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

A. 510(k) Number:

K150502

B. Purpose for Submission:

New Device

C. Measurand:

Hydrocodone

D. Type of Test:

Qualitative and semi-quantitative homogeneous immunoassay

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

DRI Hydrocodone Assay
DRI Hydrocodone Calibrator
DRI Hydrocodone Control

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
DJG	II	21 CFR § 862.3650 Opiate test system	Toxicology (91)
DLJ	II	21 CFR § 862.3200 Clinical toxicology calibrator	Toxicology (91)
LAS	I, reserved	21 CFR § 862.3280 Clinical toxicology control material	Toxicology (91)

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The DRI Hydrocodone assay is intended for the qualitative and semi-quantitative detection and estimation of Hydrocodone and its metabolites in human urine at a cutoff of 300 ng/mL.

The semi-quantitative mode is for purposes of enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as LC-MS/MS or GC-MS and permitting laboratories to establish quality control procedures.

This assay provides a preliminary analytical test result. A more specific alternative chemical method must be used in order to confirm an analytical result. Gas chromatography/mass spectrometry (GC/MS) and Liquid Chromatography/tandem mass spectrometry (LC-MS/MS) are the preferred confirmatory methods. Clinical consideration and professional judgment should be applied to any drug of abuse test result, particularly when preliminary positive results are used.

The DRI Hydrocodone assay calibrators are intended for the calibration of the DRI Hydrocodone assay. For in vitro diagnostic use only.

The DRI Hydrocodone assay controls are unassayed quality control material intended for the use in the DRI Hydrocodone assay to detect and monitor systematic deviations from accuracy resulting from reagent or instrument defects. For in vitro diagnostic use only.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Beckman Coulter AU 680 chemistry analyzer was used to generate data for this submission.

I. Device Description:

The DRI Hydrocodone assay is supplied as a liquid ready-to-use homogeneous enzyme immunoassay.

The DRI Hydrocodone Assay is a kit comprised of two reagents, Reagent A and Reagent E, which are bottled separately but sold together within the same kit.

The Reagent A solution contains: mouse monoclonal anti-hydrocodone antibody, glucose-6-phosphate (G6P) and nicotinamide adenine dinucleotide (NAD) in Tris buffer with Sodium Azide (≤0.09%) as a preservative).

The Reagent E solution contains: glucose-6-phosphate dehydrogenase (G6PDH) in Tris buffer with Sodium Azide (≤0.09%) as preservative.

The DRI Hydrocodone Enzyme Immunoassay calibrators designated for use at the 300 ng/mL cutoff contain 0 (negative), 100, 300, 500, and 1,000 ng/mL of hydrocodone in human urine with sodium azide (≤0.09%) as preservative. The calibrators are provided in liquid ready to use form as a separate kit, and are to be stored at 2º to 8º C until the expiration date on the label.

The controls are provided at a concentration of 225 and 375 ng/mL. The controls are provided in liquid ready to use form as a separate kit, and are to be stored at 2º to 8º C until the expiration date on the label.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   LZI Hydrocodone Enzyme Immunoassay

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

   K141055

3. Comparison with predicate:

Item	**DRI Hydrocodone Assay, Calibrator and Control (Candidate Device)**	**LZI Hydrocodone Enzyme Immunoassay, k141055 (Predicate Device)**
Intended use	For the qualitative and semi-quantitative determination of the presence of hydrocodone in human urine. For in vitro diagnostic use.	Same
Assay cutoff	300 ng/mL of Hydrocodone	100 or 300 ng/mL of Hydrocodone
Assay calibrated against	Hydrocodone	Same
Test system type	Homogenous enzyme immunoassay	Same
Storage conditions	2 - 8°C until expiration date	Same
Calibrator form	Liquid	Same
Control set levels	300 ng/mL Cutoff: Two levels (225 ng/mL and 375 ng/mL)	100 ng/mL Cutoff: Two levels (75 ng/mL and 125 ng/mL). 300 ng/mL Cutoff: Two levels (225 ng/mL and 375 ng/mL).
Calibrator set levels	300 ng/mL Cutoff: Five levels (0, 100, 300, 500 and 1000 ng/mL)	100 ng/mL Cutoff: Five levels (0, 50, 100, 150 and 300 ng/mL). 300 ng/mL Cutoff: Five levels (0, 150, 300, 500 and 800 ng/mL).

K. Standard/Guidance Document Referenced (if applicable):

- CLSI EP5-2A, Evaluation of Precision Performance of Quantitative Measurement Methods; Second Edition, 2004.
- CLSI EP7-A2: Interference Testing in Clinical Chemistry, 2005.
- CLSI EP9-A3; Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition, 2013.

L. Test Principle:

The DRI® Hydrocodone Assay is a homogeneous enzyme immunoassay. The assay uses specific antibodies that can detect Hydrocodone and its metabolites without any significant cross-reactivity to other opiate compounds. The assay is based on competition between a drug labeled with glucose-6-phosphate dehydrogenase (G6PDH) and free drug from the urine sample, for a fixed amount of specific antibody binding sites. In the absence of free drug from the sample, mouse monoclonal anti-hydrocodone antibody binds to the drug labeled with G6PDH and causes a decrease in enzyme activity. In the presence of free drug, the free drug occupies the antibody binding sites, allowing the drug bound G6PDH to interact with the substrate, resulting in enzyme activity. This phenomenon creates a direct proportional relationship between the drug concentration in urine and enzyme activity. The enzyme activity is determined spectrophotometrically at 340 nm by measuring the conversion of nicotinamide adenine dinucleotide (NAD) to NADH.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   A precision study was performed by one trained operator following the CLSI (EP5-A2) precision guidelines. Drug free urine samples were spiked with hydrocodone at 0, 75, 150, 225, 300, 375, 450, 525 and 600ng/mL, representing 0, 25, 50, 75, 100, 125, 150, 175 and 200% of the device cutoff (300 ng/mL). Each level sample was tested in duplicates per run, two runs per day for twenty consecutive days (total N= 80/level/reagent lot) using 2 lots on the Beckman Coulter AU680 chemistry analyzer. The results of one representative lot are shown below:

Qualitative Precision Result:

Concentration as % of the Cutoff Level	Target Hydrocodone concentration (ng/mL)	DRI Hydrocodone Assay # Neg / # Pos
0	0	80 Neg / 0 Pos
25	75	80 Neg / 0 Pos
50	150	80 Neg / 0 Pos
75	225	80 Neg / 0 Pos
100	300	46 Neg / 34 Pos
125	375	0 Neg / 80 Pos
150	450	0 Neg / 80 Pos
175	525	0 Neg / 80 Pos
200	600	0 Neg / 80 Pos

Semi-Quantitative Precision Result:

Concentration as % of the Cutoff Level	Target Hydrocodone concentration (ng/mL)	DRI Hydrocodone Assay # Neg / # Pos
0	0	80 Neg / 0 Pos
25	75	80 Neg / 0 Pos
50	150	80 Neg / 0 Pos
75	225	80 Neg / 0 Pos
100	300	40 Neg / 40 Pos
125	375	0 Neg / 80 Pos
150	450	0 Neg / 80 Pos
175	525	0 Neg / 80 Pos
200	600	0 Neg / 80 Pos

b. *Linearity/assay reportable range:*

Linearity study in the semi-quantitative mode was conducted by spiking drug free urine pool with hydrocodone (serial dilutions of a high concentration hydrocodone in negative urine pool) to achieve concentrations ranging from 0ng/mL to 1000ng/mL, and testing each level on two reagent lots in replicates of five on the Beckman

Coulter AU680 clinical chemistry analyzer. The results of one representative lot are summarized below:

Hydrocodone (ng/mL)	Recovery (ng/mL)	% Recovery
0	N/A	N/A
50	47	94
75	76	101
100	108	108
150	171	114
225	250	111
300	302	101
375	398	106
450	472	105
500	527	105
750	844	113
1000	1014	101

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

Traceability

The primary controls and calibrators are traceable to the 1 mg/mL Hydrocodone stock solution purchased from a commercial source which is established at 99.9% purity. The concentration of the primary control and calibrator stocks is confirmed by LC-MS/MS from three independent laboratories.

Value Assignment – Calibrators and Controls

The primary controls and calibrators are used to prepare secondary controls and calibrators and the performance testing is performed on AU680 analyzers against the primary controls and calibrators, in replicates of five. The testing required two passing runs on two different AU680 analyzers. The preset acceptance criteria is that replicates have less than or equal to 5% rate (mA/min) difference between the secondary and the primary controls and calibrators. The concentration of the controls and calibrators are further corroborated with validated LC-MS/MS and the values should be within 10% of the nominal values.

Calibrators and Controls Stability Studies

Accelerated a stability studies in the qualitative and semi-quantitative modes were conducted on three lots of DRI Hydrocodone Controls and DRI Hydrocodone Calibrators. Real time stability studies are ongoing. The stability protocols and acceptance criteria for open and closed vial were reviewed and found acceptable. The open vial and closed vial study results support the open vial stability claim of 60 days and closed vial stability claim of thirteen months when stored at 2 to 8 ºC for the DRI Hydrocodone Controls and DRI Hydrocodone Calibrators.

d. Detection limit:

Not applicable.

e. Analytical specificity:

An analytical specificity study to evaluate interference from non-structurally and structurally related compounds was performed in the qualitative and semi-quantitative mode. The study design and results are described below. Results were the same for each mode (qualitative and semi-quantitative modes).

Structurally Related Compounds and Other Opiates

To evaluate potential cross-reactivity for the DRI Hydrocodone assay, structurally similar compounds were spiked into drug free urine at concentrations that will yield a result that is equivalent to the 300ng/mL cutoff. Non-cross-reacting compounds were titrated to the highest levels yielding negative results in the assay. The percent cross-reactivity is presented in the table below.

Compounds	**Tested Concentration (ng/mL)**	**% Cross-Reactivity**
Hydrocodone	300	102
Hydromorphone	250	122
Hydromorphone 3β-D-Glucuronide	250	122
NorHydrocodone	10,000	3.1
Dihydrocodeine	12,000	2.7
6 -Acetyl Morphine	1000,000	< 0.3
Buprenorphine	1000,000	< 0.3
Buprenorphine 3β-D - Glucuronide	100,000	< 0.3
Codeine	150,000	< 0.2
Dextromethorphan	250,000	< 0.2
EDDP	150,000	< 0.2
Fentanyl	100,000	< 0.3
Heroin	100,000	< 0.3
Levorphanol	12,000	1.7

Methadone	100,000	<0.3
Meperidine	100,000	<0.3
Morphine	150,000	<0.2
Morphine -3β-D-Glucuronide	70,000	<0.4
Morphine -6 β-D-Glucuronide	75,000	<0.4
Nalbuphine	150,000	<0.3
Naloxone	12,000	2.0
Naltrexone	100,000	<0.3
Norbuprenorphine	100,000	<0.3
Norcodeine	150,000	<0.2
Normorphine	150,000	<0.2
Nor-Oxycodone	100,000	0.3
Oxycodone	10,000	2.5
Oxymorphone 3β-D-Glucuronide	13,000	2.2
Oxymorphone	10,000	2.5
Tapentadol	100,000	<0.3
Thebaine	100,000	<0.3
Tramadol	100,000	<0.3

Non-Structurally Related Compounds

Potential interference from non-structurally related drugs and metabolites was evaluated in the qualitative and semi-quantitative modes, by spiking these compounds at high concentrations in drug free urine spiked with hydrocodone at ± 25% of the cutoff (225 and 375 ng/mL). Results obtained with the two reagent lots are the same.

Cross Reactants	**Spiked Concentration (ng/mL)**	**Spiked Hydrocodone Concentration**		
		0 ng/mL	**-25% Cutoff (225 ng/mL)**	**+25% Cutoff (375 ng/mL)**
Acetaminophen	500,000	Negative	Negative	Positive
Acetylsalicylic acid	500,000	Negative	Negative	Positive
Amitryptyline	100,000	Negative	Negative	Positive
Amoxicillin	100,000	Negative	Negative	Positive
Amphetamine	1,000,000	Negative	Negative	Positive
Benzoylecgonine	1,000,000	Negative	Negative	Positive
Caffeine	100,000	Negative	Negative	Positive
Carbamazepine	500,000	Negative	Negative	Positive
Chlorpromazine	100,000	Negative	Negative	Positive
Clomipramine	100,000	Negative	Negative	Positive
Cimetidine	500,000	Negative	Negative	Positive
Desipramine	100,000	Negative	Negative	Positive

Diphenhydramine	100,000	Negative	Negative	Positive
Doxepine	100,000	Negative	Negative	Positive
Ephedrine	1,000,000	Negative	Negative	Positive
Fluoxethine	100,000	Negative	Negative	Positive
Fluphenazine	100,000	Negative	Negative	Positive
Ibuprofen	500,000	Negative	Negative	Positive
Imipramine	100,000	Negative	Negative	Positive
Maprotiline	100,000	Negative	Negative	Positive
Nortryptiline	100,000	Negative	Negative	Positive
Oxazepam	250,000	Negative	Negative	Positive
Phencyclidine	100,000	Negative	Negative	Positive
Phenobarbital	100,000	Negative	Negative	Positive
Ranitidine	500,000	Negative	Negative	Positive
Secobarbital	100,000	Negative	Negative	Positive
Thioridazine	100,000	Negative	Negative	Positive

Endogenous Compounds

Potential interference from endogenous compounds commonly found in urine was evaluated in the qualitative and semi-quantitative modes, by spiking these compounds into drug free urine containing hydrocodone at ± 25% of the 300 ng/mL cutoff (225 and 375 ng/mL). Results obtained with the two reagent lots are the same.

Compounds	**Concentration tested (mg/dL)**	**-25% Cutoff (225ng/mL)**	**+25% Cutoff (375ng/mL)**
No added compound	N/A	Negative	Positive
Acetaminophen	10	Negative	Positive
Acetone	500	Negative	Positive
Acetyl Salycylic Acid	10	Negative	Positive
Ascorbic Acid	150	Negative	Positive
Caffeine	10	Negative	Positive
Creatinine	400	Negative	Positive
Ethanol	10	Negative	Positive
Galactose	5	Negative	Positive
Glucose	1000	Negative	Positive
Hemoglobin	150	Negative	Positive
Human Serum Albumin (HSA)	200	Negative	Positive
Ibuprophen	10	Negative	Positive
Oxalic acid	50	Negative	Positive
Riboflavin	3	Negative	Positive
Sodium Chloride	1000	Negative	Positive
Urea	1000	Negative	Positive

pH and Specific Gravity

For potential interference from the pH of urine, device performance in the qualitative and semi-quantitative modes was tested using a range of urine pH values (4.0, 5.0, 6.0, 7.0, 8.0, 9.0 and 10.0). All test samples were prepared in drug free urine containing hydrocodone at ± 25% of the cutoff (225 ng/mL and 375 ng/mL hydrocodone concentrations). No positive or negative interference was observed at urine pH values ranging from 4.0 to 10.0 for each test mode.

For potential interference from the specific gravity of urine, device performance in the qualitative and semi-quantitative modes was tested using a range of urine specific gravity values (1.000, 1.006, 1.007, 1.010, 1.013, 1.018, 1.021, 1.025, 1.028, 1.034 and 1.036). All test samples were prepared in drug free urine containing hydrocodone at ± 25% of the cutoff (225 ng/mL and 375 ng/mL hydrocodone concentrations). No positive or negative interference was observed at urine specific gravity values ranging from 1.000 to 1.036 for each test mode.

f. Assay cut-off:

Characterization of how the device performs analytically around the claimed cutoff concentration of 300 ng/mL hydrocodone is described in the precision section, M.1.a. above.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 100 unaltered urine samples from pain management laboratories were analyzed by two lots of the candidate device in the qualitative and semi-quantitative modes on the Beckman Coulter AU680 clinical chemistry analyzer and the comparative mass spectrometry based quantitative method (LC-MS/MS). LC-MS/MS and immunoassay qualitative results are based on a 300ng/mL cutoff. The results from the study in the two modes were same and are summarized below:

Qualitative and Semi-quantitative Mode

Candidate Device Results	Negative	<50% of cutoff concentration by LC/MS (< 150ng/mL)	Near Cutoff Negative (Between 50% below the cutoff and the cutoff concentration by LC/MS) (150 ~ 299 ng/mL)	Near Cutoff Positive (Between the cutoff and 50% above the cutoff concentration by LC/MS) (300 ~ 450 ng/mL)	High Positive (Greater than 50% above the cutoff concentration by LC/MS) > 450 ng/mL
Positive	0	1*	5**	10	39
Negative	31	6	7	1	0

* and ** are oxycodone positive samples that contained 41,240 ng/mL and 37,000 ng/mL oxycodone respectively.

% Agreement among positives is 98%.

% Agreement among negatives is 88%.

% Overall agreement is 93%.

Discordant Result Table for the Discrepant Samples near cutoff

Sample #	Qualitative EIA	LC-MS/MS (ng/mL)		
		Hydrocodone	Hydromorphone	Hydormorphone 3β-D Glucuronide
33	Positive	143.3	<LLOQ♦	67.6
70*	Positive	138.4	<LLOQ	<LLOQ
75**	Positive	216.7	<LLOQ	<LLOQ
76	Positive	198.8	<LLOQ	42.6
83	Positive	78.4	<LLOQ	110.1
89	Positive	192.3	<LLOQ	56.2
96	Negative	303.3	<LLOQ	50.1

* and ** are oxycodone positive samples that contained 41,240 ng/mL and 37,000 ng/mL oxycodone respectively.

♦LLOQ = Lowest Limit of Quantitation is 40 ng/mL

b. Matrix comparison:

Not applicable. Urine is the only claimed matrix for the candidate device.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable.

b. Clinical specificity:

Not applicable.

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

Not applicable.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

Not applicable.

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.