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

A. 510(k) Number:

k182651

B. Purpose for Submission:

New Device

C. Measurand:

Glycosylated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative turbidimetric inhibition immunoassay

E. Applicant:

Beckman Coulter Ireland Inc.

F. Proprietary and Established Names:

HbA1c Advanced

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 HbA1c (Hemoglobin A1c) Advanced assay on the Beckman Coulter DxC 700 AU Clinical Chemistry Analyzer, is intended for the quantitative determination of mmol/mol HbA1c (IFCC) and % HbA1c (DCCT/NGSP) concentration in human venous whole blood. The determination of HbA1c is used as an aid in diagnosis of diabetes mellitus, for the monitoring of long-term blood glucose control in individuals with diabetes mellitus and identifying patients who may be at risk for developing diabetes mellitus. For In vitro diagnostic use only.

3. Special conditions for use statement(s):

For prescription use only.

For in vitro diagnostic use.

This assay is designed only for the measurement of mmol/mol HbA1c (IFCC) and %HbA1c (NGSP). Individual results for T-Hb and A1c concentration should not be reported.

This test should not replace glucose testing for patients with Type 1 diabetes, pediatric patients or pregnant women.

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 concentration and/or the typical clinical symptoms.

HbA1c should not be used to diagnose diabetes during pregnancy or to diagnose gestational diabetes. HbA1c reflects the average blood glucose levels over the preceding 3 months (the average life of a red blood cell), and therefore may be falsely low during pregnancy or any other condition associated with recent onset of hyperglycemia.

The HbA1c Advanced assay allows its use in patients with hemoglobin variants S, C, D and E traits. However, hemoglobinopathies might affect the red blood cell turnover or the in vivo glycation rates, and these patients may suffer from anemia and undergo transfusion. Therefore, results reported correctly by the assay may not reflect the same level of glycemic control as would be expected in patients with normal hemoglobin. In these cases, even analytically correct results do not reflect the same level of glycemic control that would be expected in patients with normal hemoglobin. Whenever, it is suspected that the presence of a Hb variant (e.g. HbSS, HbCC or HbSC) affects the correlation between the HbA1c value and glycemic control, HbA1c must not be used for the diagnosis of diabetes mellitus.

This test is not intended for analysis of samples collected from newborns.

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 T-Hb assay and as a consequence, specimens containing high amounts of HbF may result in lower than expected mmol/mol HbA1c values (IFCC) and% HbA1c values (DCCT/NGSP). HbA1c results are invalid for patients with abnormal amounts of HbF including those with known Hereditary Persistence of Fetal Hemoglobin. The following warning is included in the labeling;

> **"WARNING: The Hemoglobin A1c assay has significant negative interference from Hemoglobin F (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF, including those with known Hereditary Persistence of Fetal Hemoglobin. Refer to Limitations section."**

HbA1c should not be used to diagnose or monitor diabetes in patients with any conditions resulting in decreased erythrocyte survival, decrease in mean erythrocyte age or abnormal red blood cell turnover (e.g., hemolytic anemia, including hereditary spherocytosis, iron deficiency, thalassemias, malignancies, recovery from acute blood loss and severe chronic hepatic and renal disease). Shortened red cell survival time will reduce the exposure of red cells to glucose, with a resultant decrease in HbA1c values. The altered red blood cell turnover interferes with the relationship between mean blood glucose and HbA1c values.

4. Special instrument requirements:

   Beckman Coulter DxC 700 AU Clinical Chemistry Analyzer (k161837)

I. Device Description:

The HbA1c Advanced reagent kit is provided in a liquid format and is ready to use. It contains HbA1c R1 and HbA1c R2, Total Hemoglobin R1 and Hemolyzing reagent R1.

HbA1c R1	Anti-human HbA1c Antibody (sheep)
	MES (2-morpholino-ethanesulphonic acid) Buffer
	TRIS (tris(hydroxymethyl)aminomethane) Buffer (pH 6.2)
HbA1c R2	HbA1c Polyhapten
	MES (2-morpholino-ethanesulphonic acid) Buffer
	TRIS (tris(hydroxymethyl)aminomethane) Buffer (pH 6.2)
Total Hemoglobin R1	Phosphate Buffer, pH 7.4
Hemolyzing reagent R1	0.9% Tetradecyltrimethylammonium bromide

The HbA1c calibrator is supplied with the reagent, in a liquid, ready to use format and contains 5 x 2 mL calibrator levels (levels 2 - 6). The sample hemolysis is automated on the DxC 700 AU Clinical Chemistry analyzer.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Bio-Rad D-100™ HbA1c

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

   k151321

3. Comparison with predicate:

Similarities		
Item	Candidate Device HbA1c Advanced	Predicate Device Bio-Rad D-100™ HbA1c k151321
Intended Use	Intended for the quantitative determination of mmol/mol HbA1c (IFCC) and % HbA1c (DCCT/NGSP) concentration in human venous whole blood. The determination of HbA1c is used as an aid in diagnosis of diabetes mellitus, for the monitoring of long-term blood glucose control in individuals with diabetes mellitus and identifying patients who may be at risk for developing diabetes mellitus.	Same
Specimen Type	Venous whole blood K2-EDTA K3-EDTA Lithium Heparin Sodium Heparin	Same
Reporting Units	NGSP Equivalent Units (% HbA1c) IFCC Equivalent Units (mmol/mol)	Same

Differences		
Item	Candidate Device HbA1c Advanced	Predicate Device Bio-Rad D-100™ HbA1c k151321
Platform	DxC 700 AU Clinical Chemistry Analyzer	D-100TM Hemoglobin Testing System
Methodology	Quantitative turbidimetric inhibition immunoassay	Ion-exchange Quantitative high performance liquid chromatography (HPLC)
Measuring Range	HbA1c: 4.0 – 15% HbA1c (NGSP) 20 – 140 mmol/mol (IFCC)	HbA1c: 3.5 to 20% HbA1c (NGSP) 15 - 195 mmol/mol (IFCC)

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 EP-37 1st Edition: Supplemental tables for Interference testing in Clinical Chemistry - First edition

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

L. Test Principle:

The HbA1c Advanced assay is a turbidimetric inhibition immunoassay. The DxC 700 AU Clinical Chemistry analyzer automatically performs the whole blood hemolysis.

Tetradecyltrimethylammonium bromide (TTAB) in the hemolyzing reagent eliminates interference from leukocytes. The hemolyzed venous whole blood is then added to both the Total Hemoglobin and HbA1c assay cuvettes according to their defined assay parameters.

Total Hemoglobin reagent (R1) is used to measure Total Hemoglobin (T-Hb) concentration by a colorimetric method. Change in absorbance is measured at 570/660 nm.

HbA1c reagent (R1 and R2) is used to measure hemoglobin A1c (A1c) concentration by a turbidimetric immunoinhibition method. In the reaction, hemoglobin A1c antibodies in the reagent combine with HbA1c from the sample to form soluble antigen-antibody complexes. Polyhaptens from the reagent then bind with the excess antibodies and the resulting

agglutinated complex is measured turbidimetrically. Change in absorbance is measured at 340/700 nm.

The concentrations of both T-Hb and A1c are determined, and are used in the calculation of the reported HbA1c (A1c/T-Hb ratio), which is expressed either as mmol/mol (IFCC) or % (DCCT/NGSP).

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision of the HbA1c Advanced reagent on the DxC 700 AU Clinical Chemistry Analyzer was evaluated based on CLSI guideline EP05-A3, *Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Third Edition*. Studies were carried out at a single site by three operators over 20 days on three DxC 700 AU systems using three lots of HbA1c Advanced reagent, four levels of HbA1c K2 EDTA human venous whole blood patient samples at HbA1c concentrations of approximately 5.0%, 6.5%, 8.0% and 12%, one level of K2 EDTA human venous whole blood spiked with human based high HbA1c material at a HbA1c concentration of approximately 14% and two levels of control materials (QC) resulting in 720 measurements for each sample. The summary of precision performance results are shown in the tables below.

DxC 700 AU Clinical Chemistry Analyzer Instrument 1, % HbA1c (NGSP) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	5.06	0.04	0.88	0.04	0.80	0.03	0.64	0.05	0.92	0.08	1.63
Pool 2	6.72	0.07	1.01	0.04	0.60	0.04	0.65	0.06	0.93	0.11	1.64
Pool 3	8.06	0.06	0.77	0.04	0.47	0.06	0.73	0.09	1.06	0.13	1.57
Pool 4	11.70	0.09	0.79	0.06	0.48	0.10	0.84	0.02	0.19	0.15	1.26
Pool 5	14.02	0.10	0.74	0.07	0.49	0.10	0.72	0.04	0.32	0.17	1.19
QC 1	5.32	0.06	1.19	0.04	0.84	0.03	0.66	0.07	1.34	0.11	2.08
QC 2	9.88	0.08	0.77	0.05	0.48	0.06	0.65	0.11	1.07	0.15	1.54

DxC 700 AU Clinical Chemistry Analyzer Instrument 2, % HbA1c (NGSP) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	5.03	0.06	1.15	0.02	0.37	0.03	0.57	0.05	1.02	0.08	1.68
Pool 2	6.69	0.08	1.14	0.01	0.20	0.03	0.50	0.06	0.83	0.10	1.51
Pool 3	8.05	0.07	0.86	0.04	0.48	0.04	0.49	0.06	0.70	0.11	1.31
Pool 4	11.69	0.08	0.71	0.04	0.33	0.07	0.61	0.07	0.56	0.13	1.14
Pool 5	14.04	0.11	0.75	0.08	0.58	0.05	0.34	0.10	0.69	0.17	1.22

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
QC 1	5.28	0.06	1.23	0.02	0.41	0.04	0.75	0.07	1.32	0.11	1.99
QC 2	9.88	0.08	0.77	0.04	0.42	0.05	0.54	0.09	0.95	0.14	1.40

DxC 700 AU Clinical Chemistry Analyzer Instrument 3, % HbA1c (NGSP) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	5.03	0.04	0.83	0.02	0.45	0.04	0.70	0.05	1.02	0.08	1.55
Pool 2	6.66	0.06	0.82	0.02	0.31	0.03	0.48	0.09	1.31	0.11	1.65
Pool 3	7.98	0.06	0.73	0.05	0.58	0.04	0.47	0.14	1.68	0.16	1.98
Pool 4	11.68	0.08	0.71	0.03	0.21	0.08	0.67	0.06	0.54	0.13	1.14
Pool 5	13.99	0.09	0.66	0.06	0.44	0.08	0.56	0.09	0.66	0.17	1.18
QC 1	5.25	0.05	0.93	0.05	0.97	0.03	0.60	0.07	1.37	0.11	2.01
QC 2	9.72	0.06	0.65	0.03	0.36	0.06	0.65	0.14	1.45	0.17	1.75

DxC 700 AU Clinical Chemistry Analyzer Instruments Combined, % HbA1c (NGSP) units

Sample ID	Mean HbA1c %	Repeat-ability		Between Run		Between Day		Between Lot		Between Instrument		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	5.07	0.05	0.96	0.03	0.57	0.03	0.64	0.05	0.99	0.04	0.74	0.09	1.78
Pool 2	6.72	0.07	1.00	0.03	0.41	0.04	0.55	0.07	1.05	0.04	0.56	0.11	1.69
Pool 3	8.07	0.06	0.79	0.04	0.51	0.05	0.58	0.10	1.22	0.05	0.57	0.14	1.74
Pool 4	11.71	0.09	0.74	0.04	0.36	0.08	0.71	0.05	0.46	0.04	0.32	0.14	1.22
Pool 5	14.03	0.10	0.72	0.07	0.51	0.08	0.56	0.08	0.58	0.02	0.12	0.17	1.20
QC 1	5.29	0.06	1.12	0.04	0.78	0.04	0.67	0.07	1.34	0.03	0.50	0.11	2.09
QC 2	9.84	0.07	0.73	0.04	0.43	0.06	0.61	0.12	1.17	0.07	0.70	0.17	1.72

DxC 700 AU Clinical Chemistry Analyzer Instrument 1, mmol/mol (IFCC) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	31.84	0.48	1.51	0.46	1.43	0.34	1.08	0.51	1.60	0.90	2.84
Pool 2	49.92	0.75	1.49	0.45	0.90	0.48	0.97	0.68	1.36	1.21	2.41
Pool 3	64.65	0.68	1.06	0.40	0.61	0.65	1.01	0.93	1.43	1.38	2.14
Pool 4	104.38	1.37	1.31	0.00	0.00	1.07	1.03	0.24	0.23	1.76	1.68
Pool 5	129.76	1.13	0.87	0.74	0.57	1.11	0.86	0.49	0.37	1.82	1.40
QC 1	34.65	0.70	2.01	0.44	1.28	0.41	1.18	0.77	2.22	1.20	3.46
QC 2	84.53	0.83	0.98	0.51	0.61	0.69	0.82	1.15	1.36	1.66	1.96

DxC 700 AU Clinical Chemistry Analyzer Instrument 2, mmol/mol (IFCC) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	31.51	0.63	2.01	0.37	1.19	0.24	0.77	0.57	1.81	0.96	3.05
Pool 2	49.59	0.81	1.63	0.21	0.42	0.37	0.74	0.59	1.18	1.08	2.18
Pool 3	64.48	0.76	1.18	0.43	0.66	0.43	0.67	0.62	0.96	1.15	1.79
Pool 4	104.29	0.91	0.88	0.40	0.38	0.78	0.75	0.73	0.70	1.46	1.40
Pool 5	129.92	1.15	0.88	0.85	0.66	0.56	0.43	1.06	0.82	1.87	1.44
QC 1	34.24	0.72	2.09	0.25	0.74	0.42	1.23	0.76	2.23	1.16	3.38
QC 2	84.52	0.83	0.98	0.46	0.54	0.58	0.69	1.03	1.22	1.52	1.80

DxC 700 AU Clinical Chemistry Analyzer Instrument 3, mmol/mol (IFCC) units

Sample ID	Mean HbA1c %	Repeatability		Between Run		Between Day		Between Lot		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	31.46	0.46	1.41	0.38	1.18	0.42	1.31	0.58	1.78	0.93	2.88
Pool 2	49.27	0.61	1.21	0.23	0.46	0.35	0.70	0.97	1.93	1.22	2.42
Pool 3	63.68	0.65	1.00	0.52	0.79	0.41	0.63	1.49	2.29	1.75	2.69
Pool 4	104.18	0.92	0.87	0.26	0.25	0.85	0.81	0.70	0.66	1.46	1.39
Pool 5	129.37	1.02	0.79	0.67	0.52	0.86	0.66	1.01	0.87	1.81	1.39
QC 1	33.83	0.54	1.58	0.55	1.61	0.35	1.02	0.79	2.32	1.16	3.40
QC 2	82.77	0.69	0.83	0.38	0.46	0.69	0.83	1.55	1.86	1.87	2.24

DxC 700 AU Clinical Chemistry Analyzer Instruments Combined, mmol/mol (IFCC) units

Sample ID	Mean HbA1c %	Repeat-ability		Between Run		Between Day		Between Lot		Between Instrument		Total Precision	
		SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Pool 1	31.91	0.53	1.66	0.41	1.27	0.34	1.08	0.55	1.73	0.42	1.31	1.02	3.20
Pool 2	49.95	0.72	1.45	0.31	0.63	0.41	0.81	0.76	1.53	0.41	0.82	1.24	2.49
Pool 3	64.75	0.70	1.08	0.45	0.69	0.51	0.79	1.07	1.66	0.50	0.77	1.53	2.37
Pool 4	104.51	1.09	1.04	0.24	0.23	0.91	0.87	0.60	0.57	0.42	0.40	1.61	1.54
Pool 5	129.84	1.10	0.85	0.76	0.58	0.87	0.67	0.89	0.69	0.19	0.14	1.84	1.42
QC 1	34.32	0.66	1.91	0.43	1.26	0.39	1.15	0.78	2.26	0.30	0.87	1.21	3.52
QC 2	84.10	0.78	0.93	0.46	0.54	0.66	0.78	1.26	1.50	0.76	0.90	1.85	2.20

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 ten levels across the assay range was prepared by mixing high HbA1c and low HbA1c venous whole blood pools. Samples levels evaluated were 3.94, 4.67, 6.14, 7.60, 9.07, 10.54, 12.00, 13.47, 14.94 and 15.37% HbA1c (19.51, 29.53, 43.56, 59.59, 75.62, 91.65, 107.68, 123.71, 139.74 and 144.49 mmol/mol HbA1c) and each was run in quadruplicate with two reagent lots on

the DxC 700 AU Clinical Chemistry Analyzer. The measured values were compared to the expected values. The regression parameters (slope, intercept, and r) are shown below for one representative lot:

NGSP:

Slope	Intercept	R	Concentration Range Tested
1.030	-0.14	1.000	3.94 to 15.37 % HbA1c

IFCC:

Slope	Intercept	R	Concentration Range Tested
1.020	-0.64	1.000	19.51 to 144.49 mmol/mol HbA1c

The results of the linearity study support the claimed assay measuring range of 4-15% HbA1c (20 – 140 mmol/mol HbA1c (IFCC)).

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

The HbA1c Advanced assay standardization is traceable to the International Federation of Clinical Chemistry (IFCC) reference material. The HbA1c Advanced 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 International Federation of Clinical Chemistry (IFCC) units of mmol/mol are calculated using the Master Equation:

NGSP (%) = 0.09145 x IFCC (mmol/mol) + 2.152
IFCC Formula= (A1c / T-Hb) * 1000 = HbA1c (mmol/mol)

Results for calculated HbA1c may be reported from the DxC 700 AU analyzer in either NGSP (%) units or IFCC (mmol/mol).

d. Detection limit:

The claimed measuring range of 4-15% HbA1c (NGSP) and 20 – 140 mmol/mol HbA1c (IFCC) for HbA1c Advanced reagent is based on the linearity studies above in M.1.b.

e. Analytical specificity:

Testing to determine the interference bias of various endogenous and exogenous interferents on the HbA1c Advanced Assay was performed according to CLSI EP07-A2, *Interference Testing in Clinical Chemistry; Approved Guideline - Second Edition*; CLSI EP37 *Supplement Tables for Interference Testing in Clinical Chemistry, 1st Edition* was used in conjunction with EP07-A2.

The interfering substances analyzed were tested at two % HbA1c concentrations; approximately 6.5% HbA1c (low level human venous whole blood K2 EDTA

sample) and approximately 8.0% HbA1c (high level human venous whole blood K2 EDTA sample) using one lot of reagent on one DxC 700 AU Clinical Chemistry Analyzer.

The whole blood samples were tested at a minimum of five concentration levels for each interferent with 10 replicates tested per level on the DxC 700 AU Clinical Chemistry Analyzer to determine the magnitude of the interference. The difference in mean recovery of the samples with and without the potential interfering substances was determined.

The sponsor defines significant interference as ≥ ±7% change in the HbA1c measurements from the initial value (sample containing no interferent). The following substances demonstrated no significant interference at the concentrations described below:

Endogenous Interference Summary

Potential Interfering Substance	**Highest Concentration Tested without Significant Interference**
Conjugated Bilirubin	60 mg/dL
Unconjugated Bilirubin	60 mg/dL
Lipemia (Intralipid)	500 mg/dL
Ascorbic Acid	300 mg/dL
Rheumatoid Factor	1000 IU/mL
Total Protein	21 g/dL
Glucose	2000 mg/dL

Exogenous Interference Summary

Potential Interfering Substance	**Highest Concentration Tested without Significant Interference**
Glyburide	0.12 mg/dL
Salicyclic Acid	4.76 mg/dL
Sitagliptin	0.2 mg/dL
Rosiglitazone	0.33 mg/dL
Metformin	5 mg/dL
Cyclosporine	0.5 mg/dL
Heparin	5500 IU/L
Calcium Dobesilate	20 mg/dL
Metronidazole	200 mg/dL
Levodopa	20 mg/dL

Potential Interfering Substance	Highest Concentration Tested without Significant Interference
Acetylsalicyclic acid	1000 mg/dL
Acarbose	0.05 mg/dL
Acetaminophen	26 mg/dL
Acetylcystein	166 mg/dL
Ampicillin-Na	1000 mg/dL
Cefoxitin	2500 mg/dL
Doxycyclin	50 mg/dL
Ibuprofen	50 mg/dL
Methyldopa	20 mg/dL
Phenylbutazone	53.5 mg/dL
Rifampicin	8 mg/dL
Theophylline	10 mg/dL

Cross reactivity with Hemoglobin derivatives

Hemoglobin derivatives and potential cross reactants were tested at two %HbA1c concentrations, approximately 6.5% and 8.0% HbA1c, using one lot of reagent on one DxC 700 AU Clinical Chemistry Analyzer. Hemoglobin derivatives and potential cross reactants were tested at a minimum of five concentration levels with 10 replicates tested per level to determine the magnitude of any interference effect. The sponsor defined significant interference as recovery > 7% of the initial value (sample containing no cross reactant).

The following substances demonstrated no significant cross reactivity at the concentrations described below:

Potential Cross reacting Substance	Highest Concentration Level without Significant Cross Reactivity
Labile Hemoglobin	2000 mg/dL (Glucose)
Acetylated Hemoglobin	0.5 mg/mL (Acetylsalicylic acid)
Carbamylated Hemoglobin	1.5 mg/mL (Potassium Cyanate)
Glycated Albumin	5mg/mL
HbA0	12 mg/mL
HbA1a + b	0.16 mg/mL

Hemoglobin Variant Interference

A study was performed to assess hemoglobin variant interference with major hemoglobin variants in the HbA1c Advanced assay. Results from singlicate measurements of K2EDTA human venous whole blood samples tested using the HbA1c Advanced assay on the DxC 700 AU Clinical Chemistry Analyzer were compared to results from a FDA cleared method demonstrated to be free from

hemoglobin interference; Trinity Premier Hb9210 and Trinity Ultra Primus 2 were used to verify %HbA1c concentrations in samples containing HbC, HbD, HbE, HbS, and HbA2 variants. The Menarini HA8180V and Tosoh G8 were used to verify %HbA1c concentrations in samples containing HbF variant. Significant interference was defined by the sponsor as ≥ ±7% change in HbA1c value in the presence of the hemoglobin variant relative to control. The following tables show the samples that were measured and the range of biases that were observed.

Hemoglobin Variant Sample Ranges

Hb Variant	Number of Samples	% Concentration of Variant in Sample	%HbA1c Concentration Range
HbC	28	28.5 - 38.2	4.8 - 14.7
HbD	23	31.1 – 42.0	5.0 - 10.6
HbE	24	20.1 - 36.1	5.4 - 10.8
HbS	29	31.0 – 42.0	5.0 - 12.7
HbA2	28	3.3 - 6.2	5.4 - 7.5
HbF	22	3.2 – 34.0	4.9 - 12.8

Relative Bias Summary

Hb Variant	Relative % Bias (Range of % Bias) observed relative to Comparator Method	
	HbA1c ~6.5% A1c	HbA1c ~9% A1c
HbC	-2.57 (-4.30% to -1.80%)	-3.19 (-6.48% to 0.41%)
HbD	-0.77 (-4.81% to 2.99%)	-1.22 (-6.30% to -0.22%)
HbE	-1.12 (-9.16% to 2.48%)	0.47 (-1.76% to 4.21%)
HbS	-1.18 (-2.17% to 3.04%)	-1.04 (-3.33% to 4.41%)
HbA2	0.48 (-1.92% to 5.60%)	2.49 (-0.98% to 3.60%)
HbF	Specimens containing high amounts of HbF (> 7%) may yield lower than expected HbA1c Values	

The results show there is no significant interference for HbS (≤ 42.0%), HbC (≤ 38.2%), HbD (≤ 42.0%), HbE (≤ 36.1%), and HbA2 (≤ 6.2%). The labeling states:

"WARNING: The Hemoglobin A1c assay has significant negative interference from Hemoglobin F (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF, including those with known Hereditary Persistence of Fetal Hemoglobin. Refer to Limitations section."

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison testing was performed using 138 frozen human venous whole blood samples in K2EDTA with values spanning the assay range of 4.70 to 14.2% HbA1c. Samples were evaluated using the HbA1c Advanced assay on the DxC 700 AU Clinical Chemistry Analyzer. The HbA1c Advanced assay first replicate results were compared to results obtained for the same samples from testing at an NGSP secondary reference laboratory (SRL) on the Menarini HA8180V, a HPLC method (cleared in k162822). The distribution of samples spanning the measuring interval follows:

Distribution of Samples

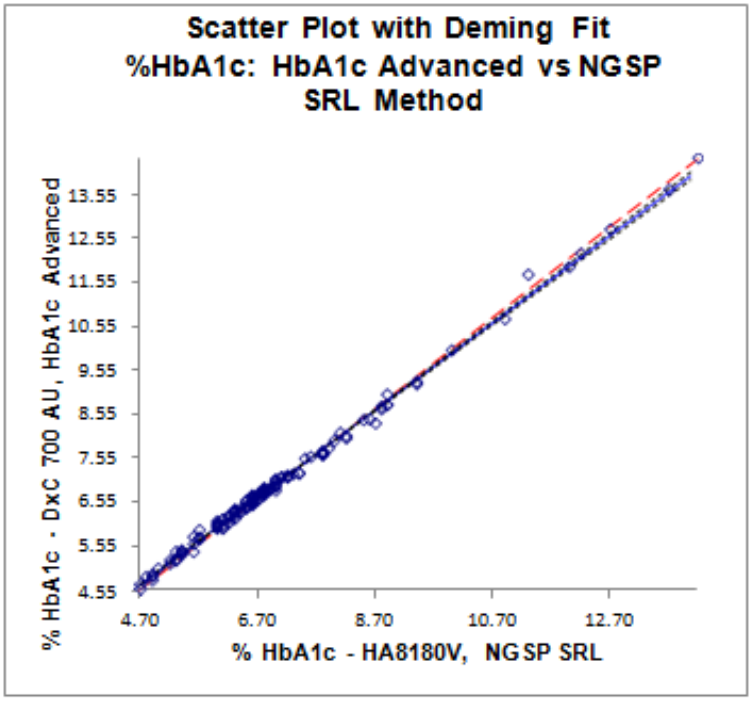
% HbA1c Level	n	% of Samples tested
<5	6	4.35%
5-6	18	13.04%
6-6.5	32	23.19%
6.5-7	35	25.36%
7-8	25	18.12%
8-9	12	8.7%
>9	10	7.25%
Total	138	100%

Deming (weighted) and Passing-Bablok regression analyses were performed for the HbA1c Advanced assay versus the comparator method. A summary of the results are provided below:

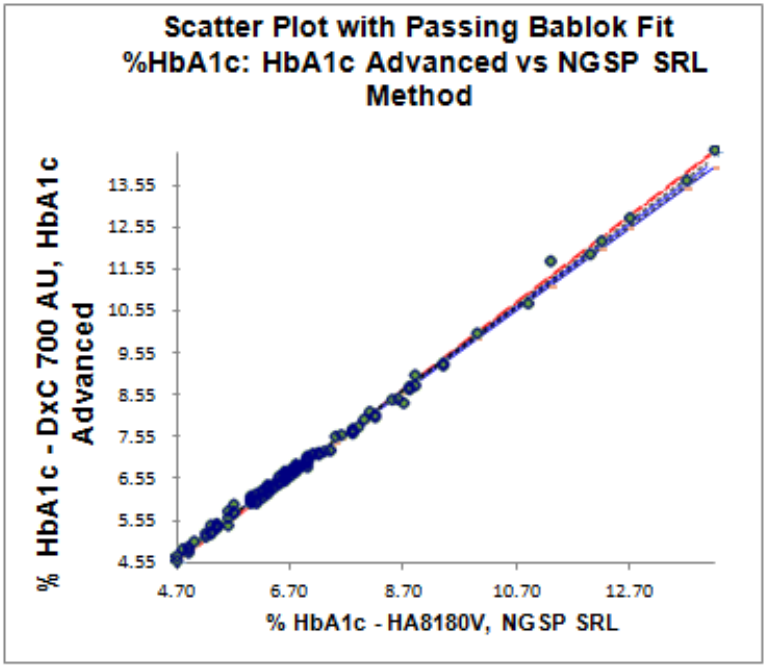
NGSP

	Slope	95 % CI	y-intercept	95% CI	R
Deming	0.990	(0.978-1.002)	0.01	(-0.070-0.089)	0.998
Passing-Bablok	0.980	(0.964-0.992)	0.090	(-0.006-0.187)	0.998

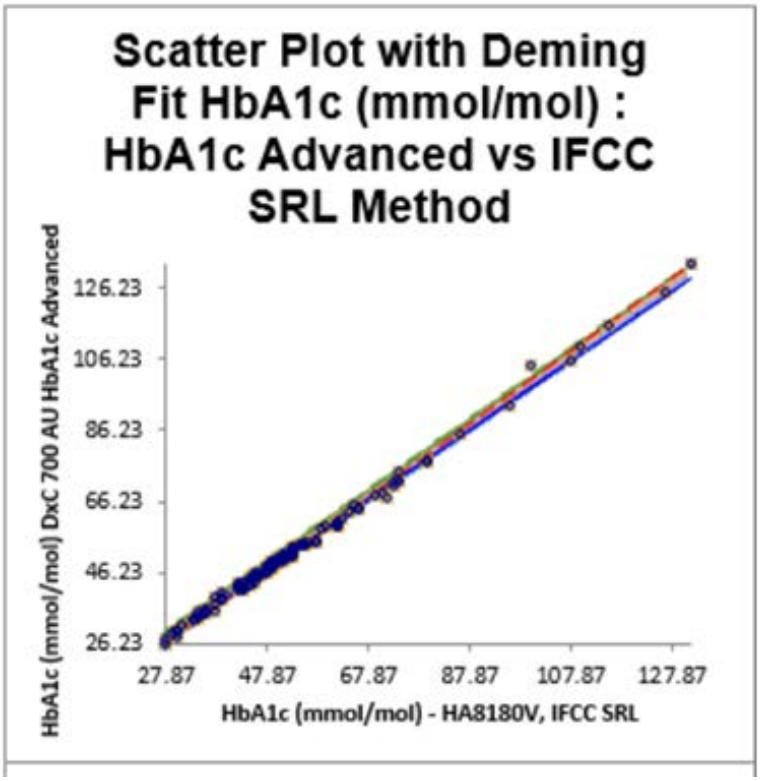
Scatter Plot using Deming Fit, %HbA1c, HbA1c Advanced vs. NGSP SRL



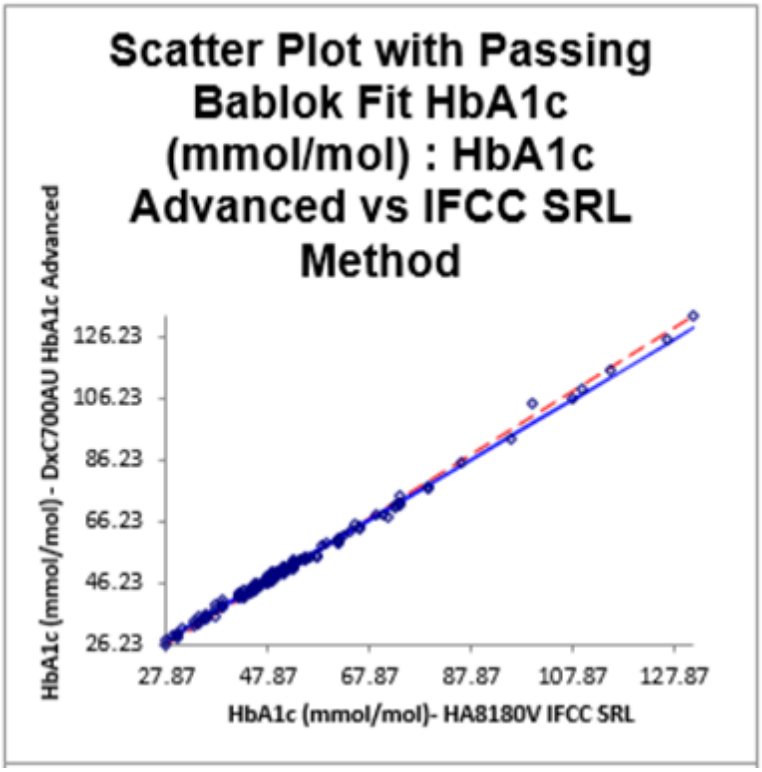
Scatter Plot using Passing-Bablok Fit, %HbA1c, HbA1c Advanced vs. NGSP SRL



Scatter Plot using Deming Fit, %HbA1c, HbA1c Advanced vs. IFCC SRL



Scatter Plot using Passing-Bablok Fit, %HbA1c, HbA1c Advanced vs. IFCC SRL



Summary of Bias Estimation table (medical decision points) Weighted Deming Analysis

Bias Estimation:

%HbA1c	Automated (Whole Blood)	
	Bias	% Bias
5.00	-0.04	-0.80
6.50	0.06	-0.85
8.00	-0.07	-0.88
12.00	-0.11	-0.92

Total Error calculations and estimation

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:

$\%TE = |\%Bias| + (1.96 \times \%CV) \times (1 + \%Bias/100)$

Total Error Summary:

%HbA1c	% Bias	%CV	%TE
5.00	-0.80	1.78	4.3
6.50	-0.85	1.69	4.2
8.00	-0.88	1.74	4.2
12.00	-0.92	1.22	3.3

b. Matrix comparison:

Testing was performed to validate the use of different anticoagulants in primary collection tubes for the HbA1c Advanced reagent on the DxC 700 AU Clinical Chemistry Analyzer. The study was carried out using one lot of HbA1c Advanced and K2 EDTA, K3 EDTA, Lithium Heparin and Sodium Heparin anticoagulant tube types. K2 EDTA values were used as the reference method for K3 EDTA, Lithium Heparin and Sodium Heparin.

Fifty native venous human whole blood specimens were drawn from each donor into each of the intended anticoagulant tube types. Values of K2-EDTA whole blood, ranging from 4.86% HbA1c to 9.83% HbA1c, were compared with values for K3-EDTA whole blood, lithium heparin whole blood and sodium heparin whole blood, yielding the following regression results:

Anticoagulant	Deming Regression Analysis
K3-EDTA	y = 1.000x + 0.043 ; r = 0.997
Lithium Heparin	y = 1.004x + 0.013; r = 0. 994
Sodium Heparin	y = 1.002x - 0.009; r = 0.997

These results support the use of the HbA1c Advanced assay with samples collected in

K2-EDTA, K3-EDTA, Lithium Heparin or Sodium Heparin tubes.

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:

Hemoglobin A1c Expected Values:

Hemoglobin A1c		Suggested Diagnosis
NGSP %	**IFCC mmol/mol**	
>6.5	>48	Diabetic
5.7 – 6.4	39-47	Pre-Diabetic
<5.7	<39	Non-Diabetic

The expected HbA1c range for non-diabetic adults is 4-6%.

The following references were cited in the labeling:

- American Diabetes Association. Position Statement: Standards of medical care in diabetes – In: Diabetes Care 2018; 41 (Suppl 1): S13-S27.
- Panteghini M, John WG. Implementation of Hemoglobin A1c results traceable to the IFCC reference system: the way forward. Clin Chem Lab Med 2007; 45(8): 942-944.

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.