January 16, 2019

Beckman Coulter Ireland Inc.
Catriona Hourigan, Regulatory Affairs Specialist
Lismeehan
O' Callaghan's Mills
Co. Clare
Ireland
V94 PP63

Re: k182651
Trade/Device Name: HbA1c Advanced
Regulation Number: 21 CFR 862.1373
Regulation Name: Hemoglobin A1c test system
Regulatory Class: Class II
Product Code: PDJ, LCP
Dated: September 20, 2018
Received: September 24, 2018

Dear Catriona Hourigan:

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. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. 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) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see https://www.fda.gov/CombinationProducts/GuidanceRegulatoryInformation/ucm597488.htm); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; 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 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2020
See PRA Statement below.

510(k) Number *(if known)*
K182651

Device Name
HbA1c Advanced

Indications for Use *(Describe)*
The HbA1c (Hemoglobin A1c) Advanced assay on the Beckman Coulter DxC700 AU Clinical Chemistry Analyzer, is intended for the quantitative determination of mmol/mol HbA1c (IFCC) or % HbA1c (DCCT/NGSP) concentration in human venous whole blood. The determination of HbA1c is used as an aid in the diagnosis of diabetes mellitus, for the monitoring of long-term 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.

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

HbA1c Advanced

1.0 Submitted By:

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2.0 Date Submitted:

15th January 2019

3.0 Device Name(s):

Proprietary Name: HbA1c Advanced
K182651

4.0 Predicate Device:

Table 1: Predicate Details

Candidate(s)	Predicate	Manufacturer	Docket Number
HbA1c Advanced	D-100™ HbA1c, D-100™HbA1c Calibrator Pack	Bio-Rad Laboratories, Inc;	K151321

5.0 Recommended Reagent Classification:

Name: Hemoglobin A1c Test System
Regulation: 862.1373
Class: II
Panel: Clinical Chemistry
Product Code: PDJ

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Name: Assay Glycosylated Hemoglobin
Regulation: 864.7470
Class: II
Panel: Hematology
Product Code: LCP

6.0 Description:

The HbA1c Advanced reagent kit is in a liquid format and is ready to use. It contains four reagents HbA1c R1 and HbA1c R2, Total Hemoglobin R1 and Hemolyzing reagent R1. The HbA1c calibrator is supplied with the reagent, in a liquid, ready to use format and contains 5 x 2mL calibrator levels. The sample hemolysis is automated on the DxC700 AU Clinical Chemistry analyzer. Sample handling is performed as follows: 200 µL of hemolyzing reagent is aspirated from the Hemolyzing Reagent R1and dispensed into a cuvette. Tetradecyltrimethylammonium bromide (TTAB) in the hemolyzing reagent eliminates interference from leukocytes. 2 µL of whole blood sample is then aspirated from the patient sample and added to the hemolyzing reagent in the cuvette. This hemolyzed whole blood is then added to the THb assay cuvette and HbA1c assay cuvette as per the assay parameters.

The concentrations of both HbA1c and Total Hemoglobin are determined. The HbA1c/Total Hemoglobin ratio is expressed either as mmol/mol (IFCC) or %HbA1c (DCCT/NGSP).

Total Hemoglobin Reagent is used to measure total hemoglobin concentration by a colorimetric method. Change in absorbance is measured at 570/660 nm.

HbA1c reagent is used to measure hemoglobin A1c concentration by a turbidimetric immunoinhibition method. In the reaction, hemoglobin A1c antibodies 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 calibrator is manufactured from human material; therefore should be handled as though capable of transmitting infectious disease. Each donor used in the preparation of this material was tested by the United States Food and Drug Administration (FDA), approved method and found to be negative for the presence of the antibodies for HIV-1/2, HCV, Hepatitis B surface antigen and was determined to not be repeatedly reactive.

Because no test method can offer complete assurance that HIV-1/2, HCV, hepatitis B virus

or other infectious agents are absent from biological materials, this product should be handled at the Biosafety Level 2 as recommended for any infectious human serum or blood specimen in the Centers for Disease Control and Prevention/National Institutes of Health manual, Biosafety in Microbiological and Biomedical Laboratories.

7.0 Intended Use:

HBA1c Advanced

The HbA1c 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.

8.0 Comparison to the Predicate(s):

Table 2: Similarities between the Predicate Device and the Proposed Device:

Test System	HbA1c Predicate	Proposed New System
Proprietary and Established Names	D-100™ HbA1c, D-100™ HbA1c Calibrator Pack	HbA1c Advanced
Similarities		
Intended use	The D-100™ HbA1c test is intended for the quantitative determination of hemoglobin A1c (IFCC mmol/mol and NGSP %) in human whole blood using ion-exchange high performance liquid chromatography (HPLC) on the D-100 Hemoglobin testing 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	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) or % HbA1c (DCCT/NGSP) concentration in human venous whole blood. The determination of HbA1c is used as an aid in the 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.

	blood glucose control in individuals with diabetes mellitus. Calibrators: The D-100^{Tm} HbA1c Calibrator pack is for the calibration of the D-100 Hemoglobin Testing System used for the quantitative determination of hemoglobin A1c (HbA1c) in human whole blood.	
Reporting Units	HbA1c results are provided to the customers using two different units: NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).	Same
Sample Types	Whole blood K2-EDTA K3-EDTA Lithium Heparin Sodium Heparin	Whole blood K2-EDTA K3-EDTA Li-Heparin Na-Heparin
Reagent Stability	**Unopened** 2° - 8^{0}C until expiration date	**Unopened** 2° - 8^{0}C until expiration date
Reference Range	Literature reference: Diabetic ≥6.5 NGSP %, ≥48 IFCC mmol/mol; Pre-Diabetic 5.7 – 6.4 NGSP%, IFCC 39 – 47 mmol/mol;: Non--Diabetic<5.7 NGSP%, <39 IFCC mmol/mol	Same
Traceability	Traceable to the Diabetes Control and Complications trial (DCCT) reference	Same

	method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP).	
Sensitivity	Not stated	Not stated
Specificity (Interference - Hb Variants)	Significant interference was defined as ≥ 7% change in HbA1c value in the presence of the hemoglobin variant relative to control. HbC, HbD, HbE, HbS HbA2, HbF	No Significant interference (NSI) is recovery within 7% of the reference value from Hb variants C, S, D, E, A2. Hemoglobin F interference shall be displayed as a disclaimer on package insert.
Specificity (Interferences - Endogenous)	NSI is observed from the following endogenous substances up to the stated concentrations (Significant interference is defined as ≥7% change in HbA1c value of the mean test value relative to mean of the reference samples): • Conjugated Bilirubin: NSI up to 60 mg/dL • Unconjugated Bilirubin: NSI up 60 mg/dL • Glucose: NSI up 2000 mg/dL • Total Protein: NSI up to 21 g/dL	The criteria for NSI is recovery within 7% of the initial value (sample containing no interferent). Similar for: • Conjugated Bilirubin: NSI up to 60 mg/dL • Unconjugated Bilirubin: NSI up to 60 mg/dL • Glucose: NSI up to 2000 mg/dL • Total Protein: NSI up to 21 g/dL
Specificity (Interference - Hb Derivatives and Cross Reactants)	Significant interference defined as % recovery of ±7% change in % HbA1c value from the control • Acetylated Hb: up to 50 mg/dL	NSI is recovery within 7% of the initial value (sample containing no interferent). • Acetylated Hb: NSI up to 0.5 mg/mL

Specificity (Interference - Drug)	Significant interference was defined as a ≥7% change in %HbA1c value from the control. Acetylcysteine: 166 mg/dL Ampicillin-Na: 1000 mg/dL Acetylsalicylic Acid: 1000 mg/dL Ascorbic Acid: 300 mg/dL Cefoxitin: 2500 mg/dL Levodopa: 20 mg/dL Methyldopa: 20 mg/dL Metronidazole: 200 mg/dL Doxycyclin: 50 mg/dL Cyclosporine: 5 mg/L Theophylline: 100 mg/L Ibuprofen: 500 mg/L Theophyline: 100mg/L	The criteria for no significant interference (NSI) is recovery within 7% of the initial value (Sample containing no interferent): Acetylcystein:166 mg/dL Ampicillin-Na: 1000 mg/dL Acetylsalicylic Acid: 1000 mg/dL Ascorbic Acid: 300 mg/dL Cefoxitin: 2500 mg/dL Levodopa: 20 mg/dL Methyldopa: 20 mg/dL Metronidazole: 200 mg/dL Doxycyclin: 50 mg/dL Cyclosporine: 0.5 mg/dL Theophylline: 10 mg/dL Ibuprofen: 50 mg/dL
Total Allowable Error	≤6%	≤6%

Table 3: Differences between the Predicate Device and the Proposed Device:

Feature	Predicate	Proposed New System
Proprietary and Established Names	D-100™ HbA1c, D-100™ HbA1c Calibrator Pack	HbA1c Advanced
Instrument Platform	D-100™ Hemoglobin Testing System	DxC 700 AU Clinical Chemistry Analyzer
Control	Commercially available Bio-Rad Lyphocheck Diabetes control materials	2 Levels of control material
Operating Principle	Ion-exchange Quantitative high performance liquid chromatography (HPLC)	Quantitative turbidimetric inhibition immunoassay

Sample Types	Capillary blood Acceptable anticoagulants are Potassium Oxalate/ Sodium Fluoride Sodium Citrate	Not Applicable for HbA1c Advanced
Analytical Range (Linearity)	HbA1c: 3.5 to 20% HbA1c (NGSP) 15 - 195 mmol/mol (IFCC)	HbA1c: 4.0 – 15% HbA1c (NGSP) 20 – 140 mmol/mol (IFCC)
Specificity (Interferences - Endogenous)	Significant interference defined as a ±7% change in % HbA1c value from the control • Lipemia (Intralipid): NSI up to 6000 mg/dL • Rheumatoid Factor: NSI up to 750 IU/mL	NSI is recovery within 7% of the initial value (sample containing no interferent). Lipemia: NSI up to 500 mg/dL Rheumatoid Factor (RF): NSI up to 1000 IU/mL
Specificity (Interference - Hb Derivatives and Cross Reactants)	Significant interference defined as % recovery of ±7% change in % HbA1c value from the control • Carbamylated Hb: up to 5% • Labile Hb: up to 1200 mg/dL of glucose does not interfere with this assay	NSI is recovery within 7% of the initial value (sample containing no interferent). • Carbamylated Hb: NSI up to 1.5 mg/mL • Labile Hb; NSI up to 2000 mg/dL • Glycated Albumin: NSI up to 5 mg/mL • HbA0: NSI up to 12 mg/mL

		• HbA1a+b: NSI up to 0.16 mg/mL
Drug Interference	Significant interference was defined as a ±7% change in %HbA1c value from the control. • Acetaminophen: 200 mg/L • Heparin: 5000 U/L • Rifampicin: 64 mg/L • Phenzylbutazone – 400 mg/L	NSI is recovery within 7% of the initial value (sample containing no interferent): • Acetaminophen: 26 mg/dL • Heparin: 5500 IU/L • Rifampicin: 8 mg/dL • Phenzylbutazone: 53.5 mg/dL • 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 • Calcium Dobsilate: 20mg/dL • Acarbose: 0.05 mg/dL
Specificity (Interference - Hb Variants)	Significant interference was defined as ≥ 7% change in HbA1c value in the presence of the hemoglobin variant relative to control. HbF concentrations up to 30% do not interfere with the test.	No Significant interference is recovery within 7% of the reference value (value assigned in Secondary Reference Laboratory). Samples containing ≥7% HbF may result in lower than expected HbA1c results

9.0 Performance Characteristics – Analytical Performance:

Precision

Precision of the HbA1c Advanced reagent on the DxC 700 AU was evaluated based on CLSI guideline EP05-A3: *"Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline - Third Edition".* Studies were carried out on 3 lots of HbA1c Advanced by testing four levels of HbA1c K2 EDTA human venous whole blood patient samples at HbA1c concentrations of approximately 5.0%, 6.5%, 8.0%, 12% and 14%. The experimental design used duplicate sample analysis, twice daily, over the course of twenty working days (n=2) in random order. NGSP results are shown in Tables 4 – 7. IFCC results are shown in Tables 8 – 11.

Table 4: DxC 700 AU: Instrument 1: NGSP units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean % HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specification
		% CV	SD	CV ≤1.5% or SD ≤0.1% HbA1c	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2% or SD ≤0.13% HbA1c
Human Whole Blood 1	5.06	0.88	0.04	Pass	0.80	0.04	0.64	0.03	0.92	0.05	1.63	0.08	Pass
Human Whole Blood 2	6.72	1.01	0.07	Pass	0.60	0.04	0.65	0.04	0.93	0.06	1.64	0.11	Pass
Human Whole Blood 3	8.06	0.77	0.06	Pass	0.47	0.04	0.73	0.06	1.06	0.09	1.57	0.13	Pass
Human Whole Blood 4	11.70	0.79	0.09	Pass	0.48	0.06	0.84	0.10	0.19	0.02	1.26	0.15	Pass
Spiked Human Whole Blood	14.02	0.74	0.10	Pass	0.49	0.07	0.72	0.10	0.32	0.04	1.19	0.17	Pass
Whole Blood Control 1	5.32	1.19	0.06	Pass	0.84	0.04	0.66	0.03	1.34	0.07	2.08	0.11	Pass
Whole Blood Control 2	9.88	0.77	0.08	Pass	0.48	0.05	0.65	0.06	1.07	0.11	1.54	0.15	Pass

Table 5: DxC 700 AU Instrument 2: NGSP units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean % HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specification
		% CV	SD	CV ≤1.5% or SD ≤0.1% HbA1c	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2% or SD ≤0.13% HbA1c
Human Whole Blood 1	5.03	1.15	0.06	Pass	0.37	0.02	0.57	0.03	1.02	0.05	1.68	0.08	Pass
Human Whole Blood 2	6.69	1.14	0.08	Pass	0.20	0.01	0.50	0.03	0.83	0.06	1.51	0.10	Pass
Human Whole Blood 3	8.05	0.86	0.07	Pass	0.48	0.04	0.49	0.04	0.70	0.06	1.31	0.11	Pass
Human Whole Blood 4	11.69	0.71	0.08	Pass	0.33	0.04	0.61	0.07	0.56	0.07	1.14	0.13	Pass
Spiked Human Whole Blood	14.04	0.75	0.11	Pass	0.58	0.08	0.34	0.05	0.69	0.10	1.22	0.17	Pass
Whole Blood Control 1	5.28	1.23	0.06	Pass	0.41	0.02	0.75	0.04	1.32	0.07	1.99	0.11	Pass
Whole Blood Control 2	9.88	0.77	0.08	Pass	0.42	0.04	0.54	0.05	0.95	0.09	1.40	0.14	Pass

Table 6: DxC 700 AU Instrument 3: NGSP units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean % HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specification
		% CV	SD	CV ≤1.5% or SD ≤0.1% HbA1c	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2% or SD ≤0.13% HbA1c
Human Whole Blood 1	5.03	0.83	0.04	Pass	0.45	0.02	0.70	0.04	1.02	0.05	1.55	0.08	Pass
Human Whole Blood 2	6.66	0.82	0.06	Pass	0.31	0.02	0.48	0.03	1.31	0.09	1.65	0.11	Pass
Human whole Blood 3	7.98	0.73	0.06	Pass	0.58	0.05	0.47	0.04	1.68	0.14	1.98	0.16	Pass
Human Whole Blood 4	11.68	0.71	0.08	Pass	0.21	0.03	0.67	0.08	0.54	0.06	1.14	0.13	Pass
Spiked Human Whole Blood	13.99	0.66	0.09	Pass	0.44	0.06	0.56	0.08	0.66	0.09	1.18	0.17	Pass
Whole Blood Control 1	5.25	0.93	0.05	Pass	0.97	0.05	0.60	0.03	1.37	0.07	2.01	0.11	Pass
Whole Blood Control 2	9.72	0.65	0.06	Pass	0.36	0.03	0.65	0.06	1.45	0.14	1.75	0.17	Pass

Table 7: Instruments Combined (Instrument 1, 2, 3): NGSP units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean % HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Between Instrument		Total Precision		Specification
		% CV	SD	CV ≤1.5% or SD ≤0.1% HbA1c	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2% or SD ≤0.13% HbA1c
Human Whole Blood 1	5.07	0.96	0.05	Pass	0.57	0.03	0.64	0.03	0.99	0.05	0.74	0.04	1.78	0.09	Pass
Human Whole Blood 2	6.72	1.00	0.07	Pass	0.41	0.03	0.55	0.04	1.05	0.07	0.56	0.04	1.69	0.11	Pass
Human Whole Blood 3	8.07	0.79	0.06	Pass	0.51	0.04	0.58	0.05	1.22	0.10	0.57	0.05	1.74	0.14	Pass
Human Whole Blood 4	11.71	0.74	0.09	Pass	0.36	0.04	0.71	0.08	0.46	0.05	0.32	0.04	1.22	0.14	Pass
Spiked Human Whole Blood	14.03	0.72	0.10	Pass	0.51	0.07	0.56	0.08	0.58	0.08	0.12	0.02	1.20	0.17	Pass
Whole Blood Control 1	5.29	1.12	0.06	Pass	0.78	0.04	0.67	0.04	1.34	0.07	0.50	0.03	2.09	0.11	Pass
Whole Blood Control 2	9.84	0.73	0.07	Pass	0.43	0.04	0.61	0.06	1.17	0.12	0.70	0.07	1.72	0.17	Pass

Table 8: DxC 700 AU Instrument 1: IFCC units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean (mmol/mol) HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specification
		% CV	SD	CV ≤2.3% or SD ≤1.1 mmol/mol	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2.9% or SD ≤1.4 mmol/mol
Human Whole Blood 1	31.84	1.51	0.48	Pass	1.43	0.46	1.08	0.34	1.60	0.51	2.84	0.90	Pass
Human Whole Blood 2	49.92	1.49	0.75	Pass	0.90	0.45	0.97	0.48	1.36	0.68	2.41	1.21	Pass
Human Whole Blood 3	64.65	1.06	0.68	Pass	0.61	0.40	1.01	0.65	1.43	0.93	2.14	1.38	Pass
Human Whole Blood 4	104.38	1.31	1.37	Pass	0.00	0.00	1.03	1.07	0.23	0.24	1.68	1.76	Pass
Spiked Human Whole Blood	129.76	0.87	1.13	Pass	0.57	0.74	0.86	1.11	0.37	0.49	1.40	1.82	Pass
Whole Blood Control 1	34.65	2.01	0.70	Pass	1.28	0.44	1.18	0.41	2.22	0.77	3.46	1.20	Pass
Whole Blood Control 2	84.53	0.98	0.83	Pass	0.61	0.51	0.82	0.69	1.36	1.15	1.96	1.66	Pass

Table 9: DxC 700 AU Instrument 2: IFCC units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean (mmol/mol) HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specification
		% CV	SD	CV ≤2.3% or SD ≤1.1 mmol/mol	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2.9% or SD ≤1.4 mmol/mol
Human Whole Blood 1	31.51	2.01	0.63	Pass	1.19	0.37	0.77	0.24	1.81	0.57	3.05	0.96	Pass
Human Whole Blood 2	49.59	1.63	0.81	Pass	0.42	0.21	0.74	0.37	1.18	0.59	2.18	1.08	Pass
Human Whole Blood 3	64.48	1.18	0.76	Pass	0.66	0.43	0.67	0.43	0.96	0.62	1.79	1.15	Pass
Human Whole Blood 4	104.29	0.88	0.91	Pass	0.38	0.40	0.75	0.78	0.70	0.73	1.40	1.46	Pass
Spiked Human Whole Blood	129.92	0.88	1.15	Pass	0.66	0.85	0.43	0.56	0.82	1.06	1.44	1.87	Pass
Whole Blood Control 1	34.24	2.09	0.72	Pass	0.74	0.25	1.23	0.42	2.23	0.76	3.38	1.16	Pass
Whole Blood Control 2	84.52	0.98	0.83	Pass	0.54	0.46	0.69	0.58	1.22	1.03	1.80	1.52	Pass

Table 10: DxC 700 AU Instrument 3: IFCC units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean (mmol/mol) HbA1c Concentration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Total Precision		Specifications
		% CV	SD	CV ≤2.3% or SD ≤1.1 mmol/mol	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2.9% or SD ≤1.4 mmol/mol
Human Whole Blood 1	31.46	1.41	0.46	Pass	1.18	0.38	1.31	0.42	1.78	0.58	2.88	0.93	Pass
Human Whole Blood 2	49.27	1.21	0.61	Pass	0.46	0.23	0.70	0.35	1.93	0.97	2.42	1.22	Pass
Human Whole Blood 3	63.68	1.00	0.65	Pass	0.79	0.52	0.63	0.41	2.29	1.49	2.69	1.75	Pass
Human Whole Blood 4	104.18	0.87	0.92	Pass	0.25	0.26	0.81	0.85	0.66	0.70	1.39	1.46	Pass
Spiked Human Whole Blood	129.37	0.79	1.02	Pass	0.52	0.67	0.66	0.86	0.87	1.01	1.39	1.81	Pass
Whole Blood Control 1	33.83	1.58	0.54	Pass	1.61	0.55	1.02	0.35	2.32	0.79	3.40	1.16	Pass
Whole Blood Control 2	82.77	0.83	0.69	Pass	0.46	0.38	0.83	0.69	1.86	1.55	2.24	1.87	Pass

Table 10: Instruments Combined (Instrument 1, 2, 3): IFCC units: Summary of 20 Day Precision Performance

Sample/ Control details	Mean (mmol/mol) HbA1c Concen-tration	Repeatability (Within-run)		Specification	Between-Run		Between-Day		Between-Lot		Between Instrument		Total Precision		Specification
		% CV	SD	CV ≤2.3% or SD ≤1.1 mmol/mol	% CV	SD	% CV	SD	% CV	SD	% CV	SD	% CV	SD	CV ≤2.9% or SD ≤1.4 mmol/mol
Human Whole Blood 1	31.91	1.66	0.53	Pass	1.27	0.41	1.08	0.34	1.73	0.55	1.31	0.42	3.20	1.02	Pass
Human Whole Blood 2	49.95	1.45	0.72	Pass	0.63	0.31	0.81	0.41	1.53	0.76	0.82	0.41	2.49	1.24	Pass
Human Whole Blood 3	64.75	1.08	0.70	Pass	0.69	0.45	0.79	0.51	1.66	1.07	0.77	0.50	2.37	1.53	Pass
Human Whole Blood 4	104.51	1.04	1.09	Pass	0.23	0.24	0.87	0.91	0.57	0.60	0.40	0.42	1.54	1.61	Pass
Spiked Human Whole Blood	129.84	0.85	1.10	Pass	0.58	0.76	0.67	0.87	0.69	0.89	0.14	0.19	1.42	1.84	Pass
Whole Blood Control 1	34.32	1.91	0.66	Pass	1.26	0.43	1.15	0.39	2.26	0.78	0.87	0.30	3.52	1.21	Pass
Whole Blood Control 2	84.10	0.93	0.78	Pass	0.54	0.46	0.78	0.66	1.50	1.26	0.90	0.76	2.20	1.85	Pass

Linearity:

Dynamic Range/ Analytical Measuring Range studies were designed using CLSI Guideline EP06-A: *"Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline".* High and low pools were prepared as per Table 1. A linearity series was prepared by inter-diluting the high and low pools to achieve a % HbA1c concentration spanning the required analytical range. The samples were mixed together in varying ratios.

Data was analyzed using Polynomial regression analysis (for first, second and third order polynomials) to determine the statistical significance of non-linearity. Where data generated was non-linear, the best fitting polynomial was applied to the data and difference between this best fitting, non-linear polynomial and the linear polynomial was calculated. Regression parameters for slope, intercept and R value were calculated.

The results of the study provides data to support the dynamic range/analytical measuring range claim for HbA1c Advanced reagent 4 – 15% (NGSP) HbA1c and 20 – 140 mmol/mol HbA1c (IFCC).

Table 12: Linearity Results Summary

Reagent	Acceptance Criteria	Results		Pass/ Fail	Acceptance Criteria	Pass/Fail
	Linear Range	Linear From	Linear To		Regression Parameters	
HbA1c Advanced	4-15% HbA1c	3.94% HbA1c	15.37% HbA1c	Pass	Slope: 1.0 ± 0.05 Intercept: ≤ ± 0.5 % HbA1c R: ≥ 0.990 N: ≥ 9	Pass Pass Pass Pass
HbA1c Advanced	20 – 140 mmol/mol	19.51 mmol/mol	144.49 mmol/mol	Pass	Slope: 1.0 ± 0.05 Intercept: ≤ ± 5.5 mmol/L R: ≥ 0.990 N: ≥ 9	Pass Pass Pass Pass

Method Comparison

Method comparison and bias estimation experiments were designed using CLSI Guideline EP09-A3; "*Measurement Procedure Comparison and Bias Estimation using Patient Samples; Approved Guideline.*" The patient correlation studies were performed using a standardized test method in an NGSP Secondary Reference Laboratory (SRL) using a test system (method X - HA8180V HPLC) with an analytical measuring range of 4-15% HbA1c (NGSP) and the proposed new Beckman Coulter HbA1c test system (method Y – HbA1c Advanced, 1 lot) with a proposed measuring range of 4-15 % HbA1c (NGSP) on a DxC 700 AU analyzer. Over a 120 (duplicates) of venous human frozen whole blood specimens (K2 EDTA anticoagulant type) with HbA1c concentrations were tested using on the DxC 700 AU Analyzer.

Table 13: Sample Distribution

Hemoglobin A1c Level	No. of Samples (SRL)	% Samples tested (SRL)	No. of Samples tested (Beckman)	% Samples tested (Beckman)
≤5%	6	4.35	6	4.35
5 – 6%	18	13.04	22	15.94
6 – 6.5%	32	23.19	32	23.19
6.5 – 7%	35	25.36	35	25.36
7 – 8%	25	18.12	23	16.67
8 – 9%	12	8.7	10	7.25
> 9%	10	7.25	10	7.25
Total Samples	138	100%	138	100%

Weighted Deming's and Passing-Bablok regression analysis was performed for the HbA1c Advancedmethod versus an NGSP SRL standardized method, results are summarized below in tables 14 and 15.

Table 14: Summary of Method Comparison for HbA1c Advanced results and specifications (Weighted Deming analysis) NGSP Units.

Sample Range:	Specifications	Results (95%CI Low; HIgh)	Pass / Fail
Method X: 4.7 - 14.2 % HbA1c Method Y: 4.6 – 14.3 % HbA1c	Slope: 1.0 ± 0.05	0.990 (0.978; 1.002)	Pass
	Intercept: ≤ ± 0.5% HbA1c	0.010 %HbA1c (-0.070; 0.089) %HbA1c	Pass
	R: ≥ 0.975	0.998	Pass
	N: ≥ 120	138	Pass

Table 15: Summary of Method Comparison for HbA1c Advanced results and specifications (Passing-Bablok analysis) NGSP Units.

Sample Range:	Specifications	Results (95% CI Low; High)	Pass / Fail
Method X: 4.7 - 14.2 % HbA1c Method Y: 4.6 – 14.3 % HbA1c	Slope: 1.0 ± 0.5	0.980 (0.964;0.992)	Pass
	Intercept: ≤ ± 0.5 %HbA1c	0.090 %HbA1c (-0.006; 0.187) % HbA1c	Pass
	R: ≥ 0.975	0.998	Pass
	N: ≥ 120	138	Pass

Total Error

Total error was evaluated using the results of the bias estimation (%Bias) from single measurements conducted of the new device compared to results of the standardised test method (method comparison) and precision estimates from the precision study. Total Error (TE) at four concentrations (5.0%, 6.5%, 8.0%, and 12.0%) was calculated as follows: "%TE = |(%Bias)| + 1.96*%CV*(1+%Bias/100)". The results are presented in Table 5.

Table 16: Total Error Estimation

%HbA1c Decision Level	% Bias	%CV	%TE	Acceptance Criteria: ≤6%
5.0	-0.80	1.78	4.3	Pass
6.5	-0.85	1.69	4.2	Pass
8.0	-0.88	1.74	4.3	Pass
12.0	-0.92	1.22	3.3	Pass

Analytical Specificity

Interference (Analytical Specificity) studies were designed based on CLSI Guideline EP07 Third Edition: *"Interference Testing in Clinical Chemistry; Approved Guideline"* and used to assess common or known substances which could interfere with the HbA1c Advanced assay.

Endogenous Interference

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 DxC700 AU analyzer. Low and high pools were prepared by interdiluting human whole blood samples.

The whole blood samples were tested at a minimum of 5 levels for each interferent (Conjugated Bilirubin, Unconjugated Bilirubin, Lipemia, Ascorbic Acid, RF, Total Protein and Glucose) with 10 replicates tested per level on the DxC700 AU Analyzer to determine the magnitude of the interference.

No Significant Interference is recovery within 7% of the initial value (sample containing no interferent). Results in Table 1 show no significant interference up to the stated concentrations.

Table 17: Specifications and Summary of Endogenous Interference data

Potential Interfering Substance	Interference pool details	Interferent Level
Conjugated Bilirubin	Whole Blood Pools spiked with Conjugated Bilirubin Stock Solution	60 mg/dL
Unconjugated Bilirubin	Whole Blood Pools spiked with unconjugated Bilirubin Stock Solution	60 mg/dL
Lipemia	Whole Blood Pools spiked with 20% w/v Intralipid	500 mg/dL
Ascorbic Acid	Whole Blood Pools spiked with Ascorbate	300 mg/dL
RF	Whole Blood Pools spiked with RF positive plasma	1000 IU/ml
Total Protein	Whole Blood Pools spiked with Human Serum Albumin	21 g/dL
Glucose	Whole Blood Pools spiked with Anhydrous Glucose	2000 mg/dL

Drug Interference

Potential drug interfering substances were analyzed to determine their effect on HbA1c Advanced reagent . All drug interferences were tested at two % HbA1c concentrations, approximately 6.5% HbA1c (low level human venous whole blood EDTA sample) and approximately 8.0% HbA1c (high level human venous whole blood EDTA sample). Testing was completed using one lot of reagent on DxC 700 AU Analyzer.

Low and high pools were prepared by inter-diluting human whole blood samples. The two whole blood sample pools were spiked with each potential interfering drug to create test samples. Ten replicates of each test and reference sample (sample containing no potential interferent) were tested on the DxC 700 AU to determine the magnitude of the interference. Each drug was tested to at least 5 times the highest drug concentration under therapeutic treatment.

No Significant Interference is recovery within 7% of the initial value (sample containing no interferent). Results outlined below showed no significant interference up to the stated concentrations.

Table 18: Specifications and Summary of Drug Interference data

Potential Interfering Substance	Interference pool details	Interferent Level
Glyburide	Whole Blood Pools spiked with Glyburide Stock Solution	0.12 mg/dL
Salicyclic Acid	Whole Blood Pools spiked with Salicyclic Acid Stock Solution	4.76 mg/dL
Sitagliptin	Whole Blood Pools spiked with Sitagliptin Phosphate stock solution	0.2 mg/dL
Rosiglitazone	Whole Blood Pools spiked with Rosiglitazone maleate stock solution	0.33 mg/dL
Metformin	Whole Blood Pools spiked with Metformin Hydrochloride stock solution	5 mg/dL
Cyclosporine	Whole Blood Pools spiked with Cyclosporine stock solution	0.5 mg/dL
Heparin	Whole Blood Pools spiked with Sodium Heparin stock solution	5500 IU/L
Calcium Dobesilate	Whole Blood Pools spiked with Calcium Dobsilate stock solution	20 mg/dL
Metronidazole	Whole Blood Pools spiked with Metronidazole stock solution	200 mg/dL
Levodopa	Whole Blood Pools spiked with Levodopa Stock solution	20 mg/dL
Acetylsalicyclic acid	Whole Blood spiked with Acetysalicyclic acid Stock Solution	1000 mg/dL

Acarbose	Whole blood spiked with Ascarbose Stock Solution	0.05 mg/dL
Acetaminophen	Whole blood spiked with Acetaminophen Stock Solution	26 mg/dL
Acetylcystein	Whole blood spiked with Acetylcystein Stock Solution	166 mg/dL
Ampicillin-Na	Whole blood spiked with Ampicillin-Na Stock Solution	1000 mg/dL
Cefoxitin	Whole blood spiked with Cefoxin Stock Solution	2500 mg/dL
Doxycyclin	Whole blood spiked with Doxycyclin Stock Solution	50 mg/dL
Ibuprofen	Whole blood spiked with Ibuprofen Stock Solution	50 mg/dL
Methyldopa	Whole blood spiked with Methyldopa Stock Solution	20 mg/dL
Phenylbutazone	Whole blood spiked with Phenylbutazone Stock Solution	53.5 mg/dL
Rifampicin	Whole blood spiked with Rifampicin Stock Solution	8 mg/dL
Theophylline	Whole blood spiked with Theophylline Stock Solution	10 mg/dL

Hemoglobin Derivative and Cross Reactants

Hemoglobin derivatives and potential interfering cross reactants 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 DxC700 AU analyzer. Low and high pools were prepared by interdiluting human whole blood samples.

Hemoglobin derivatives and potentially interfering cross reactants were tested at a minimum of 5 levels for: Labile Hemoglobin, Acetylated Hemoglobin, Carbamylated Hemoglobin, Glycated Albumin, HbA0 and HbA1a+b with 10 replicates tested per level on the DxC 700 AU analyzer to determine the magnitude of any interference effect.

No Significant Interference is recovery within 7% of the initial value (sample containing no interferent). Results in Table 19 showed no significant interference up to the stated concentrations.

Table 19: Specification and Summary of Hemoglobin Derivative and Cross Reactant Interferences

Potential Interfering Substance	Interference Pool details	Interferent Level
Labile Hemoglobin	Whole Blood Pools spiked with Glucose Stock Solution	2000 mg/dL
Acetylated Hemoglobin	Whole Blood Pools spiked with Acetylsalicylic acid Stock Solution	0.5 mg/mL
Carbamylated Hemoglobin	Whole Blood Pools spiked with Potassium Cyanate Stock Solution	1.5 mg/mL
Glycated Albumin	Whole Blood Pools spiked with Human Glycated Albumin Stock Solution	5mg/mL
HbA0	Whole Blood Pools spiked with HbA0 Stock Solution	12 mg/mL
HbA1a + 1b	Whole Blood Pools spiked with HbA1a +1b Stock Solution	0.16 mg/mL

Hemoglobin Variants

A hemoglobin variant study was performed to determine the presence of significant hemoglobin variant interference with major hemoglobin variants in the HbA1c Advanced assay. Results from singlicate measurements of samples were compared to results from a reference method, demonstrated to be free from hemoglobin interference; Trinity Biotech Hb9210 and Ultra2, Menarini HA8181V and TOSOH G8.

A minimum of 20 samples were tested for each variant (HbC, HbD, HbE, HbF, HbS and HbA2) on the DxC 700 AU Analyzer.

The following tables outline the number of samples of each variant, the range of % variant concentrations, %HbA1c concentrations and the relative % bias at 6.5% and 9.0% HbA1c.

Table 20: Hemoglobin Variant Sample Ranges

Hemoglobin Variant	Number of Samples	Range in %Variant Concentration	Range in %HbA1c Concentration
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
HbF	22	3.2 – 34.0	4.9 - 12.8
HbS	29	31.0 – 42.0	5.0 - 12.7
HbA2	28	3.3 - 6.2	5.4 - 7.5

Table 21: Relative Bias Summary

Hb Variant	Relative % bias (Range of % bias) observed relative to Reference method	
	HbA1c~6.5% HbA1c	HbA1c~9.0% HbA1c
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	

Anticoagulants

The data supports the use of the following blood collection tubes with the HbA1c Advanced reagent .

- K2 EDTA
- K3 EDTA
- Sodium Heparin
- Lithium Heparin

Expected Values/Reference Interval

Beckman Coulter used evidence recommended by the American Diabetes Association Standards of (ADA), which may be used as an aid in the diagnosis of diabetes mellitus:

Table 1: HbA1c ranges recommended by the ADA as an aid in the diagnosis of diabetes mellitus[1,2,3]

HbA1c Advanced		Suggested Diagnosis
NGSP %	IFCC mmol/mol	
≥ 6.5	≥48	Diabetic
5.7 – 6.4	39 - 47	Pre-Diabetic
< 5.7	<39	Non-Diabetic

Conclusion

The information and data in this 510(k) document demonstrate that the HbA1c Advanced reagent on the DxC700 AU Analyzer is an accurate, reliable, precise test that correlates well with current cleared methods and NGSP standardized testing for the quantitation of HbA1c.
The contents of this submission demonstrates that the HbA1c Advanced Reagent is substantially equivalent to the Biorad D-100™ HbA1c and D-100™HbA1c Calibrator Pack. It is therefore safe and effective for its intended use. The submitted information in this pre-market notification is complete and supports a substantial equivalence decision.