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

A. 510(k) Number:

k171861

B. Purpose for Submission:

Addition of a diagnostic claim to a previously cleared device

C. Measurand:

Hemoglobin A1c

D. Type of Test:

Capillary electrophoresis

E. Applicant:

Sebia, Inc.

F. Proprietary and Established Names:

CAPILLARYS Hb A1c

G. Regulatory Information:

Product Code	Regulation Name	Classification	Regulation Section	Panel
PDJ	Hemoglobin A1c Test System	Class II	21 CFR 862.1373	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

The CAPILLARYS Hb A1c kit is intended for separation and quantification of the HbA1c glycated fraction of hemoglobin (in IFCC unit (mmol/mol) and NGSP unit (%)) in venous whole human blood, by capillary electrophoresis in alkaline buffer with the CAPILLARYS 2 FLEX-PIERCING instrument. Measurement of hemoglobin A1c is used as an aid in diagnosis of diabetes, as an aid to identify patients who may be at risk for developing diabetes mellitus, and for the monitoring of long-term blood glucose control in individuals with diabetes mellitus. The CAPILLARYS Hb A1c kit is intended for in vitro Diagnostic Use Only.

3. Special conditions for use statement(s):

For In Vitro Diagnostic Use
Prescription Use Only

The CAPILLARYS Hb A1c kit should not be used:

- for point-of-care use
- in monitoring daily glucose control
- to replace daily home testing of urine and blood glucose levels
- to replace glucose testing in pediatric patients, pregnant women, or patients with Type 1 diabetes.
- for analyzing samples from patients with total hemoglobin levels of less than 2.9 or greater than 30.5 g/dL and any hemoglobinopathies that may interfere.
- 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 and/or decreased red cell survival,
- to diagnose diabetes in patients with the following conditions:
    - Any condition that alters the life span of the red blood cells, including recent blood loss, transfusion, significant iron deficiency, hemolytic anemia (including hereditary spherocytosis) or other hemolytic diseases, hemoglobinopathies and thalassemias, as the altered red blood cell turnover interferes with the relationship between mean blood glucose and HbA1c values, malignancies or severe chronic hepatic and renal disease.
- 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.

4. Special instrument requirements:

CAPILLARYS 2 FLEX-PIERCING instrument

I. Device Description:

The CAPILLARYS Hb A1c kit is to be used with the CAPILLARYS 2 FLEX-PIERCING instrument. The CAPILLARYS Hb A1c kit contains a ready to use buffer solution pH 9.4 ± 0.5 (2 vials, 700 ml each), a ready to use hemolysing solution (1 vial, 700 ml), Wash solution (1 vial, 75 ml), Green Dilution segments (1 pack of 90) and filters (4 filters per kit).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   TOSOH G8 Automated Glycohemoglobin Analyzer HLC-723G8

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

   k131580

3. Comparison with predicate:

Similarities and Differences		
Item	CAPILLARYS Hb A1c Kit (Candidate Device)	TOSOH G8 Automated Glycohemoglobin Analyzer HLC-723G8 k131580 (Predicate Device)
Intended Use	The CAPILLARYS Hb A1c kit is intended to be used as an aid in diagnosis of diabetes, as an aid to identify patients who may be at risk for developing diabetes mellitus, and for the monitoring of long-term blood glucose control in individuals with diabetes mellitus.	Same
Specimen Type	Venous whole blood (K_2EDTA and K_3EDTA)	Same
Standardization	Traceable to the Diabetes Control and Complications Trial (DCCT) reference method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP)	Same
Assay Principle	Capillary electrophoresis	Ion-exchange HPLC
Measuring Range	4.4-16.6% (NGSP) 24-158 mmol/mol (IFCC)	4.0-16.9%

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

Clinical and Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; 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 EP09-A2: Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition

L. Test Principle:

The CAPILLARYS Hb A1c kit uses the principle of capillary electrophoresis in free solution. With this technique, charged molecules of hemoglobin are separated by their electrophoretic mobility in an alkaline buffer with a specific pH. Separation of the glycated HbA1c fraction from other hemoglobins occurs according to the electrolyte pH and electroosmotic flow.

The CAPILLARYS 2 FLEX-PIERCING instrument has silica capillaries functioning in parallel allowing 8 simultaneous analyses of HbA1c quantification in a whole blood sample. A sample dilution with hemolysing solution is prepared and injected by aspiration at the anodic end of the capillary. A high voltage protein separation is then performed and direct detection of HbA1c is made at the cathodic end of the capillary at 415 nm, which is the absorbance wave length specific to HbA1c. Before each run, the capillaries are washed with a wash solution and prepared for the next analysis with buffer.

The HbA1c concentrations are reported in %HbA1c (DCCT/NGSP) and in mmol/mol (IFCC) units.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

   a. Precision/Reproducibility:

   Precision was evaluated for the CAPILLARYS Hb A1c kit based on CLSI EP05-A3 using four K_2EDTA venous whole blood samples with targeted HbA1c concentrations (5.1%, 6.4%, 8.2%, and 12.2%), two quality control solutions (5.1% and 8%), and two calibrators (5.6% and 10.1%). Samples were analyzed on three CAPILLARYS 2 FLEX-PIERCING instruments using three lots of reagents. Each sample was analyzed in duplicate on two capillaries per run, two runs per day for 20 days. The results are shown below:

Results in NGSP units (%HbA1c)

Instruments Combined (%CV by Sample, NGSP % HbA1c)

Sample	Mean (%)	Within capillary	Between capillary	Between run	Between day	Between lot	Between instrument	Total
Sample 1	5.1	1.1%	1.2%	0.0%	0.6%	0.5%	0.0%	1.8%
Sample 2	6.4	1.1%	0.6%	0.0%	0.4%	0.6%	0.0%	1.4%
Sample 3	8.2	0.9%	0.7%	0.0%	0.3%	0.4%	0.0%	1.2%
Sample 4	12.2	0.7%	0.6%	0.0%	0.4%	0.9%	0.0%	1.3%
Control 1	5.1	1.1%	1.1%	0.0%	0.7%	1.0%	0.3%	2.0%
Control 2	8.0	0.9%	1.1%	0.0%	0.9%	0.2%	1.1%	2.0%
Calibrator 1	5.6	1.3%	0.7%	0.0%	0.5%	0.9%	0.0%	1.8%
Calibrator 2	10.1	0.8%	0.6%	0.0%	0.2%	0.7%	0.0%	1.3%

Instrument 1 (%CV by Sample, NGSP % HbA1c)

Sample	Mean (%)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	5.1	1.3%	0.7%	0.0%	0.5%	0.7%	1.7%
Sample 2	6.4	1.1%	0.5%	0.0%	0.4%	0.5%	1.4%
Sample 3	8.2	0.9%	0.6%	0.0%	0.4%	0.5%	1.3%
Sample 4	12.2	0.7%	0.6%	0.0%	0.4%	0.8%	1.3%
Control 1	5.1	1.2%	0.7%	0.0%	0.7%	0.8%	1.8%
Control 2	8.0	0.9%	1.5%	0.0%	0.4%	0.3%	1.8%
Calibrator 1	5.6	1.2%	0.7%	0.0%	0.7%	0.7%	1.7%
Calibrator 2	10.1	0.9%	0.7%	0.0%	0.2%	0.7%	1.3%

Instrument 2 (%CV by Sample, NGSP % HbA1c)

Sample	Mean (%)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	5.1	1.0%	0.4%	0.3%	0.5%	0.2%	1.2%
Sample 2	6.4	1.1%	0.6%	0.0%	0.4%	0.8%	1.5%
Sample 3	8.2	0.8%	0.3%	0.2%	0.3%	0.6%	1.1%
Sample 4	12.2	0.7%	0.5%	0.0%	0.3%	1.0%	1.3%
Control 1	5.1	1.1%	1.0%	0.0%	0.5%	1.1%	1.9%
Control 2	8.0	0.7%	1.1%	0.0%	0.7%	0.3%	1.5%
Calibrator 1	5.6	1.3%	0.6%	0.0%	0.4%	1.1%	1.8%
Calibrator 2	10.1	0.8%	0.5%	0.3%	0.2%	0.7%	1.2%

Instrument 3 (%CV by Sample, NGSP % HbA1c)

Sample	Mean (%)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	5.1	1.1%	1.9%	0.0%	0.7%	0.6%	2.4%
Sample 2	6.4	1.2%	0.6%	0.0%	0.3%	0.3%	1.4%
Sample 3	8.2	0.9%	0.9%	0.0%	0.2%	0.0%	1.3%

Sample	Mean (%)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 4	12.2	0.7%	0.8%	0.0%	0.4%	0.7%	1.3%
Control 1	5.1	1.2%	1.3%	0.0%	0.7%	1.0%	2.1%
Control 2	8.0	1.0%	0.6%	0.0%	1.3%	0.0%	1.7%
Calibrator 1	5.6	1.4%	0.9%	0.0%	0.5%	0.9%	1.9%
Calibrator 2	10.1	0.9%	0.7%	0.0%	0.2%	0.5%	1.2%

Results in IFCC units (mmol/mol)

Instruments Combined (%CV by Sample, IFCC units)

Sample	Mean (mmol/mol)	Within capillary	Between capillary	Between run	Between day	Between lot	Between instrument	Total
Sample 1	32	1.9%	2.1%	0.0%	0.8%	1.1%	0.0%	3.1%
Sample 2	46	1.7%	0.9%	0.0%	0.6%	0.8%	0.0%	2.1%
Sample 3	66	1.2%	0.9%	0.0%	0.5%	0.6%	0.0%	1.6%
Sample 4	109	0.8%	0.8%	0.0%	0.5%	1.1%	0.0%	1.6%
Control 1	33	2.0%	1.8%	0.0%	1.1%	1.8%	0.1%	3.4%
Control 2	63	1.2%	1.6%	0.0%	1.2%	0.3%	1.4%	2.7%
Calibrator 1	37	2.0%	1.1%	0.0%	0.8%	1.2%	0.0%	2.7%
Calibrator 2	87	1.1%	0.8%	0.0%	0.3%	0.7%	0.0%	1.5%

Instrument 1 (%CV by Sample, IFCC units)

Sample	Mean (mmol/mol)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	32	1.9%	1.5%	0.0%	0.7%	1.3%	2.8%
Sample 2	46	1.7%	0.8%	0.0%	0.5%	0.8%	2.1%
Sample 3	66	1.2%	0.8%	0.0%	0.7%	0.6%	1.6%
Sample 4	109	0.8%	0.7%	0.0%	0.5%	1.0%	1.6%
Control 1	33	2.0%	1.5%	0.0%	1.2%	1.6%	3.2%
Control 2	63	1.2%	2.2%	0.0%	0.6%	0.5%	2.6%
Calibrator 1	37	2.1%	0.8%	0.0%	1.1%	0.8%	2.7%
Calibrator 2	87	1.1%	0.9%	0.0%	0.2%	0.7%	1.6%

Instrument 2 (%CV by Sample, IFCC units)

Sample	Mean (mmol/mol)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	32	1.9%	0.8%	0.0%	0.7%	0.7%	2.3%
Sample 2	46	1.5%	0.8%	0.0%	0.8%	1.0%	2.1%
Sample 3	66	1.1 %	0.5%	0.3%	0.4%	0.8%	1.5%
Sample 4	109	0.8%	0.7%	0.0%	0.4%	1.3%	1.7%
Control 1	33	1.9%	1.4%	0.0%	0.8%	1.8%	0.1%
Control 2	63	0.9%	1.4%	0.0%	1.0%	0.3%	1.4%

Sample	Mean (mmol/mol)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Calibrator 1	37	1.8%	0.8%	0.0%	0.7%	1.5%	2.6%
Calibrator 2	87	1.0%	0.5%	0.3%	0.4%	0.9%	1.5%

Instrument 3 (%CV by Sample, IFCC units)

Sample	Mean (mmol/mol)	Within capillary	Between capillary	Between run	Between day	Between lot	Total
Sample 1	39	1.9%	3.2%	0.0%	1.0%	1.1%	3.9%
Sample 2	46	1.7%	1.0%	0.3%	0.5%	0.5%	2.1%
Sample 3	66	1.3%	1.2%	0.0%	0.3%	0.0%	1.8%
Sample 4	109	0.8%	1.0%	0.0%	0.5%	0.9%	1.7%
Control 1	33	2.1%	2.2%	0.0%	1.3%	1.7%	3.7%
Control 2	63	1.3%	0.8%	0.0%	1.8%	0.0%	2.4%
Calibrator 1	37	2.1%	1.5%	0.0%	0.7%	1.1%	2.9%
Calibrator 2	87	1.2%	0.8%	0.0%	0.2%	0.5%	1.5%

b. *Linearity/assay reportable range:*

The linearity of the CAPILLARYS Hb A1c kit was evaluated based on CLSI EP06-A. Two blood samples, including a normal venous K_2EDTA whole blood sample with HbA1c concentration at 4.4% (24 mmol/mol) and an elevated HbA1c level venous whole blood sample with HbA1c concentration at 16.7% (159 mmol/mol) were mixed within different proportions (5.3%, 6.3%, 7.3%, 8.4%, 9.6%, 10.8%, 12.1%, 13.6%, and 15.1%) and the mixtures were electrophoresed with the CAPILLARYS Hb A1c kit. For each mixture, samples were analyzed in triplicate.

The following table summarizes the linear regression results for both NGSP (%HbA1c) and IFCC units (mmol/mol).

Units	Slope	y-intercept	Correlation coefficient (r)
NGSP (%HbA1c)	1.005	-0.124	1.000
IFCC (mmol/mol)	1.006	-1.253	1.000

The study supports the claimed reportable range of the device from 4.4% to 16.6% (24-158 mmol/mol) HbA1c.

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

Traceability:
The CAPILLARYS Hb A1c kit is traceable to the International Federation of Clinical Chemistry (IFCC) reference calibrators. The CAPILLARYS Hb A1c kit is certified with 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 derived result of the ratio (%) from the NGSP correlation is calculated from the individual quantitative results for Hemoglobin A1c (HbA1c). The International Federation of Clinical Chemistry (IFCC) units of mmol/mol are calculated using the Master Equation: IFCC = (NGSP- 2.15) / 0.092. Two different units are provided to the customers: NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).

d. Detection limit:

The claimed measuring range of 4.4 to 16.6% for the CAPILLARYS Hb A1c kit is based on linearity, see M.1.b.

e. Analytical specificity:

i. Endogenous Interference

Interference studies were performed to assess endogenous substances that could interfere with the CAPILLARYS Hb A1c kit. The interfering substances were evaluated in two venous whole blood K_2EDTA samples with one sample close to the cut-off value, ~6.3% (45 mmol/mol) HbA1c, and one sample with high levels of HbA1c, ~8.3% (67 mmol/mol) HbA1c. Test samples were prepared by spiking each endogenous substance at a single dose to simulate the expected dose into the two HbA1c samples. Test samples were assayed in replicates of 10 and the mean concentration for each test sample was compared to the mean concentration of 10 replicates of the control sample. The sponsor defined significant interference as greater than or equal to 7% mean relative deviation between the test and control sample.

The highest concentration of endogenous substances tested that show non-significant interference are summarized in the table below:

Potential interfering substance	Highest concentration tested without significant interference
Ascorbic Acid	300 mg/dL
Conjugated bilirubin	60 mg/dL
Unconjugated bilirubin	60 mg/dL
Rheumatoid factor	1076 IU/mL
Triglycerides	2.89 g/dL
Urea	265 mg/dL
D-glucose	1000 mg/dL
Total Protein	149.5 g/L

ii. Exogenous Interference

Interference studies were performed to assess various exogenous substances that could interfere with the CAPILLARYS Hb A1c kit. The interfering substances were

evaluated in two venous whole blood K_2EDTA samples with one sample close to the cut-off value, 6.3% (45 mmol/mol) HbA1c, and one sample with high levels of HbA1c, 8.3% (67 mmol/mol) HbA1c. Test samples were prepared by spiking each drug at a single dose to simulate the maximum expected dose into the two HbA1c samples. Test samples were assayed in replicates of 10 and the mean concentration for each test sample was compared to the mean concentration of 10 replicates of the control sample. The sponsor defined significant interference as greater than or equal to 7% mean relative deviation between the test and control samples.

The highest concentrations of exogenous substances tested that show no significant interference are summarized in the table below:

Potential interfering substance	Highest concentration tested without significant interference
Acetaminophen	20 mg/dL (1325 µM)
Acetylcysteine	200 mg/dL (12.3 mM)
Acetylsalicylic acid	1000 mg/dL (55,56 mM)
Ampicillin-Na	1000 mg/dL (28653 µM)
Cefoxitin	2500 mg/dL (58548 µM)
Cyclosporine	0.5 mg/dL
Doxycycline	50 mg/dL (1123.6 µM)
Glybenclamide	3 mg/dL
Heparin	5000 U/L
Ibuprofen	50 mg/dL (2427 µM)
Levodopa	40 mg/dL
Metformin	5 mg/dL (387 µM)
Methyldopa	40 mg/dL (1896 µM)
Metronidazole	200 mg/dL (11696 µM)
Phenylbutazone	40 mg/dL
Rifampicin	7 mg/dL (85.1 µM)
Theophylline	10 mg/dL (556 µM)

iii. Cross Reactivity with Hemoglobin Derivatives

To study interference from carbamylated hemoglobin, two K_2EDTA whole blood patient samples with HbA1c concentrations at ~6.3% (46 mmol/mol) and ~8.4% (69 mmol/mol) were split into two aliquots. One aliquot, at each HbA1c level, was spiked with 1 mmol/L of potassium cyanate. The other aliquot, at each HbA1c level, was not spiked and served as a control sample. Samples were then analyzed on the CAPILLARYS 2 FLEX-PIERCING instrument using the CAPILLARYS Hb A1c kit. Samples were analyzed in replicates of 10. The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the test and the control sample. The sponsor concluded that carbamylated HbA1c up to 810 mg/dL (7.2%) does not interfere with this assay.

To study interference from labile hemoglobin, two K_2EDTA whole blood patient samples with HbA1c concentrations at ~6.2% (44 mmol/mol) and ~8.1% (65 mmol/mol) were split into two aliquots. One aliquot, at each HbA1c level, was spiked with glucose (50 g/L). The other aliquot, at each HbA1c level, was not spiked and served as a control sample. Samples were then analyzed on the CAPILLARYS 2 FLEX-PIERCING instrument using the CAPILLARYS Hb A1c kit. Samples were analyzed in replicates of 10. The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the test and the control sample. The sponsor concluded that labile HbA1c up to 1970 mg/dL (18.4%) does not interfere with this assay.

To study interference from acetylated hemoglobin, two K_2EDTA whole blood samples with HbA1c concentrations at ~6.2% (45 mmol/mol) and ~ 8.5% (69 mmol/mol) were split into two aliquots. One aliquot, at each HbA1c level, was spiked with acetylsalicylic acid (10 mmol/L). The other aliquot, at each HbA1c level, was not spiked and served as a control sample. Samples were then analyzed on the CAPILLARYS 2 FLEX-PIERCING instrument using the CAPILLARYS Hb A1c kit. Samples were analyzed in replicates of 10. The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the test and the control sample. The sponsor concluded that acetylated HbA1c up to 420 mg/dL (3.6%) does not interfere with this assay.

To study interference from HbA1a+b, two K_2EDTA whole blood samples with HbA1c concentrations at ~6.5% and (48 mmol/mol) ~ 8.4% (68 mmol/mol) were split into two aliquots. One aliquot, at each HbA1c level, was spiked with HbA1a+b (20 mg/dL). The other aliquot, at each HbA1c level, was without HbA1a+b and served as a control sample. Samples were then analyzed on the CAPILLARYS 2 FLEX-PIERCING instrument using the CAPILLARYS Hb A1c kit. Samples were analyzed in replicates of 10. The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the test and the control sample. The sponsor concluded that HbA1a+b up to ≤ 20 mg/dL does not interfere with this assay.

To study interference from glycated albumin, two K_2EDTA whole blood samples with HbA1c concentrations at ~6.1% and (45 mmol/mol) ~ 8.7% (68 mmol/mol) were split into two aliquots. One aliquot, at each HbA1c level, was spiked with glycated albumin (220 mg/dL). The other aliquot, at each HbA1c level, was without glycated albumin and served as a control sample. Samples were then analyzed on the CAPILLARYS 2 FLEX-PIERCING instrument using the CAPILLARYS Hb A1c kit. Samples were analyzed in replicates of 10. The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the test and the control sample. The sponsor concluded that glycated albumin up to 220 mg/dL does not interfere with this assay.

Concentration at which no significant interference (≤7%) was observed for each hemoglobin derivative is presented below:

Interfering Factor	Highest concentration tested without significant interference
Carbamylated hemoglobin	810 mg/dL
Labile HbA1c	1970 mg/dL
Acetylated hemoglobin	420 mg/dL
HbA1a+b	20 mg/dL
Glycated Albumin	220 mg/dL

iv. Hemoglobin Variant Interference

A hemoglobin variant study was performed using a total of 121 normal and diabetic whole blood K_2EDTA patient variant samples known to contain hemoglobin variants HbS, HbC, HbE, HbD, HbA2, and HbF. Testing was performed using the CAPILLARYS Hb A1c kit on the CAPILLARYS 2 FLEX-PIERCING instrument and results were compared to results obtained by a NGSP reference method that has been demonstrated to be free from the hemoglobin interferent (Trinity Biotech Ultra2 for variants HbS, HbC, HbD, HbE and Tosoh G8 for variants HbA2 and HbF). The sponsor's definition of non-significant interference is ≤7% mean relative deviation between the CAPILLARYS Hb A1c result and the NGSP reference method. The range of hemoglobin variants and range of HbA1c that were evaluated are summarized in the table below:

Variant samples used in Hemoglobin Variant Study

Hemoglobin variant	n	Range in % Hb variant	Range in %HbA1c concentration (NGSP)	Range in mmol/mol HbA1c concentration (IFCC)
HbS	20	33 – 40.8	4.9 – 14	30 – 129
HbC	20	28 – 37.2	4.6 – 13.1	27 – 120
HbD	21	35.5 – 41.3	5.0 – 11.8	32 – 105
HbE	20	21.3 – 37.0	4.8 – 9.8	29 – 83
HbA2	20	4.0 – 7.7	7.2 – 11	55 – 97
HbF	20	1.5 – 31.4	4.9 – 15.1	85 – 141

Hemoglobin Variant Study Results

Hemoglobin Variant	Relative % Bias (range of % bias) to Comparative Method for HbA1c	
	~6.5%	~9.0%
HbS	0.8 % (0.0% – 1.6%)	0.4% (-3.1% – 3.2%)
HbC	0.0 (0.0% – 0.0%)	3.3% (1.0% – 5.7%)
HbD	0.5% (-1.4% – 1.6%)	-1.9% (-2.4% – -1.2%)
HbE	0.4% (-3.3% – 1.5%)	-0.3% (-3.7% – 2.1%)
HbA2	-3.4% (-4.5% – -1.4%)	-0.8% (-2.0% – 0.0%)
HbF	-3.3% (-4.8% – -1.6%)	-2.0% (-5.0% – 0.0%)

Significant interference was defined as ≥ 7% change in HbA1c value in the presence of the hemoglobin variant relative to control. The results show there is no significant interference for HbS (≤40.8%), HbC (≤37.6%), HbD (≤41.3%), HbE (≤26.8%), and HbA2 (≤7.8%) at the concentrations tested in this study.

The software displays the following message if the HbF level is higher than 23%: "Atypical profile—possible quantitative interference if HbF or variant > 23%."

The following prominent warning is stated in the package insert:

> "A significant negative interference has been observed with fetal hemoglobin (Hb F) concentrations >23 %. HbA1c results are invalid for patients with high amounts of Hb F (>23 %) including those with known Hereditary Persistence of Fetal Hemoglobin."

The package insert labeling states:

> No interference has been observed with HbA1c fraction quantification due to the presence of major abnormal hemoglobins Hb S (≤ 40.8 %), Hb C (≤ 37.2%), Hb D (≤ 41.3 %) and Hb E (≤ 37.0 %). However, due to the number of variants, the presence of another hemoglobin variant may be observed in the HbA1c migration zone; in the case of a shoulder on HbA1c, no result will be reported by the software (as in presence of Hb Bart's).

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study of 150 variant-free K_2EDTA whole blood samples (4.4 to 16.6% HbA1c) were evaluated using the CAPILLARYS Hb A1c kit on the CAPILLARYS 2 FLEX PIERCING instrument. Results were compared to testing

performed at a NGSP Secondary Reference Laboratory using a previously cleared HPLC HbA1c assay method (Tosoh HLC-723G8).

The distribution of samples follows in the table below:

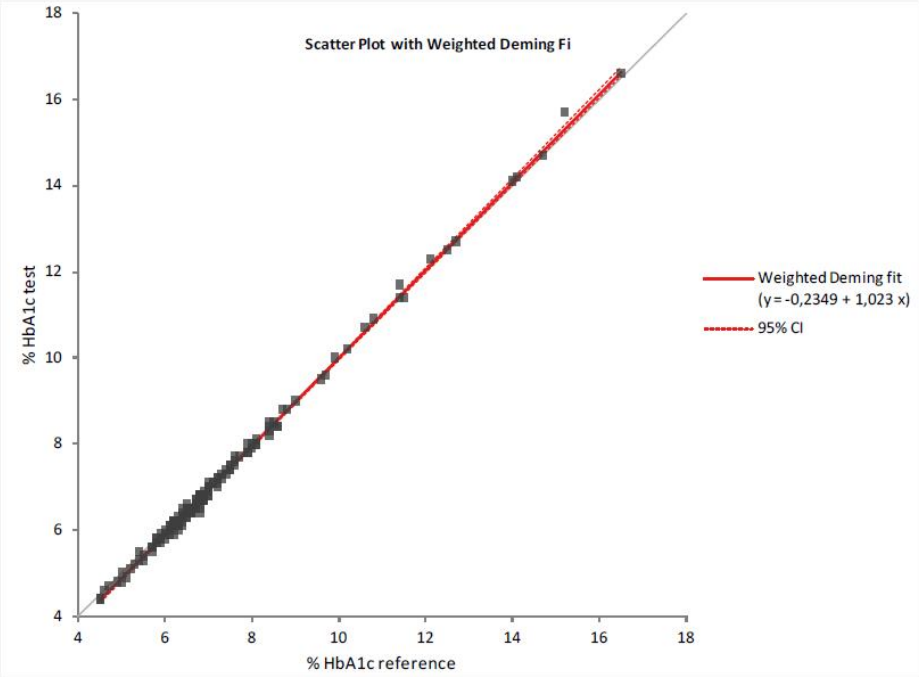
Hemoglobin A1c level	**n**	**% of Samples tested**
≤ 5%	7	5
5 – 6%	19	13
6 – 6.5%	35	23
6.5 – 7%	36	24
7 – 8%	23	15
8 – 9%	13	9
> 9%	17	11
Total samples	150	100.0

Linear, Deming (weighted), and Passing-Bablok regression analyses were performed using the CAPILLARYS HbA1c method on the CAPILLARYS 2 FLEX PIERCING instrument versus the comparative G8 HPLC method (NGSP) and are summarized below:

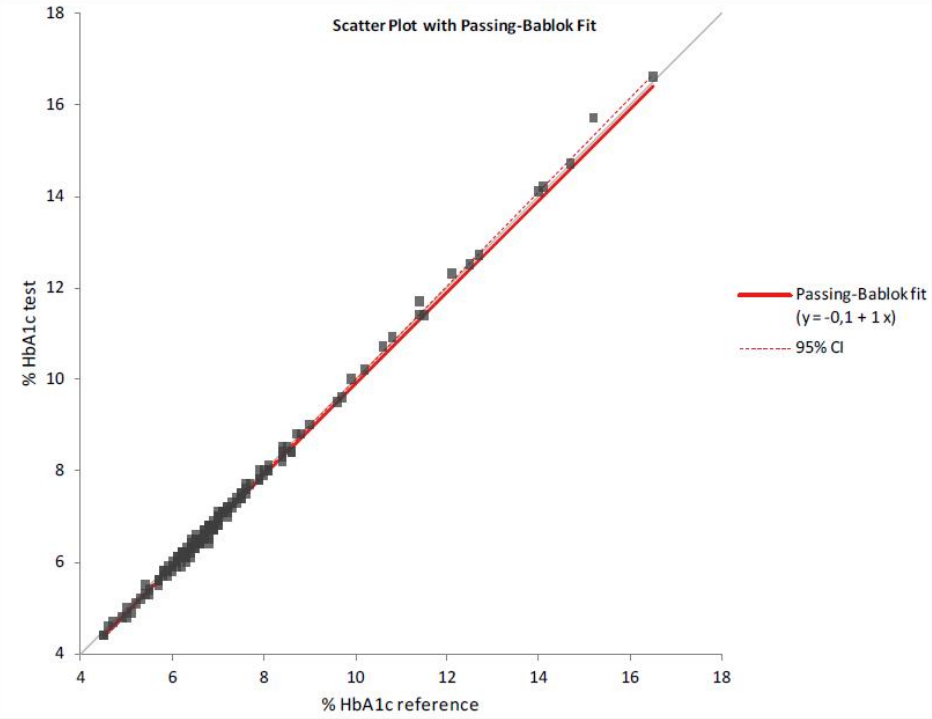
Summary of Method Comparison Results

	Slope	y-intercept	r
Linear	1.027 95% CI (1.019 to 1.035)	-0.265 95% CI (-0.325 to -0.204)	0.999
Deming	1.023 95% CI (1.012 to 1.034)	-0.235 95% CI (-0.312 to -0.158)	0.999
Passing-Bablok	1.000 95% CI (1.000 to 1.026)	-0.100 95% CI (-0.248 to -0.039)	0.999

Scatter Plot using Deming Fit, %HbA1c, NGSP vs. CAPILLARYS Hb A1c



Scatter Plot using Passing-Bablok Fit, %HbA1c, NGSP vs. CAPILLARYS Hb A1c



The following biases between CAPILLARYS Hb A1c run on the CAPILLARYS 2 FLEX-PIERCING instrument versus the NGSP Reference Method (Tosoh G8 HPLC analyzer) were observed:

Bias Estimation

% HbA1c – Decision Level	Bias	% Bias
5.1	-0.1	-2.47
6.4	-0.1	-1.42
8.2	0.0	-0.51
12.2	0.1	0.55

Total Error Calculations:
Using the results of bias estimation (%Bias) in the method comparison study and precision estimates in the reproducibility study, Total Error (TE) at four concentrations: (5.1%, 6.4%, 8.2% and 12.2%) were calculated as follows: %TE=|%Bias| + 1.96 *CV*(1 + (%Bias/100)). The results are as follows:

Total Error Estimation

% A1c – Decision Level	% Bias	% CV	% TE
5.1	-2.47	1.8	5.9
6.4	1.36	1.4	4.1
8.2	0.50	1.2	2.8
12.2	0.55	1.3	3.1

b. Matrix comparison:

Matrix comparison studies were previously reviewed in k122101. Only K_2EDTA and K_3EDTA venous whole blood samples are to be used with this assay.

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:

Category	HbA1c Range (NGSP/DCCT)
Normal	< 5.7%
Prediabetes (increased risk for diabetes)	5.7% - 6.4%
Diabetes	≥ 6.5%

The expected HbA1c range for non-diabetic adults is 4 - 6%. However, each laboratory should establish its reference range and HbA1c goal following state and federal regulations and taking into account sex, age, ethnicity and individual patient situation.

The following reference was cited: American Diabetes Association. Standards of medical care in diabetes - 2016. *Diabetes Care.* 2016 Jan, 39, Suppl 1.

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.