

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

A. 510(k) Number:

k081378

B. Purpose for Submission:

New product

C. Measurand:

2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP)

D. Type of Test:

Semi-quantitative and qualitative homogeneous enzyme immunoassay

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

DRI[®] Methadone Metabolite (100/300) Assay

DRI[®] Methadone Metabolite Urine Calibrators

DRI[®] Methadone Metabolite Urine Controls

G. Regulatory Information:

1. Regulation section:

21 CFR §862.3620, Methadone Test System

21 CFR §862.3200, Clinical Toxicology Calibrator

21 CFR §862.3280, Clinical Toxicology Control Material

2. Classification:

Class II (Reagent, Calibrator)

Class I Reserved (Control)

3. Product code:

DJR; DKB; DIF

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

See Indications for Use below.

2. Indication(s) for use:

For *in vitro* diagnostic use only.

The DRI Methadone Metabolite (100/300) Assay is intended for the qualitative and semi-quantitative determination of the presence of Methadone Metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine or EDDP) in human urine at cutoffs of 100 and 300 ng/mL.

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) is the preferred confirmatory method. Clinical and professional judgment should be applied to any drug of abuse test result, particularly when preliminary results are used. Tests for methadone metabolite cannot distinguish between abused drugs and certain prescribed medications. Certain foods or medications may interfere with test for

methadone metabolite and cause false positive results.

The DRI Methadone Metabolite Calibrators are intended for the calibration of the DRI Methadone Metabolite (100/300) Assay.

The DRI Methadone Metabolite Controls are intended for use in the DRI Methadone Metabolite (100/300) Assay to detect and monitor systematic deviations from accuracy resulting from reagent or instrument defects.

3. Special conditions for use statement(s):
This device is for use by professional laboratory personnel. For *in vitro* diagnostic use only.
4. Special instrument requirements:
Clinical chemistry analyzers. The Hitachi 917 analyzer was used to conduct performance studies below.

I. Device Description:

The DRI Methadone Metabolite (100/300) Assay utilizes liquid ready-to-use reagents. The Antibody/Substrate Reagent (R1) contains mouse monoclonal anti-EDDP antibody, glucose-6-phosphate (G6P), and nicotinamide adenine dinucleotide (NAD) in Tris buffer with sodium azide as a preservative. The Enzyme Conjugate Reagent (R2) contains EDDP-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):
CEDIA DAU EDDP Assay
CEDIA DAU Multi-Drug Calibrators
MGC DAU Control Sets: Primary, Clinical, Select
2. Predicate 510(k) number(s):
K980746; K980853; K040758,
3. Comparison with predicate:

<u>Comparison</u>	<u>DRI Methadone Metabolite (100/300) Assay</u>	<u>Predicate Device – CEDIA DAU EDDP Assay</u>
<u>Intended Use</u>	<u>Qualitative and semi-quantitative determination of the presence of Methadone Metabolite (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine or EDDP) in human urine at cutoffs of 100 and 300 ng/mL.</u>	<u>Qualitative and semi-quantitative assay of EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine or EDDP) in human urine.</u>

<u>Comparison</u>	<u>DRI Methadone Metabolite (100/300) Assay</u>	<u>Predicate Device – CEDIA DAU EDDP Assay</u>
<u>Test Principle</u>	<p><u>Homogeneous Enzyme Immunoassay 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.</u></p> <p><u>Direct relationship between drug concentration in urine and enzyme activity.</u></p> <p><u>Enzyme activity is determined spectrophotometric ally at 340 nm by measuring its ability to convert nicotinamide adenine dinucleotide (NAD) to NADH.</u></p>	<p><u>Homogeneous Enzyme Immunoassay based on competition between a drug labeled with β-galactosidase, and free drug from the urine sample for a fixed amount of specific antibody binding sites.</u></p> <p><u>Direct relationship between drug concentration in urine and enzyme activity.</u></p> <p><u>Enzyme activity is determined spectrophotometric ally at 570 nm by measuring its ability to convert CPRG to CPR.</u></p>
<u>Cutoff</u>	<u>100 and 300 ng/mL</u>	<u>100 ng/mL</u>
<u>Matrix</u>	<u>Human urine</u>	<u>Human urine</u>
<u>Reagents</u>	<u>Liquid Ready-to-Use Two reagent assay (R1 and R2)</u>	<u>Lyophilized (reconstitution required) Two reagent assay (R1 and R2)</u>
<u>Calibrators</u>	<u>Liquid ready-to-use (0, 100, 300, 500, 1000 ng/mL)</u>	<u>Liquid ready-to-use (0, 100, 500, 2000 ng/mL)</u>

<u>Comparison</u>	<u>DRI Methadone Metabolite Control</u>	<u>Predicate Device – MGC Select DAU Control Set</u>
<u>Controls</u>	<u>Liquid ready-to-use</u>	<u>Liquid ready-to-use</u>

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

CLSI EP5-A: Evaluation of Precision Performance of Quantitative Measurement Methods

L. Test Principle:

The DRI Methadone Metabolite (100/300) Assay utilizes liquid ready-to-use reagents and calibrators. The assay uses specific antibodies that can detect EDDP in human urine without cross-reactivity to the parent drug methadone. The assay is based on competition between a drug labeled with glucose-6-phosphate dehydrogenase (G6PDH) and free drug from the sample for a fixed number of specific antibody binding sites. In the presence of free drug from the sample, the free drug occupies the antibody binding sites, allowing the drug-labeled G6PDH to interact with the substrate, resulting in enzyme activity. In the absence of free drug from the sample, the specific antibody binds the drug labeled with G6PDH and causes a decrease in enzyme activity. This phenomenon creates a direct relationship between drug concentration in urine and enzyme activity. This enzyme activity is determined spectrophotometrically at 340 nm by measuring its ability to convert nicotinamide adenine dinucleotide (NAD) to NADH.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

An EDDP solution (1 mg/mL) was added to each of four samples obtained from a human urine sample pool to achieve concentrations that span the assay range. The samples were tested for precision in qualitative and semi-quantitative modes. Following a CLSI (EP5A) precision protocol, samples were tested in 2 replicates per run, 2 runs per day for 20 days, total N=80.

Qualitative – 100 cutoff

Drug	Concentration of sample, ng/mL	Number of determinations	Results # Neg / # Pos
EDDP	0	80	80 Neg / 0 Pos
EDDP	50	80	80 Neg / 0 Pos
EDDP	75	80	80 Neg / 0 Pos
EDDP	125	80	0 Neg / 80 Pos
EDDP	225	80	0 Neg / 80 Pos

Qualitative – 300 cutoff

Drug	Concentration of sample, ng/mL	Number of determinations	Results # Neg / # Pos
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Drug	Concentration of sample, ng/mL	Number of determinations	Results # Neg / # Pos
EDDP	0	80	80 Neg / 0 Pos
EDDP	125	80	80 Neg / 0 Pos
EDDP	225	80	80 Neg / 0 Pos
EDDP	375	80	0 Neg / 80 Pos
EDDP	750	80	0 Neg / 80 Pos

Semi-quantitative – 100 cutoff

Drug	Sample Conc., ng/mL	Number of determinations	Result # Neg / # Pos
EDDP	0	80	80/0
EDDP	50	80	80 / 0
EDDP	75	80	80 / 0
EDDP	125	80	0 / 80
EDDP	225	80	0 / 80

Semi-quantitative – 300 cutoff

Drug	Sample Conc., ng/mL	Number of determinations	Result # Neg / # Pos
EDDP	0	80	
EDDP	50	80	80 / 0
EDDP	75	80	80 / 0
EDDP	125	80	80 / 0
EDDP	225	80	80 / 0
EDDP	375	80	0 / 80
EDDP	750	80	0 / 80

b. *Linearity/assay reportable range:*

The assay linearity was determined by testing the recoveries of a series of samples diluted from a high concentration EDDP sample. A high patient urine sample containing around 1000 ng/mL EDDP was serially diluted with analyte-free urine in 10% increments and tested by 5 replicates in semi-quantitative mode. All samples were recovered within $\pm 10\%$ of the expected value and the r-value was 0.9990.

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

Calibrators and controls are tested on Hitachi 917 analyzers by two runs against a reference (primary) set of calibrators and controls, N=5 for all samples. The acceptance criteria require that replicates have rate imprecision less than 1.5% CV, rate difference between the secondary and the primary calibrators and controls must be within 3%, and concentration of the calibrators and controls must be within 10% error of the nominal values by GC/MS. Calibrators and controls are assigned nominal values if validation

results meet acceptance criteria. The assigned values for the calibrators and controls are traceable to the Cerilliant methadone standard catalogue E-022 and are verified by GC/MS. Real time and accelerated stability studies were conducted; protocols and acceptance criteria were described and found to be acceptable. These studies support the manufacturer's stability claims. Real time studies are ongoing.

d. *Detection limit:*

Not applicable. This assay is qualitative and semi-quantitative only. Semiquantitative values should be used to estimate concentration for dilution purposes only.

e. *Analytical specificity:*

The cross-reactivity of parent drug, metabolites, and drugs commonly found in specimens was evaluated by adding known amounts of each substance to methadone metabolite-free urine. A compound producing negative results compared to the 100 ng/mL and 300 ng/mL cutoff calibrator was considered to have no cross-reactivity. The results of the study are presented below.

Methadone, its metabolite, and structurally related compounds produced a negative result at the concentrations listed below.

Compound	Concentration, ng/mL
Methadone	500,000
EMDP	200,000
LAAM	100,000
Nor-LAAM	10,000

Structurally unrelated compounds and/or concurrently used drugs produced a negative result at the concentrations listed below.

Compound	Conc. ng/mL	Compound	Conc. ng/mL
6-AM	500,000	Imipramine	1,000,000
Acetaminophen	1,000,000	Ketamine	400,000
Acetylsalicylic acid	1,000,000	Levorphanol	200,000
Amitriptyline	100,000	Levothyroxine	500,000
Amoxicillin	500,000	Maprotiline	1,000,000
Amphetamine	1,000,000	Meperidine	1,000,000
Benzoyllecgonine	1,000,000	d-Methamphetamine	100,000
Caffeine	100,000	l-Methamphetamine	100,000
Captopril	500,000	Metronidazole	250,000
Carbamazepine	500,000	Morphine	1,000,000
Chlordiazepoxide	100,000	Nalbuphine	1,000,000
Chlorpromazine	100,000	Naloxone	3,000,000
Cimetidine	500,000	Naltrexone	3,000,000
Clomipramine	100,000	Norcodeine	1,000,000
Cocaine	200,000	Normorphine	1,000,000

Codeine	1,000,000	Nortriptyline	500,000
Desipramine	1,000,000	Oxazepam	500,000
Dextromethorphan	30,000	Oxycodone	500,000
Diazepam	30,000	Phencyclidine	50,000
Dihydrocodeine	1,000,000	Phenobarbital	1,000,000
Diphenhydramine	500,000	Phentermine	1,000,000
Disopyramide	1,000,000	Promethazine	100,000
Doxepine	200,000	Propoxyphene	50,000
Doxylamine	500,000	Ranitidine	500,000
Ephedrine	2,000,000	Salicylic acid	500,000
Fentanyl	200,000	Secobarbital	1,000,000
Fluoxetine	1,000,000	Talwin	500,000
Fluphenazine	500,000	11-Nor- Δ^9 -THC-9-COOH	10,000
Heroin	1,000,000	Thebaine	100,000
Hydrocodone	200,000	Thioridazine	150,000
Hydromorphone	200,000	Tramadol	500,000
Ibuprofen	1,000,000		

The potential effect of endogenous and exogenous urine substances, pH, and specific gravity on the recovery of methadone metabolite using DRI Methadone Metabolite (100/300) Assay was assessed by spiking known amounts of potentially interfering substances into the negative and positive levels (\pm 25% of cutoffs of 100 and 300 ng/mL cutoff) for both cutoffs. The compounds were determined to not interfere at the concentrations shown below for the 100 and 300 ng/mL cutoffs:

Compound	Cmpd. Conc.
Acetaminophen	100 ng/mL
Acetone	1 g/dL
Ascorbic acid	250 mg/dL
Aspirin	100 μ g/mL
Caffeine	100 μ g/mL
Creatinine	500 mg/dL
Ethanol	1 g/dL
Galactose	10 mg/dL
γ -globulin	500 mg/dL
Glucose	3 g/dL
Hemoglobin	150 mg/dL
Human serum albumin	500 mg/dL
Ibuprofen	100 μ g/mL
Oxalic Acid	100 mg/dL
pH range	4-11
Specific gravity range	1.004-1.035
Riboflavin	7.5 mg/dL
Sodium chloride	900 mg/dL
Urea	1.25 g/dL

f. *Assay cut-off:*

Analytical performance of the device around the claimed cutoffs is described in precision section (1 a.) above

2. Comparison studies:

a. *Method comparison with predicate device:*

One hundred unaltered clinical specimens were tested using the DRI Methadone Metabolite (100/300) Assay in both the qualitative and semi-quantitative modes, and GC/MS. The results are presented as follows:

Qualitative Stratified Results

DRI	Low Negative by GC/MS (less than -50%)	Near Cutoff Negative by GC/MS (between -50% and cutoff)	Near Cutoff Positive by GC/MS (between cutoff and +50%)	High Positive by GC/MS (greater than +50%)	Percent Agreement with GC/MS
100 ng/mL Cutoff					
Positive	0	1	6	50	93%
Negative	30	9	4	0	98%
300 ng/mL Cutoff					
Positive	0	0	9	30	100%
Negative	50	10	1	0	98%

GC/MS Summary of Discordant Qualitative Results

Cutoff Value (ng/mL)	DRI Result	GC/MS (ng/mL)	Major Drug Present by GC/MS
100	POS	96	EDDP
100	NEG	130	EDDP
100	NEG	131	EDDP
100	NEG	125	EDDP
100	NEG	128	EDDP
300	NEG	310	EDDP

Semi-quantitative Stratified Results

DRI	Low Negative by GC/MS (less than -50%)	Near Cutoff Negative by GC/MS (between -50% and cutoff)	Near Cutoff Positive by GC/MS (between cutoff and +50%)	High Positive by GC/MS (greater than +50%)	Percent Agreement with GC/MS
100 ng/mL Cutoff					
Positive	0	0	9	50	98%
Negative	30	10	*1	0	100%
300 ng/mL Cutoff					
Positive	0	0	10	30	100%
Negative	50	10	0	0	100%

*GC/MS Summary of Discordant Semi-quantitative Results

Cutoff Value (ng/mL)	DRI Result	GC/MS (ng/mL)	Major Drug Present by GC/MS
100	neg	130	EDDP

b. *Matrix comparison:*

Not applicable; this device is for use with urine only.

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.