

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

A. 510(k) Number:

k102045

B. Purpose for Submission:

Modification of previously cleared device, kit reagents and calibrators

C. Measurand:

Whole blood hemoglobin A1c (HbA1c)

D. Type of Test:

Turbidimetric inhibition immunoassay and calibration materials

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

Dimension Vista® HbA1c Kit

Dimension Vista HbA1c Calibrator

G. Regulatory Information:

| Product Code | Classification | Regulation Section | Panel |
|--|-----------------------|---------------------------|----------------|
| LCP – Assay, Glycosylated Hemoglobin | Class II | 21 CFR§ 864.7470 | 81, Hematology |
| JJX-Calibrator | Class II | 21 CFR§ 862.1150 | 75, Chemistry |

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The HbA1c assay used on the Dimension Vista® system is an in vitro diagnostic assay for the quantitative determination of per cent Hemoglobin A1c in human anticoagulated whole blood. Measurements of hemoglobin A1c are effective in monitoring long term glucose control in individuals with diabetes mellitus.

HbA1c calibrator is intended for use in the calibration of the Hemoglobin A1c (HbA1c) method on the Dimension Vista® system.

3. Special conditions for use statement(s):

The HbA1c Flex® Reagent Cartridge and HbA1c CAL are lot matched and it is required that they are used together.

Prescription use

4. Special instrument requirements:

Dimension Vista

I. Device Description:

The Dimension Vista® Hemoglobin A1c (HA1C) kit contains Flex® reagent cartridges and calibrator. Each cartridge contains liquid ready to use reagents use to measure total hemoglobin and hemoglobin A1c. The reagent wells of the cartridge contain the following reagents: sheep polyclonal anti-HbA1c antibody, MES buffer (2-morpholinoethane sulfonic acid), TRIS buffer tris(hydroxymethyl)-aminomethane, TTAB hemolyzing reagent (tetradecyl trimethyl ammonium bromide), polyhapten, and stabilizers.

The calibrator in the kit consists of lyophilized whole blood hemolysate containing five (5) specified levels of Hemoglobin A1c and Total Hemoglobin.

The calibrators contain human source material. Each donor unit used in the preparation of this product was tested by FDA-approved methods for the presence of antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2), as well as for Hepatitis B surface Antigen and antibody to Hepatitis C Virus (HCV), and found to be negative

Each calibrator level is hydrated with 2.0 mL of reagent grade water. The lot matched reagents and calibrator product are for use on the Dimension Vista® System.

The Vista only reports the result for the ratio of HbA1c to total hemoglobin, either as %HbA1c or mmol/mol HbA1c.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Dimension Vista HbA1c

2. Predicate k number(s):

k062128

3. Comparison with predicate:

| Similarities | | |
|----------------------------------|--|------------------|
| Item | Device | Predicate |
| Intended use/Indications for use | For use in monitoring long term glucose control in individuals with diabetes mellitus. | same |
| Technology | Turbidimetric inhibition immunoassay (TINIA) for the HbA1c measurement and both devices use a modification of the alkaline hematin reaction for the total hemoglobin portion of the assay. | same |
| Instrument | Dimension Vista | same |
| Sample type | Anticoagulated whole blood treated with EDTA | same |

| Differences | | |
|--------------------|--|--|
| Item | Device | Predicate |
| Reporting Units | %HbA1c and mmol/mol | %HbA1c only |
| Measuring range | 5.0 – 25.0 g/dL Hb 0.3 – 2.6 g/dL HbA1c 3.5 – 16.0 % HbA1c | 1.0 – 30.0 g/dL Hb 0.2 – 2.9 g/dL HbA1c Not stated |
| Calibrators | Five calibrator levels provided of whole blood hemolysate at specified levels of HbA1c and Hb. | Four calibrator levels provided of whole blood hemolysate at specified levels of HbA1c and Hb. |

| Differences | | |
|-------------------------|---------------|-----------|
| Item | Device | Predicate |
| Calibrator traceability | NGSP and IFCC | NGSP |

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

CLSI EP5-A: Evaluation of Precision Performance of Quantitative Measurement Methods

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP9-A: Method Comparison and Bias Estimation Using Patient Samples

CLSI C28-A2: How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline - Second Edition

CLSI EP7-A: Interference Testing in Clinical Chemistry; Approved Guideline

L. Test Principle:

The Dimension Vista® HbA1c assay measures both HbA1c and total hemoglobin. The HbA1c measurement is based on a turbidimetric inhibition immunoassay (TINIA) principle, and the measurement of total hemoglobin is based on a modification of the alkaline hematin reaction. Using the values obtained for each of these two analytes, the relative proportion of the total hemoglobin that is glycosylated is calculated and reported.

Total Hemoglobin Measurement: A sample of whole blood is added to a LOCI® reaction vessel containing lysing reagent. This reagent lyses the red blood cells and simultaneously converts the released hemoglobin to a derivative that has a characteristic absorbance spectrum. An aliquot of the lysed whole blood is transferred from the LOCI® reaction vessel to a cuvette where total hemoglobin concentration is measured at 405 nm and 700 nm.

Hemoglobin A1c Measurement: The same aliquot of the lysed whole blood that is transferred from the LOCI® reaction vessel to the cuvette for the Hb measurement is also used for the measurement of HbA1c. The cuvette contains a sheep anti-HbA1c polyclonal antibody in a buffered reagent. Hemoglobin A1c in the sample reacts with anti-HbA1c antibody to form a soluble antigen-antibody complex. A polyhapten reagent containing multiple HbA1c epitopes is then added to this cuvette. The polyhapten reacts with excess (free) anti-HbA1c antibodies to form an insoluble

antibody-polyhapten complex. The rate of this reaction is measured turbidimetrically at 340 nm and blanked at 700 nm and is inversely proportional to the concentration of HbA1c in the sample

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision testing for the HbA1c method was performed over twenty days according to CLSI/NCCLS EP5-A2. The test samples consisted of four levels of whole blood hemolysate control material tested on a single Vista instrument with one lot of reagents. On each day of testing, each sample was run in duplicate from independent sample cups, in two separate runs.

| Sample | | | | | | |
|--------|----|---------------|---------|------|------------|------|
| Level | n | Repeatability | | | Within-Lab | |
| | | Mean (%) | Std Dev | % CV | Std Dev | % CV |
| 1 | 80 | 5.31 | 0.15 | 2.8 | 0.18 | 3.4 |
| 2 | 80 | 6.16 | 0.15 | 2.4 | 0.17 | 2.7 |
| 3 | 80 | 8.25 | 0.13 | 1.6 | 0.14 | 1.7 |
| 4 | 80 | 11.71 | 0.18 | 1.6 | 0.20 | 1.8 |

A second precision study was run using five whole blood pools with %HbA1c values across the assay range. Each pool was run in duplicate for five days and two runs per day, with two reagent lots, two instruments and a single calibration for each Vista instrument.

Instrument 1, Reagent lot A

| Sample, | | | | | | |
|---------|----|---------------|---------|------|------------|------|
| Level | n | Repeatability | | | Within-Lab | |
| | | Mean (%) | Std Dev | % CV | Std Dev | % CV |
| 1 | 20 | 4.87 | 0.13 | 2.75 | 0.14 | 2.98 |
| 2 | 20 | 6.57 | 0.24 | 3.72 | 0.24 | 3.73 |
| 3 | 20 | 7.31 | 0.09 | 1.19 | 0.09 | 1.25 |
| 4 | 20 | 8.16 | 0.16 | 1.92 | 0.17 | 2.05 |
| 5 | 20 | 9.35 | 0.11 | 1.15 | 0.11 | 1.16 |

Instrument 1, Reagent lot B

| Sample, | | | | | | |
|---------|----|---------------|---------|------|------------|------|
| | | Repeatability | | | Within-Lab | |
| Level | n | Mean (%) | Std Dev | % CV | Std Dev | % CV |
| 1 | 20 | 4.78 | 0.11 | 2.34 | 0.12 | 2.56 |
| 2 | 20 | 6.46 | 0.17 | 2.59 | 0.17 | 2.60 |
| 3 | 20 | 7.21 | 0.11 | 1.49 | 0.12 | 1.68 |
| 4 | 20 | 8.11 | 0.15 | 1.81 | 0.15 | 1.85 |
| 5 | 20 | 9.43 | 0.14 | 1.54 | 0.18 | 1.93 |

Instrument 2, Reagent lot A

| Sample, | | | | | | |
|---------|----|---------------|---------|------|------------|------|
| | | Repeatability | | | Within-Lab | |
| Level | n | Mean (%) | Std Dev | % CV | Std Dev | % CV |
| 1 | 20 | 5.01 | 0.15 | 2.93 | 0.15 | 3.06 |
| 2 | 20 | 6.76 | 0.08 | 1.24 | 0.09 | 1.29 |
| 3 | 20 | 7.65 | 0.10 | 1.37 | 0.13 | 1.70 |
| 4 | 20 | 8.35 | 0.18 | 2.11 | 0.19 | 2.30 |
| 5 | 20 | 9.51 | 0.13 | 1.39 | 0.13 | 1.41 |

Instrument 2, Reagent lot B

| Sample, | | | | | | |
|---------|----|---------------|---------|------|------------|------|
| | | Repeatability | | | Within-Lab | |
| Level | n | Mean (%) | Std Dev | % CV | Std Dev | % CV |
| 1 | 20 | 4.81 | 0.17 | 3.48 | 0.18 | 3.66 |
| 2 | 20 | 6.61 | 0.12 | 1.79 | 0.12 | 1.81 |
| 3 | 20 | 7.61 | 0.15 | 1.95 | 0.17 | 2.26 |
| 4 | 20 | 8.45 | 0.13 | 1.50 | 0.16 | 1.93 |
| 5 | 20 | 9.48 | 0.11 | 1.18 | 0.15 | 1.55 |

b. *Linearity/assay reportable range:*

The claimed analytical measuring range is 3.5 – 16% (13 – 151 mmol/mol) for the ratio.

The linear range was determined according to CLSI EP06-A.

A human whole blood sample with a high concentration of 18.6% HbA1c and low sample, whole blood material from a commercial source with very low HbA1c concentration (2.4%), were used. Seven (7) dilutions ranging in concentration from 2.4 to 18.6% HbA1c were prepared from these two samples and evaluated.

Observed values were compared to expected values. The percent differences ranged from 1.5 to -7.5%.

Data was also evaluated by linear regression as follows:

$$y = 1.0272x - 0.3118, R^2 = 0.9985$$

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

Traceability:

The Dimension Vista® Hemoglobin A1c has met the requirements of the National Glycohemoglobin Standardization Program (NGSP). The NGSP certification requires annual renewal. The current list of NGSP certified methods is available on the NGSP website at:

<http://www.ngsp.org/prog/index.html>

Dimension Vista® Hemoglobin A1c Calibrators contain 5 levels and are traceable to IFCC reference materials.

Stability:

The lyophilized calibrators are stable until the expiration date on the product label. Once reconstituted the calibrators are stable for 8 hours at 25 °C and 48 hours at 2 – 8 °C. The stability protocols and acceptance criteria were reviewed and determined to be adequate.

d. *Detection limit:*

Limit of blank (LoB) and limit of detection (LoD) studies were performed for three days, one run per day, 2 replicates per run, with two reagent (Flex®) lots, on two Vista instruments.

For the LoB, a commercially available whole blood material with very low HbA1c concentration was mixed with EDTA plasma to provide low HbA1c concentrations in the presence of Hb. For the LoD EDTA treated whole blood samples obtained from eight healthy normal individuals were diluted 25% to 50% with EDTA plasma. Samples ranged in % HbA1c concentration from 3.5 – 6.5% (17 - 47 mmol/mol).

The Limit of Blank (LoB) for HbA1c was determined to be 2.2% (6 mmol/mol). The Limit of Detection (LoD) for % HbA1c (mmol/mol HbA1c) was determined to be 3.5% (15 mmol/mol)

The claimed analytical measuring range, 3.5 – 16%, is based on these results and the results of the linearity study summarized in M.1.b above.

e. Analytical specificity:

Interference testing was performed according to CLSI/NCCLS EP7-A2 to determine the effect of various endogenous and exogenous substances on the Dimension Vista[®] HbA1c method. Test samples were prepared by spiking the potential interferent into EDTA treated whole blood. A control sample without the interferant was also prepared.

Testing was performed at two HbA1c concentrations. The low range samples ranged from 4.4 - 5.5 %HbA1c (26 - 37 mmol/mol); the high level samples ranged from 9.0 to 10.4 %HbA1c (74 - 88 mmol/mol).

Each test and control sample was evaluated using the Dimension Vista[®] HbA1c method and the results were compared to each other. The sponsor's acceptance criterion for non-interference was <10% difference between test samples containing each potential interferant and the respective control sample.

The substances listed in the summary table below did not interfere with the test up to the stated concentrations.

| Substance | Concentration |
|--------------------------|----------------------|
| Acetaminophen | 20 mg/dL |
| Amikacin | 8 mg/dL |
| Ampicillin | 5.3 mg/dL |
| Ascorbic Acid | 6 mg/dL |
| Atenolol | 10 µg/mL |
| Benazepril | 25 µg/mL |
| Bilirubin (conjugated) | 60 mg/dL |
| Bilirubin (unconjugated) | 60 mg/dL |
| Caffeine | 6 mg/dL |

| | |
|--------------------------|------------|
| Carbamazepine | 3 mg/dL |
| Chloramphenicol | 5 mg/dL |
| Chlordiazepoxide | 1 mg/dL |
| Chlorpromazine | 0.2 mg/dL |
| Cholesterol | 503 mg/dL |
| Cimetidine | 2 mg/dL |
| Creatinine | 30 mg/dL |
| Dextran 40 | 6000 mg/dL |
| Diazepam | 0.51 mg/dL |
| Digoxin | 6.1 ng/mL |
| Erythromycin | 6 mg/dL |
| Ethanol | 400 mg/dL |
| Ethosuximide | 25 mg/dL |
| Fenofibrate | 45 µg/mL |
| Furosemide | 6 mg/dL |
| Gemfibrozil | 75 µg/mL |
| Gentamicin | 1 mg/dL |
| Heparin | 3 U/mL |
| Ibuprofen | 50 mg/dL |
| Immunoglobulin G | 5 g/dL |
| Intralipid | 3000 mg/dL |
| Lidocaine | 1.2 mg/dL |
| Lithium | 2.2 mg/dL |
| Metformin conc | 40 µg/mL |
| Nateglinide | 75 µg/mL |
| Niacin / Vitamin B3 | 400 µg/mL |
| Nicotine | 0.1 mg/dL |
| Penicillin G | 25 U/mL |
| Pentobarbital | 8 mg/dL |
| Phenobarbital | 10 mg/dL |
| Phenytoin | 5 mg/dL |
| Primidone | 4 mg/dL |
| Propoxyphene | 0.2 mg/dL |
| Protein: Albumin | 6 g/dL |
| Protein: Total | 12 g/dL |
| Repaglinide | 285 µg/mL |
| Rosiglitazone | 350 ng/mL |
| Salicylic Acid | 60 mg/dL |
| Simvastatin | 48 µg/mL |
| Tamsulosin hydrochloride | 165 ng/mL |
| Theophylline | 4 mg/dL |
| Triglycerides | 3000 mg/dL |
| Urea | 500 mg/dL |
| Uric Acid | 20 mg/dL |
| Valproic Acid | 50 mg/dL |
| Vancomycin | 10 mg/dL |

Glybenclamide, Sodium cyanate, Acetylsalicylic acid, Rheumatoid factor

Test samples for acetylsalicylic acid, glybenclamide, and sodium cyanate were prepared by spiking the potential interferent into EDTA treated whole blood.

Rheumatoid factor (RF) samples were 50% whole blood and 50% serum.

Testing was performed at two HbA1c concentrations: 5.9 – 6.4 %HbA1c and 9.3 – 10.2 %HbA1c. Values are the mean of three replicates for each control and test sample, using one lot of Flex[®] reagents. The difference between test and control samples were compared and a difference of $\leq 10\%$ was considered non-interference.

| Interferent | Test conc. | Sample 1 | | Sample 2 |
|----------------------|-------------------|-----------------|--|-----------------|
| Acetylsalicylic acid | 50 mg/dL | 0.5% | | 1.8% |
| Glybenclamide | 1.92 μ g/mL | 0.5% | | 0.4% |
| Sodium Cyanate | 50 mg/dL | <0.1% | | -0.4% |
| RF | 1805 IU/mL | 1.1% | | <0.1% |

Labile, Carbamyl and Acetaldehyde Hemoglobins

Three EDTA whole blood sample pools with HbA1c normal and high levels were spiked with glucose to 1500 mg/dL (labile hemoglobin HbA1c), urea to 150 mg/dL (carbamylated Hb), or acetaldehyde to 50 mg/dL (acetylated Hb).

Untreated sample pools served as controls. All specimens were incubated at 37° C for up to 5 hours and then assayed for HbA1c in triplicate.

The specimen value (control) with no added glucose or urea or acetaldehyde was used as the reference value. No interference was defined as <10% difference between the test compared to the control. There was no interference from glucose up to 1500 mg/dL, urea up to 150 mg/dL, or acetaldehyde up to 50 mg/dL, with all test samples demonstrating less than 3% difference compared to the control.

Hemoglobin Variants HbC, HbD, HbE and HbS:

Interference by samples with known Hb variants, HbC, HbD, HbE and HbS, were tested by comparison with a recognized reference method. Samples were run on the Dimension Vista[®] HbA1c method and then assayed by the Trinity Biotech *ultra*² A1c Analyzer (formerly Primus Diagnostics), an NGSP recognized secondary reference method. The Dimension Vista[®] System result was compared to the reference method result.

For all but one sample tested there was less than a 10% difference in %HbA1c values between the reference method and the Dimension Vista results. One specimen identified as having variant HbC recovered -10.9% compared to the Trinity Biotech *ultra*² method.

Hemoglobin Variant HbF:

Samples were identified as containing HbF by a recognized reference method on the Tosoh G7 Variant Analysis Mode ion-exchange HPLC.

Samples of varying HbF concentrations were prepared by mixing a high HbF sample (16.8% HbF) with a low HbF sample (0.8% HbF). Nine additional EDTA whole blood samples containing 1.7 to 15.1% HbF were prepared by mixing different amounts of the high and low HbF samples.

The sponsor defines interference as a % difference in recovery of $\geq 10\%$ between the expected and observed values. All samples up to 11.8% HbF met the acceptance criterion. The labeling states that individuals with elevated levels of HbF (>10%) may produce lower than expected results with the Dimension Vista[®] HbA1c method.

Hemoglobin concentration:

The assay is designed to measure total hemoglobin as part of the %HbA1c calculation. A linearity study was performed to support the analytical measuring range of hemoglobin 5-25 g/dL. Samples with hemoglobin values above 25 g/dL will be flagged by the instrument resulting in an error message.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Fresh, EDTA-treated whole blood samples (n=125) were evaluated in a hospital laboratory on the Dimension Vista HbA1c method and the Tosoh G7 HPLC method (k011434). Six specimens were contrived in order to cover the low end of the assay range. Samples had HbA1c ranging from 3.8 – 16.0 %HbA1c by the new device.

| Passing-Bablok Regression Dimension Vista HbA1c vs. Tosoh G7 | | | |
|---|-------------|--------|---------|
| | Coefficient | 95% CI | |
| Intercept | 0.20 | 0.12 | to 0.20 |
| Slope | 1.00 | 1.00 | to 1.01 |

The same samples were also evaluated versus the predicate Dimension Vista HbA1c device, k062128. The results are summarized below.

| Passing-Bablok Regression | | | |
|---|--------------------|---------------|---------|
| New DV HbA1c vs. Predicate DV HA1C | | | |
| | Coefficient | 95% CI | |
| Intercept | 0.71 | 0.44 | to 0.96 |
| Slope | 0.93 | 0.89 | to 0.96 |

b. Matrix comparison:

Not applicable, the device is for EDTA whole blood only.

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):

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The American Diabetes Association (ADA) expected values range is 4.0-6.0% for people without diabetes.

The sponsor performed a study to verify this range using whole blood specimens drawn at two different sites from a population of healthy adults (94 males and 89 females). The obtained range using Dimension Vista[®] HbA1c was 4.2 – 6.3 %HbA1c

The labeling also states that according to American Diabetes Association, Standards of Medical Care in Diabetes -2010, Diabetes Care, 33:Suppl 1 (2010), the primary goal of therapy should be a HbA1c of <7% and that physicians should reevaluate the treatment regimen in patients with HbA1c values consistently >8%.

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.