

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

A. 510(k) Number:

K040316

B. Purpose for Submission:

New analyte

C. Analyte:

Buprenorphine

D. Type of Test:

Homogeneous enzyme immunoassay, qualitative or semi-quantitative.

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

CEDIA Buprenorphine Assay

G. Regulatory Information:

1. Regulation section:
21CFR862.3650, 21CFR862.3200, 21CFR862.3280
2. Classification:
Class II
3. Product Code:
DJG, DLJ, LAS
4. Panel:
91

H. Intended Use:

1. Intended use(s):

The CEDIA® Buprenorphine assay is a homogeneous enzyme immunoassay for qualitative or semi-quantitative determination of the presence of at a cutoff concentration of 5 ng/ml. The assay provides a simple and rapid analytical screening procedure to detect buprenorphine in human urine.

The CEDIA Buprenorphine calibrators are used to calibrate the CEDIA Buprenorphine Assay in human urine.

The CEDIA Buprenorphine controls are used to qualify the CEDIA Buprenorphine Assay in human urine.

2. Indication(s) for use:

The assay provides a simple and rapid analytical screening procedure to detect buprenorphine in human urine.

3. Special condition for use statement(s):

The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. GCMS is the preferred confirmatory method. Clinical and professional judgement should be applied to any drug of abuse test result, particularly when preliminary results are used.

The assay does not distinguish whether buprenorphine is being taken therapeutically or abused.

4. Special instrument Requirements:

The assay is for use on automated clinical chemistry analyzers.

I. Device Description:

The assay consists of buffers (1 and 2) and lyophilized reagents (1a and 2a). The components include mouse monoclonal anti-buprenorphine antibody, recombinant microbial “enzyme donor” – buprenorphine conjugate, “enzyme acceptor”, chlorophenol red B-D-galactopyranoside, stabilizers and preservatives. Calibrators and controls are sold separately.

J. Substantial Equivalence Information:

1. Predicate device name(s):

CEDIA 6-Acetylmorphine Assay

2. Predicate K number(s):

K001178

3. Comparison with predicate:

Both devices use similar reagent and instrument systems. Both devices detect opioid derivatives. The specific antibodies used in the devices and the specific compounds detected are different for the two devices. The predicate detects 6-acetylmorphine with a cutoff concentration of 10 ng/ml. This device detects buprenorphine with a cutoff concentration of 5 ng/ml.

K. Standard/Guidance Document Referenced (if applicable): None

L. Test Principle:

The assay is based on bacterial enzyme B-galactosidase genetically engineered to 2 inactive fragments, one of which is conjugated to buprenorphine. Buprenorphine in the sample competes with the enzyme fragment-conjugated buprenorphine for binding to anti-buprenorphine antibody. In the absence of buprenorphine in the sample, the fragment binds antibody and does not reassociate to form active enzyme. If buprenorphine is present in the sample it binds to the antibody, allowing the enzyme fragments to reassociate. The reassociated enzyme cleaves the substrate,

generating a color change that can be measured spectrophotometrically (660 nm). The amount of active enzyme is proportional to the analyte present.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

Performance was evaluated at the manufacturer's site on a Hitachi 717 Analyzer.

a. Precision/Reproducibility:

Reproducibility was determined by assaying 6 replicates of each of 3 controls in 20 separate runs. Reproducibility was expressed as the %CV for the average concentration of 20 runs for each of the 3 control levels. Results of the inter-assay reproducibility evaluation are shown below.

	Low control	Mid control	High control
Total number of samples	120	120	120
Average concentration (ng/ml)	4.4	6.8	36.5
SD (ng/ml)	0.2	0.3	1.4
%CV	5.0	3.8	4.0

b. Linearity/assay reportable range:

To evaluate linearity a patient urine pool containing 76.6 ng/ml buprenorphine (as measured using the CEDIA buprenorphine assay) was sequentially diluted using a human urine pool free of buprenorphine. The resulting 10 dilutions were assayed in duplicate within one run. Within the range of 8-76.6 ng/ml, the expected/observed values ranged from 95.5%-107.4%.

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

Calibrator levels are 0, 5, 20, 50, 75 ng/ml. Control levels are approximately 3-4 ng/ml and 6-7 ng/ml i.e. approx 25% above and below the cutoff concentration.

Calibrator stability for opened calibrators is evaluated at 2-8 degrees C for up to 60 days. Closed calibrator stability is determined for calibrators stored at 25 degrees C. Acceptance criteria for recovery, with the CEDIA assay, are +/-10% of the concentration observed on day 0. Real time stability studies are ongoing.

Calibrators and controls are traceable to a USP drug standard. Master calibrators are gravimetrically prepared and values are confirmed by GCMS analysis.

d. Detection limit:

The limit of blank of the assay is based on the average plus 3 standard deviations of measurements of 21 buprenorphine-free specimens and was evaluated on 3 instruments. The limit of the blank was 1.25 ng/ml.

e. Analytical specificity

To evaluate interference by endogenous compounds, known amounts of potentially interfering substances were added to urine specimens spiked with 5 ng/ml buprenorphine. Samples containing each endogenous substance and a matched control were assayed using the CEDIA Buprenorphine Assay. The substances tested and percent recoveries are listed below.

Substance tested	Concentration (mg/dl)	% recovery (relative to control)
Acetone	1000	98.1
Ascorbin acid	1500	91.2
Creatinine	500	101.8
Galactose	10	108.2
Gamma globulin	500	93.4
Glucose	1500	93.0
Hemoglobin	300	101.2
NaCl	6000	100.0
Oxalic Acid	100	103.0
Human serum albumin	500	97.2
Urea	2000	93.5
Riboflavin	7.5	91.7
Ethanol	1000	108.0

Cross-reactivity of buprenorphine metabolites were determined by adding known amounts of metabolites to buprenorphine-free urine specimens. Concentrations were determined and compared to control samples free of metabolites. Results are tabulated below:

Metabolite	Target concentration (ng/ml)	% cross-reactivity
Buprenorphine 3-B-D	5	98
Glucuronide	20	97
Norbuprenorphine	1000	<0.01
Norbuprenorphine 3-B-D	1000	<0.01
Glucuronide		

Potential interference caused by other substances or drugs was evaluated by adding 500 ug/ml of each drug to buprenorphine-free urine and comparing results to those of controls samples. Percent cross-reactivity observed at 500 ug/ml was less than 0.1% for the compounds listed below.

Pharmacologic Compound	
10, 11 Dihydrocarbamazepine	Enalapril
11-nor-THC-COOH	Fluoxetine
Acetaminophen	Haloperidol
Acetylsalicylic Acid	Ibuprofen
Amitriptyline	Levothyroxine
Amoxicillin	Methamphetamine
Amphetamine	Nifedipine
Benzotropine methane Sulfonate	Nordiazepam
Benzoyllecgonine	Oxazepam
Bromopheniramine	Pentazocine HCL
Caffeine	Perphenazine
Captopril	Phencyclidine
Chlordiazepoxide	Phenobarbital
Chlorpromazine	Procyclidine
Cimetidine	Propoxyphene
Desipramine	Protriptyline
Diazepam	Ranitidine
Digoxin	Salicylic Acid
Diphenhydramine	Secobarbital
Disopyramide	Tolmetin
Doxepin	Triprolidine
Doxylamine	Verapamil

f. Assay cut-off:

Urine specimens (n=21) were spiked with a stock solutions of buprenorphine to final concentrations of 3.75 ng/ml and 6.25 ng/ml and evaluated using the CEDIA Buprenorphine Assay. In both the quantitative and qualitative modes, all specimens spiked to 3.75 ng/ml were determined by the assay to be below the cutoff calibrator for that run. Similarly, all specimens spiked to 6.25 ng/ml were determined to be above the cutoff calibrator. This is summarized in the table below:

Mean dose (ng/ml)	3.7	6.6
SD (ng/ml)	0.2	0.2
%cv	6.6	2.5
Cut-off dose (ng/ml)	5.4	5.4

2. Comparison studies:a. *Method comparison with predicate device:*

Ninety six clinical urine specimens were obtained from normal volunteers and individuals receiving buprenorphine. No selection criteria or pre-screening was applied. Samples spanned the range from 0-75 ng/ml buprenorphine. Results, compared to GC/MS analysis for buprenorphine (including buprenorphine glucuronide), are shown below. They were identical for qualitative and semi-quantitative mode. The discordant observation had a GC/MS buprenorphine concentration of 0 ng/mL, a negative result for qualitative mode, and a reported result of 8.3 ng/mL for semi-quantitative mode.

	GC/MS Positive	GC/MS Negative	
CEDIA Positive	45	1	46
CEDIA Negative	0	50	50
	45	51	96

b. *Matrix comparison:*

Not applicable. Urine is the only matrix for which the assay is indicated

3. Clinical studies:a. *Clinical sensitivity:*

Not applicable. Clinical sensitivity is not typically provided in a 510(k) for this type of assay.

b. *Clinical specificity:*

Not applicable. Clinical sensitivity is not typically provided in a 510(k) for this type of assay.

c. *Other clinical supportive data (when a and b are not applicable):*4. Clinical cut-off:

There are currently no SAMHSA recommendations for a clinical cutoff for buprenorphine.

5. Expected values/Reference range:

NA

N. Conclusion:

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