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

A. 510(k) Number:

k171771

B. Purpose for Submission:

New device

C. Measurand:

Glycosylated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative, enzymatic

E. Applicant:

Siemens Healthcare Diagnsotics Inc.

F. Proprietary and Established Names:

ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay

G. Regulatory Information:

Regulation Description	Product Code	Device Class	Regulation	Panel
Hemoglobin A1c Test System	PDJ	II	21 CFR 862.1373	Chemistry, 75
Glycosylated Hemoglobin Assay	LCP	II	21 CFR 864.7470	Hematology, 81

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

The ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay is an in vitro diagnostic assay for the quantitative determination of mmol/mol HbA1c (IFCC) and % HbA1c (DCCT/NGSP) in human anticoagulated venous whole blood and hemolysate for use on the ADVIA Chemistry systems. Measurement of Hemoglobin A1c is used as an aid in the diagnosis and monitoring of long-term blood glucose control in patients with diabetes mellitus, and as an aid in the identification of patients at risk for developing diabetes mellitus.

3. Special conditions for use statement(s):

For prescription use only.

For in vitro diagnostic use.

The ADVIA Chemistry A1c_E assay has significant interference with fetal hemoglobin (HbF). Samples containing HbF may produce negative bias (lower than actual results) with the ADVIA Chemistry A1c_E assay. Hemoglobin A1c results are invalid for patients with abnormal amounts of HbF, including those with known Hereditary Persistence of Fetal Hemoglobin.

Patients with hemoglobin concentrations outside of the acceptable range for the ADVIA Chemistry A1c_E assay should be assayed by a test employing a different assay principle.

Any cause of shortened red blood cell survival (for example, hemolytic anemia or other hemolytic diseases, pregnancy, or recent significant blood loss) will reduce exposure of red blood cells to glucose with a consequent decrease in HbA1c values. HbA1c results are not reliable in patients with chronic blood loss and consequent variable erythrocyte life span.

Fetal Hemoglobin (HbF) consists of 2 alpha and 2 gamma chains that are not recognized by FPOX enzyme which measures N-terminal fructosyl dipeptides on the beta-chain (refer to Principles of the Procedure). Samples that contain high amounts of HbF, usually found in some people with thalassemia, in infants, and in some pregnant women, may yield a lower than expected HbA1c result with this assay.

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.

Do not use sodium fluoride/potassium oxalate collection tubes as they may interfere with the results of the ADVIA Chemistry A1c_E assay.

4. Special instrument requirements:

   ADVIA Chemistry 1800 System

I. Device Description:

Assay
The ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay measures hemoglobin A1c in human anticoagulated venous whole blood and hemolysate. The assay consists of three reagents (R1, R2, and Pretreatment). These reagents are liquid and are ready to use.

Reagent	Reactive Ingredients
Reagent 1	10-Carboxymethylaminocarbonyl)-3,7-bis(dimethylamino)-phenothiazine sodium salt
	Protease (Bacterial)
Reagent 2	Peroxidase (Horseradish)
	Fructosyl peptide oxidase (E. coli, recombinant)
Pretreatment	Sodium nitrite

Inactive ingredients: Reagent 1 contains sodium azide as a stabilizer and preservative. Reagent 1 and pretreatment contain Proclin 300 as a preservative. Reagent 2 contains ofloxacin as a preservative.

The assay offers both an automated and a manual application. The automated application (A1c_E) lyses the anticoagulated whole blood specimen on the system for the automated application (A1c_E). Samples may also be lysed manually using the ADVIA® Chemistry A1c_E pretreatment solution to obtain hemolysate for the manual

application (A1c_EM).

Calibrator
The Enzymatic Hemoglobin A1c (A1c_E) Calibrators are available separately and consists of two levels of hemoglobin A1c and one blanking solution.

The value-assigned A1c Calibrator values are approximately the following hemoglobin A1c values:
Level 1: ~5% HbA1c
Level 2: ~11.5% HbA1c

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Abbott Architect Hemoglobin A1c

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

   k130255

3. Comparison with predicate:

Similarities and Differences		
Item	Device	Predicate
Intended Use	Intended for the the quantitative determination of mmol/mol HbA1c (IFCC) and % HbA1c (DCCT/NGSP) 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 longterm blood glucose control in individuals with diabetes mellitus.	Same
Platform	ADVIA 1800 Clinical Chemistry System	ARCHITECT c 8000 System (clinical chemistry analyzer)
Methodology	Quantitative, enzymatic	Same
Specimen Type	Venous whole blood and hemolysate: • Dipotassium EDTA • Lithium Heparin • Sodium Fluoride/Disodium EDTA	Venous whole blood and hemolysate: • Dipotassium EDTA • Lithium Heparin • Sodium Fluoride/Disodium

Similarities and Differences		
Item	Device	Predicate
	• Tripotassium EDTA	EDTA • Tripotassium EDTA • Sodium Heparin
Measuring Range	3.8 to 14.0% HbA1c (DCCT/NGSP) 18.03 -129.50 mmol/mol HbA1c (IFCC)	4.0 to 14.0% HbA1c (DCCT/NGSP) 20.22-129.51 mmol/mol HbA1c (IFCC)
Reporting Units	% HbA1c NGSP/DCCT and mmol/mol IFCC	Same

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

CLSI EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition

CLSI EP09-A3: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition

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

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

CLSI EP28-A3c: Defining, Establishing, and Verifying. Reference Intervals in the Clinical Laboratory;. Approved Guideline—Third Edition

L. Test Principle:

The ADVIA Chemistry hemoglobin A1c assay consists of two separate measurements: glycated hemoglobin (A1c_E) and total hemoglobin (tHb_E). The two measurements are used to determine the percent HbA1c (NGSP units) or the hemoglobin A1c_E/tHb_E ratio in mmol/moL (IFCC units). The individual concentration values of A1c_E and tHb_E generated by this assay are used only for calculating the %HbA1c or A1c_E/tHb_E ratio, and must not be used individually for diagnostic purposes.

The anticoagulated whole blood specimen is lysed on the system for the automated ADVIA Chemistry A1c_E assay or may be lysed manually using the ADVIA Chemistry A1c_E pretreatment solution to obtain hemolysate for manual ADVIA Chemistry A1c_E (A1c_EM) assay.

The ADVIA Chemistry A1c_E assay is an enzymatic method that specifically measures N-terminal fructosyl dipeptides on the beta-chain of HbA1c. In the pretreatment step, the erythrocytes are lysed and the hemoglobin is oxidized to methemoglobin by reaction with sodium nitrite. In the first step of the reaction (the ADVIA Chemistry A1c_E reagent 1 (R1)+ sample) , the N-terminal fructosyl dipeptide fragment is cleaved from the hemoglobin beta chain with a protease. Concurrently, methemoglobin is converted into stable azide-methemoglobin in the presence of sodium azide and the total hemoglobin concentration is determined by measuring the absorbance at 478/805 nm. In the second step of the reaction, fructosyl peptide oxidase (FPOX) is added to react with the fructosyl dipeptide to generate hydrogen peroxide. The hydrogen peroxide reacts with the chromagen in the presence of peroxidase to develop a color that is measured at 658/805 nm.

The ADVIA Chemistry A1c_E assay incorporates a turbidity normalization mechanism (cHb_E) that is measured at 884 nm to remove the effect of any sample turbidity which could impact the tHb_E measurement.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Testing was performed with both the automated pretreated and manual pretreated samples and two calibrations were performed per each method (automated and manual) over the duration of the study. Data were analyzed consistent with CLSI document EP05-A3, *Evaluation of Precision Performance of Quantitative Measurement Methods*. Samples were run in duplicate in 2 runs per day on 3 ADVIA 1800 instruments for 20 days. Testing was performed using 3 lots of reagents per instrument for a total of 720 results per sample. The pooled data from the study is shown in the tables below.

   Samples consisted of two commercial quality controls (BioRad QC) and four whole blood patient pools with target values of 5.0% HbA1c, 6.5% HbA1c, 8.0% HbA1c, and 12.0% HbA1c. The manual and automated methods were assessed and are summarized below:

Automated Pretreatment

NGSP: ADVIA 1800 Automated Pretreatment Instrument #1

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.39	0.02	0.4	0.02	0.5	0.03	0.6	0.03	0.5	0.06	1.0
MDP2	6.59	0.03	0.4	0.02	0.4	0.04	0.6	0.03	0.5	0.06	1.0
MDP3	8.02	0.03	0.4	0.03	0.4	0.05	0.6	0.03	0.4	0.07	0.9
MDP4	12.11	0.05	0.4	0.05	0.4	0.09	0.7	0.04	0.3	0.12	1.0
Control 1	4.44	0.03	0.6	0.04	0.8	0.03	0.7	0.02	0.4	0.06	1.3
Control 2	8.97	0.03	0.4	0.05	0.6	0.07	0.8	0.00	0.0	0.10	1.1

NGSP: ADVIA 1800 Automated Pretreatment Instrument #2

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.32	0.01	0.3	0.02	0.4	0.06	1.0	0.02	0.3	0.06	1.2
MDP2	6.52	0.01	0.2	0.03	0.4	0.07	1.1	0.02	0.3	0.08	1.2
MDP3	7.97	0.02	0.2	0.04	0.4	0.08	1.0	0.02	0.2	0.09	1.2
MDP4	12.11	0.03	0.2	0.06	0.5	0.12	1.0	0.02	1.0	0.14	1.1
Control 1	4.53	0.02	0.3	0.03	0.6	0.05	1.2	0.01	0.2	0.06	1.4
Control 2	9.14	0.02	0.3	0.08	0.9	0.07	0.8	0	0	0.11	1.2

NGSP: ADVIA 1800 Automated Pretreatment Instrument #3

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.38	0.02	0.4	0.02	0.4	0.02	0.5	0.01	0.2	0.05	1.0
MDP2	6.58	0.02	0.3	0.02	0.3	0.03	0.5	0.02	0.3	0.04	0.7
MDP3	8.03	0.02	0.2	0.04	0.4	0.08	1.0	0.02	0.2	0.09	1.2
MDP4	12.11	0.05	0.4	0.04	0.3	0.04	0.3	0.05	0.4	0.09	0.7
Control 1	4.50	0.03	0.6	0.03	0.7	0.02	0.5	0.01	0.2	0.05	1.0
Control 2	9.02	0.02	0.3	0.03	0.3	0.04	0.5	0.02	0.3	0.06	0.7

NGSP: ADVIA 1800 Automated Pretreatment Combined

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Instrument		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.36	0.02	0.4	0.02	0.4	0.04	0.7	0.04	0.8	0.00	0.0	0.06	1.2
MDP2	6.56	0.02	0.3	0.02	0.4	0.05	0.7	0.04	0.6	0.01	0.2	0.07	1.1
MDP3	8.01	0.02	0.3	0.03	0.4	0.06	0.7	0.03	0.4	0.02	0.3	0.08	1.0
MDP4	12.11	0.04	0.4	0.05	0.4	0.09	0.7	0.03	0.2	0.02	0.2	0.12	1.0
Control 1	4.49	0.02	0.5	0.03	0.7	0.04	0.8	0.05	1.1	0.00	0.00	0.07	1.6
Control 2	9.05	0.03	0.3	0.06	0.6	0.06	0.7	0.09	1.0	0.00	0.00	0.13	1.4

IFCC: ADVIA 1800 Automated Pretreatment Instrument #1

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	35.41	0.26	0.7	0.27	0.8	0.36	1.0	0.32	0.9	0.61	1.7
MDP2	48.49	0.30	0.6	0.26	0.5	0.41	0.9	0.38	0.8	0.69	1.4
MDP3	64.17	0.32	0.5	0.33	0.5	0.55	0.9	0.36	0.6	0.80	1.2
MDP4	108.85	0.56	0.5	0.53	0.5	0.97	0.9	0.42	0.4	1.31	1.2
Control 1	25.01	0.28	1.1	0.39	1.6	0.32	1.3	0.21	0.8	0.62	2.5
Control 2	74.52	0.36	0.5	0.60	0.8	0.80	1.1	0.00	0.0	1.06	1.4

IFCC: ADVIA 1800 Automated Pretreatment Instrument #2

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	35.41	0.15	0.4	0.22	0.6	0.60	1.7	0.17	0.5	0.68	2.0
MDP2	48.49	0.15	0.3	0.31	0.6	0.76	1.6	0.19	0.4	0.86	1.8
MDP3	64.17	0.20	0.3	0.39	0.6	0.90	1.4	0.21	0.3	1.03	1.6
MDP4	108.85	0.33	0.3	0.61	0.6	1.33	1.2	0.18	0.2	1.51	1.4
Control 1	25.01	0.17	0.6	0.30	1.1	0.59	2.3	0.10	0.4	0.69	2.7
Control 2	74.52	0.25	0.3	0.88	1.1	0.79	1.0	0.00	0.0	1.20	1.6

IFCC: ADVIA 1800 Automated Pretreatment Instrument #3

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	35.41	0.22	0.6	0.21	0.6	0.27	0.8	0.15	0.4	0.43	1.2
MDP2	48.49	0.20	0.4	0.24	0.5	0.33	0.7	0.19	0.4	0.49	1.0
MDP3	64.17	0.17	0.3	0.27	0.4	0.33	0.5	0.33	0.5	0.56	0.9
MDP4	108.85	0.53	0.5	0.46	0.4	0.39	0.4	0.58	0.5	0.99	0.9
Control 1	25.01	0.28	1.1	0.35	1.4	0.23	0.9	0.08	0.3	0.51	2.0
Control 2	74.52	0.26	0.3	0.31	0.4	0.44	0.6	0.26	0.4	0.65	0.9

IFCC: ADVIA 1800 Automated Pretreatment Combined

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Instrument		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	35.17	0.21	0.6	0.24	0.7	0.43	1.2	0.44	1.3	0.00	0.0	0.69	2.0
MDP2	48.40	0.22	0.5	0.27	0.6	0.54	1.1	0.40	0.8	0.12	0.3	0.76	1.6
MDP3	64.14	0.24	0.4	0.33	0.5	0.64	1.0	0.34	0.5	0.24	0.4	0.86	1.4
MDP4	108.90	0.49	0.4	0.53	0.5	0.98	0.9	0.29	0.3	0.23	0.2	1.27	1.2
Control 1	25.56	0.25	1.0	0.35	1.4	0.41	1.6	0.53	2.1	0.00	0.0	0.80	3.1
Control 2	75.18	0.30	0.4	0.64	0.8	0.70	0.9	0.98	1.3	0.00	0.0	1.39	1.8

Manual Pretreatment

NGSP: ADVIA 1800 Manual Pretreatment Instrument #1

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.30	0.03	0.5	0.03	0.5	0.02	0.4	0.03	0.6	0.06	1.0
MDP2	6.48	0.03	0.5	0.03	0.4	0.03	0.5	0.03	0.4	0.06	0.9
MDP3	7.91	0.04	0.5	0.03	0.3	0.04	0.6	0.03	0.4	0.07	0.9
MDP4	12.03	0.07	0.6	0.03	0.3	0.09	0.8	0.05	0.4	0.13	1.1
Control 1	4.66	0.03	0.6	0.03	0.7	0.03	0.6	0.02	0.4	0.06	1.2
Control 2	9.20	0.05	0.5	0.04	0.4	0.09	0.9	0.01	0.1	0.11	1.2

NGSP: ADVIA 1800 Manual Pretreatment Instrument #2

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.29	0.01	0.2	0.02	0.4	0.05	1.0	0.01	0.2	0.06	1.1
MDP2	6.49	0.01	0.2	0.02	0.3	0.07	1.0	0	0	0.07	1.1
MDP3	7.92	0.02	0.2	0.03	0.4	0.08	1.0	0.02	0.2	0.09	1.1
MDP4	12.08	0.04	0.4	0.05	0.4	0.11	0.9	0.02	0.2	0.13	1.1
Control 1	4.77	0.01	0.2	0.03	0.6	0.06	1.2	0.00	0.0	0.07	1.4
Control 2	9.36	0.02	0.2	0.04	0.4	0.10	1.1	0.00	0.0	0.11	1.2

NGSP: ADVIA 1800 Manual Pretreatment Instrument #3

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.28	0.02	0.3	0.03	0.5	0.03	0.6	0.02	0.3	0.05	0.9
MDP2	6.48	0.02	0.3	0.02	0.4	0.03	0.5	0.01	0.2	0.05	0.7
MDP3	7.90	0.02	0.3	0.03	0.3	0.04	0.5	0.03	0.4	0.06	0.8
MDP4	11.98	0.03	0.2	0.03	0.3	0.05	0.4	0.04	0.4	0.08	0.7
Control 1	4.72	0.02	0.4	0.03	0.7	0.04	0.7	0.01	0.2	0.05	1.1
Control 2	9.25	0.02	0.3	0.03	0.3	0.06	0.7	0.03	0.3	0.07	0.8

NGSP: ADVIA 1800 Manual Pretreatment Combined

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Instrument		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	5.29	0.02	0.4	0.03	0.5	0.04	0.7	0.01	0.2	0.02	0.3	0.05	1.0
MDP2	6.48	0.02	0.3	0.03	0.4	0.05	0.7	0.00	0.0	0.02	0.3	0.06	0.9
MDP3	7.91	0.03	0.3	0.03	0.4	0.06	0.7	0.01	0.1	0.02	0.3	0.07	0.9
MDP4	12.03	0.05	0.4	0.04	0.3	0.09	0.7	0.05	0.4	0.01	0.1	0.12	1.0
Control 1	4.72	0.02	0.4	0.03	0.7	0.04	0.9	0.05	1.1	0.00	0.0	0.08	1.6
Control 2	9.27	0.03	0.4	0.03	0.4	0.08	0.9	0.08	0.9	0.00	0.0	0.13	1.4

IFCC: ADVIA 1800 Manual Pretreatment Instrument #1

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	34.45	0.31	0.9	0.31	0.9	0.25	0.7	0.33	1.0	0.61	1.8
MDP2	47.33	0.33	0.7	0.31	0.7	0.34	0.7	0.32	0.7	0.65	1.4
MDP3	62.92	0.44	0.7	0.28	0.4	0.48	0.8	0.36	0.6	0.79	1.3
MDP4	107.92	0.75	0.7	0.34	0.3	1.03	1.0	0.57	0.5	1.43	1.3
Control 1	27.47	0.32	1.2	0.36	1.3	0.29	1.1	0.21	0.8	0.60	2.2
Control 2	77.02	0.54	0.7	0.39	0.5	0.94	1.2	0.14	0.2	1.16	1.5

IFCC: ADVIA 1800 Manual Pretreatment Instrument #2

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	34.27	0.13	0.4	0.23	0.7	0.57	1.7	0.11	0.3	0.63	1.8
MDP2	47.40	0.14	0.3	0.25	0.5	0.72	1.5	0.00	0.0	0.77	1.6
MDP3	63.08	0.17	0.3	0.35	0.6	0.83	1.3	0.18	0.3	0.93	1.5
MDP4	108.47	0.48	0.4	0.55	0.5	1.18	1.1	0.25	0.2	1.41	1.3
Control 1	28.63	0.11	0.4	0.33	1.2	0.62	2.2	0.00	0.0	0.71	2.5
Control 2	78.78	0.22	0.3	0.40	0.5	1.11	1.4	0.00	0.0	1.20	1.5

IFCC: ADVIA 1800 Manual Pretreatment Instrument #3

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	34.31	0.18	0.5	0.28	0.8	0.34	1.0	0.17	0.5	0.50	1.5
MDP2	47.34	0.23	0.5	0.26	0.6	0.36	0.8	0.16	0.3	0.53	1.1
MDP3	62.96	0.22	0.3	0.30	0.5	0.47	0.7	0.31	0.5	0.67	1.1
MDP4	107.94	0.30	0.3	0.38	0.4	0.56	0.5	0.47	0.4	0.87	0.8
Control 1	28.06	0.20	0.7	0.37	1.3	0.38	1.4	0.10	0.4	0.58	2.1
Control 2	77.78	0.26	0.3	0.28	0.4	0.66	0.9	0.29	0.4	0.82	1.1

IFCC: ADVIA 1800 Manual Pretreatment Combined

Sample ID	HbA1c %	Repeatability		Between Run		Between Day		Between Instrument		Between Lot		Toal Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
MDP1	34.31	0.22	0.6	0.27	0.8	0.41	1.2	0.14	0.4	0.18	0.5	0.59	1.7
MDP2	47.34	0.25	0.5	0.27	0.6	0.50	1.1	0.00	0.0	0.20	0.4	0.66	1.4
MDP3	62.96	0.30	0.5	0.31	0.5	0.61	1.0	0.12	0.2	0.27	0.4	0.81	1.3
MDP4	107.94	0.54	0.5	0.43	0.4	0.96	0.9	0.57	0.5	0.14	0.1	1.32	1.2
Control 1	28.06	0.23	0.8	0.36	1.3	0.45	1.6	0.58	2.1	0.00	0.0	0.85	3.0
Control 2	77.78	0.37	0.5	0.36	0.5	0.92	1.2	0.91	1.2	0.00	0.0	1.39	1.8

b. Linearity/assay reportable range:

Linearity testing was conducted based on CLSI EP06-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.* A dilution series consisting of 11 levels across the assay range were prepared by mixing high HbA1c and low HbA1c whole blood pools. Samples levels evaluated were 2.77, 3.51, 4.25, 4.99, 5.73, 7.21, 8.69, 10.16, 11.64, 13.12, and 14.60% HbA1c (6.73, 14.81, 22.90, 30.98, 39.07, 55.24, 71.41, 87.58, 103.74, 119.91, and 136.08 mmol/mol HbA1c). Three replicates were tested at each level. The measured values were compared to the expected values. The regression parameters (slope, intercept, and r^2) are the following:

NGSP:

Slope	Intercept	R^2	Concentration Range Tested
1.009	-0.111	0.999	2.77 to 14.60% HbA1c

IFCC:

Slope	Intercept	R^2	Concentration Range Tested
1.009	-0.974	0.999	6.73 to 136.08 mmol/mol HbA1c

The linearity study supports the claimed assay measuring range of 3.8 to 14.0% HbA1c (18.01 to 129.51 mmol/mol HbA1c (IFCC)).

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

Traceability

The ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay standardization is traceable to the International Federation of Clinical Chemistry (IFCC) reference calibrators. The ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay is

certified through the National Glycohemoglobin Standardization Program (NGSP). The NGSP certification expires in one year. See NGSP website for current certification at http://www.ngsp.org.

The derived results of (%) from the NGSP correlation are calculated from the individual quantitative results for Hemoglobin A1c (HbA1c).

The International Federation of Clinical Chemistry (IFCC) units of mmol/mol are calculated using the Master Equation NGSP (%) = 0.09148 x IFCC (mmol/mol) + 2.152. HbA1c results are provided to the customers using two different units: NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).

d. Detection limit:

Limit of Blank (LoB) and Limit of Detection (LoD) testing was conducted in accordance with CLSI EP17-A2, *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures*.

The LoB and LoD values were determined by measuring 180 blank measurements and 180 low-level HbA1c measurement.

To determine LoB and LoD, 4 blank and whole blood low level samples each were processed using 3 reagent lots and 1 instrument. Testing was performed for 3 days at 5 replicates per day for a total of 60 measurements per reagent lot (180 measurements total per LoB and LoD).

The detection limits are summarized in the tables below:

Hemoglobin

Limit	**%HbA1c**	**µmol/L tHb**	**µmol/L A1c**
Limit of Blank (LoB)	3.18	60.15 µmol/L	1.77 µmol/L
Limit of Detection (LoD)	3.60	69.42 µmol/L	2.50 µmol/L

The ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay has a reportable range of 3.80–14.00 % HbA1c (18.03–129.51 mmol/mol HbA1c).

e. Analytical specificity:

Testing to determine the interference bias of various endogenous and exogenous interferents on the ADVIA A1c_E Assay was performed according to CLSI EP07-A2, *Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition*.

The effect of each interferent listed below was evaluated using a paired difference analysis that compared HbA1c values of control samples (whole blood without any

added interferent) and test samples (whole blood spiked with the interferent being tested). Three replicates were tested for each of two HbA1c levels: 6.5% ± 1.0% and 8.0% ± 1.0%.

The sponsor defines significant interference as ≥±5% change in the HbA1c measurements from the control value was considered an interferent. Five pools with different concentrations of each interferent. The following substances demonstrated no significant interference at the concentrations described below:

Endogenous Interference Summary

Interferent	**Highest Concentration Level Tested with No Interference**
Conjugated Bilirubin*	10.00 mg/dL
Unconjugated Bilirubin	10.00 mg/dL
Total Protein	22 g/dL
Triglycerides	2000 mg/dL
Intralipid	1000 mg/dL
Urea	667 mg/dL
Vitamin E	8.6 mg/dL
Rheumatoid Factor	200 IU/mL
Glucose	1000 mg/dL

Exogenous Interference Summary

Interferent	**Highest Concentration Level Tested with No Interference**
Acarbose	50 mg/dL
Acetaminophen	200 µg/mL
Acetylsalicylate	50.0 mg/dL
Ascorbic Acid	3.0 mg/dL
Atorvastatin	600 µg Eq/L
Captopril	0.5 mg/dL
Chlorpropamide	74.7 mg/dL
Cyanate	64.8 mg/dL
Furosemide	6.0 mg/dL
Gemfibrozil	7.5 mg/dL
Ibuprofen	0.5 mg/mL
Insulin	450 µU/mL
Losartan	5 mg/dL

Interferent	Highest Concentration Level Tested with No Interference
Metamizole*	90.0 mg/dL
Metformin	5.1 mg/dL
N-acetylcysteine*	5.0 mmol/L
Nicotinic Acid	61 mg/dL
Propranolol	0.2 mg/dL
Repaglinide	60 ng/mL

Hemoglobin derivative interference

Testing to determine the interference bias of hemoglobin derivatives on the ADVIA A1c_E Assay was performed according to CLSI EP07-A2, *Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition*.

The effect of each hemoglobin derivative was evaluated using a paired difference analysis that compared HbA1c values between control samples (whole blood without any added derivative) and test samples (whole blood spiked with the derivative being tested). Three replicates were tested at each of two HbA1c levels: 6.5% ± 1.0% and 8.0% ± 1.0%.

Highest Derivative Concentration with No Significant Interference
Acetylated Hb (up to 50 mg/dL of acetylsalicylic acid)
Carbamylated Hb (up to10 mmol/L of Cyanate)
Labile Hb (up to 1000 mg/dL of Glucose)

To verify that HbA1a, HbA1b, or HbA0 derivatives did not interfere with assay performance, the sponsor evaluated the assay's HbA1c recovery of whole blood patient samples with known HbA1c, HbA1a, HbA1b, and HbA0 concentrations. The highest concentrations tested with no interference were 1.7, 1.4, and 86.0% for HbA1a, HbA1b, and HbA0, respectively. The data supports the sponsor's claim that HbA0, HbA1a, and HbA1b do not interfere with assay results.

Hemoglobin Variant Testing

Interference testing to determine the effect of hemoglobin variants on the ADVIA A1c_E Assay was performed according to CLSI EP07-A2, *Interference Testing in Clinical Chemistry; Approved Guideline – Second Edition*.

Anticoagulated (K_2EDTA) human venous whole blood samples with known concentrations of hemoglobin variant and HbA1c were obtained from NGSP (HbC, HbD, HbE, HbS, and HbF) and IFCC (HbA2). The effect of each hemoglobin variant on assay performance was evaluated by analyzing these samples and comparing the %HbA1c values obtained by using the candidate assay on the ADVIA 1800 to the comparator %HbA1c values. Comparator values were obtained on the Trinity Biotech Ultra 2 A1c, with the acception of HbF that was measured on the Tosoh G8 and HbC measured on the Trinity Biotech Ultra 2 A1c and Bio-Rad Variant II Turbo provided by the supplier of the sample. To obtain values across the assay range, some samples were combined into pools. Testing was performed in triplicate in the results are summarized below:

Hb Variant	**Number of Samples**	**% Concentration of Variant in Sample**	**%HbA1c Concentraiton Range**
HbC	45	26.1 – 40.0%%	4.4– 15.7%
HbD	24	22.7 – 37.5%	4.8 – 13.0%
HbE	20	19.7 – 30.4%	4.7 – 11.0%
HbS	25	23.0 – 37.4%	5.3 – 13.5%
HbA2	20	4.3 – 6.2%	5.0 – 10.0%
HbF	20	5.7 – 30.9%	4.6 – 9.3%

Hemoglobin Variant Study Summary Results

Hb Variant	**% Bias (Range of % Bias) for ~6% HbA1c**	**% Bias (95% CI) for ~9% HbA1c**
HbC	0.65% [-6.17 to 7.46%]	1.36% [-7.00% to 8.41%]
HbD	0.28% [-8.16 to 6.47%]	2.27% [-1.52 to 5.94%]
HbE	2.02% [-5.65 to 7.89%]	4.35% [-1.63 to 7.41%]
HbS	2.96% [-0.22 to 6.55%]	2.51% [-2.04 to 7.94 %]
HbA2	-1.49% [-3.87 to 5.00%]	1.47% [-1.26 to 6.63%]
HbF	Bias exceeds 5%	

Significant interference was defined by the sponsor as ≥ ±5% change in HbA1c value in the presence of the hemoglobin variant relative to control. The results show there is no significant interference for HbS (≤37.4%), HbC (≤40.0%), HbD (≤37.5%), HbE (≤30.4%), and HbA2 (≤6.2%) at the concentrations tested in this study. The labeling states:

The ADVIA Chemistry A1c_E 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.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison testing was performed in accordance with CLSI EP09-A3, *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition*. 163 human whole blood and hemolysate samples in K_2EDTA with values spanning the assay range of 3.80 to 13.60% HbA1c (18.03 to 125.14 mmol/mol HbA1c) were tested. The candidate device results were compared to those obtained from testing at a secondary NGSP reference laboratory on the Tosoh G8 HPLC method. Testing was completed in automated and manual modes. The distribution of samples spanning the measuring interval for both whole blood and hemolysate methods as follows:

Distribution of Samples, Automated (Whole Blood)

% HbA1c Level	**n**	**% of Samples tested**
<5	12	7
5-6	23	14
6-6.5	40	25
6.5-7	30	18
7-8	20	12
8-9	21	13
>9	17	10
Total	163	100

Distribution of Samples, Manual (Hemolysate)

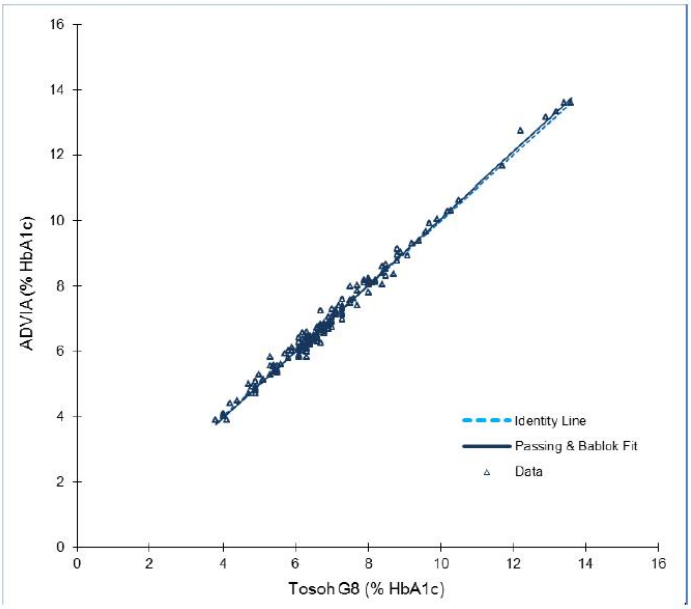
% HbA1c Level	**n**	**% of Samples tested**
<5	14	9
5-6	24	15
6-6.5	35	21
6.5-7	33	20
7-8	21	13
8-9	18	11
>9	18	11
Total	163	100

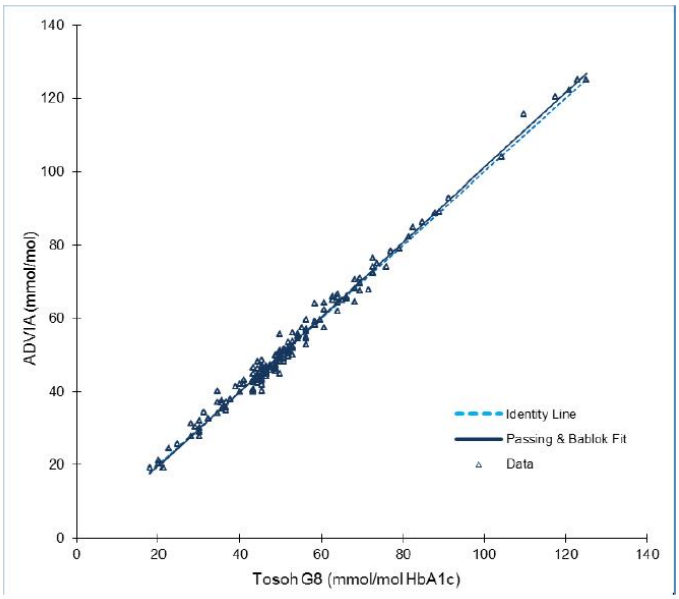
Summary of Method Comparison Results:
Deming and Passing-Bablok regression analysis was performed for the candidate system versus the Tosoh G8 method. A summary of the whole blood (automated) and manual (hemolysate) results are provided below:

N=163, sample range 3.80-13.60% HbA1c and 18.01 to 125.14 mmol/mol HbA1c

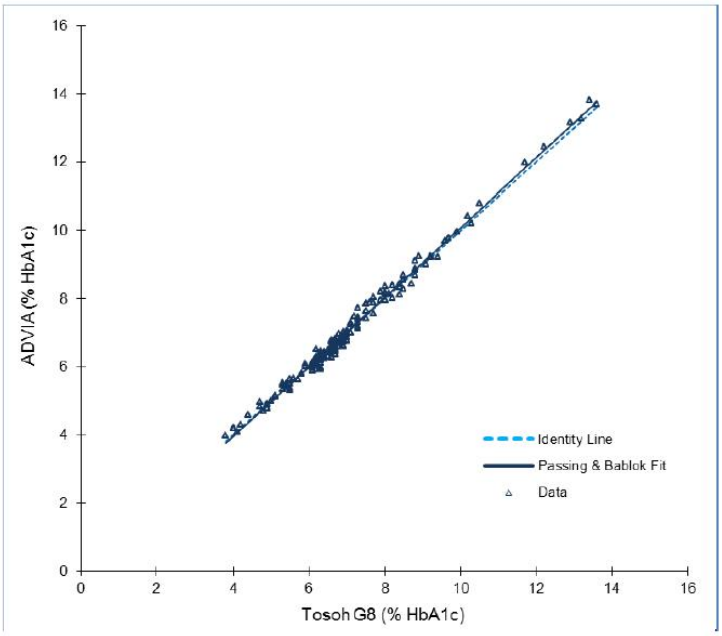
		Slope	95 % CI	y-intercept	95% CI	R^2
Passing-Bablok	NGSP (automated)	1.019	1.000 to 1.037	-0.110	-0.248 to 0.010	0.99
	NGSP (Manual)	1.022	1.004 to 1.041	-0.132	-0.280 to-0.019	1.00
	IFCC (Automated)	1.019	1.000 to 1.037	-0.761	-1.848 to 0.109	0.99
	IFCC (Manual)	1.022	1.004 to 1.041	-0.923	-2.092 to-0.109	1.00
Deming	NGSP (automated)	1.020	1.004 to 1.036	-0.120	-0.265 to-0.006	0.99
	NGSP (Manual)	1.027	1.012 to 1.042	-0.176	-0.280 to-0.072	1.00
	IFCC (Automated)	1.020	1.004 to 1.036	-0.840	-1.738 to 0.058	0.99
	IFCC (Manual)	1.027	1.012 to 1.042	-1.290	-2.098 to-0.438	1.00

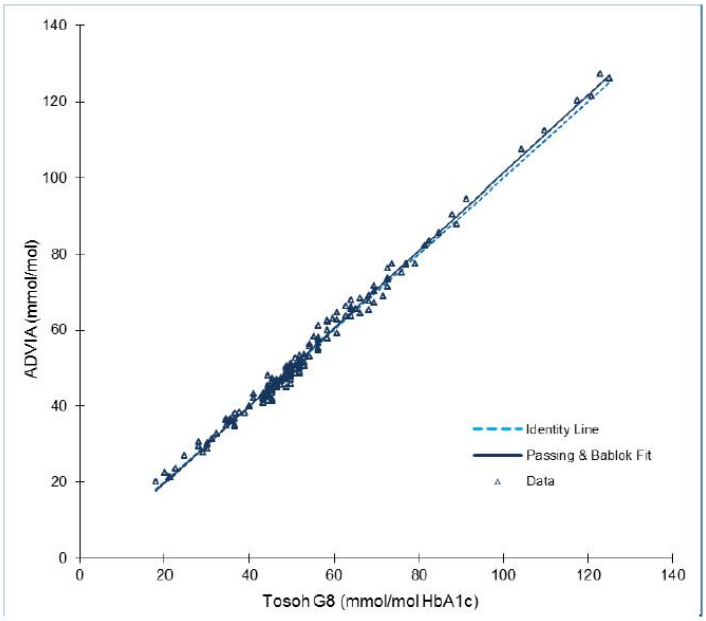
Whole blood (automated) scatter plot with Passing Bablok:



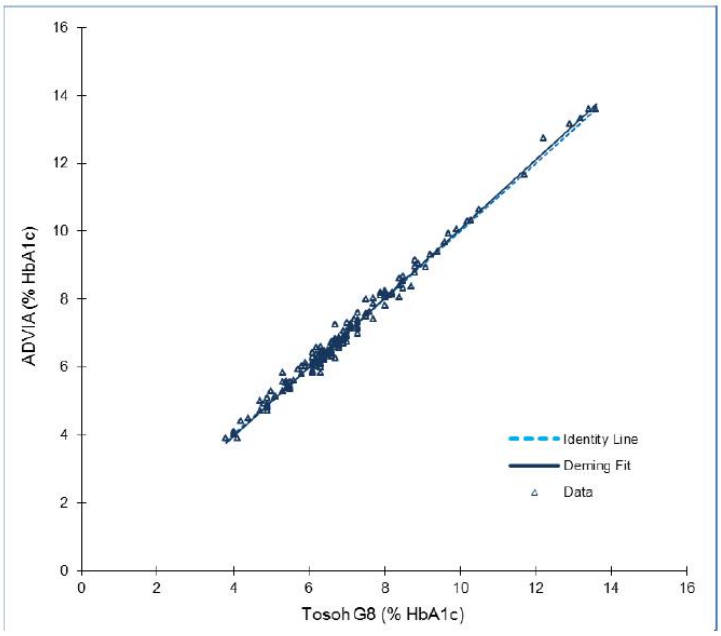


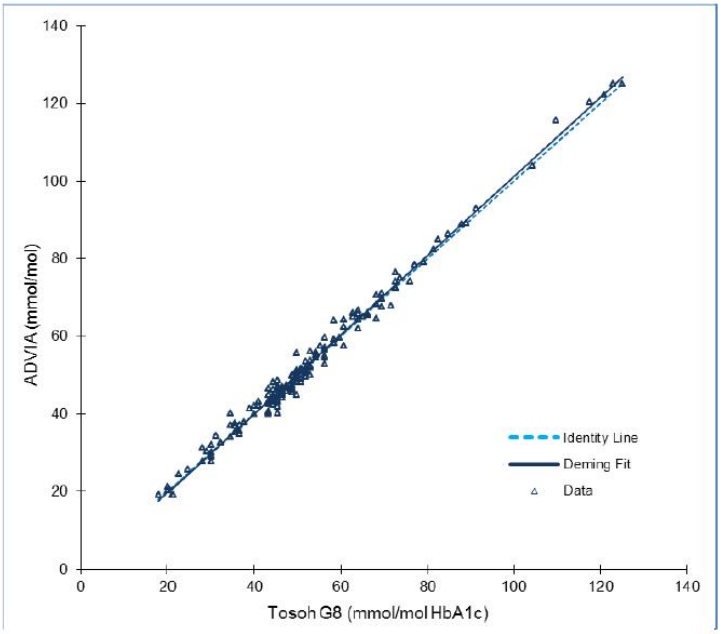
Hemolysate (manual) scatter plot with Passing Bablok:



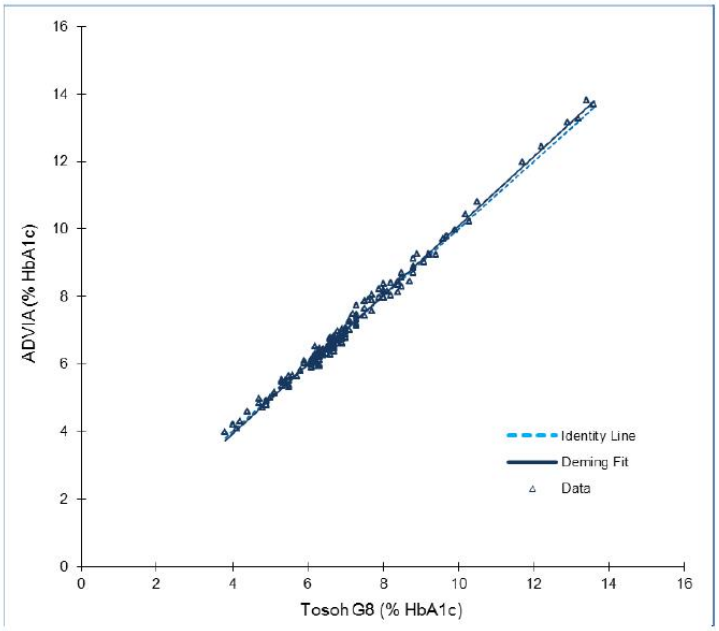


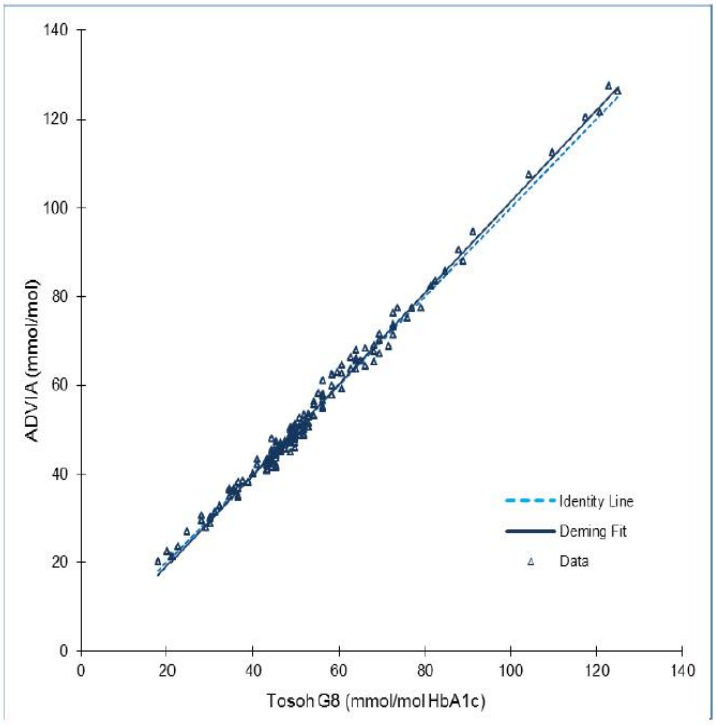
Whole blood (automated) scatter plot with Deming:





Hemolysate (manual) scatter plot with Deming:





Bias Estimation table

%HbA1c	Automated (Whole Blood)		Manual (Hemolysate)	
	Bias	**% Bias**	**Bias**	**% Bias**
5.00	-0.01	-0.20	-0.02	-0.40
6.50	0.01	0.15	0.01	0.15
8.00	0.04	0.50	0.04	0.50
12.00	0.12	1.00	0.13	1.08

Total Error calculations and estimation table

The bias estimation values determined in the method comparison study and precision estimates determined in the precision study were used to determine the total error at each of the levels listed in the tables below. Total error was calculated by the following equation:

%TE = |%Bias| + (1.96 x %CV) x (1 + %Bias/100)

Total Error Summary, Automated (Whole Blood)

%HbA1c	% Bias	%CV	%TE
5.00	-0.20	1.19	2.52
6.50	0.15	1.07	2.24
8.00	0.50	0.99	2.44
12.00	1.00	0.96	2.88

Total Error Summary, Manual (Hemolysate)

%HbA1c	% Bias	%CV	%TE
5.00	-0.40	1.01	2.38
6.50	0.15	0.93	1.97
8.00	0.50	0.93	2.33
12.00	1.08	1.01	3.06

b. Matrix comparison:

Testing was performed to demonstrate equivalence between 4 different anticoagulants in accordance with CLSI EP09-A2.

Matched sets of whole human blood were collected by Siemens Healthcare Diagnostics in four anticoagulant tubes containing K2 EDTA, K3 EDTA, Na Fluoride/Na2 EDTA, and Lithium heparin. All samples were native (unaltered).

HbA1c values were measured for each sample using the ADVIA A1c_E assay on the ADVIA 1800 using 1 reagent lot and 1 instrument. Samples were analyzed in duplicate. Only the first replicate values were used in statistical analysis. Regression analysis was used to analyze the measured values using the K2 EDTA samples as the comparator (i.e., the value plotted on the x-axis).

Deming Regression Analysis

Anticoagulant	Comparator	N	r	Slope	y-intercept
K3-EDTA	K2-EDTA	96	0.99	1.11	-0.034
Na Fluoride/Na2-EDTA	K2-EDTA	97	0.99	0.996	0.008
Lithium Heparin	K2-EDTA	96	0.99	1.033	-0.131

Passing-Bablok Regression Analysis

Anticoagulant	Comparator	N	r	Slope	y-intercept
K3-EDTA	K2-EDTA	96	0.999	1.010	-0.021
Na Fluoride/Na2-EDTA	K2-EDTA	97	0.999	0.998	-0.002
Lithium Heparin	K2-EDTA	96	0.999	1.025	-0.096

These results support the use of the ADVIA A1c_E assay with samples collected in K2-EDTA, K3-EDTA, Na Fluoride/Na2-EDTA, or Lithium Heparin tubes. In addition, the sponsor states the following in the limitations section of their labeling:

"Do not use sodium fluoride/potassium oxalate collection tubes as they may

interfere with the results of the ADVIA Chemistry A1c_E assay."

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 existing Reference Interval was taken from the American Diabetes Association, "Diagnosis and Classification of Diabetes Mellitus", Diabetes Care; 40 (Supplement 1): S11-S24; 2017.

Suggested Diagnosis	HbA1c (%)	HbA1c (mmol/mol)
Diabetic	≥ 6.5	≥ 48
Prediabetes	5.7-6.4	39-47
Normal	< 5.7	< 39

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10 and the special controls for this device type under 21 CFR 862.1373.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.