

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

A. 510(k) Number:

k140654

B. Purpose for Submission:

New Device

C. Measurand:

Glycosylated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative, enzymatic

E. Applicant:

Abbott Laboratories

F. Proprietary and Established Names:

Hemoglobin A1c Assay
Hemoglobin A1c Calibrators
Hemoglobin A1c Controls

G. Regulatory Information:

Regulatory Description	Classification	Regulation	Product Code	Panel
Hemoglobin A1c Test System	II	21 CFR 862.1373	PDJ	Chemistry, 75
Glycosylated Hemoglobin Assay	II	21 CFR 864.7470	LCP	Hematology, 81
Calibrator	II	21 CFR 862.1150	JIT	Chemistry, 75
Quality Control Material	II	21 CFR 862.1660	JJX	Chemistry, 75

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Hemoglobin A1c assay is used in clinical laboratories for the quantitative *in vitro* measurement of percent hemoglobin A1c (NGSP) or HbA1c fraction mmol/mol (IFCC) in human whole blood and hemolysate on the ARCHITECT c 4000 System.

Hemoglobin A1c measurements are used as an aid in the diagnosis of diabetes mellitus, as an aid to identify patients who may be at risk for developing diabetes mellitus, and for the monitoring of long-term blood glucose control in individuals with diabetes mellitus.

The Hemoglobin A1c Calibrators are for use in the calibration of the Hemoglobin A1c assay on the ARCHITECT c 4000 System.

The Hemoglobin A1c Controls are used for the estimation of test precision and the detection of systematic analytical deviations of the Hemoglobin A1c assay on the ARCHITECT c 4000 System.

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.
- Glycated HbF is not detected by the assay as it does not contain the β -chain that characterizes HbA1c. However, HbF is measured in the total Hb assay and as a consequence, specimens containing high amounts of HbF (>5%) may result in lower than expected mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP).
- The Hemoglobin A1c assay should not be used to diagnose diabetes during pregnancy. Hemoglobin A1c reflects the average blood glucose levels over the preceding 3 months (i.e., the average life span of a red blood cell) and therefore may be falsely low during pregnancy or any other condition associated with recent onset of hyperglycemia and/or decreased red blood cell survival.
- The Hemoglobin A1c assay should not be used to diagnose or monitor diabetes in patients with the following conditions:
 - hemoglobinopathies except as demonstrated to produce acceptable performance (e.g., sickle cell trait).
 - abnormal red blood cell turnover. (e.g., anemias from hemolysis and iron deficiency).
 - malignancies, and severe chronic hepatic and renal disease.

- In cases of rapidly evolving Type 1 diabetes, the increase of HbA1c values might be delayed compared to the acute increase in glucose concentrations. In these conditions, diabetes mellitus must be diagnosed based on plasma glucose concentrations and/or the typical clinical symptoms.
- This test should not replace glucose testing for patients with Type 1 diabetes, pediatric patients or pregnant women.

4. Special instrument requirements:

For use on the ARCHITECT c 4000 System

I. Device Description:

The Hemoglobin A1c Reagent Kit contains two working reagents, Reagent 1 and Reagent 2 and a hemolyzing reagent (Diluent) with the following constituents:

Reagent	Reactive Ingredients	Concentration
Reagent 1	10-(carboxymethylaminocarbonyl)-3,7-bis(dimethylamino)phenothiazine sodium salt	0.000817%
	Protease (bacterial)	< 1 mU/dL
Reagent 2	Peroxidase (horseradish)	5 to 15 kU/dL
	Fructosyl-peptide-oxidase (E. coli, recombinant)	300 to 900 U/dL
Diluent	Sodium nitrite	> 0.05 to < 0.3%

Inactive Ingredients: Reagent 1 contains sodium azide as a stabilizer and preservative. Reagent 1 and Diluent contain ProClin 300 as a preservative. Reagent 2 contains ofloxacin as a preservative.

The Hemoglobin A1c assay consists of two application types: The Whole Blood application used an automated on-board pretreatment with hemolyzing reagent, (Diluent). The Hemolysate application consists of a manual pretreatment step which is performed using the hemolyzing reagent before the sample is placed on the analyzer.

The Hemoglobin A1c Calibrators

The Hemoglobin A1c Calibrators are for use in the calibration of the Hemoglobin A1c assay on the ARCHITECT c 4000 System.

The Hemoglobin A1c Calibrator Kit contains two levels of calibrator material, Calibrator 1 (Cal 1) and Calibrator 2 (Cal 2). A1c Calibrators (lyophilized) contain hemoglobin and glycated hemoglobin from human whole blood. Prior to lyophilization, the calibrator matrix is an MES-buffered solution. Preservative: Ofloxacin.

The value-assigned A1c Calibrator values are within the following hemoglobin A1c ranges:
 Calibrator 1: 4.59% to 6.02% HbA1c
 Calibrator 2: 10.52% to 13.37% HbA1c
 Actual analyte concentrations for each lot of calibrators are listed in the Hemoglobin A1c Calibrator Value Sheet, packaged with the calibrator.

The Hemoglobin A1c Controls

The Hemoglobin A1c Control Kit contains: a low control (Control L) and a high control (Control H) A1c Controls (lyophilized) contain hemoglobin and glycated hemoglobin from human whole blood. Prior to lyophilization, the control matrix is an MES-buffered solution. Preservative: Ofloxacin.

The value-assigned A1c Control values are within the following hemoglobin A1c ranges:
 Control L: 4.59% to 6.02% HbA1c
 Control H: 9.42% to 11.07 % HbA1c.

Actual analyte concentrations for each lot of controls are listed in the Hemoglobin A1c Control Value Sheet, packaged with the controls.

All human source materials were tested by FDA approved methods and found to be negative for the presence of HBs Ag and antibody to HIV1/HIV2, and HCV

J. Substantial Equivalence Information:

Predicate device name(s):

Predicate Device Name	Predicate Device 510(k) Number
Hemoglobin A1c	K130255
Hemoglobin A1c Calibrators	K130255
Hemoglobin A1c Controls	K130255

Comparison with predicate:

Reagents Similarities and Differences		
Characteristics	Candidate Device Hemoglobin A1c Assay	Predicate Device Hemoglobin A1c Assay (k130255)
Intended Use and Indications for Use	Same	For the quantitative <i>in vitro</i> measurement of percent hemoglobin A _{1c} (NGSP) or HbA _{1c} fraction mmol/mol (IFCC) in human whole blood and hemolysate.

Reagents Similarities and Differences		
Characteristics	Candidate Device Hemoglobin A1c Assay	Predicate Device Hemoglobin A1c Assay (k130255)
Platform	ARCHITECT c 4000 Systems (clinical chemistry analyzer)	ARCHITECT c 8000 System (clinical chemistry analyzer)
Methodology	Same	Enzymatic
Specimen Type	Same	<u>Whole blood and Hemolysate:</u> Dipotassium EDTA Lithium Heparin Sodium Heparin Sodium Fluoride/Disodium EDTA Tripotassium EDTA
Measuring Interval	Same	4.0 to 14.0 %HbA _{1c} (DCCT/NGSP) 20.22 to 129.51 mmol/mol HbA _{1c} (IFCC)

Calibrators Similarities and Differences		
Characteristics	Candidate Device Hemoglobin A1c Calibrators	Predicate Device Hemoglobin A1c Calibrators (k130255)
Intended use	For use in the calibration of the Hemoglobin A _{1c} assay on the ARCHITECT c 4000 Systems.	For use in the calibration of the Hemoglobin A _{1c} assay on the ARCHITECT c 8000 System.
Platform	ARCHITECT c 4000 Systems (clinical chemistry analyzer)	ARCHITECT c 8000 System (clinical chemistry analyzer)
Levels	Same	2 levels (Calibrator 1 and 2) Each lot of calibrators is value-assigned and values are reported in both NGSP and IFCC units. Actual analyte concentrations for each lot of calibrators are listed in the Hemoglobin A _{1c} Calibrator Value Sheet, packaged with the calibrator. The concentration of glycated hemoglobin (HbA _{1c}) and total hemoglobin (THb) is provided for each lot.

Calibrators Similarities and Differences		
Characteristics	Candidate Device Hemoglobin A1c Calibrators	Predicate Device Hemoglobin A1c Calibrators (k130255)
Standardization/ Traceability	Same	Calibrators are prepared gravimetrically, lyophilized, and then value assigned using secondary calibrators that are traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method.

Controls Similarities and Differences		
Characteristics	Candidate Device Hemoglobin A1c Controls	Predicate Device Hemoglobin A1c Controls (k130255)
Intended use	For the estimation of test precision and the detection of systematic analytical deviations of the Hemoglobin A _{1c} assay on the ARCHITECT <i>c</i> 4000 Systems.	For the estimation of test precision and the detection of systematic analytical deviations of the Hemoglobin A _{1c} assay on the ARCHITECT <i>c</i> 8000 System.
Platform	ARCHITECT <i>c</i> 4000 Systems (clinical chemistry analyzer)	ARCHITECT <i>c</i> 8000 System (clinical chemistry analyzer)
Levels	Same	2 levels (Low and High Control) Lyophilized Assignment of values is specific for each lot.
Material	Same	Controls are prepared using hemoglobin and glycated hemoglobin from human whole blood. Prior to lyophilization, the matrix used is MES buffered solution.

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

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

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

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Second Edition

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

CLSI EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantification; Approved Guideline

L. Test Principle:

The Hemoglobin A1c assay consists of two separate concentration measurements: glycated hemoglobin (HbA1c) and total hemoglobin (THb). The two concentrations are used to determine the percent HbA1c (NGSP units) or the hemoglobin fraction in mmol/mol (IFCC units). The individual concentration values of HbA1c and THb generated by the Hemoglobin A1c assay are used only for calculating the percent hemoglobin A1c or HbA1c fraction, and must not be used individually for diagnostic purposes. The anticoagulated whole blood specimen is lysed automatically on the system for the Whole Blood application or may be lysed manually using the Hemoglobin A1c Diluent for the Hemolysate application.

Glycated Hemoglobin (HbA1c)

The Hemoglobin A1c assay utilizes an enzymatic method that specifically measures *N*-terminal fructosyl dipeptides of the β -chain of HbA1c. In the pretreatment process, the erythrocytes are lysed and the hemoglobin is transformed to methemoglobin by reaction with sodium nitrite. With the addition of Reagent 1 to the sample, the glycosylated *N*-terminal dipeptide (fructosyl-VH) of the β -chain of hemoglobin is cleaved by the action of protease. The hemoglobin is transformed to stable methemoglobin azide by the action of sodium azide and the concentration of the hemoglobin is determined by measuring absorbance. Addition of Reagent 2 starts a reaction and fructosyl peptideoxidase (FPOX) is allowed to react with fructosyl-VH. The HbA1c concentration is measured by determining the resultant hydrogen peroxide.

Total Hemoglobin (THb)

The hemoglobin is oxidized to stable methemoglobin azide by the action of sodium nitrite and sodium azide and the concentration of the hemoglobin is determined by measuring absorbance (sample + R1).

Hemoglobin A1c Calculations

The final result is expressed as %HbA_{1c} (NGSP) or mmol/mol HbA_{1c} (IFCC) and is automatically calculated by the system from the HbA_{1c}/THb ratio as follows:

mmol/mol HbA1c IFCC:

$$\text{HbA}_{1c} (\text{mmol/mol}) = (\text{HbA}_{1c}/\text{THb}) \times 1000$$

%HbA1c DCCT/NGSP:

$$\text{HbA}_{1c} (\%) = \text{IFCC} \times 0.09148 + 2.152$$

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Within-Laboratory Precision (20-Day)

A 20-day precision study was conducted to evaluate the precision performance of the Hemoglobin A1c assay based on guidance from the CLSI document EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods. Testing was performed using 3 lots of Hemoglobin A1c Reagents, 3 lots of Hemoglobin A1c Calibrators, 1 lot of Hemoglobin A1c Controls (Low and High), and 1 lot of commercially available human whole blood controls (Control Levels 1, 2, and 3) on 3 ARCHITECT c 4000 analyzers. Three levels of controls made from reconstituted lyophilized anticoagulated human whole blood and three levels of pooled human anticoagulated venous whole blood (panels) were tested a minimum of 2 replicates, twice per day, for a total of 20 testing days. Total number of measurements per sample was 720 (=3 instruments x 3 lots x 20 days x 2 runs x 2 replicates). Results are shown below in NGSP and IFCC units. The HbA1c sample abbreviations are as follows: LC= Hemoglobin A1c Low Control (target value 5.2 %), HC= Hemoglobin A1c High Control (target value 10.0%), CL3= commercially available control level 3 (target value 14.6%); PS1 = human whole blood near the lower limit of the measuring interval (target range 4.0-4.6%), PS2=human whole blood near the medical decision point (target range 6.0- 7.0%) PS3= human whole blood above the medical decision point (target range 8.0-10.0%).

Hemoglobin A1c Reproducibility

Hemolysate Application NGSP

ARCHITECT c 4000 analyzer # 1

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 5.2%	0.01	0.2	0.01	0.2	0.01	0.2	0.01	0.1	0.02	0.3
HC 10.0%	0.01	0.1	0.01	0.1	0.02	0.2	0.03	0.3	0.04	0.4
CL3 14.5%	0.04	0.2	0.02	0.2	0.04	0.3	0.13	0.9	0.14	1.0
PS1 4.5%	0.01	0.2	0.01	0.3	0.01	0.2	0.02	0.5	0.3	0.7
PS2 6.5%	0.01	0.2	0.02	0.2	0.02	0.3	0.04	0.6	0.05	0.7
PS3 9.0%	0.02	0.2	0.01	0.1	0.02	0.2	0.06	0.7	0.07	0.8

ARCHITECT c 4000 analyzer #2

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 5.3%	0.01	0.2	0.01	0.3	0.01	0.2	0.02	0.4	0.03	0.6
HC 10.1%	0.01	0.1	0.02	0.2	0.02	0.2	0.06	0.5	0.06	0.6
CL3 14.4%	0.05	0.4	0.03	0.2	0.00	0.0	0.02	0.1	0.06	0.4
PS1 4.5%	0.01	0.3	0.01	0.3	0.02	0.4	0.04	0.8	0.05	1.0
PS2 6.5%	0.01	0.2	0.01	0.2	0.02	0.4	0.05	0.8	0.06	0.9
PS3 9.0%	0.02	0.2	0.02	0.2	0.02	0.2	0.07	0.7	0.07	0.8

ARCHITECT c 4000 analyzer # 3

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 5.3%	0.01	0.2	0.01	0.2	0.00	0.0	0.03	0.7	0.04	0.7
HC 10.1%	0.01	0.1	0.01	0.1	0.01	0.1	0.07	0.7	0.07	0.7
CL3 14.3%	0.04	0.3	0.04	0.3	0.01	0.1	0.10	0.7	0.11	0.8
PS1 4.5%	0.01	0.3	0.01	0.2	0.01	0.1	0.05	1.0	0.5	1.1
PS2 6.5%	0.01	0.2	0.01	0.1	0.02	0.2	0.05	0.8	0.06	0.9
PS3 8.9%	0.02	0.2	0.01	0.1	0.02	0.2	0.06	0.6	0.07	0.7

ARCHITECT c 4000 analyzers (combined)

Reproducibility – Hemolysate Application, NGSP												
Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Between Instrument		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 5.3%	0.01	0.2	0.01	0.2	0.01	0.2	0.02	0.5	0.02	0.3	0.03	0.6
HC 10.1%	0.01	0.1	0.01	0.1	0.02	0.2	0.05	0.5	0.03	0.3	0.7	0.6
CL3 14.4%	0.04	0.3	0.04	0.3	0.02	0.1	0.09	0.7	0.11	0.8	0.16	1.1
PS1, 4.5%	0.01	0.3	0.01	0.3	0.01	0.3	0.04	0.8	0.01	0.3	0.04	1.0
PS2 6.5%	0.01	0.2	0.01	0.2	0.02	0.3	0.05	0.7	0.01	0.2	0.06	0.9
PS3 9.0%	0.02	0.2	0.01	0.2	0.02	0.2	0.06	0.7	0.02	0.2	0.07	0.8

Whole Blood Application NGSP

ARCHITECT c 4000 analyzer #1

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 4.9%	0.01	0.3	0.01	0.3	0.02	0.3	0.00	0.1	0.02	0.5
HC 9.6%	0.02	0.2	0.02	0.2	0.01	0.1	0.01	0.1	0.03	0.3
CL3 14.6%	0.03	0.2	0.05	0.4	0.03	0.2	0.03	0.2	0.07	0.5
PS1 4.4%	0.01	0.2	0.01	0.3	0.01	0.2	0.03	0.7	0.04	0.9
PS2 6.5%	0.01	0.2	0.01	0.2	0.01	0.2	0.04	0.6	0.05	0.7
PS3 9.0%	0.01	0.1	0.01	0.1	0.02	0.2	0.05	0.6	0.06	0.6

ARCHITECT c 4000 analyzer #2

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 4.9%	0.01	0.3	0.02	0.5	0.02	0.5	0.00	0.0	0.03	0.7
HC 9.6%	0.02	0.2	0.02	0.2	0.02	0.2	0.01	0.1	0.04	0.4
CL3 14.5%	0.03	0.2	0.06	0.4	0.04	0.3	0.04	0.3	0.08	0.6
PS1 4.5%	0.01	0.2	0.02	0.4	0.02	0.4	0.03	0.7	0.04	0.9
PS2 6.5%	0.01	0.1	0.02	0.3	0.02	0.3	0.04	0.5	0.04	0.7
PS3 9.0%	0.01	0.1	0.01	0.1	0.02	0.2	0.05	0.5	0.05	0.6

ARCHITECT c 4000 analyzer #3

Mean % HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 4.9%	0.01	0.2	0.02	0.4	0.00	0.0	0.02	0.4	0.03	0.6
HC 9.6%	0.02	0.2	0.02	0.2	0.01	0.1	0.03	0.3	0.04	0.4
CL3 14.5%	0.02	0.2	0.06	0.4	0.03	0.2	0.05	0.4	0.09	0.6
PS1 4.4%	0.01	0.2	0.01	0.3	0.01	0.2	0.04	0.9	0.04	1.0
PS2 6.5%	0.01	0.2	0.01	0.2	0.01	0.2	0.04	0.7	0.05	0.8
PS3 9.0%	0.01	0.2	0.02	0.2	0.01	0.2	0.05	0.6	0.06	0.6

ARCHITECT c 4000 analyzers (combined)

Reproducibility – Whole Blood Application, NGSP												
Mean	Repeatability		Between Run		Between Day		Between Lot		Between Instrument		Total	
	SD	%C V	SD	%C V	SD	%C V	SD	%C V	SD	%C V	SD	%C V
% HbA_{1c}												
LC 4.9%	0.01	0.3	0.02	0.4	0.02	0.3	0.01	0.2	0.01	0.3	0.03	0.7
HC 9.6%	0.02	0.2	0.02	0.2	0.02	0.2	0.02	0.2	0.01	0.1	0.04	0.4
CL3 14.5%	0.03	0.2	0.06	0.4	0.03	0.2	0.04	0.3	0.03	0.2	0.09	0.6
PS1 4.4%	0.01	0.2	0.01	0.3	0.01	0.3	0.04	0.8	0.01	0.2	0.04	1.0
PS2 6.5%	0.01	0.2	0.01	0.2	0.01	0.2	0.04	0.6	0.01	0.2	0.05	0.7
PS3 9.0%	0.01	0.1	0.01	0.2	0.02	0.2	0.05	0.5	0.01	0.1	0.06	0.6

Hemolysate Application IFCC

ARCHITECT c 4000 analyzer #1

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
mmol/mol HbA_{1c}										
LC 33.86	0.083	0.2	0.113	0.3	0.095	0.3	0.058	0.2	0.179	0.5
HC 86.31	0.134	0.2	0.112	0.1	0.188	0.2	0.308	0.4	0.401	0.5
CL3 135.02	0.385	0.3	0.250	0.2	0.471	0.3	1.413	1.0	1.558	1.2
PS1 25.26	0.107	0.4	0.139	0.6	0.105	0.4	0.262	1.0	0.333	1.3
PS2 47.16	0.118	0.3	0.168	0.4	0.199	0.4	0.414	0.9	0.503	1.1
PS3 74.52	0.200	0.3	0.126	0.2	0.218	0.3	0.662	0.9	0.736	1.0

ARCHITECT c 4000 analyzer #2

Mean mmol/mol HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 34.03	0.106	0.3	0.164	0.5	0.133	0.4	0.250	0.7	0.344	1.0
HC 86.86	0.149	0.2	0.167	0.2	0.174	0.2	0.605	0.7	0.688	0.8
CL3 133.68	0.569	0.4	0.369	0.3	0.000	0.0	0.185	0.1	0.703	0.5
PS1 25.36	0.147	0.6	0.161	0.6	0.182	0.7	0.404	1.6	0.494	1.9
PS2 47.27	0.127	0.3	0.152	0.3	0.256	0.5	0.543	1.1	0.633	1.3
PS3 74.56	0.191	0.3	0.185	0.2	0.277	0.2	0.724	1.0	0.792	1.1

ARCHITECT c 4000 analyzer #3

Mean mmol/mol HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 34.01	0.099	0.3	0.104	0.3	0.021	0.1	0.378	1.1	0.405	1.2
HC 86.67	0.118	0.1	0.142	0.2	0.124	0.1	0.732	0.8	0.765	0.9
CL3 133.30	0.392	0.3	0.432	0.3	0.133	0.1	1.079	0.8	1.233	0.9
PS1 25.15	0.131	0.5	0.089	0.4	0.056	0.2	0.509	2.0	0.536	2.1
PS2 47.02	0.137	0.3	0.105	0.2	0.174	0.4	0.574	1.2	0.624	1.3
PS3 74.24	0.218	0.3	0.124	0.2	0.230	0.3	0.632	0.9	0.718	1.0

ARCHITECT c 4000 analyzers (combined)

Reproducibility – Hemolysate Application, IFCC													
Mean	Repeatability		Between Run		Between Day		Between Lot		Between Instrument		Total		
	mmol/mol HbA _{1c}	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 33.97	0.097	0.3	0.130	0.4	0.095	0.3	0.261	0.8	0.169	0.5	0.363	1.1	
HC 86.61	0.135	0.2	0.142	0.2	0.164	0.2	0.577	0.7	0.333	0.4	0.713	0.8	
CL3 134.00	0.457	0.3	0.405	0.3	0.207	0.2	1.032	0.8	1.236	0.9	1.735	1.3	
PS1, 25.26	0.130	0.5	0.133	0.5	0.125	0.5	0.405	1.6	0.153	0.6	0.487	1.9	
PS2 47.15	0.127	0.3	0.144	0.3	0.213	0.5	0.515	1.1	0.146	0.3	0.608	1.3	
PS3 74.44	0.203	0.3	0.148	0.2	0.210	0.3	0.674	0.9	0.173	0.2	0.769	1.0	

Whole Blood Application IFCC

ARCHITECT c 4000 analyzer #1

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
	mmol/mol HbA _{1c}	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD
LC 30.50	0.143	0.5	0.133	0.4	0.176	0.6	0.034	0.1	0.265	0.9
HC 81.84	0.194	0.2	0.219	0.3	0.133	0.2	0.147	0.2	0.353	0.4
CL3 135.83	0.326	0.2	0.590	0.4	0.334	0.2	0.329	0.2	0.821	0.6
PS1 24.61	0.116	0.5	0.153	0.6	0.100	0.4	0.353	1.4	0.414	1.7
PS2 46.61	0.117	0.2	0.111	0.2	0.145	0.3	0.453	1.0	0.502	1.1
PS3 74.29	0.129	0.2	0.147	0.2	0.226	0.3	0.546	0.7	0.623	0.8

ARCHITECT c 4000 analyzer #2

Mean mmol/mol HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
LC 30.38	0.136	0.4	0.253	0.8	0.249	0.8	0.029	0.1	0.381	1.3
HC 81.75	0.171	0.2	0.222	0.3	0.237	0.3	0.151	0.2	0.397	0.5
CL3 135.22	0.321	0.2	0.636	0.5	0.435	0.3	0.397	0.3	0.925	0.7
PS1 25.14	0.086	0.3	0.192	0.8	0.204	0.8	0.335	1.3	0.445	1.8
PS2 47.23	0.106	0.2	0.175	0.4	0.204	0.4	0.385	0.8	0.481	1.0
PS3 74.70	0.126	0.2	0.152	0.2	0.189	0.3	0.499	0.7	0.569	0.8

ARCHITECT c 4000 analyzer #3

Mean mmol/mol HbA _{1c}	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	%CV	SD	%C V	SD	%CV	SD	%CV	SD	%CV
LC 30.32	0.125	0.4	0.199	0.7	0.000	0.0	0.220	0.7	0.	0.
HC 81.70	0.191	0.2	0.220	0.3	0.139	0.2	0.338	0.4	0.	0.
CL3 135.42	0.258	0.2	0.708	0.5	0.271	0.2	0.564	0.4	0.	0.
PS1 24.96	0.100	0.4	0.127	0.5	0.087	0.3	0.453	1.8	0.	0.
PS2 47.03	0.123	0.3	0.164	0.3	0.113	0.2	0.476	1.0	0.	0.
PS3 74.46	0.157	0.2	0.164	0.2	0.150	0.2	0.543	0.7	0.	0.

ARCHITECT c 4000 analyzers (combined)

Reproducibility – Whole Blood Application, IFCC												
Mean	Repeatability		Between Run		Between Day		Between Lot		Between Instrument		Total	
	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
mmol/mol HbA _{1c}												
LC 30.40	0.135	0.4	0.204	0.7	0.173	0.6	0.130	0.4	0.136	0.4	0.354	1.2
HC 81.76	0.186	0.2	0.221	0.3	0.176	0.2	0.230	0.3	0.096	0.1	0.420	0.5
CL3 135.49	0.303	0.2	0.646	0.5	0.353	0.3	0.442	0.3	0.299	0.2	0.959	0.7
PS1, 25.06	0.101	0.4	0.159	0.6	0.140	0.6	0.384	1.5	0.110	0.4	0.463	1.8
PS2 47.10	0.116	0.2	0.153	0.3	0.158	0.3	0.440	0.9	0.125	0.3	0.520	1.1
PS3 74.58	0.138	0.2	0.154	0.2	0.190	0.3	0.530	0.7	0.121	0.2	0.612	0.8

b. Linearity/assay reportable range:

A linearity study was performed based on guidance from the CLSI document EP6-A, Evaluation of the Linearity of Quantitative Measuring Procedures: A Statistical Approach.

Commercially available whole-blood HbA_{1c} linearity sets, comprised of Levels 1, 2, 3, and 4, were obtained. Five additional samples were prepared by combining the 4 levels of the commercially available linearity sets in specific ratios. The 9 samples were tested using the Abbott Hemoglobin A_{1c} assay on the ARCHITECT c 4000 analyzer. The mean observed %HbA_{1c} value was determined for each intermediate dilution and plotted versus the relative analyte concentration. The linear regression equation is summarized below:

NGSP:

Slope	Intercept	R ²	Sample range tested
0.9709	-0.40	0.999	3.1-19.0 %HbA _{1c}

IFCC:

Slope	Intercept	R ²	Sample range tested
0.9831	-6.17	0.999	11-184 mmol/mol HbA _{1c}

The linearity study supports the claimed assay measuring range of 4.0 to 14.0% HbA1c (20.22 to 129.51 mmol/mol HbA1c (IFCC)).

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

Traceability:

The Architect HbA1c assay standardization is traceable to the International Federation of Clinical Chemistry (IFCC) reference calibrators. The Architect HbA1c assay is NGSP certified. The NGSP certification expires in one year. See NGSP website for current certification at <http://www.ngsp.org>.

The derived result of (%) from the NGSP correlation is calculated from the individual quantitative results for total hemoglobin and Hemoglobin A1c (HbA1c). The IFCC units of mmol/mol are calculated using the Master Equation $IFCC = (NGSP - 2.15) / 0.092$. Two different units are provided to the users: NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).

Value Assignment:

The ARCHITECT HbA1c calibrators are aligned to IFCC reference calibrators through 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 calibrators is value-assigned. The concentration of glycated hemoglobin (HbA1c) and total hemoglobin (THb) is provided for each lot. Calibrators are prepared gravimetrically, lyophilized, and then value assigned using secondary calibrators that are traceable to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method.

The value-assigned A1c Calibrator values are within the following hemoglobin A1c ranges:

Calibrator 1: 4.59% to 6.02% HbA1c

Calibrator 2: 10.52% to 13.37% HbA1c

The Hemoglobin A1C Controls, low and high, are value assigned using the secondary calibrators. The values obtained must meet the sponsor's pre-determined acceptance criteria. The value-assigned A1c Control values are within the following hemoglobin A1c ranges:

Control L: 4.59% to 6.02% HbA1c

Control H: 9.42% to 11.07 % HbA1c.

Stability:

Shelf-life claims: Un-opened calibrators and controls can be stored at 2-8°C until the expiration date or for 12 months. The storage and stability study protocols and acceptance criteria provided by the sponsor were reviewed and found acceptable to

support the claimed conditions.

Open-vial claims: The recommended storage condition for in-use calibrators and controls is 2-8 °C and is stable for 10 days post-reconstitution. Labeling indicates not to freeze the control and calibrator materials. The storage and stability study protocols and acceptance criteria provided by the sponsor were reviewed and found acceptable to support the claimed conditions.

On-board stability for the ARCHITECT HbA1c was established by real time studies on the ARCHITECT c4000 analyzer and demonstrated on-board reagent stability of 50 days. The unopened ARCHITECT HbA1c reagent is stable until the expiration date printed on the label when stored at 2 to 8°C. The storage and stability study protocols and acceptance criteria provided by the sponsor were reviewed and found acceptable to support the claimed conditions.

d. Detection limit:

The claimed measuring range of 4.0-14.0% for the ARCHITECT HbA1c assay is based on linearity. See 1b. above.

e. Analytical specificity:

i.) An interference study was performed based on CLSI EP7-A2 guideline to assess common or known substances that could interfere with the HbA1c assay. The potential interferents listed below were spiked into human EDTA whole blood samples with different levels of % HbA1c (approximately 6.5 and > 8.0% HbA1c). Each sample was tested in a minimum of 12 replicates. The % HbA1c values of the spiked samples were compared to the reference samples containing no interferent. Significant interference was defined as greater or equal to $\pm 5\%$ difference from the expected concentration. The interference study results are summarized in the following table:

Potential Interferent	Highest Tested Concentration at which no significant interference ($\geq \pm 5\%$) was observed
Bilirubin, conjugated	20.0 mg/dL
Bilirubin, unconjugated	15.0 mg/dL
Total Protein	22g/dL
Triglycerides	3000 mg/dL
Rheumatoid Factor	200 IU/mL
Ascorbic Acid	3.0 mg/dL
Urea	667 mg/dL
Glucose	1000 mg/dL
Vitamin E	8.6 mg/dL

ii.) A hemoglobin variant interference

The hemoglobin variant interference study was performed according to guidance

from the CLSI EP7-A2. Interference effects were assessed by comparing the Hemoglobin A1c values to a comparative method for samples containing potentially interfering hemoglobin variants. The samples were tested in duplicate using one lot of HbA1c Reagents on one ARCHITECT c 4000 analyzer. The numbers and concentrations hemoglobin variants tested, and the range of % HbA1c concentrations in which they were tested are shown below:

Hemoglobin Variant	n	Range in % Abnormal Variant	Range in %HbA _{1c} Concentration
HbC	43	27% - 43%	4.7 – 13.6
HbD	40	34% - 43%	4.7 – 8.8
HbE	50	14% - 32%	4.7 – 11.8
HbS	31	18% - 42%	4.6 – 13.5
HbA2	24	4.1% - 6.1%	4.6 – 11.7
HbF	28	3% - 33.0%	4.2 – 7.9

The results for the hemoglobin variant study are summarized below:

Hemoglobin Variant	Relative % Difference from Reference Concentration at Low and High Concentrations			
	~ 6.0 %HbA _{1c} (5.5 to 6.5 %HbA _{1c})		~ 9.0 %HbA _{1c} (7.5 to 10.5 %HbA _{1c}) ^a	
	Relative % Difference	Range ^b	Relative % Difference	Range ^b
HbC	-3.1	-6.9 to 3.3	-0.5	-4.2 to 2.7
HbD	0.6	-3.4 to 3.2	0.2	-1.3 to 2.6
HbE	1.0	-3.3 to 7.8	2.5	-2.1 to 6.3
HbS	-0.8	-3.6 to 3.3	-0.5	-3.8 to 2.2
HbA2	0.7	0.0 to 1.7	2.9	1.4 to 4.5
HbF	Bias exceeds -5% when the amount of HbF in the sample exceeds 5% ^c			

- The HbA2 results at ~9.0 %HbA_{1c} consisted of samples between 7.2 to 11.2 %HbA_{1c}.
- The range is defined as the minimum and maximum relative % difference at each concentration level (~6.0 and ~9.0 %HbA_{1c}).
- A negative % difference with HbF is proportional in magnitude to the % HbF present in the sample. For example, when the amount of HbF in the sample was 20.4%, the % difference was -20.0% on the ARCHITECT c 4000 System.

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

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

WARNING: The Hemoglobin A1c assay has significant interference with the fetal hemoglobin (HbF). Hemoglobin A1c results are invalid for patients with abnormal amounts of HbF, including those with known Hereditary Persistence of Fetal Hemoglobin.

iii) A drug interference study was performed using a low level whole blood sample with a concentration value of between 6.0 and 7.0% HbA1c and a high whole blood sample with a concentration value of $\geq 8.0\%$ HbA1c. Test samples were prepared by spiking each drug at the interferent concentrations into the low and high samples and comparing to control samples containing no drug. The test and control samples were tested in a minimum of 12 replicates using 1 lot of HbA1c reagents and calibrators. The sponsor defined significant interference as greater or equal to $\pm 5\%$ difference from the expected concentration.

The sponsor states that the HbA1c assay is not susceptible to interference effects from the following drugs at the listed concentration levels evaluated.

Potential Drug Interferent	Highest Level Tested Showing No Significant Interference.
Acarbose	50 mg/dL
Acetaminophen	20 mg/dL
Acetylsalicylate	50.8 mg/dL
Atorvastatin	600 μg Eq/L
Captopril	0.5 mg/dL
Chlorpropamide	74.7 mg/dL
Cyanate	50 mg/dL
Furosemide	6.0 mg/dL
Gemfibrozil	7.5 mg/dL
Ibuprofen	50 mg/dL
Insulin	450 micro units/mL
Losartan	5 mg/dL
Metformin	5.1 mg/dL
Nicotinic Acid	61 mg/dL
Propranolol	0.2 mg/dL
Repaglinide	60 ng/mL

iv.) A hemoglobin derivative study was performed using a low level whole blood sample with a concentration between 6.0 and 7.0% HbA1c and a high whole blood sample with a concentration of $\geq 8.0\%$ HbA1c. The potentially interfering hemoglobin derivatives were prepared by adding the following substance at the levels shown below.

- Acetylated Hemoglobin ≥ 50 mg/dL of ASA (aspirin)
- Carbamylated Hemoglobin ≥ 10 mmol/L of Cyanate
- Labile Hemoglobin ≥ 1000 mg/dL of Glucose

The test samples were prepared by spiking the substances at the interferent concentration listed above into the low and high samples. The test and reference samples were tested in a minimum of 12 replicates. Significant interference was defined as $\pm 5\%$ when comparing test samples containing the potentially interfering hemoglobin derivatives to the corresponding reference samples.

The sponsor states that the HbA1c assay is not susceptible to interference effects from the hemoglobin derivatives at the interference levels evaluated.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study using human EDTA whole blood specimens (n=128) was performed based on CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples guidelines. Each sample was analyzed internally in replicates of two, using two lots each of HbA1c reagents and HbA1c calibrators on two ARCHITECT c 4000 analyzers over a minimum of 5 days. The samples were also tested in duplicate with an NGSP secondary reference laboratory using a FDA cleared HPLC-based method, the Tosoh G8. The total number of comparison results obtained was 256. The sample range tested was 4.1 to 13.2% HbA1c. The method comparison was performed using both the hemolysate and whole blood application. The distribution of samples spanned the measuring interval with a concentration of samples around the clinical decision points as follows:

%HbA1c Level*	Number of Samples
< 5.0%	5
5.0 – 5.9%	16
6.0 – 6.4%	32
6.5 – 7.0%	32
7.1 – 8.0%	22
8.1 – 9.0%	11
> 9.0%	10
Total	128

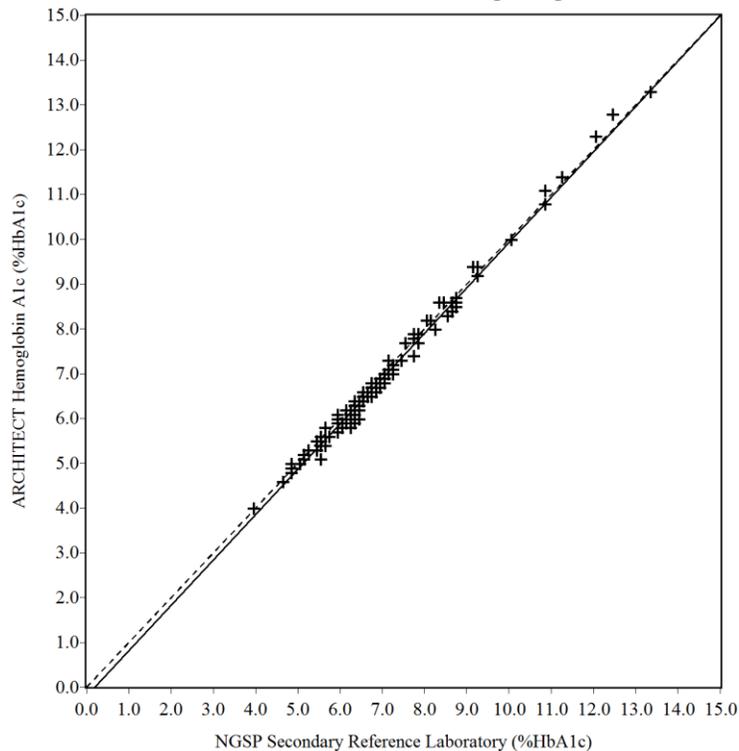
Deming (weighted) and Passing-Bablok regression analyses were performed for the ARCHITECT HbA1c versus the reference method.

Summary of the first replicate versus first replicate regression analysis results are presented in the tables below for the hemolysate and whole blood applications:

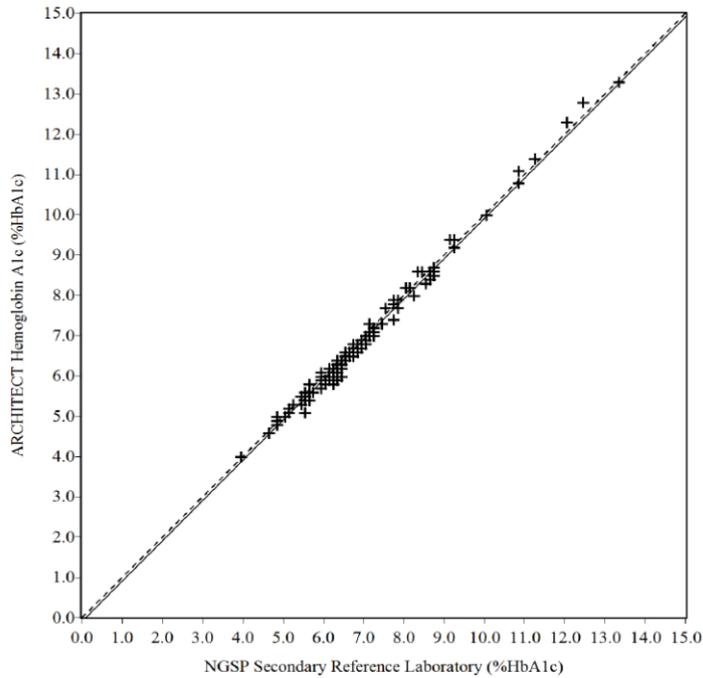
Summary of Method Comparison Results for NGSP Whole blood Application:

	y-Intercept	95% CI	Slope	95% CI
Deming	-0.2	-0.4 to 0.0	1.01	0.99 to 1.04
Passing-Bablok	-0.1	-0.3 to -0.1	1.00	1.00 to 1.03

Whole Blood Scatter Plot with Deming Regression (NGSP):



Whole Blood Scatter Plot with Passing-Bablok Regression (NGSP):



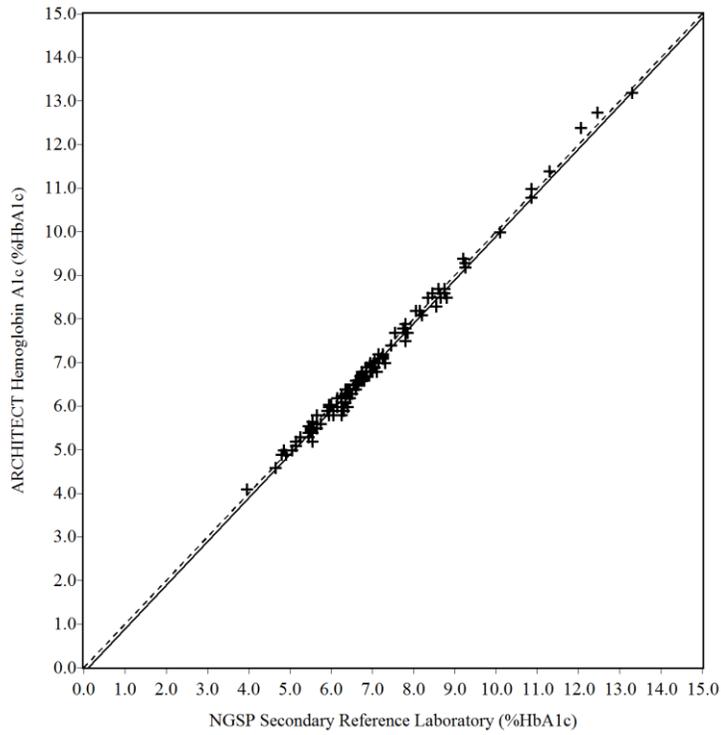
Bias and % Bias Summary for Whole Blood (NGSP)

Regression Method	%HbA _{1c}	Bias	% Bias
Deming	5.0	-0.1	-3.0
	6.5	-0.1	-2.0
	8.0	-0.1	-1.4
	12.0	-0.1	-0.6
Passing-Bablok	5.0	-0.1	-2.0
	6.5	-0.1	-1.5
	8.0	-0.1	-1.3
	12.0	-0.1	-0.8

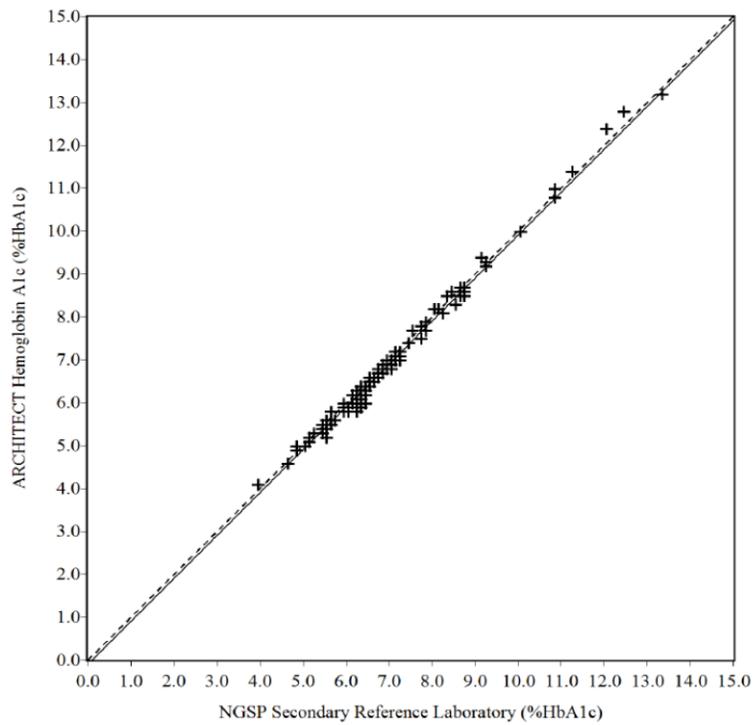
Summary of Method Comparison Results for NGSP Hemolysate Application:

	y-Intercept	95% CI	Slope	95% CI
Deming	-0.20	-0.4 to 0.0	1.01	0.99 to 1.04
Passing-Bablok	-0.01	-0.1 to -0.1	1.00	1.00 to 1.00

Hemolysate Scatter Plot with Deming Regression



Hemolysate Scatter Plot with Passing-Bablok Regression (NGSP):



**Hemoglobin A_{1c} Method Comparison (Correlation)
Bias and %Bias Summary – Hemolysate (NGSP)**

Regression Method	%HbA_{1c}	Bias	% Bias
Deming	5.0	-0.1	-2.4
	6.5	-0.1	-1.7
	8.0	-0.1	-1.3
	12.0	-0.1	-0.7
Passing-Bablok	5.0	-0.1	-2.0
	6.5	-0.1	-1.5
	8.0	-0.1	-1.2
	12.0	-0.1	-0.8

**Hemoglobin A_{1c} Method Comparison (Correlation)
Bias and %Bias Summary - Hemolysate (IFCC)**

Regression Method	HbA_{1c} mmol/mol	Bias	% Bias
Deming	31.13	-0.94	-3.0
	47.53	-1.14	-2.4
	63.93	-1.33	-2.1
	107.65	-1.85	-1.7
Passing-Bablok	31.13	-1.35	-4.3
	47.53	-1.18	-2.5
	63.93	-1.02	-1.6
	107.65	-0.57	-0.5

Bias and %Bias Summary – Whole Blood (IFCC)

Regression Method	HbA1c mmol/mol	Bias	% Bias
Deming	31.13	-1.29	-4.1
	47.53	-1.34	-2.8
	63.93	-1.39	-2.2
	107.65	-15.4	-1.4
Passing-Bablok	31.13	-1.59	-5.1
	47.53	-1.27	-2.7
	63.93	-0.95	-1.5
	107.65	-0.10	-0.1

Total Error Near the Cutoff

Using the results of bias estimation (%Bias) in the method comparison study and precision estimates in the reproducibility study, the Total Error (TE) at the following concentrations (5%, 6.5%, 8% and 12%) was calculated as follows: %TE = |%Bias| + 1.96 * %CV * (1+%Bias). The results are presented in the tables below.

Hemoglobin A_{1c} Method Comparison (Correlation)

%Total Error Summary – Hemolysate (NGSP)

%HbA _{1c}	Average % Bias	% CV	% TE
5	-2.2	0.6	3.4
6.5	-1.6	0.9	3.3
8	-1.3	0.8	2.8
12.0	-0.8	0.9	2.5

%Total Error Summary – Whole Blood (NGSP)

%HbA _{1c}	Average % Bias	% CV	% TE
5	-2.5	0.6	3.6
6.5	-1.8	0.7	3.1
8	-1.3	0.6	2.5
12.0	-0.7	0.6	1.9

b. Matrix comparison:

A matrix study was performed to determine the suitability of different anticoagulant collection tube types for use in the ARCHITECT HbA_{1c} assay. Specimens with concentration values spanning the measuring interval of the assay (4.0 to 14.0% HbA_{1c})

were collected from a minimum of 43 different donors in the control tube type (Dipotassium EDTA, plastic) and in the following tube types under evaluation:

- Lithium heparin
- Sodium heparin
- Sodium Fluoride/Disodium EDTA
- Tripotassium EDTA

The blood collection tubes collected from one individual constituted one sample set. Each sample was tested in a minimum of 2 replicates using one lot of HbA1c reagents and HbA1c calibrators on one ARCHITECT c4000 analyzer.

The regression results are as follows:

Dipotassium-EDTA Control vs Tube Types			
Tube type	Linear fit		
	Slope (95% CI)	Intercept (95% CI)	r value
Sodium Fluoride/Sodium EDTA	1.00	0.0	1.00
	1.00 to 1.00	0.0 to 0.0	
Lithium Heparin	1.02	0.0	1.00
	1.01 to 1.03	-0.1 to 0.0	
Tripotassium EDTA	1.00	0.0	1.00
	1.00 to 1.00	0.0 to 0.0	
Sodium Heparin	1.02	0.0	1.00
	1.01 to 1.03	-0.1 to 0.0	

The data support the use of the following blood collection tubes with the HbA1c assay:

- Dipotassium EDTA (control tube)
- Lithium heparin
- Sodium heparin
- Sodium Fluoride/Disodium EDTA
- Tripotassium EDTA

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 American Diabetes Association (ADA) recommendations¹ are summarized in the following table.

HbA1c Value	Glycemic Goal
< 8% HbA1c (64 mmol/mol)	Less stringent
< 7% HbA1c (53 mmol/mol)	General (Non-Pregnant Adults)
< 6.5% HbA1c (48 mol/mol)	More stringent

HbA1c values above 6.5% HbA1c (48mmol/mol) are an indication of hyperglycemia during the preceding 2 to 3 months or longer. According to the recommendations of the ADA, AbA1c values above 6.5% HbA1c (48 mmol/mol) are suitable for the diagnosis of diabetes mellitus. Patients with HbA1c values in the range of 5.7-6.4% HbA1c (39-46 mmol/mol) may be at risk of developing diabetes.^{2,3}

¹American Diabetes Association. Position Statement: Standards of medical care in diabetes - 2012. Diabetes Care 2012;35 (Suppl 1):S11–S63.

²American Diabetes Association Workgroup Report: International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32(7):1327–1334.

³American Diabetes Association. Position Statement: Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 (Suppl 1):S62–S69.

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.