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

A. 510(k) Number:

k163433

B. Purpose for Submission:

Modification of the previously cleared Glucose Slides (k955286) to reduce the surface area and amount of reagent in the slide and decrease the sample volume required for testing.

C. Measurand:

Glucose

D. Type of Test:

Quantitative, Colorimetric

E. Applicant:

Ortho Clinical Diagnostics

F. Proprietary and Established Names:

VITROS Chemistry Products GLU Slides

G. Regulatory Information:

1. Regulation section:

   21 CFR § 862.1345, Glucose test system.

2. Classification:

   Class II

3. Product code:

   CGA

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indication(s) for use below.

2. Indication(s) for use:

   For in vitro diagnostic use only. VITROS Chemistry Products GLU Slides are used on VITROS Systems to quantitatively measure glucose (GLU) concentration in serum, plasma, urine and cerebrospinal fluid. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma.

3. Special conditions for use statement(s):

   For in vitro diagnostic use only
   For prescription use only

4. Special instrument requirements:

   VITROS 4600 Systems

I. Device Description:

The VITROS GLU Slide is a multilayered, analytical element coated on a polyester support with the following reagents (reactive ingredients per cm^2):

Glucose oxidase (Aspergillus sp.) 0.77 U
Peroxidase (horseradish root) 3.6 U
1,7-dihydroxynaphthalene (dye precursor) 67 µg
4-aminoantipyrine hydrochloride (dye precursor) 0.11 mg

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITROS Chemistry Products GLU Slides

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

   k955286

3. Comparison with predicate:

Similarities		
Item	Candidate Device VITROS GLU Slide k163433	Predicate Device VITROS GLU Slide k955286
Intended Use	For quantitatively measure of glucose concentration in serum, plasma, urine, and cerebrospinal fluid	Same
Basic Principle	Enzymatic endpoint test using reflectance spectrophotometry	Same
Sample type	Serum, plasma, urine and cerebrospinal fluid	Same
Assay Range	Serum: 20 - 625 mg/dL Urine and CSF: 20 - 650 mg/dL	Same
Incubation time and temperature	5 minutes at 37°C	Same

Differences		
Item	Candidate Device VITROS® GLU Slide k163433	Predicate Device VITROS® GLU Slide k955286
Sample volume	6 µL	10 µL
Amount of slide reactive ingredients per slide (test)	Glucose oxidase 0.70 U peroxidase 3.3 U 1,7-dihydroxynaphthalene 60 µg 4- aminoantipyrine hydrochloride 0.10 mg	Glucose oxidase 0.99 U peroxidase 4.7 U 1,7- dihydroxynaphthalene 86 µg 4- aminoantipyrine hydrochloride 0.14 mg

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

CLSI-EP5-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline - Third Edition

CLSI-EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI-EP9-A3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline - Third Edition

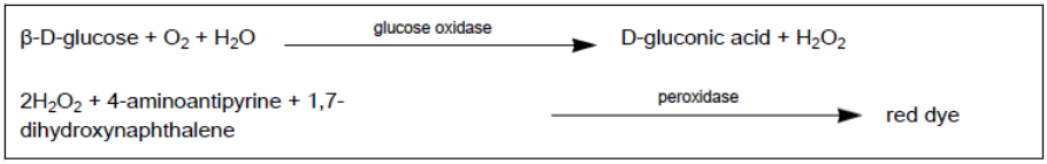
CLSI-EP7-A2: Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition

CLSI-EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline - Second Edition

L. Test Principle:

A drop of patient sample is deposited on the slide and is evenly distributed by the spreading layer to the underlying layers. The oxidation of sample glucose is catalyzed by glucose oxidase to form hydrogen peroxide and gluconate. This reaction is followed by an oxidative coupling catalyzed by peroxidase in the presence of dye precursors to produce a dye. The intensity of the dye is measured by reflected light.

Reaction Scheme



M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within-day and within-lab precision studies for the VITROS GLU assay were performed in accordance to CLSI EP5-A3 guideline. Precision studies were performed using 2 serum controls, 2 serum pools, 2 urine controls, 1 urine pool , 2 CSF controls and 3 CSF pools. Samples were analyzed in duplicate, over the course of 22 working days using 3 lots of VITROS GLU slides on VITROS 4600 chemistry system (n=88). The precision results of one representative lot are summarized in the table below:

Samples	Mean (mg/dL)	Within Day		Within Lab	
		SD	% CV	SD	%CV
Serum Control I	90.3	0.6	0.8	1.5	1.6
Serum Control II	287.2	1.6	0.7	3.4	1.2
Serum Pool 1	29.4	0.2	0.5	0.4	1.3
Serum Pool 2	571.2	3.3	0.6	5.0	0.9
Urine Control 1	31.6	0.3	1.1	0.5	1.5
Urine Control 2	301.4	2.8	0.9	4.5	1.5
Urine Pool	574.5	4.1	0.7	5.5	1.0
CSF Pool 1	37.2	0.3	0.9	0.6	1.5
CSF Control I	49.2	0.5	0.7	0.6	1.3
CSF Control II	88.9	0.6	0.9	1.1	1.2
CSF Pool 2	283.0	1.7	0.9	3.55	1.3
CSF Pool 3	609.3	2.6	0.8	4.0	0.7

b. *Linearity/assay reportable range:*

Linearity was determined following CLSI EP06-A guideline. A high glucose pool was intermixed with a low pool to generate 14 concentration levels each tested in six replicate determinations for each sample type (serum, urine and CSF) and compared to hexokinase reference value. The linearity study supports the claimed measuring range for each sample type, as shown in the table below.

Sample Type	Slope	Intercept	Correlation Coefficient	Linear Range (mg/dL)	Claimed measuring range (mg/dL)
Serum	0.98	1.56	1.00	17.1 – 662.2	20-625
Urine	0.995	0.015	0.999	17.0 - 693.0	20-650
CSF	0.98	1.47	1.00	16.0 - 672.7	20-650

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

VITROS GLU slides are calibrated with the VITROS Chemistry Products Calibrator Kit 1, which is traceable to the Certified NIST (National Institute of Standards and Technology) Reference Material, SRM 917.

Stability:

The shelf-life, on-board and on-analyzer (with system turned off) stability testing protocols and acceptance criteria were reviewed and found to be acceptable to support the following stability claims:

Shelf life at -18ºC	18 months
On-board stability	1 week
On-analyzer stability (system turned off)	Up to 2 hours

d. *Detection limit:*

The limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) of the VITROS GLU assay were determined according to CLSI EP17-A2 guideline. Detection limit summary protocols:

Serum	LoB	Four blanks samples were prepared by dialyzing serum samples with saline. Samples were tested on 6 replicates per run for 4 days using 3 VITROS GLU slide lots (n = 24 per sample).
	LoD and LoQ	Four serum samples were depleted to have 1 mg/dL glucose concentration then spiked with glucose stock solution to achieve the following target concentrations: 5, 10, 15, 20 mg/dL. Samples were tested in 16 replicates per day for 4 days using 3 VITROS GLU slide lots (n = 64 per sample).

Urine	LoB	Four blank samples were prepared by depleting glucose from urine samples. Each sample was tested in 6 replicates per run over 4 days using 3 VITROS GLU slide lots (n=48 per sample).
	LoD and LoQ	Four urine samples were spiked with glucose stock solution to target concentrations of 10 to 20 mg/dL. Each sample was tested in 6 replicates per run for 4 days using 3 lots of VITROS GLU slides (n = 24 per sample).
CSF	LoB	Four LoB fluids (plasma converted serum and 0.9% saline base pools) were run with 10 replicates per run, two runs per day over five days using 3 lots of VITROS GLU slides (n = 100 per sample).
	LoD and LoQ	Five fluids mixtures of the LoB base pool and 0.9% saline base pools were spiked with a β-D(+)glucose solution to target concentrations of 8, 12, 16, 20, 24 mg/dL. Each sample was evaluated in 6 replicates per run, with two runs per day over 5 days using 3 lots of VITROS GLU slides (n = 60 per sample).

The limit of quantitation is defined as the lowest amount of analyte in the sample that can be quantitatively determined with an imprecision of ≤20% and total allowable error of ≤30%.

The detection limits of the modified VITROS GLU Slides assay are summarized below:

Sample	LoB (mg/dL)	LoD (mg/dL)	LoQ (mg/dL)
Serum	1	2	9
Urine	7	8	18
CSF	4	5	20

The sponsor claimed measuring range is 20 - 625 mg/dL for serum and 20 - 650 mg/dL for urine and CSF.

e. *Analytical specificity:*

Interference studies were performed according to CLSI EP7-A2 guideline to determine the effects of endogenous and exogenous substances on the performance of the VITROS Chemistry Products GLU Slides assay for serum, urine and CSF on VITROS 4600 chemistry analyzer.

Serum

Two levels of glucose approximately 80 mg/dL and 215 mg/dL were spiked with different concentrations of interference substances and tested using the VITROS

Chemistry Products GLU Slides. The results of the spiked samples were compared to the results of the non-spiked samples. The bias was calculated using the formula shown below:

Bias = (mean concentration of test substance pool) – (mean concentration of control pool)

The sponsor defined no significant interference for serum as summarized in the following table:

Glu Concentration mg/dL	Bias
≤120	± 4.42 mg/dL
≥120	± 3.7% mg/dL

The substances that showed not to interfere in serum are summarized in the following table:

Substances	Highest concentration tested that showed non-significant interference
Acetaminophen	15 mg/dL
Alprazolam	0.2 mg/dL
Amlodipine	10 µg/dL
Amoxicillin	7.53 mg/dL
Ascorbic Acid	5.93 mg/dL
Atorvastatin calcium	72.6 mg/dL
Benazepril	2.21 mg/dL
Bilirubin, conjugated	57.64 mg/dL
Bilirubin, unconjugated	40 mg/dL
Cefazolin	125.9 mg/dL
Cefoxitin	69.5 mg/dL
Ceftriaxone	81.0 mg/dL
Chlorpropamide	74.7 mg/dL
Cholesterol	300 mg/dL
Creatinine	15 mg/dL
Diphenhydramine	0.50 mg/dL
Dipyrone (metamizole)	18 mg/dL
Dobutamine	30 µg/dL
Dopamine	90 µg/dL
Ethamsylate(Etamsylate)	3.14 mg/dL
Ethanol	400 mg/dL
Fructose	30 mg/dL
Furosemide	6 mg/dL
Galactose	60 mg/dL
Gentisic acid	1.80 mg/dL
Glipizide	0.20 mg/dL

Substances	Highest concentration tested that showed non-significant interference
Glyburide	0.192 mg/dL
Hydralazine HCl	0.046 mg/dL
Hydrochlorothiazide	0.60 mg/dL
Hydroxyurea	7 mg/dL
Ibuprofen	50 mg/dL
Insulin	3.12 µg/dL
Intralipid	800 mg/dL
Isomaltose	0.09 mg/dL
Isoniazid	4 mg/dL
L-Dopa	0.98 mg/dL
Levothyroxine sodium	103 µg/dL
Losartan potassium	0.091 mg/dL
Maltose	85 mg/dL
Metformin HCl	5.1 mg/dL
Methyldopa	2 mg/L
Naproxen sodium	54.7 mg/dL
Nitrofurantoin	0.4 mg/dL
Omeprazole	0.60 mg/dL
Oxycodone	0.05mg/dL
Propanolol	0.21 mg/dL
Pseudoephedrine	1 mg/dL
Rifampicin (Rifampin)	6.43 mg/dL
Salicylic acid	60 mg/dL
Sodium	1050 mg/dL
Spironolactone	0.06 mg/dL
Theophylline	4 mg/dL
Tolazamide	28 mg/dL
Tolbutamide	64.1 mg/dL
Triglycerides	800 mg/dL
Uric acid	23 mg/dL
Vancomycin	10 mg/dL
Warfarin	1 mg/dL
Xylose	134 mg/dL
Sugar Alcohols:	
Mannitol	0.09 mg/dL
Sorbitol	0.09 mg/dL
Xylitol	0.09 mg/dL
Lactitol	0.09 mg/dL
Maltitol 578	0.09 mg/dL

The results of substances that interfere with glucose determinations in serum are summarized in the table below:

Interferent	Interferent concentrations	Glucose concentrations tested	Bias
N-Acetylcysteine (NAC)	22.5	80	-5.9
	15.0	120	-4.5
	30.0	300	-12.3
Glutathione	61.5	80	-7.4
	61.5	225	-13.8
Dextran 40	3000	80	+4.7
	2000	225	+9.3

Urine

The interferent substances were tested for urine at glucose concentrations of approximately 30 mg/dL and 215 mg/dL. The sponsor defined no significant interference for urine as bias ≤ 4.42 mg/dL for glucose concentration below 120 mg/dL and bias ≤ 3.7% mg/dL for glucose concentrations above 120 mg/dL.

The substances that showed not to interfere in urine are summarized in the following table:

Substances	Highest Concentration Tested that showed non-significant interference
Boric acid	6.7 mg/mL
Boric acid with Sodium formate	6.7 mg/mL, 3.35 mg/mL
10% Thymol in Isopropanol	3.3 mL/L
Toluene	1.3 mL/L
Sodium fluoride	5 g/L
Sodium formate	3.35 mg/mL
Sodium oxalate	60 mg/dL
Urea nitrogen	100 mg/dL
Magnesium	146 mg/dL
Protein	50 mg/dL

CSF

A single human CSF patient pool containing glucose approximately 65 mg/dL was used for the hemoglobin interference evaluation. Test substance pools were made by spiking a hemolysate stock solution prepared from human hemoglobin directly into the CSF test pool. The control pool was made by spiking an equivalent volume blank solvent (water) as the hemoglobin stock. Hemoglobin was tested in concentrations of 100, 150, 500 mg/dL in CSF with 6 replicates and 3 lots. The sponsor defined no significant interference as a bias of ≤10% for glucose concentrations above 40 mg/dL.

Hemoglobin was found not to interfere up to 200 mg/dL at a glucose concentration of 65 mg/dL (bias less than 4 mg/dL).

The following limitations are listed in the package insert:

When using samples with visible hemolysis (Hb >200 mg/dL), there may be a negative bias due to catalase released from the lysis of red blood cells. On VITROS Systems capable of performing Sample Indices using the MicroSensor, the GLU result will be flagged with H (Hemolysis).

Elevated lipids may limit diffusion of oxygen to the reactants. Dilute grossly lipemic samples two-fold before analysis.

For total protein, a negative bias of -4 mg/dL (-0.22 mmol/L) is observed for total protein = 5 g/dL (50 g/L) and a positive bias of +6 mg/dL (+0.33 mmol/L) is noted for total protein = 10 g/dL (100 g/L) at a glucose concentration of 85 mg/dL.

Known interferences in urine:

High levels of ascorbic acid in urine will cause a large negative bias, potentially resulting in values less than the measuring range. The degree of bias is proportional to the ascorbic acid concentration.

Glacial acetic acid at 10 mL/L results in ~4% negative bias. The magnitude of the bias increases with higher concentrations of glacial acetic acid (60 mL/L). Do not use urine specimens with acetic acid as a preservative.

12N Hydrochloric acid (HCl) at 2.5 mL/dL results in a large negative bias, potentially resulting in values less than the measuring range. Do not use urine specimens with HCl as a preservative.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed according to CLSI EP9-A3 guideline. A total of 113 serum samples, 105 urine samples and 45 unique CSF samples (plus additional admixture CSF samples to cover claimed range) were assayed on one predicate lot and one modified lot using the VITROS 4600 System.

The results of the linear regression analysis are summarized below:

Matrix	Slope	Intercept	r	Concentration range (mg/dL)
Serum	1.01	-0.80	1.000	28-616
Urine	1.03	-0.81	0.999	20-619
CSF	1.02	-0.31	1.000	22-609

b. Matrix comparison:

A total of 68 paired serum and plasma specimens (EDTA, sodium heparin, lithium heparin, and sodium fluoride/potassium oxalate) with concentrations within the claimed measuring range (20 - 625 mg/dL) were tested using the modified VITROS GLU Slides on the VITROS 4600 Chemistry System.

The results of the linear regression analysis are summarized in the table below:

Plasma Type	Slope	Intercept	Correlation (r^2)
Sodium heparin	1.01	3.78	1.00
Lithium heparin	1.00	3.36	1.00
EDTA	0.99	4.3	1.00
Sodium fluoride/potassium oxalate	0.98	5.26	1.00

The results of the matrix comparison study support that serum and EDTA, sodium heparin, lithium heparin, and sodium fluoride/potassium oxalate plasma specimens are suitable for use with the VITROS Chemistry Products GLU Slides.

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:

The following expected values are provided in the product insert based on the literature:

Serum[1]	
Fasting adults	74 – 106 mg/dL
Urine[2]	
Random	<30 mg/dL
24-Hour	<500 mg/dL*
CSF[2]	40-70 mg/dL

*Glucose concentration (md/dL) x 24-hour volume (dL) = mg/day

[1] Tietz NW (ed). Textbook of Clinical Chemistry. ed. 3. Philadelphia: WB Saunders; 1815; 1999

[2]Tietz NW (ed). Fundamentals of Clinical Chemistry. ed. 2. Philadelphia: WB Saunders; 1213–1214; 1976.

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.