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

## I Background Information:

### A 510(k) Number

K200904

### B Applicant

Tosoh Bioscience, Inc.

### C Proprietary and Established Names

Automated Glycohemoglobin Analyzer HLC-723G8

### D Regulatory Information

| Product Code(s) | Classification | Regulation Section | Panel |
|---|---|---|---|
| PDJ | Class II | 21 CFR 862.1373 - Hemoglobin A1c Test System | CH - Clinical Chemistry |

## II Submission/Device Overview:

### A Purpose for Submission:

Modification of existing device to minimize hemoglobin variant interference

### B Measurand:

Whole Blood Glycosylated Hemoglobin (HbA1c)

### C Type of Test:

Quantitative Ion-exchange High Performance Liquid Chromatography (HPLC)

## III Intended Use/Indications for Use:

**A Intended Use(s):**

See Indications for Use below.

**B Indication(s) for Use:**

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 is intended for in vitro diagnostic use for the measurement of % hemoglobin A1c (HbA1c) (DCCT/NGSP) and mmol/mol hemoglobin A1c (IFCC) in venous whole blood specimens using ion-exchange high-performance liquid chromatography (HPLC). This test is to be used as an aid in diagnosis of diabetes and identifying patients who may be at risk for developing diabetes, and for monitoring of long-term blood glucose control in individuals with diabetes mellitus.

**C Special Conditions for Use Statement(s):**

Rx - For Prescription Use Only

Hemoglobin A1c should not be used to diagnose Diabetes Mellitus in patients with iron deficiency and hemolytic anemia, various hemoglobinopathies, thalassemias, hereditary spherocytosis, malignancies and severe chronic hepatic and renal disease.

Hemoglobin A1c should not be used in pregnant patients, patients with heterozygous sickle cell trait, hemolytic diseases and recent significant or chronic blood loss.

Hemoglobin A1c should not be used in the diagnosis of gestational diabetes.

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.

Only the percent HbA1c values measured by this device should be reported to the health care provider. The test report displays %HbF and other detected hemoglobin variants; however, the performance characteristics of the hemoglobin variants detected by this device have not been reviewed or cleared by the FDA and therefore should not be reported to the healthcare provider. The hemoglobin variants detected by this device are only to ensure the validity of the HbA1c results because increased levels of hemoglobin variants may interfere with the percent HbA1c measurement. If a hemoglobinopathy is suspected, an FDA cleared test system for their measurement should be used

Hemoglobin A1c testing should not replace glucose testing for type 1 diabetes, in pediatric patients and pregnant women.

**D Special Instrument Requirements:**

All performance data was collected using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8.

## IV Device/System Characteristics:

### A Device Description:

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 is an automated High-Performance Liquid Chromatography (HPLC) system that separates and reports stable hemoglobin A1c (sA1c) percentage in whole blood. The operational portion of the G8 is composed of a sampling unit, liquid pump, degasser, column, detector, microprocessors, sample loader, smart media card, operation panel, and a printer.

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 system consists of the following components:

- G8 Variant Elution Buffer HSi No. 1 (S), No. 2 (S), No. 3 (S)
- TSKgel® G8 Variant HSi (column)
- Hemoglobin A1c Controls Levels 1 and 2
    - 21 CFR 862.1660, Product Code JJX
- Hemoglobin A1c Calibrator Set
    - 21 CFR 862.1150, Product Code JIT
- Hemolysis and Wash Solution
    - 21 CFR 864.8540, Product Code GGK

### B Principle of Operation:

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 uses ion-exchange HPLC to separate the stable form of HbA1c (sA1c) from other hemoglobin fractions. The G8 uses a non-porous cation exchange column and separates the hemoglobin components in the blood. Separation is achieved by utilizing differences in ionic interactions between the cation and exchange group on the column resin surface and the hemoglobin components in a step gradient elution. If a sample contains a hemoglobin variant, the column elutes the fraction depending upon its charge.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

Variant II Turbo Hba1c Kit-2.0 Variant II Turbo Hemoglobin Testing System
VARIANT II TURBO HbA1c Kit - 2.0

### B Predicate 510(k) Number(s):

K122472, K142448

### C Comparison with Predicate(s):

| Device & Predicate Device(s): | K200904 | K122472 | K142448 |
|---|---|---|---|
| Device Trade Name | Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 | Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on VARIANT II TURBO Hemoglobin | Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on VARIANT II TURBO Hemoglobin |

| | | Testing System | Testing System |
|---|---|---|---|
| **General Device Characteristic Similarities** | | | |
| Intended Use/Indications For Use | This test is to be used as an aid in diagnosis of diabetes and identifying patients who may be at risk for developing diabetes, and for monitoring of long-term blood glucose control in individuals with diabetes mellitus. | Same (for Monitoring) | Same (for Diagnosis) |
| Assay Principle | Ion-Exchange HPLC | Same | Same |
| Traceability and Standardization | Traceable to the Diabetes Control and Complications Trial (DCCT) reference method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP). | Same | Same |
| **General Device Characteristic Differences** | | | |
| Measuring Range | 4.0% to 16.9% HbA1c | 3.4% to 20.6% HbA1c | 3.4% to 20.6% HbA1c |

## VI Standards/Guidance Documents Referenced:

21 CFR 862.1373 – Special controls for Hemoglobin A1c test system

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

1. Precision/Reproducibility:

Precision was evaluated for the Automated Glycohemoglobin Analyzer HLC-723G8 v5.24 based on CLSI EP05-A3 using four K2 EDTA venous whole blood samples containing approximately 5%, 6.5%, 8%, and 12% HbA1c. Samples were analyzed at two sites on three Automated Glycohemoglobin Analyzer HLC-723G8 v5.24 instruments using three lots of reagents on each instrument. Each sample was analyzed in two runs per day, two replicates per run, for 20 days. The results are shown below:

Analyzer 1

| Mean % HbA1c | Repeatability (error) | | Between-Run | | Between-Day | | Between-Lot | | Intermediate Precision (total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) |
| Sample 1 5.43% | 0.0178 | 0.33 | 0.0146 | 0.27 | 0.0230 | 0.42 | 0.0145 | 0.27 | 0.0356 | 0.66 |
| Sample 2 6.32% | 0.0204 | 0.32 | 0.0109 | 0.17 | 0.0252 | 0.40 | 0.0061 | 0.10 | 0.0348 | 0.55 |
| Sample 3 7.51% | 0.0218 | 0.29 | 0.0204 | 0.27 | 0.0276 | 0.37 | 0.0203 | 0.27 | 0.0454 | 0.60 |
| Sample 4 11.89% | 0.0288 | 0.24 | 0.0254 | 0.21 | 0.0509 | 0.43 | 0.0154 | 0.13 | 0.0656 | 0.55 |

Analyzer 2

| Mean % HbA1c | Repeatability (error) | | Between-Run | | Between-Day | | Between-Lot | | Intermediate Precision (total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) |
| Sample 1 5.48% | 0.0202 | 0.37 | 0.0151 | 0.28 | 0.0204 | 0.37 | 0.0402 | 0.73 | 0.0517 | 0.94 |
| Sample 2 6.41% | 0.0231 | 0.36 | 0.0* | 0.0* | 0.0199 | 0.31 | 0.0480 | 0.75 | 0.0569 | 0.89 |
| Sample 3 7.64% | 0.0217 | 0.28 | 0.0141 | 0.18 | 0.0278 | 0.36 | 0.0720 | 0.94 | 0.0814 | 1.07 |
| Sample 4 11.93% | 0.0266 | 0.22 | 0.0146 | 0.12 | 0.0558 | 0.47 | 0.1228 | 1.03 | 0.1383 | 1.16 |

* Negative variance component values have been sent to zero.

Analyzer 3

| Mean % HbA1c | Repeatability (error) | | Between-Run | | Between-Day | | Between-Lot | | Intermediate Precision (total) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) | SD | CV(%) |
| Sample 1 5.47% | 0.0184 | 0.34 | 0.0092 | 0.17 | 0.0317 | 0.58 | 0.0312 | 0.57 | 0.0489 | 0.89 |
| Sample 2 6.40% | 0.0201 | 0.31 | 0.0099 | 0.15 | 0.0292 | 0.46 | 0.0300 | 0.47 | 0.0475 | 0.74 |
| Sample 3 7.64% | 0.0156 | 0.20 | 0.0050 | 0.06 | 0.0395 | 0.52 | 0.0475 | 0.62 | 0.0640 | 0.84 |
| Sample 4 11.90% | 0.0277 | 0.23 | 0.0* | 0.0* | 0.0602 | 0.51 | 0.0678 | 0.57 | 0.0948 | 0.80 |

* Negative variance component values have been sent to zero.

Analyzers Combined

| Mean % HbA1c | Repeatability (error) | | Between-Run | | Between-Day | | Between-Lot | | Between-Device | | Intermediate Precision (total) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) | SD | CV (%) |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sample 1 5.46% | 0.0188 | 0.35 | 0.0132 | 0.24 | 0.0266 | 0.49 | 0.0291 | 0.53 | 0.0272 | 0.50 | 0.0532 | 0.97 |
| Sample 2 6.38% | 0.0212 | 0.33 | 0.0084 | 0.13 | 0.0288 | 0.45 | 0.0280 | 0.44 | 0.0478 | 0.75 | 0.0665 | 1.04 |
| Sample 3 7.60% | 0.0199 | 0.26 | 0.0146 | 0.19 | 0.0386 | 0.51 | 0.0441 | 0.58 | 0.0737 | 0.97 | 0.0973 | 1.28 |
| Sample 4 11.91% | 0.0277 | 0.23 | 0.0167 | 0.14 | 0.0666 | 0.56 | 0.0684 | 0.57 | 0.0239 | 0.20 | 0.1036 | 0.87 |

2. Linearity:

   Linearity was previously evaluated for this device in k071132.

3. Analytical Specificity/Interference:

   Endogenous and exogenous interference as well as cross-reactivity with acetylated hemoglobin, carbamylated hemoglobin, labile HbA1c, and aldehyde hemoglobin was previously evaluated in k131580 and k071132.

   Hemoglobin Variant Interference:
   A hemoglobin variant study was performed using a total of 130 K3 EDTA venous whole blood samples known to contain hemoglobin variants HbS, HbC, HbE, HbD, HbA2, and HbF. Testing of the samples containing hemoglobin variants were performed using the Automated Glycohemoglobin Analyzer HLC-723G8 and compared to results obtained by a comparator method that has been demonstrated to be free from interference by these hemoglobin variants (Trinity Biotech Ultra2 for HbS, HbC, HbD, HbE and Bio-Rad Variant II Turbo 2.0 for HbF and HbA2).

   Samples tested:

| Hemoglobin Variant | n | % Content of Variant in sample | Range in %HbA1c |
|---|---|---|---|
| HbC | 26 | 30.8-37.8 | 4.8-9.8 |
| HbD | 24 | 22.6-40.7 | 5.3-9.35 |
| HbE | 26 | 20.0-30.9 | 4.8-9.7 |
| HbS | 29 | 28.2-38.9 | 4.9-10.05 |
| HbA2 | 20 | 2.7-5.5 | 5.85-10.1 |
| HbF | 21 | 0.4-43.35 | 4.36-8.9 |

| Hemoglobin Variant | Percent Relative Bias from Reference Method at Low and High Concentrations of HbA1c Samples | |
|---|---|---|
| | ~6.5 % HbA1c | ~8.0 % HbA1c |
| HbC | 0.03 to 0.17 | 0.06 to 0.34 |
| HbD | 0.08 to 0.30 | -0.04 to 0.36 |
| HbE | 0.001 to 0.27 | -0.10 to 0.49 |
| HbS | -0.04 to 0.13 | -0.14 to 0.21 |
| HbA2 | -0.17 to 0.06 | -0.37 to 0.12 |
| HbF | 0.10 to 0.25 | -0.01 to 0.34 |

4. Assay Reportable Range:

   The reportable range for this device is 4.0-16.9% HbA1c.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The assigned HbA1c values of the Automated Glycohemoglobin Analyzer HLC-723G8 are certified by The National Glycohemoglobin Standardization Program (NGSP). See the NGSP website for current certification at http://www.ngsp.org.

   The final reportable result is traceable to both the International Federation of Clinical Chemistry (IFCC) and the Diabetes Control and Complications Trial (DCCT). The International Federation of Clinical Chemistry (IFCC) units of mmol/mol are calculated using the Master Equation NGSP (%) = 0.09148 × IFCC (mmol/mol) + 2.152. HbA1c results are provided to the customers using two different units: NGSP equivalent units (%) and IFCC equivalent units (mmol/mol).

6. Detection Limit:

   Not applicable.

7. Assay Cut-Off:

   Not applicable.

**B Comparison Studies:**

1. Method Comparison with Predicate Device:

   A method comparison study was conducted at two sites (one external, one internal). A total of 220 K2-EDTA venous whole blood samples ranging from 4.7% to 15.4% HbA1c were evaluated. Results obtained on the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 v5.24 were compared to results from the same samples tested on the Trinity Premier Hb9210 system.

The distribution of samples used in the study is summarized below:

| %HbA1c | # Samples Tested |
|---|---|
| <5% | 4 |
| 5.0 – 6.0% | 30 |
| 6.0 – 6.5% | 25 |
| 6.5 – 7.0% | 33 |
| 7.0 – 8.0% | 38 |
| 8.0 – 9.0% | 18 |
| >9.0% | 72 |
| Total | 220 |

The sponsor provided scatter plots demonstrating both Deming and Passing-Bablok regression between the candidate device and the Trinity Premier. The tables below summarize the bias between the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 and the Trinity Biotech reference method.

| | y-Intercept | Slope |
|---|---|---|
| **Deming** | 0.1336<br>95% CI: -0.0331 to 0.3005 | 1.013<br>95% CI: 0.9894 to 1.036 |
| **Passing-Bablok** | 0.0754<br>95% CI: -0.0472 to -0.1819 | 1.020<br>95% CI: 1.007 to 1.037 |

The predicted bias at HbA1c concentrations near clinical decision points, as determined by Passing-Bablok regression and Deming regression, are described below:

Passing-Bablok:

| Decision Level | Bias | % Bias |
|---|---|---|
| 5.0% | 0.1753 | 3.5% |
| 6.5% | 0.2068 | 3.2% |
| 8.0% | 0.2383 | 3.0% |
| 12.0% | 0.3224 | 2.7% |

Deming:

| Decision Level | Bias | % Bias |
|---|---|---|
| 5.0% | 0.1979 | 4.0% |
| 6.5% | 0.2172 | 3.3% |
| 8.0% | 0.2366 | 3.0% |
| 12.0% | 0.2884 | 2.4% |

Total Error:

Total error (%TE) was calculated using the following equation:

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

The %Bias component was generated during the method comparison studies using the Deming regression data for decision levels 5.0% and 6.5% and using the Passing-Bablok regression data for decision levels 8.0% and 12.0% and is the %Bias shown in the table below. The variance component (%CV) was generated during the precision studies and represents the total reproducibility shown in the table below:

| Sample [%HbA1c] | Passing Bablok | | Deming | | Precision (%CV) |
|---|---|---|---|---|---|
| | %TE | %Bias | %TE | %Bias | |
| Sample1 [5%] | 5.48 | 3.5 | 5.99 | 4.0 | 0.97 |
| Sample2 [6.5%] | 5.31 | 3.2 | 5.41 | 3.3 | 1.04 |
| Sample3 [8%] | 5.59 | 3.0 | 5.48 | 2.9 | 1.28 |
| Sample4 [12%] | 4.45 | 2.7 | 4.15 | 2.4 | 0.87 |

2. Matrix Comparison:

The effect on Hemoglobin A1c determination, with the HbA1c assay, in the presence of anticoagulants was determined on the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 by comparing values obtained from samples drawn into $K_2$-EDTA to results obtained from samples in $K_3$-EDTA.

47 samples of each anticoagulant were evaluated, with %HbA1c concentrations for the sample sets ranging from 5.12% to 12.86%. The sample tubes were from a total of 47 donors. Two tubes, one with each anticoagulant, were drawn from each donor. The following are results from least-squares regression analysis:

$y = 1.004x - 0.02021$ $R^2 = 0.999999$

The results support the use of the HbA1c assay with samples collected in $K_2$-EDTA and $K_3$-EDTA.

## C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

**D Clinical Cut-Off:**

Not applicable.

**E Expected Values/Reference Range:**

Reference Ranges (non-diabetic): HbA1c 4.0-6.0 % (mean 5.0 %, SD 0.5 %)

Ref: American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43(Suppl. 1):S14–S31.

The diagnosis of diabetes and identification of persons at increased risk of developing diabetes follows the ADA Guideline of 6.5% for the cut-off and values between 5.7% and 6.4% as being at increased risk.

## VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

## IX Conclusion:

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