

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

A. 510(k) Number:

k062123

B. Purpose for Submission:

New product

C. Measurand:

Benzoyllecgonine (cocaine metabolites)

D. Type of Test:

Semi-quantitative and qualitative homogeneous enzyme immunoassay

E. Applicant:

Ortho-Clinical Diagnostic

F. Proprietary and Established Names:

VITROS Chemistry Products COCM Reagent

VITROS Chemistry Products Calibrator Kit 26

VITROS Chemistry Products FS Calibrator 1

VITROS Chemistry Products DAT Performance Verifiers I, II, III, IV, and V

G. Regulatory Information:

1. Regulation section:

21 CFR §862.3250, Cocaine and Cocaine Metabolite 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:

DIO; DKB; DIF

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

See Indications for Use below.

2. Indication(s) for use:

VITROS Chemistry Products COCM Reagent is used on VITROS 5,1 FS Chemistry Systems for the semi-quantitative or qualitative determination of benzoyllecgonine (cocaine metabolites) in human urine using a cutoff of either 150 ng/mL or 300 ng/mL. Measurements obtained with the VITROS COCM method are used in the diagnosis and treatment of benzoyllecgonine use or

overdose.

The VITROS Chemistry Products COCM assay is intended for use by professional laboratory personnel. It provides only a preliminary test result. A more specific alternative chemical method must be used to confirm a result obtained with this assay. Gas chromatography/mass spectrometry (GC/MS) is the preferred confirmatory method. Clinical consideration and professional judgment should be applied to any drug-of-abuse test result, particularly when evaluating a preliminary positive result.

VITROS Chemistry Products Calibrator Kit 26 is used to calibrate VITROS 5,1 FS Chemistry Systems for the qualitative or semi-quantative measurement of the drugs of abuse.

VITROS Chemistry Products FS Calibrator 1 is used in conjunction with VITROS Chemistry Products Calibrator Kits to calibrate VITROS 5,1 FS Chemistry Systems.

VITROS Chemistry Products DAT Performance Verifiers are assayed controls used to monitor performance of urine drugs of abuse screening assays on VITROS 5,1 FS Chemistry Systems.

3. Special conditions for use statement(s):
This device is for prescription use by professional laboratory personnel. For *in vitro* diagnostic use only.
4. Special instrument requirements:
Ortho-Clinical Diagnostics VITROS 5,1 FS Chemistry System

I. Device Description:

The VITROS COCM Reagent is a dual-chambered package containing ready-to-use liquid reagents that are used to detect benzoylecgonine (cocaine metabolite) in urine. Sample, calibrators, and controls are automatically treated with surfactant (DAT Diluent 2) prior to addition of reagents. Treated sample is added to Reagent 1 containing antibody reactive to benzoylecgonine, glucose-6-phosphate and nicotinamide adenine dinucleotide (NAD⁺), followed by Reagent 2 containing benzoylecgonine labeled with the enzyme glucose-6-phosphate dehydrogenase (G6P-DH).

VITROS Chemistry Products Calibrator Kit 26 is prepared from human urine to which drugs of abuse, metabolites of drugs of abuse, organic salts, surfactants and preservative have been added.

VITROS Chemistry Products FS Calibrator 1 is prepared from sodium chloride and processed water.

VITROS DAT Performance Verifiers I, II, III, IV & V are prepared from a human urine pool to which analytes, surfactant and preservative have been added.

The product labeling for the Calibrator Kit 26 and Performance Verifiers contain

warnings regarding the presence of human sourced materials and recommend the use of Universal Precautions when handling these products.

J. Substantial Equivalence Information:

1. Predicate device name(s):
EMIT II Plus Cocaine Metabolite Assay
Liquicheck Urine Toxicology Controls
2. Predicate 510(k) number(s):
k031512; k022707
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	For use in the qualitative and semi-quantitative analysis of methadone in human urine.	Same
Reagent	Liquid, ready to use	Same
Principle	Homogeneous enzyme immunoassay	Same
Matrix	Urine	Same
Antibody	Sheep polyclonal	Same

Differences		
Item	Device	Predicate
Instrumentation	VITROS 5,1 FS Chemistry Systems	Multiple automated clinical chemistry analyzers
Calibrators	Six levels	Five levels
Controls	Five levels	Two levels

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

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples
 CLSI EP5-A: Evaluation of Precision Performance of Clinical Chemistry Devices
 CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures, A Statistical Approach
 CLSI EP7-P: Interference Testing in Clinical Chemistry
 CLSI EP17-A: Protocols for Demonstration, Verification and Evaluation of Limits of Detection and Quantitation
 CLSI EP12-A: User Protocols for Evaluation of Qualitative Test Performance

L. Test Principle:

The VITROS COCM assay is a homogeneous enzyme immunoassay that is performed using the VITROS Chemistry Products COCM Reagent in conjunction with the VITROS Chemistry Products Calibrator Kit 26 and VITROS Chemistry Products FS Diluent Pack 4 (DAT Diluent/DAT Diluent 2) on VITROS 5,1 FS Chemistry Systems.

The assay is based on competition between benzoylecgonine in the treated urine sample and the benzoylecgonine labeled with the enzyme glucose-6-phosphate dehydrogenase (G6P-DH) for antibody binding sites. Enzyme activity decreases upon binding to the antibody, therefore the concentration of benzoylecgonine in the urine sample is directly proportional to measured enzyme activity. Active enzyme converts oxidized nicotinamide adenine dinucleotide (NAD⁺) to NADH, resulting in an absorbance change that is measured spectrophotometrically at 340 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Imprecision was evaluated with human urine-based quality control materials on the VITROS 5,1 FS Chemistry System following CLSI Protocol EP5 and CLSI protocol EP12.

The sponsor cautions that variables such as instrument maintenance, environment, reagent storage/handling, control material reconstitution, and sample handling can affect the reproducibility of test results.

Imprecision for COCM: Semi-Quantitative

System	Conventional Units (ng/mL) and SI Units (µg/L)			Within Lab CV%**	No. Observ.	No. Days
	Mean Conc.	Within Day SD*	Within Lab SD**			
VITROS 5,1 FS	98	4.8	9.4	9.6	86	22
	181	5.6	11.5	6.4	86	22
	227	7.1	13.5	5.9	86	22
	369	10.3	19.2	5.2	84	22
	567	21.0	46.7	8.2	86	22

* Within Day imprecision was determined using one to two runs per day with two replications per run.

** Within Lab imprecision was determined using a single lot of reagents with one analyzer and four calibrations.

Qualitative imprecision was assessed using test fluids targeted at $\pm 25\%$ of each cutoff. The imprecision was determined as the confidence level of obtaining a correct result with known positive or negative fluids.

Imprecision for COCM: Qualitative*

System	Cutoff Level (ng/mL & µg/L)	Test Fluid at $\pm 25\%$ Cutoff	Number of Observations	Number of Correct Interpretations	Confidence Level
VITROS 5,1 FS	150	-25%	86	86	>95% negative reading
	150	+25%	86	86	>95% positive reading
	300	-25%	86	86	>95% negative reading
	300	+25%	84	84	>95% positive reading

* Determined using one to two runs per day with two replicates per run for 22 days, using a single lot of reagents with one analyzer and four calibrations

b. *Linearity/assay reportable range:*

The sponsor followed CLSI EP6-A in determining the linear range of their device. Two urine pools were prepared with benzoylecgonine concentrations at the low (0 ng/mL) and high (1200 ng/mL) end of the calibration range. The two pools were mixed to give 18 admixtures of intermediate concentrations. Linearity was evaluated using three assay reagent lots and comparing the measured results against the expected results from 18 pooled samples. A linear regression was performed and the results indicated acceptable linearity across the benzoylecgonine concentration range tested 47 to 1007 ng/mL. This linearity determination in conjunction with determination of the limit of quantitation was used to establish the semi-quantitative range of the VITROS COCM assay (50-1000 ng/mL).

Recovery study

Eleven admixtures were prepared from two human urine pools. Benzoylecgonine values for the admixtures were calculated based on the gravimetric addition with GC/MS verification of the high pool and the percentage of high pool to the low pool (a drug-free urine based matrix). Percent recovery was calculated using the concentration obtained by the VITROS Chemistry Products COCM Assay versus the calculated benzoylecgonine value.

Recovery of Benzoylecgonine

Benzoylecgonine (ng/mL)	VITROS COCM Assay (ng/mL)	% Recovery
50	57	113.3
100	105	105.1
200	219	109.4
300	316	105.3
400	403	100.6
500	484	96.9
600	593	98.8
700	721	103.0
800	774	96.8
900	880	97.8
1000	998	99.8

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

The assigned values for the calibrators and controls are traceable to the Cerilliant benzoylecgonine standard catalogue B-028 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:*

The limit of quantitation (LOQ) is defined as the minimum amount of analyte whose presence can be quantitatively determined with stated acceptable precision and trueness under defined experimental conditions.

The limit of detection (LOD) is the minimum amount of analyte whose presence can be quantitatively detected under defined conditions. For the VITROS COCM assay, the LOD was determined to be 31 ng/mL. The limit of quantitation (LOQ) was determined to be 50 ng/mL.

e. *Analytical specificity:*

The specificity of the VITROS COCM assay for various cocaine metabolites and structurally similar compounds was estimated by generating a dose response curve for each of the compounds listed below. The quantity (ng/mL) of compound that produces a value equivalent to the benzoylecgonine quantity (ng/mL) at each cutoff value is listed below. The combined effects of more than one compound detected in a sample may cause levels lower than those listed below to produce a value approximately equivalent to or greater than the cutoff value.

Substances that Cross-react with COCM

Compound	Quantity (ng/mL) equivalent to 150 ng/mL of BE	% cross- reactivity *	Quantity (ng/mL) equivalent to 300 ng/mL of BE	% cross- reactivity *
Benzoylecgonine (BE)	150	100.0	300	100.0
m- hydroxybenzoylecgonine	153	98.0	304	98.7
ecognine	4450	3.4	15,325	2
cocaine	39,500	0.4	81,300	0.4
ecognine methyl ester	>100,000	<0.2%	>100,000	<0.3%
cocaethylene	>100,000	<0.2%	>100,000	<0.3%

* The VITROS COCM Assay cutoff value (ng/mL) divided by the amount of cross-reactant (ng/mL) that produces a value equivalent to the cutoff value, multiplied by 100.

The substances listed in the table, at the concentrations shown, were tested according to CLSI Protocol EP7 and found not to interfere (defined by the sponsor as bias <28.7 ng/mL at 150 ng/mL COCM and bias <57.4 ng/mL at 300 ng/mL COCM).

Substances that Do Not Interfere with COCM

Compound	Concentration	
ammonia	570 mg/dL	335 µmol/L
amobarbital	10 mg/dL	442 µmol/L
ascorbic acid	500 mg/dL	28 mmol/L
benzocaine	10 mg/dL	605 µmol/L
bilirubin	26 mg/dL	445 µmol/L
brompheniramine	0.01 mg/dL	313 µmol/L
calcium	30 mg/dL	8 mmol/L
ciprofloxacin	10 mg/dL	300 µmol/L
citric Acid	100 mg/dL	5 mmol/L
cloxacillin	10 mg/dL	229 µmol/L
creatinine	300 mg/dL	27 mmol/L
desipramine HCl	10 mg/dL	330 µmol/L
dextromethorphan	10 mg/dL	369 µmol/L
dicyclomine	10 mg/dL	289 µmol/L
diethylpropione	10 mg/dL	487 µmol/L
doxylamine	10 mg/dL	370 µmol/L
ethacrynic acid	10 mg/dL	330 µmol/L
ethanol	780 mg/dL	169 mmol/L
glucose	4000 mg/dL	222 mmol/L
hemoglobin	500 mg/dL	5 g/L
human IgG	200 mg/dL	2 g/L
human serum albumin	200 mg/dL	2 g/L
imipramine HCl	10 mg/dL	357 µmol/L
indomethacin	10 mg/dL	280 µmol/L
iron	100 µg/dL	18 µmol/L
KCl	1118 mg/dL	150 mmol/L
L-hyoscyamine	10 mg/dL	346 µmol/L

Compound	Concentration	
lidocaine	10 mg/dL	427 µmol/L
magnesium	60 mg/dL	25 mmol/L
meperidine	10 mg/dL	404 µmol/L
methoxyphenamine HCl	10 mg/dL	371 µmol/L
metronidazole	10 mg/dL	584 µmol/L
NaCl	6000 mg/dL	1027 mmol/L
nylidrine HCl	10 mg/dL	334 µmol/L
ofloxacin	10 mg/dL	277 µmol/L
oxalic Acid	300 mg/dL	24 mmol/L
pH = 4	4	4
pH = 9	9	9
phenylbutazone	10 mg/dL	324 µmol/L
phenyltoloxamine	10 mg/dL	392 µmol/L
phosphate	1420 mg/dL	100 mM/L
promethazine	10 mg/dL	312 µmol/L
propranolol HCl	10 mg/dL	338 µmol/L
pyruvate	100 mg/dL	11 mmol/L
ranitidine HCl	10 mg/dL	285 µmol/L
riboflavin	2 mg/dL	53 µmol/L
tolmetin/tolectin	10 mg/dL	389 µmol/L
triethylphenidyl	10 mg/dL	296 µmol/L
trimethobenzamide HCl	10 mg/dL	257 µmol/L
tripelannamine	10 mg/dL	392 µmol/L
triprolidine	10 mg/dL	359 µmol/L
tyramine	10 mg/dL	729 µmol/L
urea	3000 mg/dL	500 mmol/L
uric acid	120 mg/dL	7 mmol/L

f. Assay cut-off:

The stated cutoff of this assay is either 150ng/mL or 300 ng/mL.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 108 human urine samples were assayed using the VITROS Chemistry Products COCM Reagent and a commercially available immunoassay method. Percent agreement was evaluated at assay cutoff values of 150 and 300 ng/mL.

Commercial Method Comparison for COCM

Cutoff Value (ng/mL)		Commercial Method**				%Agreement		
		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	%Agreement Negative	%Agreement Positive	%Agreement Overall
150		(<-50%) <75 ng/mL	(-50% to cutoff) 75-150 ng/mL	(cutoff to +50%) 150-225 ng/mL	(>+50%) >225 ng/mL	97.6%	100.0%	99.1%
	VITROS Positive	0	1*	11	56			
	VITROS Negative	31	9	0	0			
300		(<-50%) <500 ng/mL	(-50% to cutoff) 150-300 ng/mL	(cutoff to +50%) 300-450 ng/mL	(>+50%) >450 ng/mL	100.0%	100.0%	100.0%
	VITROS Positive	0	0	11	38			
	VITROS Negative	41	18	0	0			

* See Summary of Discordant Results below

** Syva® Emit® II Plus Cocaine Metabolite Assay

Summary of Discordant Results: Commercial Method

Cutoff Value (ng/mL)	VITROS COCM Assay (ng/mL)	Commercial Method (ng/mL)
150	154	141

A total of 116 human urine samples were assayed using the VITROS Chemistry Products COCM Reagent and a GC/MS reference method for benzoylecgonine (a cocaine metabolite). Percent agreement was evaluated at assay cutoff values of 150 and 300 ng/mL.

To challenge performance at the 150 ng/mL cutoff value, 34 of the 116 samples tested had concentrations within +/-50% of the cutoff value, 21 samples below the cutoff value and 13 samples above the cutoff value.

To challenge performance at the 300 ng/mL cutoff value, 34 of the 116 samples tested had concentrations within +/-50% of the cutoff value, 25 samples below the cutoff value and 9 samples above the cutoff value

GC/MS Reference Method Comparison for COCM

		GC/MS Reference Method				% Agreement		
Cutoff Value (ng/mL)		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	% Agreement Negative	% Agreement Positive	% Agreement Overall
150		(<-50%) <75 ng/mL	(-50% to cutoff) 75-150 ng/mL	(cutoff to +50%) 150-225 ng/mL	(>+50%) >225 ng/mL	69.1%	96.7%	83.6%
	VITROS Positive	3*	14*	11	48			
	VITROS Negative	31	7	2*	0			
300		(<-50%) <150 ng/mL	(-50% to cutoff) 150-300 ng/mL	(cutoff to +50%) 300-450 ng/mL	(>+50%) >450 ng/mL	76.3%	100.0%	83.6%
	VITROS Positive	2*	17*	9	27			
	VITROS Negative	53	8	0	0			

*See GC/MS Summary of Discordant Results below

Summary of Discordant Results: GC/MS			
Cutoff Value (ng/mL)	VITROS COCM (ng/mL)	GC/MS (ng/mL)	Major Drug Present by GC/MS
150	104	170	benzoylecgonine
	120	187	
	171	142	
	172	131	
	178	90	
	184	81	
	184	61	
	184	134	
	185	61	
	191	119	
	199	104	
	204	97	
	217	126	
	234	146	
	250	117	
	267	92	
	276	134	
	314	76	
	442	62	
300	314	76	benzoylecgonine
	323	184	
	350	299	
	368	277	
	373	290	

Summary of Discordant Results: GC/MS			
Cutoff Value (ng/mL)	VITROS COCM (ng/mL)	GC/MS (ng/mL)	Major Drug Present by GC/MS
	377	169	
	393	253	
	423	232	
	434	299	
	441	235	
	442	62	
	445	181	
	452	259	
	479	221	
	531	224	
	555	186	
	575	214	
	788	243	
	>1000	296	

- 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.