

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE**

A. 510(k) Number:

k122472

B. Purpose for Submission:

Modification to a marketed device to revise hemoglobin variant interference claim and updated software, hardware and firmware.

C. Measurand:

Hemoglobin A_{1c} (HbA_{1c})

D. Type of Test:

Quantitative ion-exchange high-performance liquid chromatography (HPLC)

E. Applicant:

Bio-Rad Laboratories, Inc.

F. Proprietary and Established Names:

VARIANT II TURBO HbA_{1c} Kit – 2.0 and VARIANT II TURBO Hemoglobin Testing System.

G. Regulatory Information:

Regulation Description	Product Code	Device Class	Regulation	Panel
Glycosylated Hemoglobin Assay	LCP	II	21 CFR § 864.7470	Hematology, 81

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

The Bio-Rad VARIANT II TURBO HbA_{1c} Kit – 2.0 is intended for the quantitative determination of hemoglobin A_{1c} in human whole blood using ion-exchange high performance liquid chromatography (HPLC) on the VARIANT II TURBO Hemoglobin Testing System. Measurement of hemoglobin A_{1c} is effective in monitoring long-term glycemic control in individuals with diabetes mellitus. The Bio-Rad VARIANT II TURBO HbA_{1c} Kit – 2.0 is intended for Professional Use Only.

3. Special conditions for use statement(s):

For prescription use only.

4. Special instrument requirements:

For use with the Bio-Rad VARIANT II TURBO Hemoglobin Testing System (cleared under k040872 and k090699; modified in the current submission).

I. Device Description:

The VARIANT II TURBO HbA_{1c} Kit – 2.0 contains an analytical cartridge, five prefilters, Elution Buffers A and B, Calibrator Level 1, Calibrator Level 2, Whole Blood Primer, sample vials and a CD-ROM with test parameters.

The Calibrators and the Whole Blood Primer contain lyophilized human red blood cell hemolysate with gentamicin, tobramycin, and EDTA as preservatives.

Each unit of whole blood used in the manufacture of the calibrators and whole blood primer was tested by FDA accepted methods and found non-reactive for HIV-1, HIV-2, Hepatitis B (HBV), Hepatitis C (HCV), and syphilis.

The items in the VARIANT II TURBO HbA_{1c} Kit – 2.0 are described in the table below.

Component	Description
Analytical Cartridge	One cation exchange cartridge (2500 tests), 4.6 ID x 27.5 mm. Five prefilter elements (500 tests each) are included with the cartridge.
Elution Buffer A	Five bottles containing 2500 mL of a sodium perchlorate buffer. Contains <0.05% sodium azide as preservative.
Elution Buffer B	One bottle containing 2500 mL of a sodium perchlorate buffer. Contains <0.05% sodium azide as preservative.
Calibrator/Diluent Set	One set consisting of two vials of Calibrator Level 1, two vials of Calibrator Level 2, and one bottle of Calibrator Diluent. The calibrator vials contains lyophilized human red blood cell hemolysate with gentamicin, tobramycin, and EDTA as preservatives. Reconstituted volume is 7 mL per vial. Calibrator Diluent contains 100 mL of deionized water with <0.05% sodium azide as a preservative.
Whole Blood Primer	Two vials of lyophilized human red blood cell hemolysate with gentamicin, tobramycin, and EDTA as preservatives. Reconstituted volume is 1.0 mL per vial.
Sample Vials	100 polypropylene vials with pierceable caps, 1.5 mL.
CD-ROM	VARIANT II TURBO HbA _{1c} Kit – 2.0 parameters.

The VARIANT II TURBO Hemoglobin Testing System provides an integrated method for sample preparation, separation and the percent determination of HbA_{1c} in EDTA human whole blood. The VARIANT II TURBO Hemoglobin Testing System is a fully automated, high-throughput hemoglobin analyzer. It consists of two modules - the VARIANT II Chromatographic Station (VCS) and the VARIANT II Sampling Station (VSS). There have been hardware updates due to obsolescence of parts and firmware updates to support the

replacement hardware components. A personal computer is used to control the VARIANT II TURBO Hemoglobin Testing System using Clinical Data Management (CDM) software version 5.1.1.

J. Substantial Equivalence Information:

Predicate device name	Predicate 510(k) number
Bio-Rad VARIANT II TURBO HbA _{1c} Kit – 2.0	k090699

Comparison with predicate:

Item	Candidate Device	Predicate Device
Intended Use	Measurement of hemoglobin A1c is effective in monitoring long-term glycemic control in individuals with diabetes mellitus.	Same
Test Principle	Ion-exchange high performance liquid chromatography	Same
Sample Type	Anticoagulated whole blood (EDTA)	Same
Detection Wavelength	415 nanometers	Same
Reporting Units	% HbA1c (NGSP) mmol/mol HbA1c (IFCC)	Same
Expected Range	3.5 to 19.0% HbA1c (NGSP)	Same
Interference from HbF	HbF up to 25% had no significant effect on HbA1c determination.	Same
Interference from variants HbC, HbD, HbE, HbS	No significant interference was observed at the following concentrations: • HbC <72% • HbD <55% • HbE <41% • HbS <67%	Hemoglobin variants: Two out of 7 hemoglobin AD-trait, 2 out of 11 hemoglobin AS-trait, 1 out of 12 hemoglobin AE-trait, and 3 out of 9 hemoglobin AC-trait patient samples at the clinically significant levels of 6% and 9% HbA1c exhibited differences of more than +10% from values obtained using boronate affinity reference method.
Interference from HbA2	β-thalassemia trait, as indicated by increased HbA ₂ concentrations up to 10%, does not interfere with the assay.	No claim previously
Instrument	VARIANT II TURBO Hemoglobin Testing System	Same
Software	CDM Version 5.1.1	CDM Version 4.03
Calibrator	2 levels	Same

Calibration frequency	Once every 500 injections/ 2500 injections total column life	Same
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K. Standard/Guidance Document Referenced (if applicable):

CLSI EP7-A2: Interference Testing in Clinical Chemistry.

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples.

L. Test Principle:

The VARIANT II TURBO HbA1c Kit- 2.0 is based on chromatographic separation of HbA1c on a cation exchange cartridge. The various forms of hemoglobin exhibit charge differences (positive) at the acidic pH of the mobile phase, and thus can be separated on a support that is negatively charged (cation exchange). The use of ion-exchange chromatography allows molecules to be separated based upon a molecule's charge.

Separation is optimized to eliminate interferences from hemoglobin variants (HbS, HbC, HbD and HbE trait), labile A1c, hemoglobin F and carbamylated hemoglobin.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Previously established in submission k090699.

b. *Linearity/assay reportable range:*

The reportable range of 3.5 to 19.0% HbA_{1c} was previously established in submission k090699.

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

Calibrators were previously cleared in k070452. The recommended control materials were cleared in k070546 and k052838.

The modified device is certified by the National Glycohemoglobin Standardization Program (NGSP) as having documented traceability to the Diabetes Control and Complications Trial (DCCT) reference method.

d. *Detection limit:*

Previously established in submission k090699.

e. *Analytical specificity:*

The interference claims for icterus (bilirubin), lipemia (triglyceride), EDTA, hemoglobin F, labile A_{1c} and carbamylated hemoglobin were previously established in submission k090699.

The possible interferant effects from hemoglobin variants C, D, E, F, S and A2 (HbC, HbD, HbE, HbF, HbS and HbA2) were evaluated. Two fresh, EDTA non-variant

human blood sample pools at 6.5% and 8.0-9.0% HbA_{1c} were collected. Fresh, homozygous EDTA-whole blood samples containing each of the hemoglobin variants (E, D, S, and C) were obtained. EDTA-whole blood samples were prepared by spiking purified HbF or HbA₂. For the interference testing of each variant, a series of test sample pools (0, 25, 50, 75, 100% and additional intermediate pools) were prepared by the dilution of a homozygous variant patient sample (as interferant) in the non-variant patient sample pool. The samples were run in duplicate on two VARIANT II TURBO Hemoglobin Testing Systems. Non-significant interference was defined by the sponsor as less than $\pm 10\%$ bias from control.

Based upon the data in the study, the sponsor claims no interference at the following concentrations: HbC $\leq 72\%$, HbD $\leq 55\%$, HbE $\leq 41\%$, HbF $\leq 25\%$, HbS $\leq 67\%$ and HbA₂ $\leq 10\%$.

- f. *Assay cut-off:*
Not applicable.

2. Comparison studies:

- a. *Method comparison with predicate device:*

To demonstrate the correlation between samples analyzed on devices using CDM Software Versions 5.1 (candidate device) and samples run on devices using CDM Software Version 4.03 (predicate device), 40 EDTA whole blood patient samples, 60 commercially purchased EDTA whole blood patient samples and 16 contrived samples prepared by mixing EDTA whole blood samples with either purified HbA₀ or purified HbA_{1c} (8 samples cover 3.5% to 4.5% and 8 samples cover 14.2% to 19.5%) were analyzed by the VARIANT II TURBO HbA_{1c} Kit - 2.0 run on the VARIANT II TURBO Hemoglobin Testing System using both software versions. . The samples were run in singlet on the subject device and on the predicate device. The results of the linear regression analysis are presented in the table below.

Reporting Unit	Regression Data	Sample Range
%HbA _{1c} (NGSP)	$y = 0.99x + 0.06$, $R^2 = 0.9996$	3.5% to 19.5%
mmol/mol (IFCC)	$y = 0.99x + 0.48$, $R^2 = 0.9996$	15 to 190 mmol/mol

- b. *Matrix comparison:*
Not applicable.

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:
Hemoglobin A_{1c} expected value range was cited from American Diabetes Association Standards of Medical Care in Diabetes 2012, 35 (Supplement 1), S11-S63.

Hemoglobin A _{1c} (%)	Glycemic Goal
<8	Less Stringent
<7	General Goal
<6.5	More Stringent
<5.7	Non-Diabetic Goal

N. Instrument Name:

Bio-Rad VARIANT II TURBO Hemoglobin Testing System

O. System Descriptions:

1. Modes of Operation:

A completely closed, fully automated, high-throughput analyzer consisting of a chromatographic and a sampling station.

2. Software:

FDA has reviewed applicant's Hazard Analysis and software development processes for this line of product types:

Yes X or No

3. Specimen Identification:

Samples are identified from the barcode on blood collection test tube. The code is read automatically by the analyzer. The system software (CDM 5.1.1) detects and prevents mismatch of results with sample ID. If a mismatch is detected, the sample result will not be sent to the Laboratory Information System (LIS) and the operator will be notified.

4. Specimen Sampling and Handling:

Blood is drawn into normal vacuum test tube. The blood collection tube is placed directly into a sample rack, which is part of the analyzer. A volume of sample is automatically drawn from the tube through its rubber seal.

5. Calibration:

The calibrators were previously cleared in k070452.

6. Quality Control:

The recommended control materials were cleared in k052838 and k070452.

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The “Performance Characteristics” Section above:

The software documentation was reviewed and it supports that the device was developed under good software cycle processes.

Q. Proposed Labeling:

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

R. Conclusion:

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