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

A. 510(k) Number:

k173195

B. Purpose for Submission:

Adding a previously cleared test (DRI Hydrocodone Assay) to the Indiko Family Analyzer

C. Measurand:

Hydrocodone

D. Type of Test:

Qualitative and semi-quantitative homogeneous enzyme immunoassay

E. Applicant:

Microgenics Corporation

F. Proprietary and Established Names:

DRI Hydrocodone Assay

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.3650, Opiate test system

2. Classification:

   Class II

3. Product code:

   DJG

4. Panel:

   Toxicology (91)

H. Intended Use:

1. Intended use(s):

   Refer to Indications for Use below

2. Indication(s) for use:

   The DRI Hydrocodone Assay is a homogeneous enzyme immunoassay for the qualitative and/or semi-quantitative determination of the presence of hydrocodone and its metabolites in human urine at a cutoff concentration of 300 ng/mL. The assay is intended to be used in laboratories and provides a simple and rapid analytical screening procedure to detect hydrocodone and its metabolites in human urine. The assay is designed for use with a number of clinical chemistry analyzers.

   The semi-quantitative mode is for the purpose of enabling laboratories to determine an appropriate dilution of the specimen for confirmation by a confirmatory method such as liquid chromatography/tandem mass spectrometry (LC-MS/MS) or permitting laboratories to establish quality control procedures. The assay provides only a preliminary analytical test result. A more specific alternative chemical method must be used to obtain a confirmed analytical result. Gas chromatography/ mass spectrometry (GC/MS) or liquid chromatography/tandem mass spectrometry (LC-MS/MS) is the preferred confirmatory method.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   Performance characteristics provided in this submission were determined on the Indiko Plus Analyzer.

I. Device Description:

The DRI Hydrocodone assay is supplied as a liquid ready-to-use homogeneous enzyme immunoassay, comprised of two reagents (Reagent A and Reagent E) which are bottled separately but sold together within the same kit.

Reagent A: Contains mouse monoclonal anti-Hydrocodone antibody, glucose-6-phosphate (G6P), and nicotinamide adenine dinucleotide (NAD) in Tris buffer with sodium azide as a preservative.

Reagent E: Contains Hydrocodone derivative labeled with glucose-6-phosphate dehydrogenase (G6PDH) in Tris buffer with sodium azide as a preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   DRI Hydrocodone assay

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

   k150502

3. Comparison with predicate:

Similarities and Differences		
Item	Candidate Device k173195	Predicate Device k150502
Intended Use	Homogeneous enzyme immunoassay for the qualitative and/or semi-quantitative determination of the presence of hydrocodone and its metabolites in human urine.	Same
Measured Analyte	Hydrocodone and its metabolites	Same
Test Matrix	Urine	Same
Cutoff Levels	300 ng/mL	Same
Methodology	Homogeneous Enzyme Immunoassay	Same
Antibody	Mouse Monoclonal	Same
Storage	2–8°C until expiration date	Same
Platform	Indiko Plus	Beckman AU680

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

- CLSI EP5-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline -Third Edition, 2014.
- CLSI EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline -Second Edition, 2005.
- CLSI EP9-A3: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline -Third Edition, 2013.
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures, a Statistical Approach; Approved Guideline, 2003.

- CLSI EP25-A: Evaluation of Stability ofTn Vitro Diagnostic Reagents; Approved Guideline, 2009.

L. Test Principle:

The DRI Hydrocodone Assay is a homogeneous enzyme immunoassay. The assay uses specific antibodies that can detect Hydrocodone and its metabolites. 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. Analytical performance:

   a. *Precision/Reproducibility:*

   A precision study was performed following CLSI EP5-A3. Drug free urine samples were spiked with hydrocodone at 0, 75, 150, 225, 300, 375, 450, 525 and 600 ng/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 duplicate per run, two runs per day for twenty consecutive days (total n= 80/level/reagent lot) using 2 lots on one Indiko Plus analyzer in both qualitative and semi-quantitative modes. The results of one representative lot are shown below:

   Qualitative Precision Result:

Concentration as % of the Cutoff Level	**Target Hydrocodone spiked concentration (ng/mL)**	**Hydrocodone concentration determined by LC-MS/MS (ng/mL)**	**DRI Hydrocodone Assay # Negative / # Positive**
0	0	0	80 Neg / 0 Pos
25	75	89.5	80 Neg / 0 Pos
50	150	174.85	80 Neg / 0 Pos
75	225	243.37	80 Neg / 0 Pos
100	300	318.50	4 Neg / 76 Pos
125	375	410.66	0 Neg / 80 Pos
150	450	501.62	0 Neg / 80 Pos
175	525	592.11	0 Neg / 80 Pos
200	600	667.52	0 Neg / 80 Pos

Semi-Quantitative Precision Result:

Concentration as % of the Cutoff Level	Target Hydrocodone spiked concentration (ng/mL)	Hydrocodone concentration determined by LC-MS/MS (ng/mL)	DRI Hydrocodone Assay # Negative / # Positive
0	0	0	80 Neg / 0 Pos
25	75	89.5	80 Neg / 0 Pos
50	150	174.85	80 Neg / 0 Pos
75	225	243.37	80 Neg / 0 Pos
100	300	318.50	7 Neg / 73 Pos
125	375	410.66	0 Neg / 80 Pos
150	450	501.62	0 Neg / 80 Pos
175	525	592.11	0 Neg / 80 Pos
200	600	667.52	0 Neg / 80 Pos

b. *Linearity/assay reportable range:*

A drug recovery study in the semi-quantitative mode was conducted by spiking a drug free urine pool with hydrocodone and using serial dilutions with a negative urine pool to achieve concentrations ranging from 100 ng/mL to 1000ng/mL, and testing each level on one lot of reagent, calibrators and controls. Each concentration was tested in five replicates on the Indiko Plus analyzer. The mean of the five replicates tested was defined as the observed drug concentration value. The percent recovery range was defined as the range in observed percent recoveries amongst the five replicates at each concentration. The results of are summarized below:

Target concentration (ng/mL)	Observed concentration (ng/mL)	% Recovery Range
0	0	N/A
100	95	80-120
200	219	160-240
300	331	240-360
400	427	320-480
500	529	400-600
600	624	480-720
700	696	560-840
800	798	640-960
900	893	720-1080
1000	911	800-1200

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

Calibrators for this device were previously cleared in k150502.

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 modes. The study design and results were the same for each mode (qualitative and semi-quantitative modes) and are shown in the tables below.

Cross-Reactivity of Hydrocodone and Its Metabolites

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. Percent cross-reactivity for compounds with no observed cross-reactivity was calculated using the highest concentration tested. The percent cross-reactivity is presented in the table below.

Hydrocodone and its metabolites	Tested Concentration (ng/mL)	Pos/neg	% Cross-Reactivity
Hydrocodone	300	Pos	100
Hydromorphone	325	Pos	92
Hydromorphone-3β-glucuronide	185	Pos	162
Norhydrocodone	13,000	Pos	2
Dihydrocodeine	12,500	Pos	2

Cross-Reactivity of Opiates and Structurally Related Compounds

Compounds	Tested Concentration (ng/mL)	% Cross-Reactivity
6 -Acetyl Morphine	100,000	< 0.3
Buprenorphine	100,000	< 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	22,000	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	17,000	2.0
Naltrexone	75,000	<0.3
Norbuprenorphine	100,000	<0.3
Norcodeine	150,000	<0.2
Normorphine	150,000	<0.2
Nor-Oxycodone	110,000	0.3
Oxycodone	14,000	2.5
Oxymorphone 6β-D- Glucuronide	14,000	2.2
Oxymorphone	14,000	2.5
Tapentadol	100,000	<0.3
Thebaine	100,000	<0.3
Tramadol	100,000	<0.3

Structurally Unrelated Compounds

Potential interference from non-structurally related drugs 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 two reagent lots were the same, and results from one representative lot are provided in the table below.

Compounds	Spiked Concentration (ng/mL)	-25% Cutoff (225 ng/mL)	+25% Cutoff (375 ng/mL)
Acetaminophen	500,000	Neg	Pos
Acetylsalicylic acid	500,000	Neg	Pos
Amitryptyline	100,000	Neg	Pos
Amoxicillin	100,000	Neg	Pos
Amphetamine	1,000,000	Neg	Pos
Benzoylecgonine	1,000,000	Neg	Pos
Caffeine	100,000	Neg	Pos
Carbamazepine	500,000	Neg	Pos
Chlorpromazine	100,000	Neg	Pos
Clomipramine	10,000	Neg	Pos

Cimitidine	500,000	Neg	Pos
Desipramine	100,000	Neg	Pos
Diphenhydramine	100,000	Neg	Pos
Doxepine	100,000	Neg	Pos
Ephedrine	1,000,000	Neg	Pos
Fluoxethine	100,000	Neg	Pos
Fluphenazine	100,000	Neg	Pos
Ibuprofen	500,000	Neg	Pos
Imipramine	100,000	Neg	Pos
Maprotiline	100,000	Neg	Pos
Nortryptiline	100,000	Neg	Pos
Oxazepam	250,000	Neg	Pos
Phencyclidine (PCP)	100,000	Neg	Pos
Phenobarbital	100,000	Neg	Pos
Ranitidine	500,000	Neg	Pos
Secobarbital	100,000	Neg	Pos
Thioridazine	100,000	Neg	Pos

Endogenous Compounds, pH and Specific Gravity

Potentially interfering substances were spiked into drug free urine spiked with 225 ng/mL or 375 ng/mL of hydrocodone. Samples were tested in replicates of five (n=5) in both qualitative and semi-quantitative modes. Results obtained in both modes were identical, and results are provided in the below table.

Potential Interfering Substances	**Concentration tested (mg/dL)**	**-25% Cutoff (225ng/mL)**	**+25% Cutoff (375ng/mL)**
Acetaminophen	10	Negative	Positive
Acetone	500	Negative	Positive
Acetylsalycylic 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	1,000	Negative	Positive
Hemoglobin	150	Negative	Positive
Human Serum Albumin (HSA)	200	Negative	Positive
Ibuprofen	10	Negative	Positive
Oxalic acid	50	Negative	Positive
Riboflavin	3	Negative	Positive
Sodium Chloride	1,000	Negative	Positive
Urea	1,000	Negative	Positive

pH: Drug free urine specimens spiked with 225 or 375 ng/mL of hydrocodone were adjusted to varying pH (between pH 4.0 and pH 10.0). Samples were tested in replicates of five (n=5) in both qualitative and semi-quantitative modes. No positive or negative interference was observed at urine pH values ranging from 4.0 to 10.0 for each test mode.

Specific Gravity: Urine with specific gravity spanning the range within 1.003–1.031 was spiked with 225 and 375 ng/mL of hydrocodone. Samples were tested in replicates of five (n=5) in both qualitative and semi-quantitative. No positive or negative interference was observed at urine specific gravity values ranging from 1.003 to 1.031 in either test mode.

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 136 unaltered urine samples were analyzed by one lot of the DRI Hydrocodone Assay in one replicate, in both Qualitative and Semi-quantitative modes, and the results were compared to LC-MS/MS (liquid- chromatography-tandem mass spectroscopy). The results from the study in the two modes were identical and are summarized in the table below.

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	7*	17*	9	48
Negative	42	3	10	0	0

*Discordant Result Table

Sample #	Immunoassay result	LC-MS/MS (ng/mL)	
		Hydrocodone	Hydromorphone 3β-D Glucuronide
46	Positive	126	179
47	Positive	132	160
48	Positive	126	314
49	Positive	82.7	128
50	Positive	138	677
51	Positive	131	126
52	Positive	73.3	262
63	Positive	162	218
64	Positive	249	356
65	Positive	253	265
66	Positive	160	739
67	Positive	270	88.6
68	Positive	217	158
69	Positive	236	90.4
70	Positive	282	242
71	Positive	295	433
72	Positive	167	149
73	Positive	193	756
74	Positive	214	434
75	Positive	207	706
76	Positive	298	190
77	Positive	198	262
78	Positive	157	124
79	Positive	287	79.9

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 Parts 801 and 809, as applicable.

O. Conclusion:

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