

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

A. 510(k) Number:

k062460

B. Purpose for Submission:

New device

C. Measurand:

Opiates

D. Type of Test:

Qualitative and semi-quantitative enzyme immunoassay

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products OP Reagent
VITROS Chemistry Products Calibrator 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 862.3650 Opiate test system
21 CFR 862.3200, Clinical Toxicology Calibrator
21 CFR 862.3180, Clinical Toxicology Control

2. Classification:

II (reagent, calibrator)
I, reserved (control)

3. Product code:

DJG, DKB and DIF

4. Panel:

Toxicology (91)

H. Intended Use:

1. Intended use(s):

See Indications for use.

2. Indication(s) for use:

VITROS Chemistry Products OP Reagent: For in vitro diagnostic use only. VITROS Chemistry Products OP Reagent is used on VITROS 5,1 FS Chemistry Systems for the semi-quantitative or qualitative determination of opiates (OP) in human urine using a cutoff of either 300 ng/mL or 2000 ng/mL. Measurements obtained with the VITROS OP method are used in the diagnosis and treatment of opiate use or overdose.

The VITROS Chemistry Products OP 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 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: For in vitro diagnostic use only. VITROS Chemistry Products Calibrator Kit 26 is used to calibrate VITROS 5,1 FS Chemistry Systems for the qualitative or semi-quantitative measurement of drugs of abuse.

VITROS Chemistry Products DAT Performance Verifiers I, II, III, IV & V: For in vitro diagnostic use only. 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):

For 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 Chemistry Products OP Reagent is a dual chambered reagent pack containing two ready-to-use liquid reagents. The reactive ingredients in Reagent 1 include sheep polyclonal antibodies reactive to morphine, Glucose 6-phosphate and

Nicotinamide adenine nucleotide (NAD). The other ingredients in Reagent 1 include inorganic salt, organic salt, proteins, inorganic polymer, protease inhibitor, stabilizer, surfactant and preservative. The reactive ingredients in Reagent 2 include morphine labeled with glucose-6-phosphate dehydrogenase. The other ingredients in Reagent 2 include buffers, organic salt, inorganic salt, proteins, inorganic polymer, protease inhibitor, biological material, surfactant and preservatives.

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 DAT Performance Verifiers I, II, III, IV & V are prepared from a human urine pool to which analytes, surfactant and preservative have been added. These are assayed controls used to monitor performance of the VITROS PCP Reagent on VITROS 5,1 FS Chemistry Systems.

The product labeling for Calibrator Kit 26 and Performance Verifiers contain warnings regarding the presence of human source materials and recommend the use of Universal Precautions when handling these products.

J. Substantial Equivalence Information:

1. Predicate device name(s):
 Syva EMIT II Plus Opiate assay
 Bio-Rad Liquicheck Urine Toxicology Controls
2. Predicate 510(k) number(s):
 k011289
 k022707
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	For use in the qualitative and semi-quantitative analysis of opiates 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	Qualitative: two levels Semi-quantitative: four 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 OP assay is a homogenous immunoassay based on the competition between morphine in the treated urine sample and morphine 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 morphine 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
 - a. Precision/Reproducibility:
 Precision was evaluated with quality control materials on the VITROS 5,1 FS Chemistry System following CLSI EP5-A. The samples were run in duplicate, twice a day for twenty-two days using two reagent lots and four instruments. The results are presented in the table below.

Semi-quantitative-LO (300)					
Mean Conc. ng/mL	Within-Day SD	Within-Lab SD	Within-Lab %CV	No. Observations	No. Days
213	5.1	10.5	4.9	88	22
294	5.4	12.4	4.2	88	22
371	5.5	14.5	3.9	88	22

Semi-quantitative-HI (2000)					
Mean Conc. ng/mL	Within-Day SD	Within-Lab SD	Within-Lab %CV	No. Observations	No. Days
1459	24.1	65.2	4.5	88	22
1995	37.3	88.0	4.4	80	20
2441	46.4	112.9	4.6	88	22
2901	62.7	139.2	4.8	88	22

Qualitative imprecision was assessed using drug-spiked human urine pools with concentrations targeted at approximately $\pm 25\%$ of the 300 and 2000 ng/mL cutoff concentrations. The concentrations of the targeted test fluids were confirmed by GC/MS. The sponsor performed two runs per day with two replicates per run for 22 days using a single lot of reagent on one analyzer. The results are presented below:

Qualitative				
Cutoff ng/mL	Test Fluid Concentration ng/mL	Test Fluid % of Cutoff	No. Observations	No. of Correct Results
300	213	-25% of the cutoff	88	88
300	371	+25% of the cutoff	88	88

Qualitative				
Cutoff ng/mL	Test Fluid Concentration ng/mL	Test Fluid % of Cutoff	No. Observations	No. of Correct Results
2000	1459	-25% of the cutoff	88	88
2000	2441	+25% of the cutoff	88	88

- b. Linearity/assay reportable range:
The sponsor followed CLSI EP6-A in determining the linear range of their device.

Number of reagent lots: 3

Replicates of each solution: 3

OP-LO (300 ng/mL)

Two urine pools were prepared with a high urine based morphine pool (4000 ng/mL) and a negative urine based pool (0 ng/mL). The two pools were mixed to give 16 admixtures of intermediate concentrations. Linearity was evaluated using three assay reagent lots and comparing the measured results against the expected results from 16 pooled samples. A linear regression was performed and the results indicated acceptable linearity across the concentration range tested (69 to 1009 ng/mL). The claimed reportable range of the VITROS OP-LO assay is 100 - 900 ng/mL.

OP-HI (2000 ng/mL)

Two urine pools were prepared with a high urine based morphine pool (5000 ng/mL) and a negative urine based pool (0 ng/mL). The two pools were mixed to give 11 admixtures of intermediate concentrations. Linearity was evaluated using three assay reagent lots and comparing the measured results against the expected results from 11 pooled samples. A linear regression was performed and the results indicated acceptable linearity across the concentration range tested (503 to 4000 ng/mL). The claimed reportable range of the VITROS OP-HI assay is 700 - 4000 ng/mL.

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

The assigned values for the calibrators are traceable to the Cerilliant morphine standard catalogue M-109 and are verified by GC/MS.

The assigned values for the controls are traceable to USP 14447002 (Morphine Monohydrate CII). They are prepared through gravimetric addition to drug free urine and 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 for the following products:

Reagent	Storage	Stability*
Unopened	2-8°C	5 months
Opened	On board analyzer, system turned off	≤28 days
Opened	On board analyzer, system turned on	≤30 minutes

Calibrator	Storage	Stability*
Unopened	≤18°C	8 months
Opened	2-8°C	4 weeks

Controls	Storage	Stability*
Unopened	2-8°C	6 months
Opened	2-8°C	4 weeks.

*Note: Real time studies are ongoing.

d. Detection limit:

The detection limit was determined according to protocol recommendations in CLSI EP-17 on three different lots of reagent and one instrument platform. The claimed lowest detectable limit for VITROS OP-LO is 97 ng/mL. The claimed lowest detectable limit for VITROS OP-HI is 338 ng/mL.

e. Analytical specificity:

The sponsor conducted interference studies following CLSI EP7-A2. The substances listed in the table below were determined not to interfere in the concentration tested at 300 ng/mL morphine and 2000 ng/mL morphine cutoffs, up to the concentrations shown:

Compound	Concentration Tested	
	Conventional	SI
ammonia	570 mg/dL	316 mmol/L
ascorbic Acid	500 mg/dL	28.4 mmol/L
Bilirubin	26 mg/dL	444 µmol/L
buprenorphine	5 mg/dL	106 µmol/L
Calcium	30 mg/dL	7.5 mmol/L
ciprofloxacin	10 mg/dL	302 µmol/L

Compound	Concentration Tested	
	Conventional	SI
citric acid	100 mg/dL	5.2 mmol/L
Cloxacillin	10 mg/dL	230 µmol/L
creatinine	300 mg/dL	26.5 mmol/L
Diethylpropione	10 mg/dL	487 µmol/L
ethacrylnic 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
Indomethacin	10 mg/dL	279 µmol/L
Iron	0.1 mg/dL	17.9 µmol/L
Magnesium	60 mg/dL	24.7 mmol/L
Methoxyphenamine	10 mg/dL	558 µmol/L
Metronidazole	10 mg/dL	584 µmol/L
Nylidrine	10 mg/dL	334 µmol/L
Oxalic acid	300 mg/dL	23.8 mmol/L
pH = 4		
pH = 9		
Phenylbutazone	10 mg/dL	324 µmol/L
Phosphate	950 mg/dL	100 mmol/L
Potassium	587 mg/dL	150 mmol/L
Propoxyphene	10 mg/dL	295 µmol/L
Propanolol	10 mg/dL	385 µmol/L
Pyruvate	200 mg/dL	22.8 mmol/L
Ranitidine	10 mg/dL	318 µmol/L
Riboflavin	2 mg/dL	53 µmol/L
Tolmetin/tolectin	10 mg/dL	390 µmol/L
Trihexylphenidyl	10 mg/dL	332 µmol/L
Trimethobenzamide	10 mg/dL	257 µmol/L
Tyramine	10 mg/dL	576 µmol/L
Urea	3000 mg/dL	499.5 mmol/L
Uric acid	120 mg/dL	7.14 mmol/L

The sponsor determined that a high specific gravity does not interfere with the assay by evaluating the primary causes of high specific gravity: high concentrations of NaCl, protein, and glucose in urine.

The specificity of VITROS OP assay for morphine and structurally similar compounds was determined by generating a dose response curve for each of the compounds and determining the approximate quantity of each compound that is equivalent in assay reactivity to the 300 ng/mL and 2000 ng/mL

cutoffs.

Compound	Quantity equivalent to 300 ng/mL	Approx. % Cross-reactivity	Quantity equivalent to 2000 ng/mL	Approx. % Cross-reactivity
Ethylmorphine	165	181.8%	1175	170.2%
Codeine	190	157.9%	950	210.5%
Hydrocodone	240	125%	1510	132.5%
Dihydrocodeine	250	120%	1420	140.8%
Morphine	300	100%	2000	100%
Thebaine	400	75%	2900	69%
Hydromorphone	420	71.4%	4100	48.8%
6-acetyl morphine	430	69.8%	3920	51%
Heroin (diacetylmorphine)	490	61.2%	3850	51.9%
Dihydromorphone	535	56.1%	6025	33.2%
Levorphanol	550	54.5%	10800	18.5%
Morphine-3-glucuronide	700	42.9%	11100	18%
Oxycodone	2175	13.8%	56500	3.5%
Norcodeine	2840	10.6%	50000	4%
Nalorphine	10025	3%	290000	0.7%
Oxymorphone	12600	2.4%	>200000	<1%
Normorphine	24000	1.3%	458000	0.4%
Meperidine	33500	0.9%	459000	0.4%
Naloxone	466000	0.1%	>1000000	<0.2%
Fluphenazine	>100,000	<0.3%	>1000000	>0.2%

f. Assay cut-off:

There are two cutoffs for this assay: 300 ng/mL and 2000 ng/mL. The 2000 ng/mL cutoff concentration is currently recommended by the Substance Abuse and Mental Health Services Administration (SAMHSA).

Characterization of how the device performs analytically around the claimed cutoff concentrations appear in the precision section, above.

2. Comparison studies:

a. Method comparison to the predicate device

The results obtained on the new device were compared to the reference method, Gas Chromatography/Mass Spectrometry, and a commercially marketed (predicate) device. Results are summarized below:

OP-LO 300 ng/mL cutoff

One hundred and eighteen unaltered human urine samples were assayed on the device and the results were compared to GC/MS. The results are corrected for cross-reactivity.

Comparison of VITROS OP-LO to GC/MS is presented in the following table.

Cutoff ng/mL		<50% <150 ng/mL	-50% to cutoff 150-300 ng/mL	Cutoff to +50% 300-450 ng/mL	>+50% >450 ng/mL	% Agreement Negative	% Agreement Positive	% Agreement Overall
300	VITROS +	0	2*	9	55	95.8	91.4	93.2
	VITROS -	29	17	5*	1*			

*The summary of discordant results is presented in the table below:

Discordant Results		
Cutoff ng/mL	VITROS OP-LO ng/mL	GC/MS ng/mL
300	333	268 Morphine
	303	277 Morphine
	295	311 Morphine
	277	331 Morphine
	270	368 Morphine
	282	376 Morphine
	296	313 Morphine 69 Hydromorphone
	280	463 Morphine

OP-HI 2000 ng/mL cutoff

One hundred and fifty three unaltered human urine samples were assayed on the device and the results were compared to GC/MS. The results are corrected for cross-reactivity.

Comparison of VITROS OP-HI to GC/MS is presented in the following table.

Cutoff ng/mL		<50% <1000 ng/mL	-50% to cutoff 1000-2000 ng/mL	Cutoff to +50% 2000-3000 ng/mL	>+50% >3000 ng/mL	% Agreement Negative	% Agreement Positive	% Agreement Overall
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Cutoff ng/mL		<50% <1000 ng/mL	-50% to cutoff 1000-2000 ng/mL	Cutoff to +50% 2000-3000 ng/mL	>+50% >3000 ng/mL	% Agreement Negative	% Agreement Positive	% Agreement Overall
2000	VITROS +	1*	1*	5	35	98.1	81.6	92.8
	VITROS -	87	15	8*	1*			

*The summary of the discordant results is presented in the table below:

Discordant Results		
Cutoff ng/mL	VITROS OP-HI ng/mL	GC/MS ng/mL
2000	2669	421 Morphine
	3986	720 Hydrocodone 971 Hydromorphone
	1296	2090 Morphine
	1428	2330 Morphine
	1668	2373 Morphine
	1292	2425 Morphine
	1270	2612 Morphine
	1898	2593 Morphine 113 Hydromorphone
	1797	2690 Morphine
	1605	2826 Morphine
	1653	3440 Morphine

The sponsor notes that the primary form of morphine in urine is morphine-3-glucuronide, a morphine conjugate. The VITROS Chemistry Product OP Assay has lower recovery with morphine conjugates than with free morphine. As part of sample preparation for GC/MS analysis, morphine conjugates are commonly hydrolyzed to morphine. This may lead to an apparent under-recovery of opiates when comparing VITROS OP Assay results to GC/MS.

OPI-LO 300 ng/mL cutoff

One hundred and twenty one human urine samples were assayed on the device and were compared to results from the predicate device.

Comparison of VITROS OP-LO to the Predicate Device is presented in the following table.

Cutoff ng/mL		<50% <150 ng/mL	-50% to cutoff 150-300 ng/mL	Cutoff to +50% 300-450 ng/mL	>+50% >450 ng/mL	% Agreement Negative	% Agreement Positive	% Agreement Overall
300	VITROS +	0	0	5	63	100	93.2	95.9
	VITROS -	27	21	5*	0			

*The summary of discordant results is presented in the table below.

Discordant Results		
Cutoff ng/mL	VITROS OP-LO ng/mL	Predicate Assay ng/mL
300	251	321
	261	304
	284	333
	295	399
	296	414

OPI-HI: 2000 ng/mL cutoff

One hundred and fifty five human urine samples were assayed on the device and were compared to results from the predicate device.

Comparison of VITROS OP-HI to the Predicate Device are presented in the following table.

Cutoff ng/mL		<50% <1000 ng/mL	-50% to cutoff 1000-2000 ng/mL	Cutoff to +50% 2000-3000 ng/mL	>+50% >3000 ng/mL	% Agreement Negative	% Agreement Positive	% Agreement Overall
2000	VITROS +	0	1*	8	34	99.1	91.3	96.8
	VITROS -	77	31	4*	0			

The summary of the discordant results is presented in the table below.

Discordant Results		
Cutoff ng/mL	VITROS OP-HI ng/mL	Predicate ng/mL
2000	1653	2107
	1797	2135
	1898	2472
	1993	2098
	2005	1966

b. Matrix comparison:

Not applicable

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.