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

A. 510(k) Number:

k140829

B. Purpose for Submission:

New device

C. Measurand:

Glycosylated Hemoglobin A1c (HbA1c)

D. Type of Test:

Quantitative turbidimetric inhibition immunoassay

E. Applicant:

Beckman Coulter, Inc**.**

F. Proprietary and Established Names:

UniCel DxC Synchron Systems Hemoglobin (HbA1c3) Reagent

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
LCP	II	864.7470	Hematology,81

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The UniCel DxC Synchron Systems Hemoglobin A1c3 (HbA1c3) Reagent, when used in conjunction with UniCel DxC 600/800 SYNCHRON Systems, UniCel DxC SYNCHRON Systems HbA1c3 Calibrators and HbDil reagent, is intended for the

quantitative determination of hemoglobin A1c concentration in human whole blood.

The A1c3 and Hb3 values generated as part of the HbA1c3 assay are intended for use in the calculation of the A1c3/Hb3 ratio and must not be used individually.

Measurement of hemoglobin A1c is accepted as a method to measure long-term glucose control in patients with diabetes mellitus.

Special conditions for use statement(s):

- For Prescription use Only
- This assay is designed only for the measurement of mmol/mol HbA1c (IFCC) and %HbA1c (NGSP). The individual results for Hb and A1c concentration should not be reported.
- Do not use this test for the screening or diagnosis of diabetes mellitus. Performance characteristics for this use have not been determined.
- This assay is not useful in evaluating day-to-day glucose control and should not be used to replace daily home testing of glucose.
- Caution should be exercised when interpreting the HbA1c results from patients with hemolytic disease or other conditions characterized by shortened erythrocyte survival, acute blood loss and iron deficiency.
- Erythrocytes in a whole blood sample will settle over time. An inaccurate result could be produced from an unmixed whole blood sample.
- Samples containing >10% HbF may result in lower than expected HbA1c results
- Specimens with elevated Erythrocyte Sedimentation (ESR) may generate inaccurate results. The hemolysate should be manually prepared and assayed for HbA1c3 using "OTHER" as sample type.

3. Special instrument requirements:
   UniCel DxC 600 SYNCHRON Systems
   UniCel DxC 800 SYNCHRON Systems

I. Device Description:

Each UniCel DxC Synchron Systems Hemoglobin A1c3 (HbA1c3) reagent kit is comprised of the following items:

- Two A1c3 Cartridges (125 tests/cartridge)
- Two Hb3 Cartridges (125 tests/cartridge)
- One bottle A1c3 Calibrator Level 1 (lyophilized, 2 ml when reconstituted)
- One bottle Hb3/A1c3 Calibrator Level 2 (lyophilized, 2 ml when reconstituted)
- One bottle A1c3 Calibrator Level 3 (lyophilized, 2 mL when reconstituted)
- One bottle A1c3 Calibrator Level 4 (lyophilized, 2 mL when reconstituted)
- One bottle A1c3 Calibrator Level 5 (lyophilized, 2 mL when reconstituted)
- One calibrator Diskette

- One calibrator Value Assignment Sheet

Reagent Constituents

Antibody Reagent (50 ml):
Anti-human HbA1c Antibody (sheep) - ≥ 0.5 mg/dL
MES (2-morpholino-ethanesulfonic acid) Buffer - 0.025 mol/L
TRIS (tris (hydroxymethyl)aminomethane) Buffer – 0.015 mol/L

Polyhapten Reagent (12.7 mL):
HbA1c Polyhapten - ≥ µg/mL
MES buffer – 0.025 mol/L
TRIS Buffer (pH 6.2)-0.015 mol/L

Hemoglobin Reagent (42 mL):
Phosphate Buffer (pH 7.4) - 0.02 mol/L

Calibrator Constituents
Hemolysate (human and sheep)
0.9% tetradecyltrimethylammonium bromide

The HbDil reagent is sold separately and is not part of the kit. The HbDil reagent was previously cleared in k042459

J. Substantial Equivalence Information:

1. Predicate device name(s):

UniCel DxC Synchron Systems Hemoglobin A1c (HbA1c) Reagent

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

k121492

3. Comparison with predicate:

Similarities and Differences		
Item	Candidate Device UniCel DxC Synchron Systems Hemoglobin A1c (HbA1c3) Reagent (k140829)	Predicate Device UniCel Synchron Systems Hemoglobin A1c (HbA1c) reagent (k121492)
Intended Use/Indications for Use	Quantitative determination of hemoglobin A1c concentration in human whole blood.	Same
Technology	Colorimetric	Same

Similarities and Differences		
Item	Candidate Device UniCel DxC Synchron Systems Hemoglobin A1c (HbA1c3) Reagent (k140829)	Predicate Device UniCel Synchron Systems Hemoglobin A1c (HbA1c) reagent (k121492)
Analytical Measuring Range	4-17% HbA1c (NGSP)/20-140 mmol/mol (IFCC)	Same
Methodology	Turbidimetric Inhibition	Same
Sample Types	K_2-EDTA, K^3-EDTA, Li-Heparin or Na-Heparin	Same
Reagent volumes/tests per kit	Two A1c3 cartridges (125 tests/cartridge), Antibody Reagent (50 mL), Polyhapten Reagent (12.7 mL); Two Hb3 Cartridges (125 tests/cartridge), Hemoglobin Reagent (42 mL)	Two A1c Cartridges (200 tests/cartridge) Antibody Reagent (64mL), Polyhapten Reagent (16.9 mL); One Hb- Cartridge (400 tests/cartridge) Hemoglobin Reagent (103 mL)
Calibrators:		
Calibrator base matrix	Hemolysate (human and sheep)	Same
Calibrator Format and Levels	Lyophilized 5 levels THb=two point calibration HbA1c=multi point calibration	Lyophilized 5 levels THb=single point HbA1c=multi point calibration

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

CLSI EP05-A2-Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second 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-A2-Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline-Second Edition

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

CLSI EP28-A3-Defining, Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline- Third Edition

L. Test Principle:

The Hb3 reagent is used to measure total hemoglobin concentration by a colorimetric method. The analyzer system automatically proportions the appropriate sample and reagent volumes in to the cuvette. The ratio used is one part samples to 8.6 parts reagent. The system monitors the change in absorbance at 410 nm. This change in absorbance is directly proportional to the concentration of total hemoglobin in the sample and is used by the system to calculate and express total hemoglobin concentration.

The A1c3 reagent is used to measure the hemoglobin concentration by a turbidimetric immunoinhibition method. In the reaction, hemoglobin A1c antibodies combine with hemoglobin A1c 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 nm. This change in absorbance is inversely proportional to the concentration of hemoglobin A1c in the sample and is used by the analyzer system to calculate and express hemoglobin A1c concentration as a ratio of total hemoglobin.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision studies were performed according to CLSI EP05-A2. Within-run and Total precision were evaluated by testing a low and high whole blood commercial control. Three individual human whole blood samples at low, mid and high levels were also evaluated. Each sample was assayed in duplicate, twice a day over the course of twenty working days (n=80) on the Unicel DxC 600 and 800 SYNCHRON Systems analyzers.

UniCel DxC 600 SYNCHRON Systems

Sample	N	Mean (%HbA1c)	Within Run		Total Imprecision	
			SD	%CV	SD	%CV
Whole Blood Control 1	80	5.5	0.07	1.24	0.09	1.56
Whole Blood Control 2	80	10.0	0.11	1.13	0.15	1.46
Human Whole Blood Sample 1	80	8.9	0.09	0.96	0.14	1.56
Human Whole Blood Sample 2	80	6.3	0.08	1.30	0.10	1.62
Human Whole Blood Sample 3	80	4.8	0.07	1.52	0.09	1.93

UniCel DxC 800 SYNCHRON Systems

Sample	N	Mean (%HbA1c)	Within Run		Total Imprecision	
			SD	%CV	SD	%CV
Whole Blood Control 1	80	5.4	0.06	1.13	0.09	1.61
Whole Blood Control 2	80	9.9	0.08	0.80	0.13	1.34
Human Whole Blood Sample 1	80	8.9	0.07	0.81	0.13	1.47
Human Whole Blood Sample 2	80	6.3	0.07	1.16	0.11	1.72
Human Whole Blood Sample 3	80	4.6	0.06	1.34	0.09	1.89

An additional within run precision study was performed in order to demonstrate the precision of the UniCel DxC Synchron Systems Hemoglobin A1c3 Reagent on the UniCel DxC 600 and 800 SYNCHRON systems analyzers for samples with elevated HbA1c levels. A human whole blood was analyzed in replicates of twenty. The results are shown below:

	Sample	N	Mean (%HbA1c)	SD	%CV
Within-run (DxC 600)	Human Whole Blood Sample 4	20	14.6	0.16	1.10
Within-run (DxC 800)	Human Whole Blood Sample 4	20	14.6	0.15	1.10

b. Linearity/assay reportable range:

Linearity was evaluated according to CLSI EP-06A. A series of thirteen analyte concentrations, covering the measuring range of the assay, were prepared by inter-mixing a high (18.8 %) and low (3.4 %) HbA1c sample. Each dilution was assayed in quadruplicate on the UniCel DxC 600 and 800 SYNCHRON Systems analyzers. Sample range tested was between 3.4 -18.8% HbA1c. The results from regression analysis between the target values and the measured values are summarized below:

Platform/Method	**Linear Equation**
UniCel DxC 600 SYNCHRON Systems	y=0.991x+0.038,r=0.999
UniCel DxC 800 SYNCHRON Systems	y=0.984x+0.052, r=0.999

The results of the linearity study support the claimed measuring range of 4-17% HbA1c on the UniCel DxC 600/800 SYNCHRON System analyzers

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

The UniCel Synchron Systems Hemoglobin A1c3 (HbA1c3) assay is traceable to the IFCC (International Federation of Clinical Chemistry). The UniCel Synchron

Systems Hemoglobin (HbA1c3) assay is certified with the National Glycohemoglobin Standardization Program (NGSP). The NGSP certification expires one year from the certification date. See NGSP website for current certification http://www.ngsp.org.

Two different units of measure are provided to the customers. NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).

Stability-The UniCel DxC Synchron Systems HbA1c (HbA1c3) calibrators are stable until the expiration date printed on the calibrator bottle if stored unopened at 2°C to 8°C. Reconstituted calibrators are stable for 8 hours stored at 15°C to 25°C, or 48 hours stored at 2°C to 8°C unless the expiration date is exceeded. Calibrators that are aliquoted immediately after reconstitution and stored at -15°C to 20°C are stable for 60 days. Frozen calibrators should be thawed only once.

Calibrator value assignment- calibrator values are lot specific values which are assigned using multiple analyzers and multiple runs over several days. The data generated provides set points for use on the UniCel DxC 600/800 SYNCHRON Systems platforms. Once the calibration set points are established on the analyzers; principal samples (IFCC calibrators, IFCC controls, freshly prepared test calibrators, and NGSP traceable samples to cover the NGSP range) are analyzed in several replicates and must meet the sponsor's pre-determined acceptance criteria.

Controls- the sponsor recommends the use of any commercially available control for HbA1c. Alternatively, the user may use the Canterbury Scientific extendSURE ® Hemoglobin A1c Liquid Controls previously cleared in k043070.

d. Detection limit:

The claimed measuring range of 4.0-17.0% HbA1c for the Unicel DxC 600 and 800 SYNCHRON Systems analyzers, is based on linearity. See 1b above.

e. Analytical specificity:

i.) Endogenous Interference

Interference studies were performed to assess common or known substances that could potentially interfere with the Unicel DxC Synchron Systems Hemoglobin A1c3 (HbA1c3) assay. The potential interfering substances were evaluated using human EDTA whole blood sample pools at three HbA1c concentrations (5%, 7% and 10%). Each sample was spiked with the potential interferant and tested in quadruplicate to give a total of four replicates per sample on the UniCel DxC 600 and 800 SYNCHRON Systems analyzers. The % HbA1c values of the spiked samples were compared to reference samples (samples containing no interferent). The sponsor defined non- significant interference as the % recovery +/- 6%.

The sponsor claims there is no significant interference by the following substances:

- Unconjugated Bilirubin up to 30 mg/dL
- Triglycerides (Intralipid) up to 1000 mg/dL
- Rheumatoid Factor up to 2000 IU/mL
- Ascorbic Acid 50 mg/dL

ii.) Cross Reactivity

Potential Interference from from HbA0, HbA1(a+b), acetylated hemoglobin HbA0, glycated albumin and Carbamylated HbA0 were evaluated using EDTA whole blood samples with HbA1c values of ~5%, ~7% and ~10% HbA1c. The sponsor defined non-significant interference as the % recovery +/- 10%. The results were concluded as follows:

- HbA0 (up to 600 mg/mL) does not interfere with this assay
- HbA1(a+b) (up to 8 mg/mL) does not interfere with this assay
- Acetylated HbA0 (up to 10 mg/mL) does not interfere with this assay.
- Glycated albumin (up to 50 mg/mL) does not interfere with this assay
- Carbamylated HbA0 (up to 10 mg/mL) does not interfere with this assay.

In addition, interference from Labile glycated hemoglobin was evaluated using human whole blood samples at three HbA1c concentrations (5%, 7% and 10% HbA1c). Each sample was spiked with a glucose stock solution and incubated at 37°C for 5 hours and analyzed in quadruplicate on the UniCel DxC 600 and 800 SYNCHRON System analyzers. The percent difference of the samples with and without the potential interfering substance was calculated. The sponsor defined non-significant interference as the % recovery +/- 10%. The results concluded as follows:

- Labile Glycated hemoglobin (up to 2000 mg/dL) does not interfere with this assay.

iii.) Hemoglobin Variant Interference:

A hemoglobin variant study was performed using commercially available samples known to contain Hemoglobin variants C, D, E, S, F. These variant samples were tested on the UniCel DxC 600 and 800 SYNCHRON Systems analyzers using the UniCel DxC Synchron Systems Hemoglobin A1c3 (HbA1c3) assay. Samples were analyzed in quadruplicate and compared to the target values which were obtained using an HPLC reference analyzer. The sponsor defined non-significant interference as +/- 7% between the candidate method and the reference method for Hemoglobin variants C, D, E, and S. Non-significant interference was defined as +/- 10% between the candidate and reference method for HbF.

The testing results indicate there is no significant interference for HbC (≤36.4%), HbD (≤35.1%), HbE (≤21.7%) and HbS (≤31.9%).

The labeling states "Samples containing >10% HbF may result in lower than expected HbA1c results"

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed using the UniCel DxC Synchron Systems Hemoglobin A1c3 (HbA1c3) assay on the UniCel DxC 600 and 800 SYNCHRON Systems analyzers versus the UniCel DxC Synchron Systems HbA1c Reagent (predicate) on the UniCel DxC 600 and 800 SYNCHRON Systems analyzers. The study was conducted using between 118 and119 whole blood (K2-EDTA) samples. A total of 11 samples were altered (3 diluted and 8 spiked). Each sample was analyzed in singlicate using the candidate and predicate devices. Sample range tested was 4.4-16.6% HbA1c. The data was assessed using Deming regression analysis and is provided below:

Analyzer	Sample Range	n	R	Slope	Intercept
UniCel DxC600	4.4-16.6% HbA1c	119	0.998	1.031	-0.267
UniCel DxC800	4.3-15.9% HbA1c	118	0.999	1.031	-0.294

b. Matrix comparison:

A matrix comparison study was conducted using K_2EDTA, K_3EDTA, Lithium Heparin and Na-Heparin. K_2EDTA was used as the reference anticoagulant. Each single set of samples were analyzed in singlicate on the UniCel DxC 800 SYNCHRON System. Samples ranged from 4.8% - 16.0% HbA1c. The results using Deming regression analysis are as follows:

Anticoagulant	n	Deming Regression Analysis
K_2EDTA vs K_3EDTA	62	Y=1.012x-0.043 ; r=0.999
K_2EDTA vs Lithium Heparin	61	Y=1.007x-0.034 ; r=0.999
K_2EDTA vs Na-Heparin	62	Y=1.007x-0.034 ; r=0.999

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 expected normal HbA1c range in adults is 4.0-6.0% (NGSP); 20-42 mmol/mol (IFCC units) [1,2,3]

[1]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.

[2]Wu, A.,ed., Tietz clinical guide to Laboratory Tests, 4th edition, 2006

[3]McPherson, R.A, Pincus, M.R., Henry's Clinical Diagnosis and Management by Laboratory Methods, 22nd Edition, 2011

The sponsor recommends in the labeling that each clinical laboratory should establish its own reference range/expected values as dictated by good laboratory practices.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

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