LZI Hydrocodone 100 Enzyme Immunoassay

IVD For In Vitro Diagnostic Use Only

REF 0380 (100/37.5 mL R_1/R_2 Kit)
0381 (1000/375 mL R_1/R_2 Kit)

2°C 8°C

Lin-Zhi International, Inc.

Intended Use

The Lin-Zhi International, Inc. (LZI) Hydrocodone Enzyme Immunoassay is intended for the qualitative and semi-quantitative determination of hydrocodone in human urine at a cutoff value of 100 ng/mL. The assay is designed for prescription use with a number of automated clinical chemistry analyzers.

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

Hydrocodone is an opioid compound derived from codeine. Hydrocodone acts on μ-opioid receptors (3). It is prescribed as a narcotic analgesic to treat moderate to severe pain and as an antitussive to treat cough (4). As an opioid compound, it is more potent than codeine but 1.5 times less potent than oxycodone (5). Hydrocodone can be addictive, causing physical and psychological dependence. Its risk of abuse is similar to morphine and lower than oxycodone's (6).

Hydrocodone is often administered in combination with paracetamol (acetaminophen) or ibuprofen. Combination with other medication is often used to increase efficacy and reduce adverse side effects (7, 8). Use of Hydrocodone in combination with alcohol, other opioids, antihistamines, antipsychotics, antianxiety medication, or other central nervous system (CNS) depressants can cause additive CNS depression (9). Hydrocodone may also interact with serotonergic medications (10).

The analgesic properties of hydrocodone begin 20-30 minutes after consumption and last between four to eight hours (3). Hydrocodone is metabolized in the liver by the cytochrome p450 enzyme CYP2D6 which converts it to hydromorphone, an even more potent opioid than hydrocodone itself (11).

In 72-hour urine, 26 % of the hydrocodone dose is eliminated as unchanged drug (12 %), norhydrocodone (5 %), conjugated hydromorphone (4 %), 6-hydrocodol (3 %) and conjugated 6-hydromorphol (0.1 %) (12, 13).

The hydrocodone metabolite, hydromorphone, is also a minor urinary metabolite of morphine. Initial studies suggest that hydromorphone may have advantages as an analgesic as compared to morphine and is seven to ten times more potent than morphine (14, 15). Hydromorphone is often prescribed by itself under the brand name Dilaudid. In the 24-hour urine, an average of 6 % of the dosage is eliminated as free hydromorphone and 30 % as conjugated hydromorphone (16). The metabolite of hydromorphone, hydromorphone-3-glucuronide, has also been shown to have significant pharmacological activity (17).

Assay Principle

The LZI Hydrocodone Enzyme Immunoassay 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 (18). 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, hydrocodone-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 would bind to free drug; the unbound hydrocodone-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 340 nm.

Reagents Provided

Antibody/Substrate Reagent (R_1): Contains a mouse monoclonal anti-hydrocodone 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 hydrocodone 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.*

HYDROCODONE 100 ng/mL Calibrators	REF
Negative Calibrator	0001
Low Calibrator: Contains 50 ng/mL hydrocodone	0382
Cutoff Calibrator: Contains 100 ng/mL hydrocodone	0383
Intermediate Calibrator: Contains 150 ng/mL hydrocodone	0384
High Calibrator: Contains 300 ng/mL hydrocodone	0385

HYDROCODONE 100 ng/mL Controls	REF
Level 1 Control: Contains 75 ng/mL hydrocodone	0387
Level 2 Control: Contains 125 ng/mL hydrocodone	0388

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 (19).*
- *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 samples may be collected in plastic or glass containers. Some plastics may absorb drugs. Use of plastics such as polyethylene is recommended (20). 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 (21, 22). For longer storage, keep sample frozen at -20ºC and then thaw before use. Studies have shown hydrocodone samples in urine are stable at -20ºC for up to three years (23). Samples should be equilibrated to 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 a laboratory for testing.

Handle all urine specimens as if they are potentially infectious.

Instrument

Clinical chemistry analyzers capable of maintaining a constant temperature, pipetting sample, 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 Beckman Coulter® AU480. If other instruments are used, performance will need to be validated by the laboratory (24, 25).

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 Beckman Coulter AU480 analyzer include a 18 μL sample, 120 μL of antibody reagent (R_1), 45 μL of enzyme conjugate reagent (R_2), 10 μL dilution following addition of R_2 in 37ºC incubation temperature, 14-18 reading points, and 340 nm primary wavelength.

For qualitative analysis use the 100 ng/mL as the cutoff calibrator. For semi-quantitative analysis, use all five calibrators. Recalibration should be performed after reagent bottle change or a change in calibrators or reagent lot. Two levels of controls are also available for monitoring the cutoff level: 75 ng/mL and 125 ng/mL.

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, as well as all 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 100 ng/mL of hydrocodone, is used as a reference for distinguishing preliminary positive from negative samples. A sample with a change in absorbance (ΔmAU) equal to or greater than that obtained with the cutoff calibrator is considered preliminary positive. A sample with a change in absorbance (ΔmAU) 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 hydrocodone 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 hydrocodone. The test is not intended for quantifying this single analyte 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 Beckman Coulter AU480 automated chemistry analyzer.

Precision:

Semi-quantitative analysis: The following concentrations were determined with reference curves from five calibrators. Typical results were measured in ng/mL. Positive/Negative results are as follows:

100 ng/mL Cutoff		Within Run (N=22)		Run-to-Run (N=88)	
Concentration	**% of Cutoff**	**# Samples**	**EIA Result**	**# Samples**	**EIA Result**
0 ng/mL	0 %	22	22 Neg	88	88 Neg
25 ng/mL	25 %	22	22 Neg	88	88 Neg
50 ng/mL	50 %	22	22 Neg	88	88 Neg
75 ng/mL	75 %	22	22 Neg	88	88 Neg
100 ng/mL	100 %	22	14 Neg/ 8 Pos	88	45 Neg/ 43 Pos
125 ng/mL	125 %	22	22 Pos	88	88 Pos
150 ng/mL	150 %	22	22 Pos	88	88 Pos
175 ng/mL	175 %	22	22 Pos	88	88 Pos
200 ng/mL	200 %	22	22 Pos	88	88 Pos

Qualitative analysis: The following concentrations were evaluated. Typical qualitative results (measured by ΔOD, mAU) are as follows:

100 ng/mL Cutoff		Within Run (N=22)		Run-to-Run (N=88)	
Concentration	**% of Cutoff**	**# Samples**	**EIA Result**	**# Samples**	**EIA Result**
0 ng/mL	0 %	22	22 Neg	88	88 Neg
25 ng/mL	25 %	22	22 Neg	88	88 Neg
50 ng/mL	50 %	22	22 Neg	88	88 Neg
75 ng/mL	75 %	22	22 Neg	88	88 Neg
100 ng/mL	100 %	22	15 Neg/ 7 Pos	88	60 Neg/ 28 Pos
125 ng/mL	125 %	22	22 Pos	88	88 Pos
150 ng/mL	150 %	22	22 Pos	88	88 Pos
175 ng/mL	175 %	22	22 Pos	88	88 Pos
200 ng/mL	200 %	22	22 Pos	88	88 Pos

Accuracy: Eighty (80) unaltered clinical urine specimens were tested with the LZI Hydrocodone Enzyme Immunoassay and confirmed with GC/MS or LC/MS. Specimens having a hydrocodone and hydromorphone total concentration greater than 100 ng/mL by GC/MS or LC/MS are defined as positive, and specimens with total concentrations below 100 ng/mL by GC/MS or LC/MS are defined as negative in the table below. Near cutoff samples are defined as ± 50 % of the cutoff value. Adjusted GC/MS or LC/MS values have been corrected for cross-reactivity (12, 13). The correlation results are summarized as follows:

Semi-Quantitative Accuracy Study:

100 ng/mL Cutoff	Neg	< 50 % below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	% Agree-ment
Positive	0	0	3*	5	32	92.5 %
Negative	20	4	13	3**	0	92.5 %

The following table summarizes the result for the discordant samples:

100 ng/mL Cutoff	GC/MS or LC/MS	LZI EIA	Adjusted Total Hydrocodone + Hydromorphone GC/MS or LC/MS (ng/mL)	LZI EIA (ng/mL)
Sample #37*	-	+	85.1	100.5
Sample #39*	-	+	97.0	105.4
Sample #40*	-	+	97.0	101.6
Sample #44**	+	-	128.8	93.1
Sample #45**	+	-	138.5	93.7
Sample #46**	+	-	146.5	88.1

Qualitative Accuracy Study:

100 ng/mL Cutoff	Neg	< 50 % below the cutoff	Near Cutoff Neg	Near Cutoff Pos	> 50 % above the cutoff	%Agree-ment
Positive	0	0	3*	5	32	92.5 %
Negative	20	4	13	3**	0	92.5 %

Analytical Recovery: To demonstrate linearity for purposes of sample dilution and quality control (see semi-quantitative results section) of the entire assay range, a drug-free urine pool spiked with hydrocodone at 300 ng/mL was serially diluted. Each sample was run in 10 replicates and the average was used to determine percent recovery compared to the expected target value. When comparing the result (y) and target (x) value, using the least squares regression technique, the regression equation and correlation are as follows:

$y = 1.0139x - 1.174$, $r^2 = 0.9995$

Expected Value (ng/mL)	Observed Value (ng/mL)	% Recovery
300	299.0	99.7 %
250	254.2	101.7 %
200	205.6	102.8 %
175	177.3	101.3 %
150	152.6	101.7 %
125	124.9	99.9 %
100	98.2	98.2 %
75	73.3	97.8 %
50	48.1	96.1 %
25	24.1	96.4 %
5	3.7	73.6 %

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 below lists the concentration of each test compound that gave a response approximately equivalent to that of the cutoff calibrator (as preliminary positive) or the maximal concentration of the compound tested that gave a response below the response of the cutoff calibrator (as negative).

Hydrocodone and Metabolites:

Compound	Target [ ] (ng/mL)	% Cross-Reactivity
Hydrocodone	100	101.6 %
Hydromorphone	125	85.1 %
Hydromorphone Glucuronide	200	52.2 %
Dihydrocodeine	2000	5.0 %
Norhydrocodone	18,000	0.6 %

Structurally Related Compounds:

Compound	Target [ ] (ng/mL)	% Cross-Reactivity
6-Mono Acetylmorphine	6500	1.6 %
Codeine	3000	3.5 %
Codeine-6-glucuronide	15,000	0.6 %
Dextromethorphan	100,000	0.0 %
Levorphanol	20,000	0.5 %
Morphine	5000	2.0 %
Morphine 3-glucuronide	13,000	0.8 %
Morphine 6-glucuronide	50,000	0.2 %
Nalbuphine	100,000	0.0 %
Naloxone	100,000	0.0 %
Naltrexone	100,000	0.0 %
Norbuprenorphine	100,000	0.0 %
Norcodeine	100,000	0.0 %
Noroxycodone	100,000	0.0 %
Noroxymorphone	100,000	0.0 %
Oxycodone	5000	2.1 %
Oxymorphone	7500	1.3 %
Thebaine	12,000	0.8 %

Structurally Unrelated Compounds:

Compound	Spiked [ ] (ng/mL)	Spiked Hydrocodone Concentration		
		0 ng/mL (ng/mL)	75 ng/mL Control (ng/mL)	125 ng/mL Control (ng/mL)
d-Amphetamine	250,000	Neg	Neg	Pos
Benzoylecgonine	100,000	Neg	Neg	Pos
MDA (3,4-Methylenedioxy-Amphetamine)	100,000	Neg	Neg	Pos
MDMA (3,4-Methylenedioxy-Methamphetamine)	100,000	Neg	Neg	Pos
d-Methamphetamine	250,000	Neg	Neg	Pos
Phencyclidine	250,000	Neg	Neg	Pos
THC-COOH (11-Nor-Delta-9-THC-9-Carboxylic Acid)	1000	Neg	Neg	Pos
Acetaminophen	500,000	Neg	Neg	Pos
Acetylsalicylic Acid	500,000	Neg	Neg	Pos
Albuterol (Salbutamol)	500,000	Neg	Neg	Pos
Amitriptyline	500,000	Neg	Neg	Pos
Amobarbital	500,000	Neg	Neg	Pos
Bupropion	500,000	Neg	Neg	Pos
Caffeine	500,000	Neg	Neg	Pos
Carbamazepine	500,000	Neg	Neg	Pos
Chlorpheniramine	500,000	Neg	Neg	Pos
Chlorpromazine	500,000	Neg	Neg	Pos
Clomipramine	500,000	Neg	Neg	Pos
Desipramine	250,000	Neg	Neg	Pos
Ephedrine	500,000	Neg	Neg	Pos
Fentanyl	10,000	Neg	Neg	Pos
Fluoxetine	100,000	Neg	Neg	Pos
Fluphenazine	500,000	Neg	Neg	Pos
Ibuprofen	500,000	Neg	Neg	Pos
Imipramine	50,000	Neg	Neg	Pos
Lidocaine	500,000	Neg	Neg	Pos
Maprotiline	500,000	Neg	Neg	Pos
Meperidine	50,000	Neg	Neg	Pos
Methadone	100,000	Neg	Neg	Pos
Methapyrilene	500,000	Neg	Neg	Pos
Methaqualone	500,000	Neg	Neg	Pos
Metronidazole	500,000	Neg	Neg	Pos
Nicotine	500,000	Neg	Neg	Pos
Nortriptyline	500,000	Neg	Neg	Pos
Oxazepam	100,000	Neg	Neg	Pos
Phenobarbital	500,000	Neg	Neg	Pos
d-Propoxyphene	100,000	Neg	Neg	Pos
Propranaolol	100,000	Neg	Neg	Pos
Ranitidine	500,000	Neg	Neg	Pos
Secobarbital	100,000	Neg	Neg	Pos
Sertraline	100,000	Neg	Neg	Pos
Pentazocine	20,000	Neg	Neg	Pos
Thioridazine	100,000	Neg	Neg	Pos
Tramadol	100,000	Neg	Neg	Pos
Valproic Acid	500,000	Neg	Neg	Pos

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

Endogenous Compound Interference Study:

Endogenous Substance	Spiked [ ] (mg/dL)	Spiked Hydrocodone Concentration		
		0 ng/mL (ng/mL)	75 ng/mL Control (ng/mL)	125 ng/mL Control (ng/mL)
Acetone	1000	Neg	Neg	Pos
Ascorbic Acid	500	Neg	Neg	Pos
Creatinine	500	Neg	Neg	Pos
Ethanol	1000	Neg	Neg	Pos
Galactose	10	Neg	Neg	Pos
γ-Globulin	500	Neg	Neg	Pos
Glucose	3000	Neg	Neg	Pos
Hemoglobin	300	Neg	Neg	Pos
HSA	500	Neg	Neg	Pos
Oxalic Acid	100	Neg	Neg	Pos
Riboflavin	7.5	Neg	Neg	Pos
Urea	6000	Neg	Neg	Pos
Sodium Chloride	1000	Neg	Neg	Pos

pH Interference Study:

pH	Spiked Hydrocodone Concentration		
	0 ng/mL (ng/mL)	75 ng/mL Control (ng/mL)	125 ng/mL Control (ng/mL)
pH 3	Neg	Neg	Pos
pH 4	Neg	Neg	Pos
pH 5	Neg	Neg	Pos
pH 6	Neg	Neg	Pos
pH 7	Neg	Neg	Pos
pH 8	Neg	Neg	Pos
pH 9	Neg	Neg	Pos
pH 10	Neg	Neg	Pos
pH 11	Neg	Neg	Pos

Specific Gravity: Samples ranging in specific gravity from 1.000 to 1.030 were split into three portions each and either left unspiked or further spiked to a final hydrocodone concentration of either 75 ng/mL or 125 ng/mL (the negative and positive control concentrations, respectively). These samples were then evaluated in semi-quantitative and qualitative modes. No interference was observed.

Open-Vial Calibrator/Control Stability: Real-time data for open-vial calibrator/control stability studies at cold temperature (2-8ºC) have been carried out and support stability up to 18 months. Open-vial calibrators/controls should be stored at 2-8ºC for maximum shelf life.

Closed-Vial Calibrator/Control Stability: Real-time data for closed-vial calibrator/control stability studies at cold temperature (2-8ºC) have been carried out and support stability up to 18 Months. Closed-vial calibrators/controls should be stored at 2-8ºC for maximum shelf life.

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. Vallejo, R., Barkin, R. L., and Wang, V.C. Pharmacology of opioids in the treatment of chronic pain syndromes. *Pain physician* **14** (4): E343–E360. (2011)
4. Karch, S.B. Pharmacokinetics and pharmacodynamics of abused drugs. CRC Press, Boca Raton; **55–56** (2008).
5. Zacny, J. P., and Gutierrez, S. Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. *Drug and Alcohol Dependence* **101**(1–2): 107–114 (2009).
6. Wightman, R., Perrone, J., Portelli, I., and Nelson, L. Likeability and Abuse Liability of Commonly Prescribed Opioids. *J Med Tox* **8**(4): 335–340 (2012).
7. Beaver, W. T., and McMillan, D. Methodological considerations in the evaluation of analgesic combinations: Acetaminophen (paracetamol) and hydrocodone in postpartum pain". *British journal of clinical pharmacology*. **10** (Suppl 2): 215S–223S (1980).
8. Raffa, R. B. Pharmacology of oral combination analgesics: Rational therapy for pain. *J Clin Pharm and Ther* **26** (4): 257–264 (2001).
9. "REPREXAIN(hydrocodone bitartrate, ibuprofen) tablet, film coated". *http://dailymed.nlm.nih.gov*. (2013).
10. Gnanadesigan, N., Espinoza, R.T., and Smith, R.L. The serotonin syndrome. *N Engl J Med* **352**(23): 2454–6 (2005).
11. Gardiner, S. J., and Begg, E. J., Pharmacogenetics, Drug-Metabolizing Enzymes, and Clinical Practice. *Pharmacological Reviews* **58** (3): 521–590 (2006).

Bibliography, continued:

12. Cone, E.J. and Darwin, W.D., Simultaneous determination of hydromorphone, hydrocodone and their 6α- and 6β-hydroxy metabolites in urine using selected ion recording with methane chemical ionization., *Biomed. Mass Spect.* **5**:291-295 (1978).
13. Valtier, S. and Bebarta, V.S., Excretion profile of hydrocodone, hydromorphone, and norhydrocodone in urine following single dose administration of hydrocodone to healthy volunteers. *J. Anal. Toxicol.* **36**(7):507-14 (2012).
14. Felden, L., Walter, C., Harder, S., Treede, R.-D., Kayser, H., Drover, D., Geisslinger, G., and J. Lötsch. Comparative Clinical Effects of Hydromorphone and Morphine. *British Journal of Anaesthesia* **107**(3): 319–328 (2011).
15. Baselt, R.C., Disposition of Toxic Drugs and Chemicals in Man. 9th edition. Biomedical Publications, Seal Beach, CA. 818-820 (2011).
16. Cone, E.J., Phelps, B.A., and C.W. Gorodetzky. Urinary excretion of hydromorphone and metabolites in humans, rats, dogs, guinea pigs, and rabbits. *J. Pharm. Sci*. **66**:1709-1713 (1977).
17. Wright, A.W., Nocente, M.L., and M.T. Smith. Hydromorphone-3-glucuronide: biochemical synthesis and preliminary pharmacological evaluation. *Life Sci*. **63**:401-411 (1998)
18. Rubenstein, K.E., R.S. Schneider, and E.F. Ullman, Homogeneous Enzyme Immunoassay: A New Immunochemical Technique, *Biochem Biophys Res Commun*, **47**: 846 (1972).
19. 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
20. Yahya, A.M., McElnay, J.C., and P.F. D'Arcy. Drug sorption to glass and plastics. *Drug Metabol Drug Interact*. **6**(1):1-45 (1988).
21. Gonzales, E.G., Ng, G., Pesce, A.J., West, C., West, R., Mikel, C., Latyshev, S., and Almazan, P. Stability of Commonly Prescribed Opioids and Other Pain Medications in Urine. 2012 AAPM Annual Meeting Presentation.
22. Dixon, R. B., Stability study of opioids and benzodiazepines in urine samples by liquid chromatography tandem mass spectrometry, Journal of Analytical Science and Technology, **6**:17 (2015).
23. ARUP Consult Physician's Guide. http://www.aruplab.com/guides/ug/tests/0090364.jsp
24. J. Nichols. Instrument Validation: The Road to Success. CLN's Lab 2004: From Basic to Advanced Series. 14-16 (2004).
25. CDRH Guidance for Industry and FDA Staff: Replacement Reagent and Instrument Family Policy (2003).

Additions, deletions, or changes are indicated by a change bar in the margin.
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