September 14, 2021

Tosoh Bioscience, Inc.
Louise Musante
Regulatory Compliance Consultant, Senior Regulatory Specialist
6000 Shoreline Court, Suite 101
South San Francisco, California 94080

Re: K200904
Trade/Device Name: Tosoh Automated Glycohemoglobin Analyzer HLC-723G8
Regulation Number: 21 CFR 862.1373
Regulation Name: Hemoglobin A1c test system
Regulatory Class: Class II
Product Code: PDJ, LCP

Dear Louise Musante:

The Food and Drug Administration (FDA) is sending this letter to notify you of an administrative change related to your previous substantial equivalence (SE) determination letter dated August 5, 2021. Specifically, FDA is updating this SE Letter as an administrative correction to correct a typo in the sponsor's 510(k) summary.

Please note that the 510(k) submission was not re-reviewed. For questions regarding this letter please contact Leslie Landreee, OHT7: Office of In Vitro Diagnostics and Radiological Health, (301) 796-6147, leslie.landree@fda.hhs.gov.

Sincerely,

Leslie Landree -S

Digitally signed by Leslie Landree -S
Date: 2021.09.14 17:43:06 -04'00'

Leslie Landree
Acting Diabetes Diagnostic Devices Branch Chief
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

August 5, 2021

Tosoh Bioscience, Inc.
Louise Musante
Regulatory Compliance Consultant, Senior Regulatory Specialist
6000 Shoreline Court, Suite 101
South San Francisco, California 94080

Re: K200904
Trade/Device Name: Tosoh Automated Glycohemoglobin Analyzer HLC-723G8
Regulation Number: 21 CFR 862.1373
Regulation Name: Hemoglobin A1c test system, Glycosylated hemoglobin assay
Regulatory Class: Class II
Product Code: PDJ, LCP
Dated: September 25, 2020
Received: September 29, 2020

Dear Louise Musante:

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/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); 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 https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). 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 (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Marianela Perez-torres -S

Marianela Perez-Torres, Ph.D.
Deputy Director
OHT7: Office of In Vitro Diagnostics
and Radiological Health
Office of Product Evaluation and Quality
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)*
k200904

Device Name
Tosoh Automated Glycohemoglobin Analyzer HLC-723G8

Indications for Use *(Describe)*
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.

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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TOSOH BIOSCIENCE

Section 5 - 510(k) Summary or 510(k) Statement

k200904 510(k) Summary
Tosoh Bioscience, Inc.'s
Tosoh Automated Glycohemoglobin Analyzer HLC-723G8

DATE PREPARED: May 26, 2020

1. COMPANY NAME/CONTACT

Tosoh Bioscience, Inc.
6000 Shoreline Court, Suite 101
South San Francisco, CA 94080

2. CONTACT:

Louise Musante
Regulatory Compliance Consultant
Email: louise.musante@tosoh.com
Cell Phone: (650) 242-5563

3. DEVICE INFORMATION

Device Trade Name: Tosoh Automated Glycohemoglobin Analyzer HLC-723G8
Regulation Numbers: 21 CFR Part 862.1373 and 21 CFR Part 864.7470
Regulation Names: Hemoglobin A1c test system, Glycosylated hemoglobin assay
Product Code: PDJ, LCP
Device Class: Class II
510(k) Review Panel: Clinical Chemistry

4. PREDICATE DEVICE

Trade name: VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System

510(k) submitter/holder: Bio-Rad Laboratories, Inc.,
Clinical Diagnostics Group
4000 Alfred Nobel Drive Hercules, CA 94547

510(k) Numbers:
k122472 (monitoring claim)
k142448 (diagnostic claim)

5. REFERENCE DEVICES USED IN NON-CLINICAL PERFORMANCE TESTING

Method Comparison testing:

Trinity Biotech Premier Hb9210™ HbA1c Analyzer, by Primus Corporation DBA Trinity Biotech, k112015, Product Code LCP

Hemoglobin Variant Interference (HbC, HbD, HbE and HbS) testing:

Primus Model CLC 330, aka Ultra2 Affinity HbA1c Analyzer, by Primus Corporation DBA Trinity Biotech, k891235, Product Code LCP

Hemoglobinopathy Interference (HbF and HbA2) testing:

VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System by Bio-Rad Laboratories, Inc., k142448, Product Code LCP

6. 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 venous 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, which are 510(k) exempt and clearance is not required;

- 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

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 uses ion-exchange HPLC for rapid, accurate, and precise separation of 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. The hemoglobin fractions (designated as A1a, A1b, F, LA1c+, SA1c, A0, and, if present, H-V0, H-V1, H-V2 and H-V3) are subsequently removed from the column by performing a step-wise elution gradient using the varied salt concentrations in the Variant Elution Buffers HSi 1, 2 and 3. The peaks, H-V0, H-V1, H-V2 and H-V3 are typically presumptive HbAD, HbAS, HbAC and HbAE respectively.

The software compares the retention times of hemoglobin fractions in a sample to the expected "windows of retention" and labels each fraction that correctly elutes within a defined expected window of retention. The software designates a hemoglobin fraction as P0X (where X is the order of the peak as it elutes from the column) if it does not match a defined window of retention. All automated processes in the G8 are controlled by internal microprocessors, using software downloaded via a smart media card.

The result report is printed and can be stored on the instrument. The data can be transmitted to a host computer through a bi-directional interface. The result report includes the sample ID, date, percentage and retention time of each fraction of hemoglobin, sA1c percentage and total A1 percentage, along with a chromatogram of the elution pattern of the hemoglobin fractions. If a sample contains a hemoglobin variant, the column elutes the fraction depending upon its charge.

7. INDICATION FOR USE STATEMENT

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.

8. INTENDED USE STATEMENTS:

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.

9. SUBSTANTIAL EQUIVALENCE COMPARISON

The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24, is substantially equivalent to the claimed predicate device; the Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K122472 and K142448), based on comparisons of the intended use and technological characteristics.

Section 5 - 510(k) Summary or 510(k) Statement

Table 1 – Comparison Table of Subject Device to Predicate Device

Attributes	Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 (Subject Device)	VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K142448)	VARIANT II TURBO HbA1c Kit - 2.0 on VARIANT II TURBO Hemoglobin Testing System (K122472)	Differences	Differences raise any additional safety issues?
General Information					
Regulation #	• 21 CFR 862.1373 • 21 CFR 864.7470 • 21 CFR 862.1150	21 CFR 862.1373	21 CFR 864.7470	Same	N/A
Regulation Name	• Hemoglobin A1c Test System • Glycosylated Hemoglobin Assay • Calibrator	Hemoglobin A1c test system	Glycosylated Hemoglobin Assay	Same	N/A
Regulatory Class	Class II	Class II	Class II	Same	N/A
Product Code	PDJ, LCP, JIS	PDJ	LCP	Same	N/A
Indications 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.	The VARIANT II TURBO HbA1c Kit – 2.0 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 VARIANT™ II TURBO Hemoglobin Testing System and VARIANT II TURBO Link Hemoglobin Testing System. This test is to be used as an aid in diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes. The VARIANT™ II TURBO HbA1c Kit – 2.0 is intended for Professional Use Only. The Hemoglobin Capillary Collection System (HCCS) is intended for the collection of human whole blood for the percentage	The Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 is intended for the quantitative determination of hemoglobin A1c in human whole blood using ion-exchange high performance liquid chromatography (HPLC) on the VARIANT II TURBO Hemoglobin Testing System. Measurement of hemoglobin A1c is effective in monitoring long-term glycemic control in individuals with diabetes mellitus. The Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 is intended for Professional Use Only.	Different	No

Attributes	Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 (Subject Device)	VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K142448)	VARIANT II TURBO HbA1c Kit - 2.0 on VARIANT II TURBO Hemoglobin Testing System (K122472)	Differences	Differences raise any additional safety issues?
		determination of hemoglobin A1c using Bio-Rad HPLC methods.			

Table 2 – Comparison Table of Technological Characteristics: Subject Device to Predicate Device

Attributes	Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 (Subject Device)	Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K142448)	VARIANT II TURBO HbA1c Kit - 2.0 on VARIANT II TURBO Hemoglobin Testing System (K122472)	Differences	Differences raise any additional safety issues?
Product Specifications					
Instrument Platform	Automated Glycohemoglobin Analyzer HLC-723G8	VARIANT™ II TURBO Hemoglobin Testing System and VARIANT™ II TURBO Link Hemoglobin Testing System	VARIANT™ II TURBO Hemoglobin Testing System and VARIANT™ II TURBO Link Hemoglobin Testing System	Different	No
Detection Method	Analyte passes through a flow cell where changes in absorbance are measure at 415nm and recorded as a digital chromatogram. An additional filter at 500nm corrects for background absorbance.	Analyte passes through a flow cell where changes in absorbance are measure at 415nm and recorded as a digital chromatogram. An additional filter at 690nm corrects for background absorbance.	Analyte passes through a flow cell where changes in absorbance are measure at 415nm and recorded as a digital chromatogram. An additional filter at 690nm corrects for background absorbance.	Different	No
Assay Principle	Ion-exchange HPLC	Ion-exchange HPLC	Ion-exchange HPLC	Same	N/A
Specimen Types	Human Venous Whole Blood	Human Venous Whole Blood	Human Venous Whole Blood	Same	N/A
Methodology	Dilutes whole blood specimen with Hemolysis & Wash Solution, and then injects a small volume of this specimen onto the TSKgel G8 Variant HSi column.	Dilutes whole blood specimen and then injects a small volume of this specimen onto the analytical cartridge.	Dilutes whole blood specimen and then injects a small volume of this specimen onto the analytical cartridge.	Same	N/A

Section 5 - 510(k) Summary or 510(k) Statement

Attributes	Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 (Subject Device)	Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K142448)	VARIANT II TURBO HbA1c Kit - 2.0 on VARIANT II TURBO Hemoglobin Testing System (K122472)	Differences	Differences raise any additional safety issues?
Performance Specifications					
Measuring Range	4.0 to 16.9% HbA1c (NGSP)	3.4 to 20.6% HbA1c (NGSP)	3.4 to 20.6% HbA1c (NGSP)	Different	No
Traceability and Standardization	Traceable to the Diabetes Control and Complications Trial (DCCT) reference method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP)	Traceable to the Diabetes Control and Complications Trial (DCCT) reference method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP)	Traceable to the Diabetes Control and Complications Trial (DCCT) reference method and IFCC. Certified via the National Glycohemoglobin Standardization Program (NGSP)	Same	N/A
Matrix	K2-EDTA and K3-EDTA Venous Whole Blood	K2-EDTA, K3-EDTA, Capillary blood in Hemoglobin Capillary Collection System (HCCS)	K2-EDTA, K3-EDTA, Capillary blood in Hemoglobin Capillary Collection System (HCCS)	Same	N/A
Hemoglobin Variant Interference	Accurate and reportable HbA1c% results in the presence of HbC (39%), HbD (39.5%), HbS (39%). Non-clinically significant interference is defined as </= 6% relative difference in the results from a comparative method at 6% or 9% HbA1c.	Accurate and reportable HbA1c% results in the presence of HbC, HbD, HbS. Non-clinically significant interference defined as ±7% from the control.	Accurate and reportable HbA1c% results in the presence of HbC, HbD, HbS. Non-clinically significant interference defined as ±7% from the control.	Different	No
	Accurate HbA1c% in the presence of HbF up to 25%. Non-clinically significant interference is defined as </= 6% relative difference in the results from a comparative method at 6% or 9% HbA1c.	Accurate HbA1c% in the presence of HbF up to 25%.	Accurate HbA1c% in the presence of HbF up to 25%.		
	Accurate HbA1c% in the presence of HbA2 up to 12%. Non-clinically significant interference is defined as </= 6% relative difference in the results from a comparative	Accurate HbA1c% in the presence of HbA2 up to 10%.	Accurate HbA1c% in the presence of HbA2 up to 10%.	Different	No

Attributes	Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 (Subject Device)	Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K142448)	VARIANT II TURBO HbA1c Kit - 2.0 on VARIANT II TURBO Hemoglobin Testing System (K122472)	Differences	Differences raise any additional safety issues?
	method at 6% or 9% HbA1c.				
	Accurate and reportable HbA1c% results in the presence of 26% HbE. Non-clinically significant interference is defined as </= 6% relative difference in the results from a comparative method at 6% or 9% HbA1c.	Accurate and reportable HbA1c% results in the presence of HbE. Non-clinically significant interference defined as ±7% from the control.	Accurate and reportable HbA1c% results in the presence of HbE. Non-clinically significant interference defined as ±7% from the control.	Different	No

10. SUMMARY OF TECHNOLOGICAL DIFFERENCES

Indications for Use:

The predicate device is cleared separately for the monitoring claim (K122472) and diagnostic claim (K142448). Tosoh seeks clearance for both the monitoring and diagnostic claim combined in this pre-market submission by combining the claims sought and obtained separately for previously cleared Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 submissions; k071132 for the long-term monitoring of people diagnosed with diabetes under 21 CFR 864.7470 as well as the same analyzer cleared in k131580 as a diagnostic HbA1c device under 21 CFR 862.1373. As both clearances are for the same device, with incremental changes, the combination of "Indications for Use" does not raise any additional safety or efficacy questions for the subject device.

Instrument Platform:

The subject device and predicate device are both automated High-Performance Liquid Chromatography (HPLC) systems that separate and report hemoglobin A1c percentage in venous whole blood. Aside for the sample volume requirement (3µL of whole blood and 80µL of diluted samples for the subject device and 50µL of venous whole blood and diluted samples for the predicate device), both systems use software algorithms to measure HbA1c concentrations, in the presence of variants. The difference in instrument platform does not raise any additional safety or efficacy questions for the subject device.

Detection Method:

The subject device allows the analyte to pass through a flow cell where changes in absorbance are measure at 415nm and recorded as a digital chromatogram. An additional filter at 500nm corrects for background absorbance. The predicated device uses the same absorbance wavelength to detect and record the sample as a digital chromatogram. The additional filter, however, uses a wavelength of 690nm, correcting for background absorbance. The difference in background wavelength subtraction does not raise any additional safety or efficacy questions for the subject device.

Measuring Range:

The subject device has a measuring range of 4.0 to 16.9% HbA1c (NGSP), whereas the predicate device has a measuring range of 3.4 to 20.6% HbA1c (NGSP). The difference in measuring range does not raise any additional safety or efficacy questions for the subject device.

11. SUMMARY OF NON-CLINICAL PERFORMANCE TESTING

Non-clinical performance tests were conducted to support the substantial equivalence determination of this 510(k) submission. No clinical performance tests were conducted to support the substantial equivalence determination of this 510(k) submission. The non-clinical performance tests and summary of results are as follows;

a) Precision/Repeatability

The precision repeatability study was performed in compliance with CLSI EP05-A3*, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition*, to verify whether or not the previously established claim of imprecision at ≤ 2% was affected by the software modification to version 5.24 of the Tosoh Automated Glycohemoglobin Analyzer HLC723-G8. Four concentrations of HbA1c% in K_2EDTA venous whole blood were tested. The concentrations were approximately 5.0%, 6.5%, 8.0% and 12.0%. A total of seven-hundred and twenty measurements per concentration were measured using the study design; three analyzers over twenty non-consecutive days with three reagent lots. Specimens were run in duplicate, two times per day for a total of seven-hundred and twenty unique results per concentration.

Section 5 - 510(k) Summary or 510(k) Statement

Table 3 - Summary of Precision Analysis of All Analyzers Combined

HbA1c% (Target) Mean	Repeatability		Between Run		Between Day		Between Lot		Between Instruments		Total	
	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample1 [5%] 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
Sample2 [6.5%] 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
Sample3 [8%] 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
Sample4 [12%] 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
*: Negative variance component's values have been set to '0'.												

Abbreviations: CV = coefficient of variation, SD = standard deviation

Table 4 - Summary of Precision Analysis for Analyzer 1 (SN 14736306)

HbA1c% (Target) Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample1 [5%] 5.43%	0.0178	0.33	0.0146	0.27	0.0230	0.42	0.0145	0.27	0.0356	0.66
Sample2 [6.5%] 6.32%	0.0204	0.32	0.0109	0.17	0.0252	0.40	0.0061	0.10	0.0348	0.55
Sample3 [8%] 7.51%	0.0218	0.29	0.0204	0.27	0.0276	0.37	0.0203	0.27	0.0454	0.60
Sample4 [12%] 11.89%	0.0288	0.24	0.0254	0.21	0.0509	0.43	0.0154	0.13	0.0656	0.55
*: Negative variance component's values have been set to '0'.										

Abbreviations: CV = coefficient of variation, SD = standard deviation

Table 5 - Summary of Precision Analysis for Analyzer 2 (SN 14927602)

HbA1c% (Target) Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample1 [5%] 5.48%	0.0202	0.37	0.0151	0.28	0.0204	0.37	0.0402	0.73	0.0517	0.94
Sample2 [6.5%] 6.41%	0.0231	0.36	0.0*	0.0*	0.0199	0.31	0.0480	0.75	0.0569	0.89
Sample3 [8%] 7.64%	0.0217	0.28	0.0141	0.18	0.0278	0.36	0.0720	0.94	0.0814	1.07
Sample4 [12%] 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's values have been set to '0'.										

Abbreviations: CV = coefficient of variation, SD = standard deviation

Table 6 - Summary of Precision Analysis for Analyzer 3 (SN 12521504)

`Mean´ HbA1c	`Repeatability´		`Between Run´		`Between Day´		`Between Lot´		`Total´	
	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)	SD	CV (%)
Sample1 [5%] 5.47%	0.0184	0.34	0.0092	0.17	0.0317	0.58	0.0312	0.57	0.0489	0.89
Sample2 [6.5%]6.40%	0.0201	0.31	0.0099	0.15	0.0292	0.46	0.0300	0.47	0.0475	0.74
Sample3 [8%]7.64%	0.0156	0.20	0.0050	0.06	0.0395	0.52	0.0475	0.62	0.0640	0.84
Sample4 [12%]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's values have been set to '0'.										

b) Method Comparison

The method comparison study was performed in compliance to CLSI EP09c: *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline – Third Edition*. The study was conducted at two separate sites with the candidate device; Tosoh G8 v5.24 Analyzer, located at a moderate complexity clinical laboratory and the comparator device; Trinity Biotech Premier Hb9210^{TM} HbA1c Analyzer, located at an NGSP SRL. Two Hundred and Twenty (220) K_2EDTA venous whole blood specimens with HbA1c concentrations that span the G8 v5.24 measuring range (4.0-16.9%) were tested in duplicate on both analyzers.

Table 7 - Sample Distribution Across HbA1c Concentration Range

Target A1c Concentration (%)	No. of Specimens	Percent of Total Samples
<5%	4	1.8%
5.0 – 6.0%	30	13.6%
6.0 – 6.5%	25	11.4%
6.5 – 7.0%	33	15.0%
7.0 – 8.0%	38	17.3%
8.0 – 9.0%	18	8.2%
>9.0%	72	32.7%
Total	220	100%

Table 8 - Summary of Method Comparison Results

	y-Intercept	95% CI	Slope	95% CI
Deming	0.1336	-0.0331 to 0.3005	1.013	0.9894 to 1.036
Passing-Bablok	0.0720	-0.0472 to -0.1819	1.021	1.007 to 1.037

Figure 1 - Method Comparison Deming Regression Analysis of G8 v5.24 vs NGSP SRL (Trinity Premier)

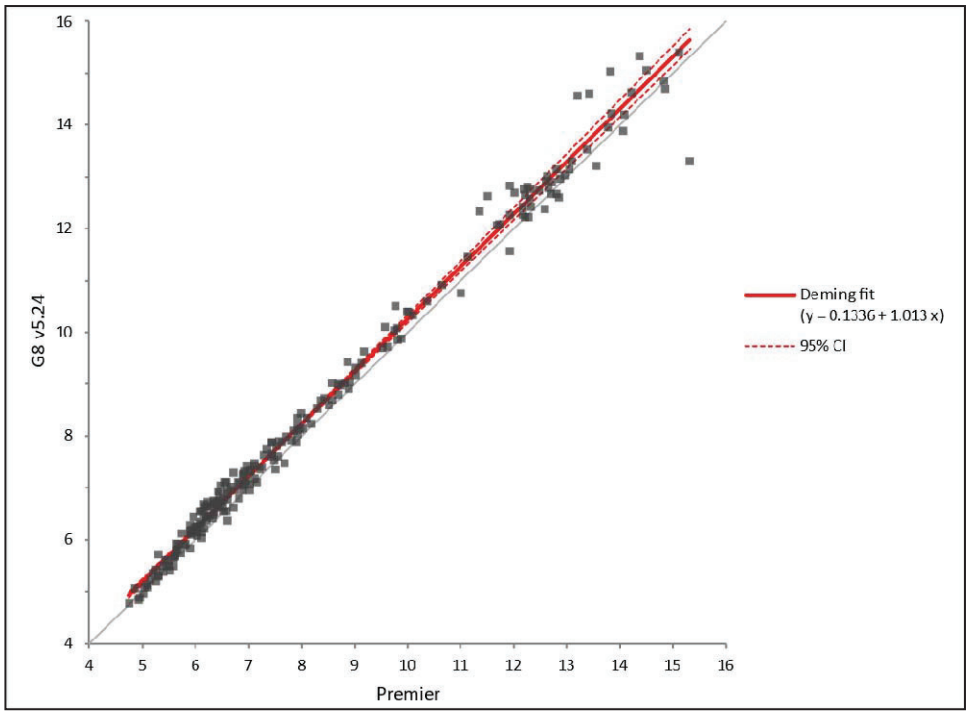

Table 9 - Method Comparison Bias Results – Passing Bablok

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%

Table 10 - Method Comparison Bias Results – 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%

Table 11 - Total Error Estimation

Total Error [%]					
	Passing Bablok		Deming		
HbA1c Level	`%TE´*	%Bias	`%TE´*	%Bias	$\%CV_{Total}$
Sample1 [5%]	5.48	3.5	5.99	4.0	0.974054
Sample2 [6.5%]	5.31	3.2	5.41	3.3	1.042108
Sample3 [8%]	5.59	3.0	5.59	3.0	1.281173
Sample4 [12%]	4.45	2.7	4.15	2.4	0.870450
*: Calculated as: `|%Bias| + 1.96 x $\%CV_{Total}$ x (1+ %Bias/100)´					

c) Matrix Comparison

The data supports the use of K2-EDTA and K3-EDTA blood collection tubes, as they show no clinical or statistical difference and thus may be used interchangeably for testing HbA1c on the G8 HPLC Analyzer.

d) Traceability and Expected Values (calibrators)

The assigned HbA1c values of the Tosoh Automated Glycohemoglobin Analyzer are 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 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 x 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).

Calibrators (Tosoh A1c Calibrator Set) and Controls (Canterbury Scientific Hemoglobin A1c Control) are recommended for use with this device. The calibrators and controls were previously cleared under 510(k) k071132 and k021484, respectively.

e) Linearity and Detection Limit

Linearity and Detection Limit was previously established for this assay under 510(k) k071132. The reportable range for this device is 4.0 to 16.9% HbA1c.

f) Analytical Specificity

i. Endogenous Interfering Substances

The endogenous interference study was performed in compliance to CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition. Significant interference was defined as percent recovery ± 5% of the expected 100% recovery. Interference studies were conducted on known concentrations of HbA1c%. Specimens were spiked with increasing amounts of the interfering substance.

Table 12 - Endogenous Interfering Substances Tested

Potential Interfering Substance	Range Tested	HbA1c% Concentrations	Concentration with No Interference
Albumin	500 to 5000 mg/dL	6.6 and 14.7	5000 mg/dL
Ascorbic Acid	3.0 to 25 mg/dL	6.4 and 10.8	25 mg/dL
Bilirubin C	2.0 to 21 mg/dL	6.5 and 14.3	21 mg/dL
Bilirubin F	2.0 to 18 mg/dL	6.5 and 14.3	18 mg/dL
Lipemia	1 to 1000 mg/dL	6.4 and 14.1	1000 mg/dL
Rheumatoid Factor	110 to 550 IU/mL	6.3 and 12.6	550IU/mL

ii. Drug Interference

The exogenous drug interference study was performed under clearance of k071132. Acetylsalicylic Acid was tested because it does form acetylated hemoglobin, which may interfere with the %HbA1c when measured by HPLC. Acetaldehyde was tested because it can form aldehyde hemoglobin, which can cause an increase in the LA1c fraction.

With HPLC, the red cells are lysed and eluted across the column for separation of the hemoglobin fractions. Research of the FDA website and others show no contraindication of Levodopa, Methyldopa, Acetaminophen and Ibuprofen when used by pre-diabetic or diabetic patients, and the drugs do not interfere with the HPLC technology as they might during an antigen/antibody reaction. FDA stated that based on the technology of the device, it has been shown that the additional substances do not appear to interfere with this type of device; therefore, the additional interference data on these drugs was not needed.

iii. Cross Reactivity with Hemoglobin Derivatives

A cross-reactivity study was performed with potential interferences from Acetylated hemoglobin (Hb), Carbamylated Hb, Aldehyde Hb, and Labile HbA1c with HbA1c values of ~6.5% and ~8% HbA1c. The following results were concluded as not interfering with the assay.

- Acetylated Hb up to 50 mg/dL
- Carbamylated Hb up to 25 mg/dL
- Aldehyde Hb up to 25 mg/dL
- Labile HbA1c up to 1000 mg/dL

iv. Hemoglobin Variant Interference

The hemoglobin variant interference study was performed in compliance to CLSI EP07-A2, Interference Testing in Clinical Chemistry; Approved Guideline-Second Edition. Interference when measuring %HbA1c in clinical specimens due to certain levels of Hb variants (HbC, HbD, HbE, and HbS) and hemoglobinopathies (HbA2 and HbF) is well-known. To reduce possible interference and to enhance the performance of the G8 in the presence of these variants and hemoglobinopathies, Tosoh modified the software algorithms. The modified software, version 5.24, reduces interference when measuring %HbA1c.

An interference study was performed to identify the level of Hb variants and hemoglobinopathies likely to cause interference, thus verifying that the G8 software modification (version 5.24) did reduce measurement interference of %HbA1c under these conditions. Non-clinically significant interference was defined as </= 6% relative difference in the results from a comparative method at 6.5% or 8.0% HbA1c.

Table 13 - Variant Samples Used in Hemoglobin Variant Study

Hemoglobin Variant/ Hemoglobinopathy	n	Range in % Abnormal Variant/ Hemoglobinopathy	Range in % HbA1c Concentration
HbC	26	30.8 to 37.8	4.8 to 9.8
HbD	24	22.6 to 40.7	5.3 to 9.347
HbE	26	20.0 to 30.9	4.763 to 9.7
HbS	29	28.2 to 38.9	4.9 to 10.05
HbA2*	20	2.7 to 5.5	5.85 to 10.1

HbF*	21	0.4 to 43.35	4.36 to 8.9

*Hemoglobinopathies

Table 14 - Hemoglobin Variant Study - Reporting Percent Relative Bias

Hemoglobin Variant/ Hemoglobinopathy	Percent Relative Bias from Reference Method at Low and High Concentrations of HbA1c Samples			
	~6.5 % HbA1c		~8.0 % HbA1c	
	Calibrated Relative % Difference	Range	Calibrated Relative % Difference	Range
HbAD	-0.5	0.08 to 0.30	-1.7	-0.04 to 0.36
HbAS	-2.7	-0.04 to 0.13	-3.2	-0.14 to 0.21
HbAC	-1.9	0.03 to 0.17	-1.1	0.06 to 0.34
HbAE	-1.3	0.001 to 0.27	-1.2	-0.10 to 0.49
HbA2	-4.2	-0.17 to 0.06	-5.1	-0.37 to 0.12
HbF	-0.7	0.10 to 0.25	-1.6	-0.01 to 0.34

All performance testing results met their pre-determined acceptance criteria. In all instances, the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 performed as intended. Additionally, a risk hazard analysis and design FMEA were performed for the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24. The risk management report concluded that all identified risks were mitigated to an acceptable risk level through design and/or labeling, and that the benefits of using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 for its intended use outweigh any residual risk from use of the device.

12. CONCLUSION

Tosoh Bioscience, Inc. believes that the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24, is substantially equivalent in intended use and technological characteristics to the Bio-Rad VARIANT II TURBO HbA1c Kit – 2.0 on the VARIANT II TURBO Hemoglobin Testing System (K122472 and k142448). The Tosoh Automated Glycohemoglobin Analyzer HLC-723G8, v5.24 therefore meets the Federal Food, Drug and Cosmetic Act criteria for 510(k) clearance of this device.