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

A. 510(k) Number:

k062165

B. Purpose for Submission:

New device

C. Measurand:

Barbiturates

D. Type of Test:

Qualitative and semi-quantitative enzyme immunoassay

E. Applicant:

Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:

VITROS Chemistry Products BARB 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 862.3150, Barbiturates test system
   21 CFR 862.3200, Clinical Toxicology Calibrator
   21 CFR 862.3180, Clinical Toxicology Control
2. Classification:
   Class II, (reagent, calibrator)
   Class I, reserved (control)
3. Product code:
   DIS, DLJ 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 BARB Reagent: For in vitro diagnostic use only. VITROS Chemistry Products BARB Reagent is used on VITROS 5,1 FS Chemistry Systems for the semi-quantitative or qualitative determination of barbiturates (BARB) in human urine using a cutoff of 200 ng/mL or 300 ng/mL. Measurements obtained with the VITROS BARB method are used in the diagnosis and treatment of barbiturates use or overdose.

   The VITROS Chemistry Products BARB 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 Chromatograpy/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. VITROSChemistry 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 BARB Reagent consists of two dual chambered reagent packs containing two ready-to-use liquid reagents. The reactive ingredients in Reagent 1 include sheep polyclonal antibodies reactive to secobarbital, Glucose 6-phosphate and Nicotinamide adenine nucleotide (NAD). The other ingredients in Reagent 1 include inorganic salt, organic salt, inorganic polymer, protease inhibitor, surfactant and preservative. The reactive ingredients in Reagent 2 include secobarbital labeled with glucose-6-phosphate dehydrogenase. The other ingredients in Reagent 2 include buffers, organic salt, inorganic salt, proteins, protease inhibitors, 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 Chemistry Products FS Calibrator 1 is prepared from sodium chloride and processed water. These products are used to calibrate VITROS 5,1 FS Chemistry Systems for the qualitative and semi-quantitative measurement of barbiturates (BARB).

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 VITROS BARB Reagent on VITROS 5,1 FS Chemistry Systems.

The product labeling for the calibrator and controls 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):
   Syva EMIT II Plus Barbiturate assay
   Bio-Rad Liquicheck Urine Toxicology Controls

2. Predicate 510(k) number(s):
   k993987
   k022707

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	For use in the semi-quantitative or qualitative determination of barbiturates 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	6 levels	Qualitative: 3 levels Semi-quantitative: 5 levels
Controls: Number of levels	5 levels	Two levels

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

CSLI 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 BARB assay is a homogenous immunoassay based on the competition between barbiturates in the treated urine sample and secobarbital 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 barbiturates 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:

   Semi-quantitative precision was assessed with quality control materials on the VITROS 5,1 FS Chemistry System following CLSI Protocol EP5 and EP12. The samples were run in duplicate, twice a day for twenty-two days using two reagent lots and four instruments. Each run consisted of five control fluids to assess assay imprecision at approximately ± 25% of the 200 and 300 ng/mL cutoff concentrations. The results are presented in the table below.

Mean Conc. ng/mL	Within-Day SD	Within-Lab SD	Within-Lab %CV	No. Observations
143	6.8	10.3	7.2	86
215	6.0	10.5	4.9	84
240	6.2	11.5	4.8	86
378	7.9	14.1	3.7	84
632	12.8	20.5	3.2	86

Qualitative imprecision was assessed using drug-spiked human urine pools with concentrations targeted at approximately ± 25% of the 200 and 300 ng/mL cutoff concentrations. The concentrations of the targeted test fluids were confirmed by GC/MS. The sponsor performed one to 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:

Cutoff ng/mL	Test Fluid Concentration ng/mL	No. Observations	Number of Correct Results
200	143	86	86/86
200	240	86	86/86
300	215	84	84/84
300	378	84	84/84

b. Linearity/assay reportable range:

The sponsor followed CLSI EP6-A: "Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline" in determining the linear range of their device.

Number of reagent lots: 3
Replicates of each solution: 3

Two urine pools were prepared with barbiturate concentrations at the low (0 ng/mL) and high (1000 ng/mL) end of the calibration range. The two pools were mixed to give 13 admixtures of intermediate barbiturate concentrations. Linearity was evaluated using three assay reagent lots and comparing the measured results against the expected results from 13 pooled samples. A linear regression was performed and the results indicated acceptable linearity across the concentration range tested (3 – 890 ng/mL). The claimed reportable range of the VITROS BARB assay is 60 - 800 ng/mL.

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

The assigned values for the calibrators and controls are traceable to the Cerillant secobarbital standard catalogue S-005 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 sponsor's stability claims for the following products:

Reagent	Storage	Stability*
Unopened	2-8˚C	12 months
Opened	On board analyzer, system tu	≤14 days
Opened	On board analyzer, system tu	≤30 minutes

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

Controls	Storage	Stability*

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

*NOTE: Real time stability 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 lower limit for VITROS BARB assay is 60 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 two secobarbital concentrations tested, 200 and 300 ng/mL, up to the concentrations shown:

Compound	Concentration Tested	
	Conventional	SI
Ammonia	570 mg/dL	334.6 µmol/L
Ascorbic Acid	500 mg/dL	28.4 mmol/L
Bilirubin	26 mg/dL	444.6 µmol/L
Brompheniramine	100,000 ng/mL	313.2 µmol/L
Calcium	30 mg/dL	7.5 mmol/L
Ciprofloxacin	100,000 ng/mL	300.3 µmol/L
Citric acid	100 mg/dL	5.2 mmol/L
Cloxacillin	100,000 ng/mL	229.4µmol/L
creatinine	300 mg/dL	26.5 mmol/L
Desipramine	100,000 ng/mL	330.2 µmol/L
dextromethorphan	100,000 ng/mL	368.5 µmol/L
Dicyclomine	100,000 ng/mL	289.1 µmol/L
Dipethylpropione	100,000 ng/mL	487.1 µmol/L
Doxylamine	100,000 ng/mL	369.8 µmol/L
Ethacrylnic acid	100,000 ng/mL	329.9 µmol/L
Ethanol	780 mg/dL	169.3 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 album	200 mg/dL	2 g/L
Imipramine	10 mg/dL	357 µmol/L
Indomethacin	10 mg/dL	280 µmol/L

Compound	Concentration Tested	
	Conventional	SI
Iron	100 ug/dL	18 µmol/L
KCl	1118 mg/dL	150 mmol/L
l-hyoscyamine	10 mg/dL	346 µmol/L
Magnesium	60 mg/dL	24.7 mmol/L
Meperidine	10 mg/dL	404 µmol/L
Methoxyphenamine	10 mg/dL	558 µmol/L
Metronidazole	10 mg/dL	584 µmol/L
NaCl	6000 mg/dL	1027 mmol/L
Nylidrine	10 mg/dL	334 µmol/L
Ofloxacin	10 mg/dL	277 µmol/L
Oxalic acid	300 mg/dL	24 mmol/L
pH = 4		
pH = 9		
Phenytoloxamine	10 mg/dL	392 µmol/L
Phenylbutazone	10 mg/dL	324 µmol/L
Phosphate	1420 mg/dL	100 mmol/L
Promethazine	10 mg/dL	312 µmol/L
Propanolol	10 mg/dL	386 µmol/L
Pyruvate	100 mg/dL	11 mmol/L
Riboflavin	2 mg/dL	53 µmol/L
Tolmetin/tolectin	10 mg/dL	389 µmol/L
Trihexylphenidyl	10 mg/dL	296 µmol/L
Trimethobenzamide	10 mg/dL	257 µmol/L
Tripelannamine	10 mg/dL	392 µmol/L
Triprolidine	10 mg/dl	359 µmol/L
Tyramine	10 mg/dL	576 µmol/L
Urea	3000 mg/dL	500 mmol/L
Uric acid	120 mg/dL	7 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 BARB assay for common barbiturates 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 a secobarbital 200 ng/mL and 300 ng/mL cutoff.

Compound	Conc. equivalent to 200 ng/mL	Approx. % Cross-reactivity	Conc. equivalent to 300 ng/mL	Approx. % Cross-reactivity
Alphenal	100	200	230	130.2
Talbutal	188	106.7	311	96.5
Secobarbital	200	100	300	100
Aprobarbital	219	91.4	415	72.3
Butabarbital	238	84.2	472	63.5
Butalbital	263	76.2	472	63.5
Pentobarbital	281	71.1	472	63,5
Cyclopentobarbital	350	57.1	611	49.1
Butobarbital	375	53.3	864	34.7
Amobarbital	450	44.4	922	32.6
Allobarbital	563	35.6	1152	26.0
Phenobarbital	1000	20	3456	8.7
Barbital	1875	10.7	6106	4.9
5-ethyl-5-(4-hydroxyphenyl) barbituric acid	2250	8.9	9792	3.1
Thiopental	6250	3.2	40320	0.7

f. Assay cut-off:

There is a description of the analytical performance of the device around the 200 ng/mL and 300 ng/mL cutoffs in section M.1.d. The test is designed to yield a positive result when the drug exceeds these cutoff concentrations in the urine sample.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 102 human urine samples were assayed using the VITROS Chemistry Products BARB Reagent and GC/MS reference method. Percent agreement was evaluated at assay cutoff values of 200 ng/mL and 300ng/mL.

GC/MS Reference Method Comparison for BARB

		Commercial Method				%Agreement		
Cutoff Value (ng/mL)		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	%Agreement Negative	%Agreement Positive	%Agreement Overall
200		(<-50%) <100 ng/mL	(-50% to cutoff) 100-200 ng/mL	(cutoff to +50%) 200-300 ng/mL	(>+50%) >300 ng/mL	68.4	100.0	82.4
	VITROS Positive	0	18	18	27			
	VITROS Negative	27	12	0	0			
300		(<-50%) <150 ng/mL	(-50% to cutoff) 150-300 ng/mL	(cutoff to +50%) 300-450 ng/mL	(>+50%) >450 ng/mL	73.3	100.0	80.4
	VITROS Positive	1	19	11	16			
	VITROS Negative	41	14	0	0			

Summary of Discordant Samples: GC/MS

200 ng/mL Cutoff	VITROS BARB Assay (ng/mL)	GC/MS Reference Method (ng/mL)
	203	369 phenobarbital
	208	408 phenobarbital
	203	434 phenobarbital
	204	451 phenobarbital
	212	496 phenobarbital
	201	520 phenobarbital
	203	663 phenobarbital
	213	803 phenobarbital
	376	119 butalbital
	352	170 butalbital
	276	177 butalbital
	286	185 butalbital
	327	215 butalbital
	305	221 butalbital
	369	224 butalbital
	351	236 butalbital
	341	248 butalbital
	369	253 butalbital

Summary of Discordant Samples: GC/MS

300 ng/mL Cutoff	VITROS BARB Assay (ng/mL)	GC/MS Reference Method (ng/mL)
	376	119 butalbital
	352	170 butalbital
	327	215 butallbital
	305	221 butalbital
	369	224 butalbital
	351	236 butalbital
	341	248 butalbital
	369	253 butalbital
	334	308 butalbital
	381	322 butalbital

	VITROS BARB Assay (ng/mL)	GC/MS Reference Method (ng/mL)
	325	322 butalbital
	322	1731 butalbital
	309	331 butalbital
	376	101 butalbital & 236 phenobarbital
	341	366 butalbital
	390	374 butalbital
	449	392 butalbital
	322	123 butalbital & 419 phenobarbital
	419	453 butalbital
	408	464 butalbital

A total of 102 unaltered human urine samples were assayed on the device and a commercially available immunoassay method for barbiturates. Percent agreement was evaluated at assay cutoff values of 200 and 300 ng/mL. To challenge performance at the 200 ng/mL cutoff value, 25 of the 102 samples tested had concentrations within +/- 50% of the cutoff value, 10 samples below the cutoff value and 15 above the cutoff value. To challenge performance at the 300 ng/mL cutoff value, 54 of the 102 samples tested had concentrations within +/- 50% of the cutoff value, 25 samples below the cutoff value and 29 above the cutoff value.

Commercial Method Comparison for BARB

		Commercial Method				%Agreement		
Cutoff Value (ng/mL)		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	%Agreement Negative	%Agreement Positive	%Agreement Overall
200		(<-50%) <100 ng/mL	(-50% to cutoff) 100-200 ng/mL	(cutoff to +50%) 200-300 ng/mL	(>+50%) >300 ng/mL	100.0	94.0	96.1
	VITROS Positive	0	0	11	52			
	VITROS Negative	25	10	4	9			
300		(<-50%) <150 ng/mL	(-50% to cutoff) 150-300 ng/mL	(cutoff to +50%) 300-450 ng/mL	(>+50%) >450 ng/mL	100.0	90.4	95.1
	VITROS Positive	0	0	24	23			
	VITROS Negative	25	25	5	0			

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.