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

A. 510(k) Number:

k142595

B. Purpose for Submission:

New Device

C. Measurand:

Whole Blood Glycated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative turbidimetric, inhibition immunoassay

E. Applicant:

Ortho-Clinical Diagnostic, Inc.

F. Proprietary and Established Names:

VITROS® Chemistry Products HbA1c Reagent Kit

VITROS® Chemistry Products Calibrator Kit 31

VITROS® Chemistry Products %A1c Performance Verifiers I and II

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
PDJ	Class II	862.1373	Chemistry (75)
JIT	Class II	862.1150	Chemistry (75)
JJY	Class I, reserved	862.1660	Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indications for use below

2. Indication(s) for use:

   For in vitro diagnostic use only. VITROS Chemistry Products HbA1c Reagent Kit is used on VITROS 5,1 FS Chemisty System, VITROS 4600 Chemistry System and the VITROS 5600 Integrated System for the quantitative determination of percent glycated hemoglobin A1c (DCCT/NGSP) and mmol/mol hemoglobin A1c (IFCC) in human whole blood. The test is to be used as an aid in diagnosis of diabetes, as an aid in identifying patients who may be at risk for developing diabetes and for the monitoring of long-term blood glucose control in individuals with diabetes mellitus.

   For in vitro diagnostic use only. VITROS Calibrator Kit 31 is used to calibrate the VITROS 5,1 FS Chemistry System, VITROS 4600 Chemistry System and the VITROS 5600 Integrated System for the determination of percent glycated hemoglobin (HbA1c) in human whole blood.

   For in vitro diagnostic use only. VITROS Chemistry Products %A1c Performance Verifiers I and II are assayed controls used on the VITROS 5,1 FS Chemistry System, the VITROS 4600 Chemistry System and the VITROS 5600 Integrated System to monitor performance of the VITROS d%A1c and VITROS HbA1c Reagent Kits.

3. Special conditions for use statement(s):

   For Prescription Use Only

   This device has significant negative interference with fetal hemoglobin (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF including those with known Hereditary Persistence of Fetal Hemoglobin."

   The result from this or any other diagnostic test should be used and interpreted only in the context of the overall clinical picture.

   Hemoglobin A1c should not be used to diagnose diabetes mellitus in patients with a hemoglobinopathy but normal red cell turnover (e.g. sickle cell trait).

   Hemoglobin A1c should not be used in patients with homozygous sickle cell trait, hemolytic anemia, or other hemolytic diseases and recent significant or chronic blood loss.

Hemoglobin A1c should not be used to diagnose gestational diabetes. It reflects the average blood glucose levels over the preceding 3 months (the average life of a red blood cell) and therefore may be falsely low during pregnancy or any condition associated with reset onset of hyperglycemia.

In very rare cases of rapidly evolving type 1 diabetes, the increase of HbA1c values might be delayed compared to the acute increase in glucose concentrations and/or the typical clinical symptoms.

Hemoglobin A1c should not be used to diagnose diabetes mellitus in patients with malignancies or severe chronic hepatic and renal disease.

Hemoglobin A1c testing should not replace glucose testing for type 1 diabetes, in pediatric patients and in pregnant women.

4. Special instrument requirements:
   VITROS 5,1 FS Chemisty System
   VITROS 4600 Chemistry System
   VITROS 5600 Integrated System

I. Device Description:

The determination of % glycated hemoglobin (HbA1c) is performed using the VITROS Chemistry Products HbA1c Reagent Kit in conjunction with the VITROS Chemistry Products Calibrator Kit 31 on the VITROS 5,1 FS and VITROS 4600 Chemistry Systems and the VITROS 5600 Integrated System. The VITROS Chemistry Products HbA1c Reagents are two dual chambered packages containing ready-to use liquid reagents.

The VITROS® Chemistry Products HbA1c Reagent Kit:
Reactive ingredients:
Reagent 1 (R1): Hba1c anitibody (ovine serum) ≥0.5 mL
Reagent 2 (R2): HbA1c Polyhapten ≥ 8µg/mL
DIL5 (R1): Tetradecyltrimethlylammonium bromide (TTAB) <1% (w/v).
Other ingredients:
Reagent 1 (R1): Buffers, surfactant, stabilizers and preservatives
Reagent 2 (R2): Buffers, surfactant, stabilizers and preservatives
DIL5 (R1): Surfactants, stabilizers and preservatives

VITROS Chemistry Products Calibrator Kit 31:
The VITROS® Chemistry Products Calibrator Kit 31 is prepared for a hemolysate derived from human and ovine blood to which surfactants, stabilizer, and preservative have been added. The single calibrator is provided as a lyophilate that is reconstituted with 2 mL of FS Reconstitution Diluent. In the calibration process the instrument produces 4 calibrator levels by dilution.

VITROS® Chemistry Products Performance Verifiers I and II:
The VITROS® Chemistry Products %A1c Performance Verifiers I and II are prepared from a hemolysate derived from human and ovine blood to which surfactants, stabilizer and preservatives have been added.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   COBAS Integra 800 Tina Quant HbA1c Dx. Gen. 2 Assay
   VITROS® Chemistry Products %A1c Performance Verifiers
   Roche (Calibrator for Automated Systems) C.f.a.s. HbA1c calibrator

2. Predicate 510(k) number(s):
   k121291
   k041764
   k052101

3. Comparison with predicate:

Similarities and Differences		
Item	**The VITROS® Chemistry Products HbA1c Reagent Kit**: Candidate Device	**COBAS Integra 800 Tina Quant HbA1c Dx. Gen. 2 Assay k121291** Predicate Device
Indication For Use/Intended Use	For in vitro diagnostic use. Quantitative determination of % HbA1c in human whole blood. Used as an aid in diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes.	Same
Sample Type	EDTA Whole Blood	Same
Test Principle	Whole blood samples are lysed. Hemoglobin is converted to a hematin derivative that is measured bichromatically. HbA1c is measured by turbidimetric inhibition. %A1c is derived from the quantitative measurements of	Same

Similarities and Differences		
Item	The VITROS® Chemistry Products HbA1c Reagent Kit: Candidate Device	COBAS Integra 800 Tina Quant HbA1c Dx. Gen. 2 Assay k121291 Predicate Device
	hemoglobin and hemoglobin A1c.	
Traceability	Traceable to the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) Reference Method	Same
Final Results	Final result are expressed as mmol/mol HbA1c or %A1c (NGSP)	Same
Sample Type	EDTA Whole Blood	Li-Heparin, Na-heparin, K_2EDTA, K_3EDTA, potassium fluoride/Na_2EDTA, NaF/Sodium EDTA and NaF/Potassium Oxalate
Measuring Range	4-14% HbA1c	4.2-20.1% HbA1c

Similarities and Differences: Controls		
Item	VITROS Chemistry Products %A1c Performance Verifiers I and II Candidate Device	VITROS Chemistry Products %A1c Performance Verifiers I and II k041764 Predicate Device
Indication for Use/ Intended Use	Quality Control material used for monitoring the accuracy and precision of the VITROS HbA1c assay	Same
Product Type	Assayed Control	Same
Number of levels	Two	Same
Matrix	Lyophilized	Same

Similarities and Differences: Calibrators		
Item	**VITROS Chemistry Products Calibrator Kit 31** Candidate Device	**Roche C.f.a.s. HbA1c calibrator k052101** Predicate Device
Indication for Use/Intended Use	For use in the calibration of the VITROS HbA1c assay on the VITROS 5,1 FS Chemistry System, VITROS 4600 Chemistry System and the VITROS 5600 Integrated System	Same
Levels	1 level diluted automatically by the analyzer system to achieve 4 levels	1 level diluted automatically by the analyzer system
Traceability	Traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Reference Method	Same

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

CLSI EP05-A2- Evaluation of Precision Performance of Clinical Devices; Approved Guideline

CLSI EP06-A- Evaluation of the Linearity of Quantitative Measurement Procedure: A statistical Approach; Approved Guideline

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

EP9-A2-IR – Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline

CLSI EP12-A2- User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline

EP17-A2-Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

CLSI EP25-A-Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

CLSI EP28-A3-Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline

L. Test Principle:

Whole blood samples are hemolyzed on the VITROS 5,1 FS and VITROS 4600 Chemistry Systems and the VITROS 5600 Integrated System. Calibrators, controls and hemolyzed whole blood samples are mixed with Reagent 1 containing anti-HbA1c antibody to form a soluble antigen-antibody complex. Hemoglobin in the hemolyzed whole blood is converted with Reagent 1 to a hematin derivative that is measured bichromatically at 340 nm and 700 nm. Unbound anti-HbA1c antibody reacts with polyhapten (hexapeptide-glycan, A1c Reagent 2) to form an insoluble antibody-polyhapten immune complex, which is measured turbidimetrically at 340 nm. %A1c is a derived test calculated from the quantitative measurements of hemoglobin and hemoglobin A1c.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

   A precision study was performed according to CLSI EP05-A2- Evaluation of Precision Performance of Clinical Devices; Approved Guideline using three VITROS Chemistry HbA1c Reagents lots tested on each of three VITROS 5,1 FS Chemistry Systems, three VITROS 4600 Chemistry Systems and three VITROS 5600 Integrated Systems analyzers. Two runs were performed for a minimum of 20 days on each of three VITROS 5,1 FS Chemistry Systems, VITROS 4600 Chemistry Systems and VITROS 5600 Integrated Systems analyzers. Each run included four whole blood based control fluids (~5, ~6.5, ~8 and ~12% HbA1c). The whole blood based control fluids were analyzed in duplicate for a minimum of 720 measurements per sample.

   An additional precision study was also performed with three VITROS Chemistry HbA1c reagent lots tested on each of three VITROS 5,1 FS Chemistry Systems, three VITROS 4600 Chemistry Systems and three VITROS 5600 Integrated Systems analyzers. Two runs were performed for 4 consecutive days on each of three VITROS 5,1 FS Chemistry Systems, three VITROS 4600 Chemistry Systems and three VITROS 5600 Integrated Systems analyzers. Each run included four whole blood patient samples (~5, ~6.5, ~8 and ~12% HbA1c). Each of the whole blood patient samples were analyzed in duplicate for a total of 144 measurements per patient sample.

   The results of the two precision studies are as follows:

VITROS 5,1 FS Chemistry System-Analyzer #1-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 5.0	0.02	0.6	0.02	0.4	0.01	0.3	0.01	0.4	0.04	0.9
Control 6.4	0.05	0.8	0.04	0.6	0.03	0.4	0.03	0.6	0.08	1.3
Control 8.2	0.06	0.8	0.02	0.3	0.03	0.4	0.09	1.2	0.12	1.6
Control 11.8	0.16	1.4	0.05	0.5	0.07	0.7	0.00	0.0	0.18	1.6
Patient 5.0	0.02	0.4	0.02	0.5	0.00	0.0	0.01	0.4	0.03	0.7
Patient 6.5	0.04	0.7	0.02	0.4	0.03	0.5	0.00	0.0	0.06	0.9
Patient 8.2	0.05	0.7	0.04	0.5	0.04	0.6	0.00	0.0	0.08	1.1
Patient 11.9	0.15	1.2	0.23	1.9	0.00	0.0	0.00	0.0	0.28	2.4

VITROS 5,1 FS Chemistry System-Analyzer #1-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 31.1	0.31	1.0	0.24	0.8	0.17	0.6	0.19	0.6	0.46	1.5
Control 47.5	0.55	1.2	0.45	1.0	0.34	0.7	0.42	0.9	0.89	1.9
Control 63.9	0.73	1.1	0.31	0.5	0.39	0.6	1.07	1.6	1.39	2.1
Control 107.7	1.77	1.7	0.62	0.6	0.86	0.8	0.00	0.0	2.07	2.0
Patient 31.1	0.24	0.8	0.26	0.8	0.00	0.0	0.20	0.6	0.40	1.3
Patient 47.5	0.48	1.0	0.32	0.7	0.33	0.7	0.00	0.0	0.66	1.4
Patient 63.9	0.64	1.0	0.46	0.7	0.51	0.8	0.00	0.0	0.94	1.4
Patient 107.7	1.66	1.6	2.57	2.4	0.00	0.0	0.00	0.0	3.06	2.9

VITROS 5, 1 FS Chemistry System-Analyzer #2-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 5.0	0.02	0.5	0.04	0.8	0.02	0.4	0.04	0.7	0.06	1.3
Control 6.5	0.04	0.7	0.05	0.8	0.03	0.6	0.09	1.3	0.12	1.6
Control 8.3	0.06	0.8	0.04	0.5	0.06	0.7	0.08	1.0	0.13	1.6
Control 11.9	0.14	1.3	0.09	0.8	0.09	0.8	0.17	1.4	0.26	2.1
Patient 5.1	0.02	0.6	0.03	0.7	0.03	0.7	0.04	0.9	0.07	1.4
Patient 6.6	0.03	0.5	0.03	0.5	0.02	0.4	0.08	1.2	0.09	1.5
Patient 8.3	0.04	0.6	0.08	0.9	0.00	0.0	0.10	1.2	0.13	1.6
Patient 12.1	0.14	1.2	0.18	1.5	0.06	0.5	0.14	1.1	0.27	2.3

VITROS 5, 1 FS Chemistry System-Analyzer #2 -IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 31.5	0.30	1.0	0.46	1.5	0.22	0.7	0.44	1.4	0.73	2.3
Control 47.2	0.48	1.0	0.59	1.3	0.43	0.9	0.98	2.1	1.31	2.8
Control 67.6	0.75	1.1	0.49	0.7	0.68	1.0	0.94	1.4	1.48	2.2
Control 107.0	1.63	1.5	1.02	1.0	0.98	0.9	1.88	1.8	2.86	2.7
Patient 48.7	0.32	1.0	0.36	1.1	0.38	1.2	0.52	1.6	0.81	2.5
Patient 47.5	0.39	0.8	0.33	0.7	0.32	0.7	0.90	1.8	1.08	2.2
Patient 66.8	0.50	0.7	0.90	1.3	0.00	0.0	1.11	1.7	1.51	2.3
Patient 108.5	1.53	1.4	1.99	1.8	0.66	0.6	1.60	1.5	3.04	2.8

VITROS 5, 1 FS Chemistry System- Analyzer #3-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.02	0.4	0.02	0.5	0.04	0.8	0.06	1.2	0.08	1.6
Control 6.2	0.05	0.8	0.05	0.9	0.07	1.1	0.01	0.2	0.10	1.6
Control 7.9	0.05	0.7	0.04	0.5	0.08	1.0	0.05	0.6	0.12	1.5
Control 11.8	0.13	1.1	0.11	0.9	0.16	1.4	0.07	0.3	0.24	2.0
Patient 4.9	0.01	0.3	0.03	0.6	0.04	0.9	0.02	0.4	0.06	1.3
Patient 6.4	0.03	0.5	0.05	0.8	0.05	0.9	0.04	0.6	0.09	1.4
Patient 8.0	0.05	0.7	0.08	1.0	0.04	0.5	0.05	0.6	0.12	1.5
Patient 11.8	0.21	1.8	0.04	0.3	0.15	1.3	0.14	1.2	0.30	2.5

VITROS 5, 1 FS Chemistry System- Analyzer #3-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.1	0.25	0.8	0.31	1.0	0.46	1.5	0.67	2.2	0.90	3.0
Control 45.2	0.55	1.2	0.63	1.4	0.77	1.7	0.14	0.3	1.15	2.5
Control 63.6	0.64	1.0	0.50	0.8	0.94	1.5	0.58	0.9	1.38	2.2
Control 105.4	1.42	1.3	1.27	1.2	1.83	1.7	0.40	0.4	2.67	2.5
Patient 30.2	0.20	0.7	0.37	1.2	0.49	1.6	0.26	0.9	0.70	2.3
Patient 46.4	0.37	0.8	0.56	1.2	0.64	1.4	0.45	1.0	1.03	2.2
Patient 64.3	0.63	1.0	0.91	1.4	0.49	0.8	0.56	0.9	1.33	2.1
Patient 105.8	2.33	2.2	0.49	0.5	1.72	1.6	1.62	1.5	3.36	3.2

VITROS 5,1 FS Chemistry System – All analyzers combined-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.02	0.5	0.03	0.6	0.02	0.5	0.04	0.8	0.06	1.2	0.09	1.8
Control 6.3	0.04	0.7	0.05	0.8	0.05	0.7	0.05	0.8	0.08	1.3	0.13	2.1
Control 8.1	0.06	0.8	0.04	0.5	0.06	0.8	0.08	0.9	0.17	2.1	0.22	2.7
Control 11.8	0.14	1.2	0.09	0.7	0.11	1.0	0.10	0.8	0.05	0.4	0.24	2.0
Patient 5.0	0.02	0.4	0.03	0.6	0.03	0.6	0.03	0.6	0.09	1.8	0.11	2.2
Patient 6.5	0.03	0.5	0.03	0.5	0.04	0.6	0.05	0.8	0.09	1.5	0.13	2.0
Patient 8.1	0.05	0.6	0.07	0.8	0.03	0.3	0.06	0.7	0.10	1.3	0.16	1.9
Patient 11.9	0.17	1.4	0.17	1.4	0.09	0.7	0.11	0.9	0.10	0.8	0.30	2.5

The between-analyzer and between –lot precision was equal to or less than 2.1% for concentrations in the range of 4.9% to 11.9% HbA1c.

VITROS 5,1 FS Chemistry System- All analyzers combined-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.7	0.28	0.9	0.35	1.1	0.32	1.0	0.47	1.5	0.69	2.2	0.99	3.2
Control 46.2	0.52	1.1	0.57	1.2	0.55	1.2	0.62	1.3	0.92	2.0	1.45	3.1
Control 65.7	0.71	1.1	0.45	0.7	0.71	1.1	0.89	1.4	1.95	3.0	2.4	3.7
Control 106.0	1.61	1.5	1.01	1.0	1.30	1.2	1.11	1.0	0.63	0.6	2.6	2.5
Patient 31.3	0.25	0.8	0.34	1.1	0.35	1.1	0.36	1.2	1.03	3.3	1.2	3.9
Patient 47.7	0.42	0.9	0.42	0.9	0.46	1.0	0.58	1.2	1.08	2.3	1.4	3.0
Patient 65.6	0.59	0.9	0.78	1.2	0.34	0.5	0.70	1.1	1.17	1.8	1.7	2.6
Patient 106.9	1.87	1.7	1.89	1.8	0.98	0.9	1.25	1.2	1.09	1.0	3.3	3.1

The between-analyzer and between –lot precision was equal to or less than 3.0% for concentrations in the range of 30.7 to 106.9 mmol/mol HbA1c.

VITROS 4600 Chemistry System – Analyzer #1-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.02	0.48	0.02	0.44	0.01	0.34	0.04	0.86	0.05	1.14
Control 6.3	0.05	0.80	0.05	0.92	0.00	0.00	0.01	0.23	0.08	1.25
Control 8.1	0.05	0.66	0.03	0.47	0.03	0.42	0.03	0.39	0.08	1.00
Control 11.9	0.15	1.33	0.10	0.87	0.06	0.54	0.07	0.63	0.21	1.80
Patient 5.0	0.02	0.50	0.02	0.40	0.01	0.26	0.00	0.18	0.03	0.70
Patient 6.5	0.03	0.57	0.03	0.52	0.00	0.00	0.00	0.00	0.05	0.77
Patient 8.1	0.07	0.92	0.09	1.11	0.00	0.00	0.00	0.00	0.11	1.44
Patient 12.0	0.16	1.38	0.05	0.47	0.08	0.68	0.00	0.00	0.19	1.61

VITROS 4600 Chemistry System – Analyzer #1-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.9	0.26	0.8	0.24	0.8	0.19	0.6	0.47	1.5	0.62	2.0
Control 46.6	0.56	1.2	0.64	1.4	0.00	0.0	0.16	0.3	0.87	1.9
Control 65.3	0.59	0.9	0.42	0.6	0.37	0.6	0.35	0.5	0.89	1.4
Control 106.7	1.74	1.6	1.14	1.1	0.70	0.7	0.82	0.8	2.34	2.2
Patient 31.4	0.27	0.9	0.22	0.7	0.14	0.4	0.10	0.3	0.38	1.2
Patient 47.7	0.40	0.8	0.37	0.8	0.00	0.0	0.00	0.0	0.55	1.2
Patient 65.1	0.82	1.3	0.98	1.5	0.00	0.0	0.00	0.0	1.28	2.0
Patient 107.9	1.81	1.7	0.61	0.6	0.90	0.8	0.00	0.0	2.12	2.0

VITROS 4600 Chemistry System- Analyzer #2-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.03	0.6	0.00	0.1	0.03	0.6	0.02	0.5	0.05	1.1
Control 6.4	0.05	0.8	0.02	0.4	0.05	0.88	0.07	1.1	0.11	1.7
Control 8.1	0.08	1.0	0.00	0.1	0.07	0.8	0.03	0.4	0.11	1.4
Control 11.9	0.18	1.5	0.00	0.0	0.17	1.4	0.03	0.3	0.25	2.1
Patient 5.0	0.03	0.6	0.02	0.56	0.02	0.4	0.00	0.0	0.04	0.9
Patient 6.4	0.05	0.8	0.00	0.0	0.02	0.4	0.01	0.3	0.0	0.9
Patient 8.1	0.07	0.9	0.06	0.7	0.02	0.3	0.03	0.4	0.10	1.
Patient 11.9	0.15	1.2	0.15	1.2	0.20	1.7	0.00	0.0	0.29	2.49

VITROS 4600 Chemistry System- Analyzer #2-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.4	0.35	1.2	0.09	0.3	0.37	1.2	0.31	1.0	0.60	2.0
Control 45.8	0.60	1.3	0.32	0.7	0.61	1.3	0.81	1.8	1.22	2.7
Control 64.8	0.92	1.4	0.10	0.2	0.79	1.2	0.36	0.6	1.27	2.0
Control 106.8	1.99	1.9	0.00	0.0	1.90	1.8	0.43	0.4	2.79	2.6
Patient 30.7	0.37	1.2	0.31	1.0	0.24	0.8	0.00	0.0	0.54	1.8
Patient 46.8	0.57	1.2	0.00	0.0	0.32	0.7	0.21	0.4	0.69	1.5
Patient 64.7	0.84	1.3	0.69	1.1	0.26	0.4	0.37	0.6	1.17	1.8
Patient 107.0	1.66	1.6	1.65	1.5	2.25	2.1	0.00	0.0	3.25	3.0

VITROS 4600 Chemistry System – Analyzer #3-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.02	0.5	0.01	0.3	0.01	0.3	0.02	0.5	0.04	0.9
Control 6.3	0.04	0.6	0.04	0.6	0.02	0.4	0.05	0.9	0.08	1.3
Control 8.0	0.07	0.9	0.05	0.6	0.00	0.0	0.05	0.7	0.10	1.3
Control 11.8	0.19	1.6	0.06	0.5	0.03	0.3	0.14	1.1	0.24	2.0
Patient 5.0	0.02	0.4	0.02	0.5	0.01	0.2	0.02	0.4	0.04	0.8
Patient 6.4	0.05	0.8	0.01	0.2	0.02	0.4	0.05	0.8	0.08	1.3
Patient 8.0	0.11	1.4	0.02	0.2	0.07	0.9	0.08	1.0	0.16	2.0
Patient 11.9	0.15	1.2	0.18	1.5	0.00	0.0	0.15	1.2	0.28	2.4

VITROS 4600 Chemistry System – Analyzer #3-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.2	0.30	1.0	0.19	0.6	0.1	0.5	0.28	0.9	0.48	1.6
Control 45.2	0.47	1.0	0.45	1.0	0.28	0.6	0.62	1.4	0.95	2.1
Control 64.0	0.79	1.2	0.56	0.9	0.08	0.1	0.63	1.0	1.16	1.8
Control 105.9	2.08	2.0	0.66	0.6	0.39	0.4	1.53	1.4	2.69	2.5
Patient 30.7	0.24	0.8	0.30	1.0	0.11	0.4	0.25	0.8	0.47	1.5
Patient 46.9	0.61	1.3	0.20	0.4	0.30	0.6	0.61	1.3	0.94	2.0
Patient 63.9	1.22	1.9	0.23	0.4	0.81	1.3	0.95	1.5	1.77	2.8
Patient 106.8	1.68	1.6	2.03	1.9	0.00	0.0	1.68	1.6	3.13	2.9

VITROS 4600 Chemistry System-All analyzers combined-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.02	0.5	0.01	0.3	0.02	0.4	0.03	0.6	0.02	0.5	0.06	1.3
Control 6.3	0.05	0.7	0.04	0.7	0.03	0.5	0.05	0.8	0.04	0.6	0.10	1.6
Control 8.1	0.07	0.8	0.03	0.4	0.04	0.5	0.04	0.5	0.05	0.6	0.12	1.4
Control 11.8	0.17	1.4	0.06	0.5	0.10	0.9	0.09	0.8	0.00	0.0	0.23	2.0
Patient 5.0	0.02	0.5	0.02	0.5	0.01	0.3	0.01	0.2	0.03	0.7	0.05	1.1
Patient 6.5	0.04	0.7	0.01	0.2	0.02	0.3	0.03	0.5	0.04	0.6	0.07	1.2
Patient 8.1	0.09	1.1	0.06	0.7	0.03	0.4	0.05	0.6	0.04	0.5	0.13	1.7
Patient 11.9	0.15	1.3	0.14	1.1	0.11	0.9	0.06	0.5	0.00	0.0	0.25	2.1

The between-analyzer and between –lot precision was equal to or less than 0.8% for concentrations in the range of 4.9% to11.9% HbA1c.

VITROS 4600 Chemistry System-All analyzers combined-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.5	0.31	1.0	0.19	0.6	0.26	0.9	0.36	1.2	0.31	1.0	0.64	2.1
Control 45.9	0.55	1.2	0.49	1.1	0.37	0.8	0.60	1.3	0.48	1.0	1.1	2.5
Control 64.7	0.78	1.2	0.40	0.6	0.50	0.8	0.47	0.7	0.59	0.9	1.2	1.9
Control 106.5	1.93	1.8	0.75	0.7	1.19	1.1	1.04	1.0	0.00	0.0	2.6	2.5
Patient 30.9	0.30	1.0	0.27	0.9	0.17	0.6	0.13	0.4	0.39	1.3	0.6	1.9
Patient 47.1	0.54	1.1	0.21	0.4	0.22	0.5	0.37	0.8	0.44	0.9	0.8	1.8
Patient 64.6	0.98	1.5	0.70	1.1	0.35	0.5	0.57	0.9	0.48	0.7	1.5	2.3
Patient 107.2	1.72	1.6	1.55	1.4	1.28	1.2	0.70	0.7	0.00	0.0	2.7	2.5

The between-analyzer and between –lot precision was equal to or less than 1.3% for concentrations in the range of 30.5 to 107.2 mmol/mol HbA1c.

VITROS 5600 Integrated System-Analyzer #1-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 4.9	0.03	0.6	0.01	0.2	0.01	0.3	0.07	1.5	0.08	1.8
Control 6.4	0.05	0.9	0.03	0.5	0.00	0.0	0.02	0.4	0.07	1.1
Control 8.1	0.07	0.8	0.01	0.2	0.02	0.2	0.03	0.3	0.08	1.0
Control 11.8	0.18	1.5	0.07	0.6	0.01	0.1	0.00	0.0	0.19	1.7
Patient 5.0	0.02	0.4	0.01	0.2	0.02	0.5	0.05	1.0	0.06	1.3
Patient 6.5	0.04	0.6	0.00	0.1	0.02	0.3	0.00	0.0	0.04	0.8
Patient 8.1	0.06	0.7	0.01	0.2	0.03	0.4	0.00	0.0	0.07	0.9
Patient 12.0	0.17	1.43	0.11	0.9	0.00	0.0	0.00	0.0	0.20	1.7

VITROS 5600 Integrated System-Analyzer #1-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.9	0.35	1.1	0.11	0.4	0.16	0.5	0.86	2.8	0.95	3.1
Control 46.1	0.64	1.4	0.36	0.8	0.00	0.0	0.31	0.7	0.77	1.7
Control 65.0	0.78	1.2	0.17	0.3	0.23	0.4	0.33	0.5	0.89	1.4
Control 105.7	1.98	1.9	0.83	0.8	0.19	0.2	0.00	0.0	2.15	2.0
Patient 31.5	0.23	0.7	0.12	0.4	0.27	0.9	0.59	1.9	0.70	2.2
Patient 47.7	0.46	1.0	0.08	0.2	0.26	0.5	0.00	0.0	0.54	1.1
Patient 65.4	0.70	1.1	0.21	0.3	0.37	0.6	0.00	0.0	0.82	1.3
Patient 107.6	1.88	1.7	1.22	1.1	0.00	0.0	0.00	0.0	2.24	2.1

VITROS 5600 Integrated System-Analyzer #2-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 5.0	0.03	0.7	0.01	0.3	0.01	0.3	0.04	0.8	0.06	1.2
Control 6.3	0.05	0.9	0.02	0.3	0.04	0.7	0.05	0.8	0.09	1.5
Control 8.0	0.08	1.0	0.00	0.0	0.04	0.5	0.06	0.7	0.11	1.4
Control 11.9	0.20	1.6	0.00	0.0	0.05	0.4	0.02	0.2	0.21	1.8
Patient 5.0	0.03	0.6	0.01	0.3	0.02	0.5	0.00	0.0	0.04	0.9
Patient 6.5	0.05	0.7	0.01	0.2	0.01	0.1	0.05	0.8	0.07	1.2
Patient 8.1	0.07	0.9	0.07	0.8	0.00	0.0	0.05	0.6	0.11	1.5
Patient 12.0	0.16	1.3	0.10	0.8	0.10	0.8	0.00	0.0	0.21	1.8

VITROS 5600 Integrated System-Analyzer #2-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.6	0.40	1.3	0.17	0.6	0.21	0.7	0.46	1.5	0.67	2.2
Control 45.6	0.64	1.4	0.23	0.5	0.48	1.1	0.56	1.2	1.01	2.2
Control 64.4	0.94	1.5	0.00	0.0	0.47	0.7	0.66	1.0	1.24	1.9
Control 106.3	2.19	2.1	0.00	0.0	0.60	0.6	0.31	0.3	2.30	2.2
Patient 31.3	0.37	1.2	0.20	0.6	0.27	0.9	0.00	0.0	0.50	1.6
Patient 47.5	0.56	1.2	0.20	0.4	0.13	0.3	0.61	1.3	0.86	1.8
Patient 65.0	0.85	1.3	0.78	1.2	0.00	0.0	0.56	0.9	1.28	2.0
Patient 107.5	1.76	1.6	1.13	1.1	1.10	1.0	0.00	0.0	2.36	2.2

VITROS 5600 Integrated System – Analyzer #3-NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 5.0	0.03	0.6	0.00	0.0	0.01	0.3	0.04	0.9	0.05	1.1
Control 6.4	0.05	0.8	0.03	0.5	0.03	0.6	0.00	0.0	0.07	1.1
Control 8.1	0.05	0.7	0.02	0.3	0.02	0.2	0.06	0.8	0.09	1.1
Control 12.0	0.14	1.2	0.06	0.5	0.10	0.8	0.02	0.2	0.19	1.5
Patient 5.1	0.02	0.4	0.01	0.2	0.01	0.2	0.01	0.2	0.03	0.6
Patient 6.6	0.03	0.4	0.04	0.6	0.01	0.2	0.03	0.5	0.06	1.0
Patient 8.1	0.03	0.4	0.07	0.7	0.00	0.0	0.05	0.7	0.10	1.3
Patient 12.1	0.18	1.5	0.02	0.2	0.13	1.0	0.13	1.1	0.26	2.2

VITROS 5600 Integrated System – Analyzer #3-IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 31.2	0.35	1.1	0.00	0.0	0.19	0.6	0.51	1.6	0.64	2.1
Control 46.6	0.56	1.2	0.35	0.8	0.43	0.9	0.00	0.0	0.79	1.7
Control 65.5	0.63	1.0	0.30	0.5	0.22	0.3	0.72	1.1	1.03	1.6
Control 107.2	1.61	1.5	0.66	0.6	1.09	1.0	0.28	0.3	2.08	1.9
Patient 31.9	0.26	0.8	0.11	0.3	0.13	0.4	0.13	0.4	0.34	1.1
Patient 48.3	0.34	0.7	0.46	1.0	0.20	0.4	0.40	0.8	0.73	1.5
Patient 65.9	0.42	0.6	0.86	1.3	0.00	0.0	0.64	1.0	1.16	1.8
Patient 109.2	2.03	1.9	0.27	0.2	1.43	1.3	1.49	1.4	2.92	2.7

VITROS 5600 Integrated System – All analyzers combined - NGSP

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
HbA1c%	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 5.0	0.03	0.6	0.01	0.2	0.01	0.3	0.05	1.1	0.00	0.0	0.07	1.2
Control 6.4	0.05	0.9	0.02	0.4	0.03	0.5	0.03	0.5	0.04	0.6	0.08	1.4
Control 8.1	0.07	0.8	0.01	0.2	0.03	0.3	0.05	0.6	0.03	0.4	0.10	1.4
Control 12.0	0.17	1.5	0.05	0.4	0.06	0.5	0.01	0.1	0.06	0.5	0.21	1.3
Patient 5.0	0.02	0.5	0.01	0.2	0.02	0.4	0.03	0.6	0.02	0.4	0.05	1.8
Patient 6.5	0.04	0.6	0.02	0.4	0.01	0.2	0.03	0.5	0.0	0.4	0.07	1.1
Patient 8.1	0.06	0.7	0.06	0.7	0.00	0.0	0.04	0.5	0.03	0.3	0.10	1.3
Patient 12.0	0.17	1.4	0.08	0.7	0.08	0.7	0.06	0.5	0.07	0.5	0.23	1.9

The between-analyzer and between –lot precision was equal to or less than 1.1% for concentrations in the range of 4.9% to 11.9% HbA1c.

VITROS 5600 Integrated System – All analyzers combined - IFCC

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Analyzer		Total	
mmol/mol	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Control 30.9	0.37	1.2	0.12	0.4	0.19	0.6	0.63	2.0	0.00	0.0	0.77	2.5
Control 46.1	0.62	1.3	0.32	0.7	0.37	0.8	0.36	0.8	0.45	1.0	0.97	2,1
Control 65.0	0.79	1.2	0.19	0.3	0.33	0.5	0.59	0.9	0.40	0.6	1.13	1.7
Control 106.4	1.95	1.8	0.60	0.6	0.73	0.7	0.20	0.2	0.72	0.7	2.28	2.1
Patient 31.5	0.30	1.0	0.14	0.4	0.23	0.7	0.35	1.1	0.22	0.7	0.58	1.8
Patient 47.8	0.46	1.0	0.28	0.6	0.21	0.4	0.42	0.9	0.35	0.7	0.80	1.7
Patient 65.4	0.68	1.0	0.68	1.0	0.00	0.0	0.48	0.7	0.35	0.5	1.14	1.7
Patient 108.1	1.89	1.7	0.97	0.9	0.96	0.9	0.70	0.6	0.77	0.7	2.56	2.4

The between-analyzer and between –lot precision was equal to or less than 2.0% for concentrations in the range of 30.9 to 108.1 mmol/mol HbA1c.

b. *Linearity/assay reportable range:*

A linearity study was conducted according to CLSI EP06-A- Evaluation of the
Linearity of Quantitative Measurement Procedure: A statistical Approach. Linearity
was assessed by taking a low (2.54% HbA1c) pool and a high (20.9% HbA1c) pool
and inter-mixing the two pools to create 17 intermediate pools. The measured values
were compared to the theoretical values based upon the dilution factor. Polynomial
regression analysis (for first, second, and third order polynomials) were performed to
determine the statistical significance of non-linearity. The higher order coefficients
were found not to be significant and linearity was demonstrated using the second
order regression analysis. The regression parameters (slope, intercept and r^2) were the
following:

NGSP:

Analyzer	Intercept	Slope	r^2	Concentration Range Tested
VITROS 5,1 FS	0.005	0.9995	0.999	2.39 to 17.35 %HbA1c
VITROS 4600	0.030	0.9957	0.997	3.03 to 15.44 %HbA1c
VITROS 5600	0.012	0.9988	0.999	2.89 to 15.79 %HbA1c

IFCC:

Analyzer	Intercept	Slope	r^2	Concentration Range Tested
VITROS 5,1 FS	0.044	0.9995	0.999	2.6 to 166.1 mmol/mol
VITROS 4600	0.223	0.9957	0.997	9.6 to 145.3 mmol/mol
VITROS 5600	0.099	0.9988	0.999	8.1 to 149.1 mmol/mol

The results of the linearity studies support the sponsor's claim that the VITROS
Chemistry HbA1c assay is linear across the measuring range of 4-14% HbA1c when
using the VITROS 5,1 FS Chemistry System, the VITROS 4600 Chemistry System
and the VITROS 5600 Integrated System analyzers.

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

Traceability

The values assigned to the VITROS Chemistry Products Calibrator Kit 31 for %A1c
are traceable to the IFCC (International Federation of Clinical Chemistry and
Laboratory Medicine) Reference Method. The VITROS® Chemistry Products HbA1c
Reagent Kit is certified by The National Glycohemoglobin Standardization Program
(NGSP). See the website for current certification at: http://www.ngsp.org

The derived result (%A1c) is calculated from the individual quantitative results for hemoglobin (Hb) and glycated hemoglobin (HbA1c). The International Federation of Clinical Chemistry (IFCC) units of mmol/mol are calculated using the Master Equation IFCC = (NGSP- 2.15) / 0.092. Two different units are provided to the customers: NGSP equivalent units (%) and IFCC equivalents units (mmol/mol).

Value Assignment

The values assigned to the VITROS Chemistry Products Calibrator Kit 31 and VITROS Chemistry Products %A1c Products %A1c Performance Verifiers are aligned to IFCC reference calibrators through an internal value assignment in which calibrator values must meet the sponsor's pre-determined acceptance criteria within a set specification, determined by the manufacturer. Each lot of VITROS Chemistry Products Calibrator and VITROS Chemistry Products %A1c Products %A1c Performance Verifiers are value-assigned. The concentration of glycated hemoglobin (HbA1c and total hemoglobin (Thb) is provided for each lot.

Stability:

The shelf life for the VITROS® Chemistry Products HbA1c Reagent Kit and calibrators is 24 months when stored at 2-8°C. The reconstituted open vial stability of the VITROS Chemistry Products Calibrator Kit 31 is 1 day when stored at 2-8°C. The in-use or on-board stability of the VITROS Chemistry products HbA1c Reagent Kit is up to 28 days.

The stability protocols and acceptance criteria were reviewed and determined to be adequate.

d. *Detection limit:*

The claimed measuring range of 4-14% HbA1c for the VITROS HbA1c Assay is based on linearity. See 1*b*. above.

e. *Analytical specificity:*

i. Endogenous Interference

Studies were performed to assess common or known substances that could interfere with the VITROS Chemistry Products HbA1c reagent kit. To determine endogenous interference, two samples pools containing %A1c at approximate concentrations of 6.5% and 8.5% were used as control pools. These pools were spiked with the test substances and the %A1c result was compared to the control pool with no interferent present. Samples were analyzed in replicates of ten on the VITROS 5,1 FS Chemistry System the VITROS 4600 Chemistry System and the VITROS 5600 Integrated System. Significant interference was defined as greater or equal to +/- 7% difference from the expected concentration. Results showed that no significant interference was

observed with the following substances up to the stated concentrations below:

Potential Interferent	Highest Concentration in which no significant interference was observed
Bilirubin	50 mg/dL
Cholesterol	350 mg/dL
Glucose	1000 mg/dL
Lipemia (Intralipid)	500 mg/dL
Rheumatoid Factor	750 IU/mL
Total Protein	22 g/dL
Triglyceride	500 mg/dL

ii. Cross –Reactivity with Hemoglobin Derivatives: To determine interference from labile, acetylated, and carbamylated hemoglobin as well as HbA0, HbA1a and HbA1b, 3 EDTA whole blood patient samples for each interferent containing %A1c concentrations of ~5%, ~6.5% and ~8.5% were used. Samples were treated to create labile, acetylated and carbamylated hemoglobin and the % A1c result was compared to the control samples with heat treatment but no chemical addition. Samples were analyzed in replicates of ten. Significant interference was defined as greater or equal to +/- 7% difference from the expected concentration. Results showed that no significant interference was observed with the following substances up to the stated concentrations below:

Potential Interferent	Highest Concentration in which no significant interference was observed
Acetylated hemoglobin	50 mg/dL
Carbamylated Hemoglobin	150 mg/dL
Labile glycated Hemoglobin	1500 mg/dL
Glycated Albumin	500 mg/dL
HbA0	Up to 90%
HbA1a	Up to 1.5%
HbA1b	Up to 4%

iii. Drug Interference: Drug interferences were evaluated using by testing common drugs that could interfere with the VITROS Chemistry Products HbA1c reagent kit.

Two samples pools containing %A1c at approximate concentrations of 6.5% and 8.5% were used as control pools. These pools were spiked with the test substances and the %A1c result was compared to the control pool with no interferent present. Samples were analyzed in replicates of ten. Significant interference was defined as greater or equal to +/- 7% difference from the expected concentration. Results showed that no significant interference was observed with the following substances up to the stated concentrations below:

Potential Interferent	Highest Concentration in which no significant interference was observed
Acetaminophen	20 mg/dL
Acetylsalicylic acid	100 mg/dL
Ampicillin	100mg/dL
Ascorbic Acid	80 mg/dL
Ca-dobesilate	20 mg/dL
Cefoxin sodium	250 mg/dL
Cyclosporin	0.5 mg/dL
Doxycyclin hyclate	5 mg/dL
Ibuprofen	50 mg/dL
Levodopa	2 mg/dL
Metformin	4 mg/dL
Methyldopa	2 mg/dL
Metronidazole	20 mg/dL
N-acetylcysteine	166.3 mg/dL
Phenylbutazone	40 mg/dL
Rifampicin	6 mg/dL
Rosiglitazone maleate	0.8 mg/dL
Theophylline	10 mg/dL

iv. Hemoglobin Variant Interference

A hemoglobin variant interference study was performed using a total of 108 samples known to contain Hemoglobin variants C, D, E, F and S. Testing of the samples was performed in replicates of 10 on the VITROS 5, 1 FS Chemistry System, VITROS 4600 Chemistry System and VITROS 5600 Integrated System and compared to results obtained by a reference method that demonstrated to be free of interferences from the hemoglobin variant being tested. The numbers and concentrations of hemoglobin variants tested, and the range of %HbA1c concentrations in which they were tested on each analyzer are shown below:

Hemoglobin Variant	# samples tested	Variant Concentration Range (%)	Range of %A1c Concentration
HbA2	22	4.9 – 6.1	5.7 – 9.0
HbC	31	24.5-38.4	5.1 – 9.8
HbD	21	29.0-38.0	5.2 – 11.3
HbE	30	14.3-26.3	5.4 – 9.1
HbS	40	28.2-41.6	4.6 – 12.7
HbF	43	0.2 - 34.8	5.5 - 12.8

The results obtained from the hemoglobin variant study are summarized below:

VITROS 5,1 FS Chemistry System

Hemoglobin Variant	Relative % Difference from Reference Concentration at Low and High HbA1c Concentrations			
	~ 6.0 %HbA1c		~ 9.0 %HbA1c	
	Relative %Bias	Range %Bias	Relative %Bias	Range %Bias
HbA2	-1.80	-7.25% to 0.68%	-2.67	-5.08% to -2.13%
HbC	-2.56	-7.13% to 3.24%	-2.85	-4.00% to 0.30%
HbD	-1.52	-7.65% to 2.86%	-2.95	-4.34% to 0.05%
HbE	-0.37	-6.45% to 3.95%	-1.00	-1.26% to 6.01%
HbS	0.76	-4.72% to 5.95%	0.70	-1.60% to 7.86%
HbF	HbF Interferes with this assay			

VITROS 4600 Integrated System

Hemoglobin Variant	Relative % Difference from Reference Concentration at Low and High HbA1c Concentrations			
	~ 6.0 %HbA1c		~ 9.0 %HbA1c	
	Relative %Bias	Range %Bias	Relative %Bias	Range %Bias
HbA2	-1.78	-7.07% to 1.60%	-1.81	-4.52% to -1.40%
HbC	-1.92	-6.44% to 2.68%	-2.67	-2.58% to -0.26%
HbD	-1.33	-6.09% to 1.25%	-3.74	-4.61% to -2.58%
HbE	2.38	-3.41% to 7.92%	-0.69	-5.13% to 1.46%
HbS	-0.84	-4.07% to 4.29%	0.30	-1.05% to 7.85%
HbF	HbF Interferes with this assay			

VITROS 5600 Integrated System

Hemoglobin Variant	Relative % Difference from Reference Concentration at Low and High HbA1c Concentrations			
	~ 6.0 %HbA1c		~ 9.0 %HbA1c	
	Relative %Bias	Range %Bias	Relative %Bias	Range %Bias
HbA2	-3.25	-8.12% to 1.33%	-4.12	-8.03% to -1.66%
HbC	-2.86	-6.46% to 1.18%	-3.52	-4.05% to -1.26%
HbD	-2.71	-7.18% to 0.45%	-5.37	-6.65% to -4.98%
HbE	-0.49	-6.15% to 3.94%	-2.39	-7.11% to -0.62%
HbS	-0.74	-7.40% to 4.24%	-1.87	-1.83% to 4.21%
HbF	HbF Interferes with this assay			

The sample data shown for the ~6.0% column spanned from 5.5-6.5% HbA1c. The sample data shown for the ~9.0% column spanned from 8.5-9.5% HbA1c.

The sponsor claims that no significant interference was observed for the HbC, HbD, HbE, HbS and HbA2 variants at the concentrations tested above.

Additionally, the device labeling contains the following prominent boxed warning in the package insert labeling:

"This device has significant negative interference with fetal hemoglobin (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF including those with known Hereditary Persistence of Fetal Hemoglobin."

f. *Assay cut-off:*

Not applicable

2. Comparison studies:

a. *Method comparison with predicate device:*

A method comparison study was conducted based on CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples Guideline. A total of 125 samples with a sample range of 4.2 to 13.4% HbA1c were evaluated on the VITROS 5,1 FS Chemistry System, the VITROS 4600 Chemistry System and the VITROS 5600 Integrated System using the candidate VITROS Chemistry Products HbA1c assay versus the reference laboratory method (Tosoh G8-HPLC method). Samples were distributed across the claimed measuring range of the assay. Samples were tested in singlicate, over a 10 day period. Two lots of the candidate reagent were used on each of the VITROS 5,1 FS, VITROS 4600 and VITROS 5600 platforms. The

distribution of samples spanned the measuring interval (with a concentration of samples around the clinical decision points) as follows:

| Hemoglobin A1c level	Number of samples	%samples tested
≤ 5%	5	4%
5 – 6%	16	12.8%
6 – 6.5%	23	18.4%
6.5 – 7%	31	24.8%
7 – 8%	20	16%
8 – 9%	11	8.8%
> 9%	19	15.2%
Total samples	125	100%

Bias between Candidate and NGSP method

Deming (weighted) and Passing-Bablok regression analysis were performed for the VITROS Chemistry Product HbA1c Reagent using the VITROS 5,1 FS Chemistry System, the VITROS 4600 Integrated System and the VITROS 5600 Integrated System versus the Tosoh G8-HPLC reference method.

Summary of results are as follows:

Analyzer	Regression	Slope	95% CI	Intercept	95% CI
5,1 FS	Passing-Bablok	0.998	0.991 to 1.006	-0.019	-0.072 to 0.031
	Deming	1.007	0.995 to 1.02	-0.076	-0.16 to 0.008
4600	Passing-Bablok	1.012	1.004 to 1.02	-0.079	-0.133 to -0.025
	Deming	1.020	1.007 to 1.032	-0.139	-0.222 to -0.056
5600	Passing-Bablok	1.004	0.996 to 1.011	-0.056	-0.107 to -0.005
	Deming	1.004	0.992 to 1.015	-0.056	-0.132 to 0.021

Scatter Plot for Passing & Bablok regression on the VITROS 5,1 FS Chemistry System
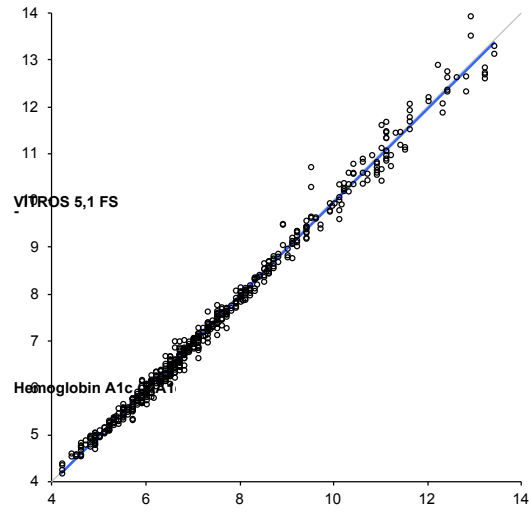
Scatter Plot for the Deming Regression on the VITROS 5,1 FS Chemistry System
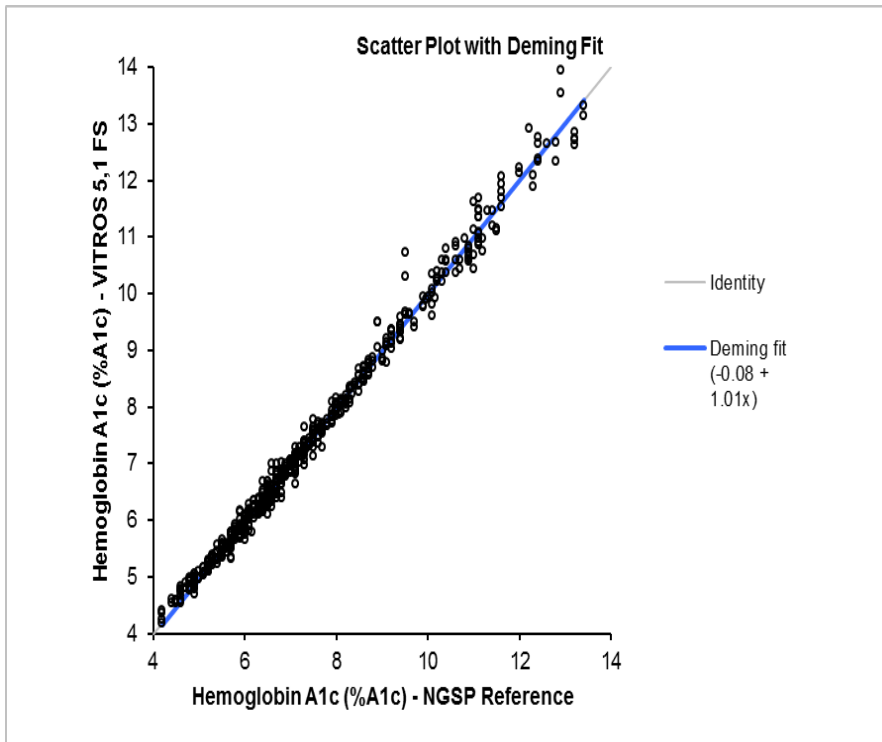
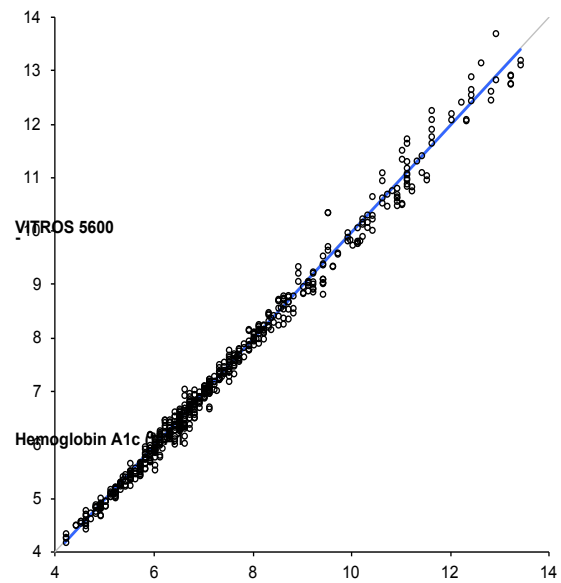Scatter Plot for the Passing & Bablok regression on the VITROS 4600 Integrated System
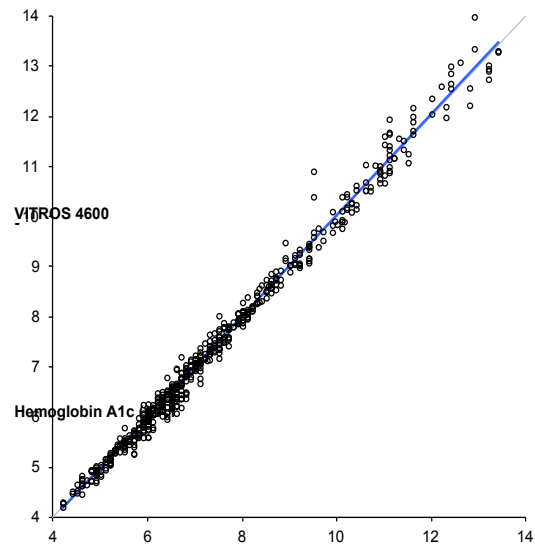
Scatter Plot for the Deming regression on the VITROS 4600 Integrated System
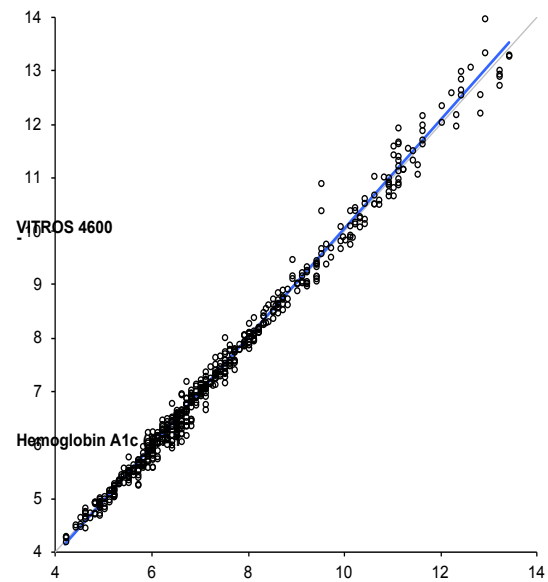
Scatter Plot for the Passing & Bablok regression on the VITROS 5600 Integrated System
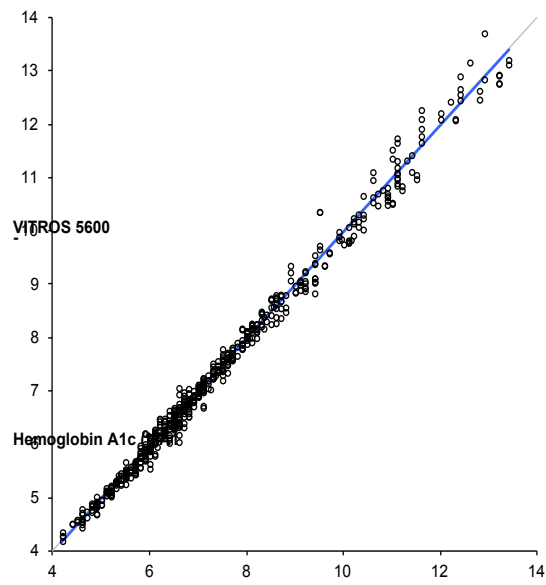
Scatter Plot for the Deming regression on the VITROS 5600 Integrated System

The following biases between the VITROS Chemistry Product HbA1c Reagent using the VITROS 5,1 FS Chemistry System, the VITROS 4600 Integrated System and the VITROS 5600 Integrated System versus the Tosoh G8-HPLC reference method were observed:

Deming Regression Analysis (NGSP):

	Decision Level (%NGSP)	Bias	%Bias
VITROS 5,1 FS	5.0	-0.040	-0.798
	6.5	-0.029	-0.447
	8.0	-0.018	-0.228
	12.0	0.011	0.089
	Decision Level (%NGSP)	Bias	%Bias
VITROS 4600	5.0	-0.040	-0.805
	6.5	-0.011	-0.164
	8.0	0.019	0.236
	12.0	0.098	0.814
	Decision Level (%NGSP)	Bias	%Bias
VITROS 5600	5.0	-0.036	-0.723
	6.5	-0.030	-0.467
	8.0	-0.024	-0.306
	12.0	-0.009	-0.075

Passing & Bablok (NGSP):

	Decision Level (%NGSP)	Bias	%Bias
VITROS 5,1 FS	5.0	-0.027	-0.543
	6.5	-0.030	-0.454
	8.0	-0.032	-0.398
	12.0	-0.038	-0.317
VITROS 4600	Decision Level (%NGSP)	Bias	%Bias
	5.0	-0.019	-0.380
	6.5	-0.001	-0.016
	8.0	0.017	0.211
	12.0	0.065	0.540
VITROS 5600	Decision Level (%NGSP)	Bias	%Bias
	5.0	-0.038	-0.760
	6.5	-0.033	-0.501
	8.0	-0.027	-0.338
	12.0	-0.012	-0.104

Deming Regression Analysis (IFCC):

	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
VITROS 5,1 FS	31.1	-0.373	-1.199
	47.5	-0.296	-0.622
	63.9	-0.218	-0.341
	107.7	-0.011	-0.010
VITROS 4600	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
	31.1	-0.367	-1.179
	47.5	-0.091	-0.192
	63.9	0.185	0.289
	107.7	0.920	0.855
VITROS 5600	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
	31.1	-0.332	-1.066
	47.5	-0.309	-0.651
	63.9	-0.287	-0.448
	107.7	-0.226	-0.210

Passing & Bablok (IFCC)

	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
VITROS 5,1 FS	31.1	-0.297	-0.954
	47.5	-0.323	-0.679
	63.9	-0.348	-0.545
	107.7	-0.416	-0.387
	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
VITROS 4600	31.1	-0.208	-0.667
	47.5	-0.011	-0.024
	63.9	0.185	0.289
	107.7	0.708	0.658
	Decision Level (mmol/mol)	Bias (mmol/mol)	%Bias
VITROS 5600	31.1	-0.415	-1.334
	47.5	-0.356	-0.748
	63.9	-0.296	-0.463
	107.7	-0.137	-0.127

Total Error Near the Cutoff

Using the results of bias estimation (%Bias) in the method comparison study and precision estimated in the reproducibility study. Total Error (TE) at four concentrations: (5.0, 6.5, 8.0 and 12.0%) was calculated as the following:

	Decision Level (%NGSP)	%Bias	%CV	%TE*	%TE^
VITROS 5,1 FS	5.0	-0.798	2.21	5.14	5.10
	6.5	-0.447	2.01	4.39	4.37
	8.0	-0.228	1.92	4.00	3.99
	12.0	0.089	2.52	5.03	5.04

*TE = |Bias| + 1.96*SD
^%TE = |%Bias| + 1.96*%CV*(1+%Bias)

	Decision Level (%NGSP)	%Bias	%CV	%TE*	%TE^
VITROS 4600	5.0	-0.805	1.10	2.97	2.95
	6.5	-0.164	1.19	2.50	2.49
	8.0	0.236	1.66	3.50	3.50
	12.0	0.814	2.09	4.91	4.94

*TE = |Bias| + 1.96*SD
^%TE = |%Bias| + 1.96*%CV*(1+%Bias)

	Decision Level (%NGSP)	%Bias	%CV	%TE*	%TE^
VITROS 5600	5.0	-0.723	1.05	2.79	2.77
	6.5	-0.467	1.12	2.66	2.65
	8.0	-0.306	1.28	2.81	2.80
	12.0	-0.075	1.94	3.88	3.88

*TE = |Bias| + 1.96*SD
^%TE = |%Bias| + 1.96*%CV*(1+%Bias)

b. *Matrix comparison:*

K_2 and K_3-EDTA whole blood samples are to be used with this assay. Matrix equivalence was previously established in k060650 and k041764.

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 labeling indicates: The expected normal HbA1c range in adults is 4.0-6.0% (NGSP)[1] The Standards of Medical Care in Diabetes – 2015 recommend to diagnose diabetes using a HbA1c method that is NGSP-certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay and a cut point of HbA1c $\geq$ 6.5%.[2,3]

[1]Implementation of haemoglobin A1c results traceable to the IFCC reference system: the way forward; *Clin Chem Lab Med* 2007; 45(8):942-944.

[2]International Expert Committee Report in the Role of the A1c Assay in the Diagnosis of Diabetes. *Diabetes Care*. 32: (7):1327-1334; 2009.

[3]Standards of Medical Care in Diabetes. *Diabetes Care. 38:* Supplement 1; S8-S16, 2015

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.