

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

A. 510(k) Number:

k063164

B. Purpose for Submission:

New device

C. Measurand:

Cannabinoids in urine

D. Type of Test:

Homogenous enzyme immunoassay with associated calibrators and controls

E. Applicant:

Ortho Clinical Diagnostics, inc.

F. Proprietary and Established Names:

Vitros Chemistry Products THC Reagent

VITROS Chemistry Products Calibrator Kit 30

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 862.3870 Cannabinoid test system

21 CFR 862.3200 Clinical toxicology calibrator

21 CFR 862.3280 Clinical toxicology control material

2. Classification:

Reagent and calibrators are Class II, control materials are class I

3. Product code:

THC reagent: LDJ – Enzyme immunoassay, cannabinoids

Calibrator kit 30: DLJ – Calibrators drug specific

Calibrator 1: DKB – Calibrators drug mixture

Control material: DIF - Drug mixture control materials

4. Panel:

91 - toxicology

H. Intended Use:

1. Intended use(s):

See indications for use below.

1. Indication(s) for use:

VITROS Chemistry Products THC Reagent: For *in vitro* diagnostic use only. VITROS Chemistry Products THC Reagent is used on VITROS 5,1 FS Chemistry Systems for the semi-quantitative or qualitative determination of cannabinoids (THC) in human urine using a cutoff of either 20 ng/mL or 50 ng/mL. Measurements obtained with the VITROS THC method are used in the diagnosis and treatment of cannabinoid use or overdose.

The VITROS Chemistry Products THC 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 30: For *in vitro* diagnostic use only. VITROS Chemistry Products Calibrator Kit 30 is used to calibrate VITROS 5,1 FS Chemistry Systems for the qualitative or semi-quantitative measurement of cannabinoids (THC).

VITROS Chemistry Products FS Calibrator 1: For *in vitro* diagnostic use only. 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 I, II, III, IV and 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 prescription use only

4. Special instrument requirements:

VITROS 5,1 FS Chemistry System

I. Device Description:

The VITROS THC assay is a homogeneous enzyme immunoassay that is performed using the VITROS THC Reagent with the VITROS Calibrator Kit 30, VITROS FS Calibrator 1 and VITROS FS Diluent Pack 4 (DAT Diluent / DAT Diluent 2) on VITROS 5,1 FS Chemistry Systems. The VITROS THC Reagent is a dual chambered package containing ready-to-use liquid reagents that are used to detect cannabinoids 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 antibodies reactive to delta-9-tetrahydrocannabinol (delta-9-THC), glucose-6-phosphate and nicotinamide adenine dinucleotide (NAD⁺), followed by Reagent 2 containing delta-9-THC labeled with the enzyme glucose-6-phosphate dehydrogenase (G6P-DH). The assay is based on competition between delta 9-THC metabolites in the treated urine sample and the delta 9 -THC 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 delta-9-THC metabolites 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.

VITROS Calibrator Kit 30 is prepared from human urine to which analyte, surfactant, and preservatives have been added. The VITROS FS Calibrator 1 is composed of processed water and 0.9% w/v sodium chloride (Saline). These calibrators are used to calibrate VITROS 5,1 FS Chemistry Systems for the qualitative or semiquantitative measurement of cannabinoids (THC).

VITROS DAT Performance Verifiers I, II, III, IV and 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 THC assay on VITROS 5,1 FS Chemistry Systems.

J. Substantial Equivalence Information:

1. Predicate device name(s):

SYVA® EMIT® II Plus Cannabinoid Assay

BIO-RAD® Liquechek™ Urine Toxicology Controls

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

k011300, k022707 respectively

3. Comparison with predicate:

Similarities		
Item	VITROS THC assay (device)	SYVA EMIT II Plus Cannabinoid assay and Liquechek Controls (predicate)
Test Principle	Homogeneous enzyme immunoassay	Homogeneous enzyme immunoassay
Sample Type	Human Urine	Human Urine
Reagent Format	Liquid ready to use	Liquid ready to use
Antibody	Monoclonal anti delta 9-tetrahydrocannabinol	Monoclonal anti delta 9-tetrahydrocannabinol
Calibrator	11-nor-delta-9-THC-9-COOH in human urine	11-nor-delta-9-THC-9-COOH in human urine
Calibrator and control format	Refrigerated: Liquid, ready to use	Refrigerated: Liquid, ready to use
Control Matrix	Human urine	Human urine

Differences		
Item	VITROS THC assay (device)	SYVA EMIT II Plus Cannabinoid assay and Liquechek Controls (predicate)
Number of Calibrators	Six	Three for Qualitative Four for Semi-Quantitative
Instrumentation	VITROS 5,1 FS Chemistry Systems	Multiple clinical chemistry systems

Differences		
Item	VITROS THC assay (device)	SYVA EMIT II Plus Cannabinoid assay and Liquichek Controls (predicate)
Cutoff Values	20 and 50 ng/mL	20, 50, and 100 ng/mL
Control claimed analytes	Cocaine metabolites (benzoylecgonine), benzodiazepines (lormetazepam), methadone, amphetamines (dmethamphetamine), Opiates (morphine), cannabinoids (11-nor-delta-9-THC-9-COOH), phencyclidine and barbiturates (secobarbital).	Methamphetamine, secobarbital, lormetazepam, Tetrahydrocannabinol(THC), benzoylecgonine, ethanol, lysergic acid diethylamide (LSD), methadone, methaqualone, morphine, (Free), phencyclidine, propoxyphene, nortriptyline and addition of creatinine, pH, specific gravity.
Control: Number of levels	Five	Two

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

Not applicable

L. Test Principle:

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 antibodies reactive to delta-9-tetrahydrocannabinol (delta-9-THC), glucose-6-phosphate and nicotinamide adenine dinucleotide (NAD+), followed by Reagent 2 containing delta-9-THC labeled with the enzyme glucose-6-phosphate dehydrogenase (G6P-DH). The assay is based on competition between delta-9-THC metabolites in the treated urine sample and the delta-9-THC 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 delta-9-THC metabolites 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:*

The evaluation was conducted on the VITROS 5,1 FS Chemistry System on each of 22 calendar days using three lots of reagents on two different systems. Each run consisted of seven control fluids to challenge system precision at approximately $\pm 25\%$ of the cut-off values (20 and 50 ng/mL), at the cut-off values, and at a high THC level (75 ng/mL). Control fluids are drug-spiked, pooled human urine with concentrations verified by GC/MS. Four calibrations were performed over the 22-day testing period. Multiple runs within a day were separated by at least two hours. All fluids were run in duplicate in each run. Final results and the calculation of within lab imprecision are based on weekly calibrations.

The results of the test samples were analyzed by ANOVA as detailed in NCCLS EP5-A2. The mean within lab CV of the three lots tested was 3.5% (range 1.7 – 9.0%).

Qualitative precision was estimated by determining the percentage of negative controls that produced a negative result versus the cutoff value and the percentage of positive controls that produced a positive result versus the cutoff value.

Cut-off Level	Cut-off	Number Tested	Correct Results	Confidence Level
20 ng/mL	0.75x	262	262	> 95% negative reading
20 ng/mL	1.25x	264	263	> 95% positive reading
50 ng/mL	0.75x	264	264	> 95% negative reading
50 ng/mL	1.25x	264	264	> 95% positive reading

One result pair (0.75x) 20ng/mL cutoff was excluded because the wrong fluid was tested.

The results demonstrated acceptable imprecision on the VITROS THC Reagent lots and VITROS 5,1 FS Systems evaluated.

b. *Linearity/assay reportable range:*

The reportable range of the assay is from 5.0 to 80 ng/mL. A linearity study was performed according to NCCLS EP6-A. Urine pools containing low and high concentrations of 11-nor-delta-9-THC-9-COOH were mixed together resulting in 16 samples with 11-nor-delta-9-THC-9-COOH concentrations that spanned the measuring range of the assay. The linearity was evaluated with multiple reagent lots and assessed by comparing the measured VITROS THC assay values against the percent high pool to determine if the data conformed to a straight line. The linear regression calculations gave R^2 values of 0.999 and all samples were within the acceptance criteria when measured results

were compared to expected results across the sample range tested (2.5 – 82.5 ng/mL).

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

The values assigned to the VITROS calibrators and controls for 11-nor-delta-9-THC-9-COOH are traceable to NIST standard SRM 1507b, verified by GC/MS.

Working Calibrators that are value assigned by a GC/MS method with reference to NIST SRM 1507b are used to assign values to master calibrators using the Vitros 5,1 Chemistry system. These master calibrators are then used to assign values to final product calibrators. Controls are manufactured and verified by GC/MS traceable to NIST SRM 1507b. Final control values are assigned using the Vitros 5,1 Chemistry system. Real time stability studies are used to support both long term and open vial storage dates.

d. Detection limit:

The Limit of Blank (LOB), Limit of Detection (LOD) and Limit of Quantitation (LOQ) were determined following NCCLS EP17-A. The Limit of Blank, Limit of Detection and Limit of Quantitation were calculated for three reagent lots and determined to be 1.7 ng/mL, 4.9 ng/mL, and 5.0 ng/mL, respectively. The limit of quantitation is used when determining the reportable range of the assay.

e. Analytical specificity:

Determination of Cross-reactivity

Cross-reactivity was examined by adding potential cross-reactant compounds into a drug free calibrator. The compounds were evaluated using the VITROS 5,1 FS Chemistry System to determine the VITROS THC Assay value equivalent to that of the calibration 11-nor-delta-9-THC-9-COOH analyte, at the cutoff values of 20 ng/mL and 50 ng/mL. Screened compounds exceeding the cutoff responses were further diluted with drug free calibrator to determine the approximate compound concentration required to generate a VITROS THC Assay value equivalent to 11-nor-delta-9-THC-9-COOH at the cutoff values.

Cross Reacting Substances

Cross-reactant	Quantity (ng/mL) equivalent to 20 ng/mL of 11-nor-D9-THC-9-COOH	% Cross-reactivity*	Quantity (ng/mL) equivalent to 50 ng/mL of 11-nor-D9-THC-9-COOH	% Cross-reactivity*
8- <i>b</i> -11-dihydroxy- Δ^9 -THC	24	83.3%	60	83.3%
Δ^9 -THC	30	66.7%	86	58.1%
cannabinol	36	55.6%	121	41.3%
11-hydroxy- Δ^9 -THC	38	52.6%	105	47.6%
cannabidiol	6550	0.3%	24500	0.2%

*The VITROS THC 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.

Exogenous Compounds

Exogenous compounds were evaluated with a single test fluid spiked with the featured compound at a high concentration level (100,000 ng/mL). These compounds were spiked into commercially available calibrators with THC concentrations of 20 ng/mL or 50 ng/mL. Exogenous compounds demonstrating biases that exceeded the acceptance criteria were considered to interfere with the VITROS THC Assay at the cutoff value tested. When interference was observed, on-board dilutions of the test fluid were performed to estimate the highest interferent concentration that did not exceed the acceptance criteria at the cutoff value.

Compounds tested that do not interfere		
Compound	Concentration Tested Conventional	Concentration Tested SI
ammonia	570 mg/dL	316 mmol/L
amobarbitol	10 mg/dL	442 mmol/L
ascorbic acid	500 mg/dL	28.4 mmol/L
bilirubin	26 mg/dL	444 mmol/L
brompheneramine	10 mg/dL	313 mmol/L
calcium	30 mg/dL	7.5 mmol/L
ciprofloxacin	10 mg/dL	302 mmol/L
citric acid	100 mg/dL	5.2 mmol/L
cloxacillin	10 mg/dL	230 mmol/L

Compounds tested that do not interfere		
Compound	Concentration Tested Conventional	Concentration Tested SI
creatinine	300 mg/dL	26.5 mmol/L
desipramine HCl	10 mg/dL	330 mmol/L
dextromethorphan	10 mg/dL	369 mmol/L
dicyclomine HCl	10 mg/dL	289 mmol/L
diethylpropione	10 mg/dL	487 mmol/L
doxylamine	10 mg/dL	370 mmol/L
ethacrynic acid	10 mg/dL	330 mmol/L
ethanol	780 mg/dL	169 mmol/L
glucose	4000 mg/dL	222 mmol/L
hemoglobin	500 mg/dL	5.00 g/L
human IgG	200 mg/dL	2.00 g/L
human serum albumin	200 mg/dL	2.00 g/L
imipramine	10 mg/dL	357 mmol/L
indomethacin	10 mg/dL	279 mmol/L
iron	0.1 mg/dL	17.9 mmol/L
L-hyoscyamine	10 mg/dL	346 mmol/L
magnesium	60 mg/dL	24.7 mmol/L
meperidine	10 mg/dL	404 mmol/L
methoxyphenamine	10 mg/dL	558 mmol/L
metronidazole	10 mg/dL	584 mmol/L
nylidrine	10 mg/dL	334 mmol/L
ofloxacin	10 mg/dL	277 mmol/L
oxalic acid	300 mg/dL	23.8 mmol/L
pH= 9	N/A	N/A
phenylbutazone	10 mg/dL	324 mmol/L
phenyltoloxamine	10 mg/dL	391 mmol/L
phosphate	950 mg/dL	100 mmol /L
potassium	587 mg/dL	150 mmol /L
promethazine HCl	10 mg/dL	312 mmol/L
propranolol	10 mg/dL	386 mmol/L
pyruvate	200 mg/dL	22.8 mmol/L
ranitidine	10 mg/dL	318 mmol/L
riboflavin	2 mg/dL	53 mmol/L
sodium	6000 mg/dL	2608 mmol/L
tetrahydrozoline	10 mg/dL	499 mmol/L
tolmetin/tolectin	10 mg/dL	390 mmol/L
trihexylphenidyl HCl	10 mg/dL	296 mmol/L

Compounds tested that do not interfere		
Compound	Concentration Tested Conventional	Concentration Tested SI
trimethobenzamide	10 mg/dL	257 mmol/L
tripelannamine	10 mg/dL	392 mmol/L
tripolidine	10 mg/dL	359 mmol/L
tyramine HCl	10 mg/dL	576 mmol/L
urea	3000 mg/dL	500 mmol/L
uric acid	120 mg/dL	7.1 mmol/L

Endogenous Compounds

Solutions for the evaluation of potential endogenous interferents were prepared by addition of endogenous compounds a commercial calibrator containing THC. The test fluids and their control blanks were run on a VITROS 5,1 FS Chemistry. The effects of variations in pH were tested by adjusting the calibrator pH. Endogenous compounds demonstrating biases that exceeded the acceptance criteria were considered to interfere with the VITROS THC Assay for the appropriate cutoff value tested. When interference was observed, on-board dilutions of the test fluid were performed to estimate the highest interferent concentration that did not exceed the acceptance criteria at the cutoff value.

Known Interfering Substances

Cutoff Value (ng/mL or µg/L)	Interferent	Interferent Concentration*		Bias** (ng/mL or µg/L)
		Conventional	SI	
20	pH	=4.0	=4.0	-3.9

*The degree of interference at concentrations other than those listed might not be predictable from these results. Other interfering substances may be encountered in the patient population.

**The bias is an estimate of the maximum difference observed.

f. Assay cut-off:

The cutoffs identified for this assay are 20 and 50 ng/mL. Performance around the cutoff was found to be acceptable and is shown in section 1.a., above.

2. Comparison studies:

a. Method comparison with predicate device:

A total of 113 unaltered human urine samples were assayed using the

VITROS THC Reagent, and the predicate device. Percent agreement was evaluated at each of the assay cutoff values (20 and 50 ng/mL).

Cutoff Value		Commercial Method				% Agreement		
		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	% Agreement Negative	% Agreement Positive	% Agreement Overall
20 ng/mL		(< -50%) < 10 ng/mL	(-50% to cutoff) 10-20 ng/mL	(cutoff to + 50%) 20-30 ng/mL	(> + 50%) > 30 ng/mL	97.6%	95.8%	96.5%
	VITROS positive	0	1	15	53			
	VITROS negative	30	11	3	0			
50 ng/mL		(< -50%) < 25 ng/mL	(-50% to cutoff) 25-50 ng/mL	(cutoff to + 50%) 50-75 ng/mL	(> + 50%) > 75 ng/mL	100%	87.0%	94.7%
	VITROS positive	0	0	4	36			
	VITROS negative	54	13	6	0			

A total of 113 human urine samples were assayed using the VITROS THC Reagent and a GC/MS reference method specific for 11-nor-delta-9-THC-9-COOH. Percent agreement was evaluated at assay cutoff values of 20 and 50 ng/mL.

Cutoff Value		GC/MS Reference Method				% Agreement		
		Low Negative	Near Cutoff Negative	Near Cutoff Positive	High Positive	% Agreement Negative	% Agreement Positive	% Agreement Overall
20 ng/mL		(< -50%) < 10 ng/mL	(-50% to cutoff) 10-20 ng/mL	(cutoff to + 50%) 20-30 ng/mL	(> + 50%) > 30 ng/mL	62.9%	100.0%	77.0%
	VITROS positive	9	17	10	33			
	VITROS negative	43	1	0	0			
50 ng/mL		(< -50%) < 25 ng/mL	(-50% to cutoff) 25-50 ng/mL	(cutoff to + 50%) 50-75 ng/mL	(> + 50%) > 75 ng/mL	84.9%	100.0%	88.5%
	VITROS positive	5	8	11	16			
	VITROS negative	70	3	0	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.