal. Toxicol.*, **24**(6):442-447 (2000).
12. Moody, D.E., Monti, K.M., Spanbauer, A.C., and Hsu, J.P., Long-Term Stability of Abused Drugs and Antiabuse Chemotherapeutical Agents Stored at -20ºC, J Anal Toxicol. 23:535-540 (1999).
13. Nichols, J., Instrument Validation: The Road to Success. CLN's Lab 2004: From Basic to Advanced Series. 14-16 (2004).
14. CDRH Guidance for Industry and FDA Staff: Replacement Reagent and Instrument Family Policy (2003).
15. Baselt, R.C., Disposition of toxic drugs and chemicals in man. 7th edition. Chemical Toxicology Institute, Foster City, CA. 532 (2000).
16. Lalovic, et al., Pharmacokinetics and pharmacodynamics of oral oxycodone in healthy human subjects: Role of circulating active metabolites, *Clinical Pharm. & Therapeutics*, **79**(5):461-479 (2006).

Additions, deletions, or changes are indicated by a change bar in the margin.
For technical assistance please call: (408) 970-8811

Manufacturer:
Lin-Zhi International, Inc.
2945 Oakmead Village Court
Santa Clara, CA 95051
USA
Tel: (408) 970-8811
Fax: (408) 970-9030
www.lin-zhi.com

EC REP

Authorized European Rep. within the EU:
CEpartner4U
Esdoornlaan 13
3951 DB Maarn
The Netherlands
www.cepartner4u.eu

CE

© November 2023 Rev. 8