



December 4, 2017

Siemens Healthcare Diagnostics Inc.
Alan Haley
Regulatory Clinical Affairs Specialist
500 GBC Drive
Newark, Delaware 19714-6101

Re: K171771

Trade/Device Name: ADVIA Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay
Regulation Number: 21 CFR 862.1373
Regulation Name: Hemoglobin A1c Test System
Regulatory Class: Class II
Product Code: PDJ, LCP
Dated: October 16, 2017
Received: October 17, 2017

Dear Alan Haley:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR

Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/>) and CDRH Learn (<http://www.fda.gov/Training/CDRHLearn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<http://www.fda.gov/DICE>) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Kellie B. Kelm -S

for Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known)

K171771

Device Name

ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay

Indications for Use (Describe)

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.

Type of Use (Select one or both, as applicable)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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510(k) Summary – K171771

This 510(k) Summary of Safety and Effectiveness is being submitted in accordance with the requirements of Safe Medical Device Act of 1990 and 21 CFR 807.92.

1. Submitter

Company Siemens Healthcare Diagnostics Inc.
Address 500 GBC Drive
 Newark, DE 19702
Contact Alan Haley
Telephone 302.631.9883
Fax 302.631.6299
Date of Preparation November 29, 2017

2. Device Information

Trade Name	ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay	
Common Name	Hemoglobin A1c Test System	Assay, Glycosylated Hemoglobin
Classification Name	Hemoglobin A1c Test System	Glycosylated hemoglobin assay
Regulation	21 CFR 862.1373	21 CFR 864.7470
Device Class	Class II	Class II
Product Code	PDJ	LCP
Panel	Clinical Chemistry	Hematology

3. Identification of Predicate

Trade Name	ARCHITECT Hemoglobin A1C
510(k) Submitter	Abbott Laboratories Diagnostics Division
510(k) Number	K130255
Clearance Date	February 28, 2014

4. Device Description

The ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay measures hemoglobin A1c in human anticoagulated whole blood and hemolysate. The assay consists of three reagents (R1, R2, and Pretreatment). These reagents are liquid and are ready to use. 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). The two applications yield the same results.

5. Intended Use Statement

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.

6. Technological Characteristics

(a) Similarities and Differences

Device Characteristic	Proposed Device ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay	Predicate Device Abbott Architect Hemoglobin A1c (K130255)
Intended 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.	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 8000 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.
Type of Test	Quantitative, enzymatic	Same
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) 20.22-129.50 mmol/mol HbA1c (IFCC)
Specimen Types	Whole blood and Hemolysate	Same
Anticoagulant Types	<ul style="list-style-type: none"> • Dipotassium EDTA • Lithium Heparin • Sodium Fluoride/Disodium EDTA • Tripotassium EDTA 	<ul style="list-style-type: none"> • Dipotassium EDTA • Lithium Heparin • Sodium Fluoride/Disodium EDTA • Tripotassium EDTA • Sodium Heparin

Device Characteristic	Proposed Device ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) Assay	Predicate Device Abbott Architect Hemoglobin A1c (K130255)
Standardization and Certification	Assay standardization is traceable to International Federation of Clinical Chemistry (IFCC) reference calibrators. Assay is certified with the National Glycohemoglobin Standardization Program (NGSP). The NGSP certification expires in one year.	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.
Instrument Platform	ADVIA® 1800 Clinical Chemistry System	ARCHITECT c 8000 System (clinical chemistry analyzer)
Reporting Units	% HbA1c NGSP/DCCT and mmol/mol IFCC	% HbA1c NGSP/DCCT and mmol/mol IFCC

(b) Non-Clinical Performance Evaluation

(i) Method Comparison

Method comparison testing was performed in accordance with CLSI EP09-A3, *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition*.

One hundred sixty-three (163) human whole blood samples with values spanning the assay range were tested on the ADVIA® 1800 Clinical Chemistry System. Testing was performed in both automated (A1c_E) and manual (A1c_EM) modes.

Results on the ADVIA® 1800 were compared to results from NGSP reference method testing performed at an NGSP primary reference laboratory. Sample distribution is shown in Tables A and B. Slope and Y-intercept results were generated with both Passing-Bablok regression and Deming analysis. Correlation (r) values are Pearson correlation coefficients. Results are presented in Tables C, D, E, and F.

Table A. Method Comparison Sample Distribution, Automated (Whole Blood)

Range of Results (%HbA1c)	Percentage of Samples	Number of Samples
<5	7%	12
5 - 6	14%	23
6 - 6.5	25%	40
6.5 - 7	18%	30
7 - 8	12%	20
8 - 9	13%	21
>9	10%	17
Total	100%	163

Table B. Method Comparison Sample Distribution, Manual (Hemolysate)

Range of Results (%HbA1c)	Percentage of Samples	Number of Samples
<5	9%	14
5 - 6	15%	24
6 - 6.5	21%	35
6.5 - 7	20%	33
7 - 8	13%	21
8 - 9	11%	18
>9	11%	18
Total	100%	163

Table C. Method Comparison, Passing-Bablok

Units	Option	N	r	Slope [95% CI]	y-int. [95% CI]	Sample Range
NGSP (%HbA1c)	Automated (Whole Blood)	163	0.99	1.019 [1.000 to 1.037]	-0.110 [-0.248 to 0.010]	3.80 to 13.60
	Manual (Hemolysate)	163	1.00	1.022 [1.004 to 1.041]	-0.132 [-0.280 to -0.019]	3.80 to 13.60
IFCC (mmol/mol HbA1c)	Automated (Whole Blood)	163	0.99	1.019 [1.000 to 1.037]	-0.761 [-1.848 to 0.109]	18.01 to 125.14
	Manual (Hemolysate)	163	1.00	1.022 [1.004 to 1.041]	-0.923 [-2.092 to -0.109]	18.01 to 125.14

Table D. Bias Estimations, Passing-Bablok

%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

Table E. Method Comparison, Deming

Units	Option	N	r	Slope [95% CI]	y-int. [95% CI]	Sample Range
NGSP (%HbA1c)	Automated (Whole Blood)	163	0.99	1.020 [1.004 to 1.036]	-0.120 [-0.265 to -0.006]	3.80 to 13.60
	Manual (Hemolysate)	163	1.00	1.027 [1.012 to 1.042]	-0.176 [-0.280 to -0.072]	3.80 to 13.60
IFCC (mmol/mol HbA1c)	Automated (Whole Blood)	163	0.99	1.020 [1.004 to 1.036]	-0.840 [-1.738 to 0.058]	18.01 to 125.14
	Manual (Hemolysate)	163	1.00	1.027 [1.012 to 1.042]	-1.290 [-2.098 to -0.438]	18.01 to 125.14

Table F. Bias Estimations, Deming

%HbA1c	Automated (Whole Blood)		Manual (Hemolysate)	
	Bias	% Bias	Bias	% Bias
5.00	-0.02	-0.40	-0.04	-0.80
6.50	0.01	0.15	0.00	0.00
8.00	0.04	0.50	0.04	0.50
12.00	0.12	1.00	0.15	1.25

(ii) Precision

Precision testing was performed in accordance with CLSI EP05-A3, *Evaluation of Precision Performance of Quantitative Measurement Methods: Approved Guideline – Third Edition*.

Samples consisted of two (2) commercial quality controls and four whole blood patient pools with target values of 5.0% HbA1c, 6.5% HbA1c, 8.0% HbA1c, and 12.0% HbA1c. Whole blood pools were aliquoted and frozen prior to the start of the study. Each testing day, whole blood pool aliquots were thawed. QC materials were handled according to manufacturer’s instructions.

Testing was performed over twenty (20) days, two (2) runs per day (with a minimum of 2 hours in between), a single test from two (2) independent cups were analyzed for each test material. Testing was performed using three (3) reagent lots and three (3) ADVIA® 1800 instruments for a total of nine (9) sets of data. Testing was performed in both automatic and manual modes. Two calibrations were performed over the duration of the study. Data were analyzed using Analysis of Variance (ANOVA), consistent with the recommendations of CLSI EP05-A3. Results are presented in Tables I, J, K, and L.

Table I. Precision, All Instruments, Automated (Whole Blood), NGSP Units (%HbA1c)

SAMPLE	Mean	Repeat-ability		Between Run		Between Day		Between Instrument		Between Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
QC 1	4.49	0.02	0.5	0.03	0.7	0.04	0.8	0.05	1.1	0.00	0.0	0.07	1.6
QC 2	9.05	0.03	0.3	0.06	0.6	0.06	0.7	0.09	1.0	0.00	0.0	0.13	1.4
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

Table J. Precision, All Instruments, Automated (Whole Blood), IFCC Units (mmol/mol)

SAMPLE	Mean	Repeat-ability		Between Run		Between Day		Between Instrument		Between Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
QC 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
QC 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
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

Table K. Precision, All Instruments, Manual (Hemolysate), NGSP Units (%HbA1c)

SAMPLE	Mean	Repeat-ability		Between Run		Between Day		Between Instrument		Between Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
QC 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
QC 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
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

Table L. Precision, All Instruments, Manual (Hemolysate), IFCC Units (%HbA1c)

SAMPLE	Mean	Repeat-ability		Between Run		Between Day		Between Instrument		Between Lot		Total	
		SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
QC 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
QC 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
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

(iii) Total Error at Decision Levels

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 Tables M and N. Total error was calculated as follows:

$$\%TAE = |\%Bias| + 1.96 \times \%CV \times \left(1 + \frac{\%Bias}{100}\right)$$

Table M. Total Error Summary, Passing-Bablok

Option	%HbA1c Decision Level	% Bias	% CV	%TE
Automated (Whole Blood)	5.0	-0.20	1.19	2.52
	6.5	0.15	1.07	2.24
	8.0	0.50	0.99	2.44
	12.0	1.00	0.96	2.88
Manual (Hemolysate)	5.0	-0.40	1.01	2.38
	6.5	0.15	0.93	1.97
	8.0	0.50	0.93	2.33
	12.0	1.08	1.01	3.06

Table N. Total Error Summary, Deming

Option	%HbA1c Decision Level	% Bias	% CV	%TE
Automated (Whole Blood)	5.0	-0.40	1.19	2.72
	6.5	0.15	1.07	2.24
	8.0	0.50	0.99	2.44
	12.0	1.00	0.96	2.88
Manual (Hemolysate)	5.0	-0.80	1.01	2.78
	6.5	0.00	0.93	1.81
	8.0	0.50	0.93	2.33
	12.0	1.25	1.01	3.22

(iv) Endogenous Interference

Testing to determine the interference bias of various endogenous 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 was evaluated using a paired difference analysis. Three replicates were tested at each of two HbA1c levels: 6.5% ± 1.0% and 8.0% ± 1.0%. No significant interference (greater than ± 5.0%) was observed for the potential interferents at the concentrations listed in Table O.

Table O. Endogenous Interference

Interferent	Interferent Level	Approximate HbA1c Level
Ascorbic Acid	3.0 mg/dL	~6.5 %
	3.0 mg/dL	~8.0 %
Conjugated Bilirubin	10 mg/dL	~6.5 %
	10 mg/dL	~8.0 %
Unconjugated Bilirubin	10 mg/dL	~6.5 %
	10 mg/dL	~8.0 %
Total Protein	22 g/dL	~6.5 %
	22 g/dL	~8.0 %
Triglycerides	2000 mg/dL	~6.5 %
	2000 mg/dL	~8.0 %
Urea	667 mg/dL	~6.5 %
	667 mg/dL	~8.0 %
Vitamin E	8.6 mg/dL	~6.5 %
	8.6 mg/dL	~8.0 %

(v) Exogenous Interference

Testing to determine the interference bias of various 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 was evaluated using a paired difference analysis. Three replicates were tested at each of two HbA1c levels: 6.5% ± 1.0% and 8.0% ± 1.0%. No significant (bias greater than ± 5.0%) interference was observed for the potential interferents at the concentrations listed in Table P.

Table P. Exogenous Interference

Interferent	Interferent Level	Approximate HbA1c Level
Acarbose	50 mg/dL	~6.5 %
	50 mg/dL	~8.0 %
Acetaminophen	200 µg/mL	~6.5 %
	200 µg/mL	~8.0 %
Acetylsalicylate	50.0 mg/dL	~6.5 %
	50.0 mg/dL	~8.0 %
Atorvastatin	600 µg Eq/L	~6.5 %
	600 µg Eq/L	~8.0 %
Captopril	0.5 mg/dL	~6.5 %
	0.5 mg/dL	~8.0 %
Chlorpropamide	74.7 mg/dL	~6.5 %
	74.7 mg/dL	~8.0 %
Cyanate	64.8 mg/dL	~6.5 %
	64.8 mg/dL	~8.0 %
Furosemide	6.0 mg/dL	~6.5 %
	6.0 mg/dL	~8.0 %
Gemfibrozil	7.5 mg/dL	~6.5 %
	7.5 mg/dL	~8.0 %
Glucose	1000 mg/dL	~6.5 %
	1000 mg/dL	~8.0 %
Ibuprofen	0.5 mg/mL	~6.5 %
	0.5 mg/mL	~8.0 %
Insulin	450 µU/mL	~6.5 %
	450 µU/mL	~8.0 %
Intralipid	1000 mg/dL	~6.5 %
	1000 mg/dL	~8.0 %
Losartan	5 mg/dL	~6.5 %
	5 mg/dL	~8.0 %
Metamizole	90 mg/dL	~6.5 %
	90 mg/dL	~8.0 %
Metformin	5.1 mg/dL	~6.5 %
	5.1 mg/dL	~8.0 %
N-acetylcysteine	5 mmol/L	~6.5 %
	5 mmol/L	~8.0 %
Nicotinic Acid	61 mg/dL	~6.5 %
	61 mg/dL	~8.0 %
Propranolol	0.2 mg/dL	~6.5 %
	0.2 mg/dL	~8.0 %
Repaglinide	60 ng/mL	~6.5 %
	60 ng/mL	~8.0 %
Rheumatoid Factor	200 IU/mL	~6.5 %
	200 IU/mL	~8.0 %

(vi) Hemoglobin Derivative Interference

Hemoglobin derivative interference was determined per CLSI EP7-A2. No significant interference was observed for HbA0, HbA1a, HbA1b and for the hemoglobin derivatives listed below.

- Acetylated Hemoglobin with ≥ 50 mg/dL of acetylsalicylic acid
- Carbamylated Hemoglobin with ≥ 10 mmol/L of Cyanate
- Labile Hemoglobin with ≥ 1000 mg/dL of Glucose

(vii) Hemoglobin Variant Interference

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 human blood samples with known concentrations of hemoglobin variant and HbA1c were analyzed. The effect of each hemoglobin variant on assay performance was evaluated comparing the *mean observed %HbA1c* values to the *mean expected %HbA1c* values. Three replicates were tested for each sample.

No significant interference bias (i.e., greater than $\pm 5.0\%$) was observed for HbC, HbD, HbE, and HbA2. Significant interference bias was observed for HbF. Results are presented in Tables Q and R.

Table Q. Hemoglobin Variant Samples

Hb Variant	n	Range (% Variant)	Range (%HbA1c)
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%	5.3 – 9.3%

Table R. Hemoglobin Variant Interference

Hb Variant	Relative %Bias [Range of %Bias] Observed to Reference Method	
	HbA1c ~6%	HbA1c ~9%
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%	

(viii) Linearity

Linearity testing was conducted CLSI EP06-A, *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline*.

A dilution series consisting of eleven (11) levels across the assay range were prepared by mixing high HbA1c and low HbA1c whole blood pools. The high pools were prepared by spiking whole blood with HbA1c. The low pools were prepared by mixing whole blood with cord blood. The expected value for each level was calculated from the measurand concentrations and volumes of the low and high samples. Three replicates were tested at each level. Samples ranged from 2.77 to 14.60% HbA1c.

No deviations from linearity were observed for results from 2.77 to 14.60% HbA1c. The regression analysis equation is Observed %HbA1c = 1.0088 x Expected %HbA1c – 0.1110 with an R² of 0.9998.

(ix) Limit of Blank (LoB) and Limit of Detection (LoD)

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*.

To determine LoB, four (4) blank samples were processed using three (3) reagent lots and one (1) instrument. Testing was performed for three (3) days at five (5) replicates per day for a total of 60 measurements per reagent lot (180 measurements total).

To determine LoD, four (4) low samples were processed using three (3) reagent lots and one (1) instrument. Testing was performed for three (3) days at five (5) replicates per day for a total of 60 measurements per reagent lot (180 measurements total). Results are presented in Table S.

Table S. Limit of Blank / Limit of Detection

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

(x) Anticoagulant Comparison

Testing was performed to demonstrate equivalence between five different anticoagulants in accordance with CLSI EP09-A2, *Method Comparison and Bias Estimation Using Patient Samples*.

Testing was performed to demonstrate equivalence between K₂ EDTA, K₃ EDTA, Na Fluoride/Na₂ EDTA, and Lithium Heparin collection tubes. HbA1c values were measured for each sample using the ADVIA A1c_E assay on the ADVIA 1800. Regression analysis was used to analyze the measured values using the K₂ EDTA samples as the comparator. Results are presented in Tables T and U.

Table T. Passing-Bablok Regression Analysis Summary for Anticoagulant Equivalency

Anticoagulant	Comparator	N	r	Slope [95% CI]	y-intercept [95% CI]
K ₃ -EDTA	K ₂ -EDTA	96	0.9996	1.010 [1.000 to 1.018]	-0.021 [-0.077 to 0.035]
Na Fluoride/ Na ₂ -EDTA	K ₂ -EDTA	97	0.9989	0.998 [0.986 to 1.005]	-0.002 [-0.049 to 0.072]
Lithium Heparin	K ₂ -EDTA	96	0.9992	1.025 [1.016 to 1.034]	-0.096 [-0.146 to -0.039]

Table U. Deming Regression Analysis Summary for Anticoagulant Equivalency

Anticoagulant	Comparator	N	r	Slope [95% CI]	y-intercept [95% CI]
K ₃ -EDTA	K ₂ -EDTA	96	0.9996	1.011 [1.000 to 1.023]	-0.034 [-0.102 to 0.033]
Na Fluoride/ Na ₂ -EDTA	K ₂ -EDTA	97	0.9989	0.996 [0.986 to 1.006]	0.008 [-0.045 to 0.062]
Lithium Heparin	K ₂ -EDTA	96	0.9992	1.033 [1.023 to 1.042]	-0.131 [-0.183 to -0.079]

(xi) Conclusion

The proposed ADVIA® Chemistry Enzymatic Hemoglobin A1c (A1c_E) assay is substantially equivalent to the legally marketed predicate based on intended use, principle and the performance characteristics presented above.