

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

A. 510(k) Number:

k112015

B. Purpose for Submission:

New device

C. Measurand:

Glycosylated Hemoglobin (HbA1c)

D. Type of Test:

Quantitative, HPLC with boronate affinity method

E. Applicant:

Primus Corporation DBA Trinity Biotech

F. Proprietary and Established Names:

Premier Hb9210

G. Regulatory Information:

1. Regulation section:

21CFR 864.7470

2. Classification:

Class II

3. Product code:

LCP

4. Panel:

H. Intended Use:

1. Intended use(s):

See Indications for use below

2. Indication(s) for use:

The Premier Hb9210 System is intended for the quantitative measurement of hemoglobin A1c (HbA1c) in human capillary and venous whole blood. HbA1c is used for the monitoring of long-term glycemic control in individuals with diabetes mellitus. For in vitro diagnostic use only

3. Special conditions for use statement(s):

For prescription use only.

In the package insert the manufacturer has stated the following limitations:

Abnormal RBC survival- Correct HbA1c analysis depends on stable hemoglobin with typical lifespan. As with all HbA1c analytical methodologies, patients with shortened RBC life, such as occurs in hemolytic anemia, will exhibit decreased HbA1c values, with the decreased life span dependent upon the severity of the anemia and/or the presence of unstable hemoglobins like Hb SS, Hb CC, and Hb SC. Patients with extended red cell life such as polycythemia or after splenectomy, may exhibit increased HbA1c results. Iron deficiency anemia may yield falsely high results. GPP and/or fructosamine assays are recommended for these conditions.

4. Special instrument requirements:

Premier Hb9210 Instrument

I. Device Description:

Premier Hb9210 system is a compact (21"W x26"Lx29"H) integrated HPLC system and workstation with Trinity Biotech AFFINITY software using boronate affinity chemistry with high performance liquid chromatography. The instrument contains integrated HPLC, sample preparation/transport, computer and printer. The four main components to fractionate and quantitate HbA1c are: liquid chromatography, integrated sample handling system, integrated PC, and windows XP software.

Components required for operations include:

1. Reagents: buffer A reagent, buffer B reagent, wash reagent, and diluent reagent (to make hemolysate from whole blood sample). Buffer A reagent, buffer B reagent, and wash reagent come in a 940 mL bottle. The diluent reagent comes in a 3.8L bottle.
2. Two levels of calibrators and two levels of controls made from human whole blood.
3. The Premier Hb9210 Boronate Affinity Column.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Primus Boronate Affinity HPLC method, Ultra2 analyzer

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

k891235

3. Comparison with predicate:

Similarities and differences between the predicate and candidate devices		
Item	Predicate Device (k891235)	Candidate Device
Intended use/Indications for use	For quantitative measurement of hemoglobin A1c in whole blood. It is intended for health care providers in the monitoring of long-term glycemic control in individuals with diabetes mellitus.	Same
Instrument	Boronate Affinity HPLC method, Ultra2 analyzer	Premier Hb9210 analyzer
Method	Conventional HPLC column chromatography with a boronate affinity matrix suitable for HPLC	Same
Reporting units	% HbA1c	% HbA1c and mmol/mol (IFCC)
Sample type	Venous EDTA or finger-stick	Venous EDTA, heparin, and sodium fluoride or finger-stick
Calibration	With each run	Same
Traceability	Traceable to NGSP, Diabetes Control and Complications Trial (DCCT) method	Same

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

1. CLSI Guideline, EP5-A2 *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline Second edition*
2. CLSI Guideline, EP6-A *Evaluation of the Linearity of Quantitative Analytical Methods; Approved Guideline*
3. CLSI Guideline, EP7-A2 *Interference Testing in Clinical Chemistry; Approved Guideline- Second edition*
4. CLSI Guideline, EP9-A2 *Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline Second edition*
5. EN ISO 17511: 2003, *Metrological Traceability of Values Assigned to Calibrator and Control Materials.*

L. Test Principle:

The Premier Hb9210 employs the principles of boronate affinity and high-performance liquid chromatography (HPLC). The pumps transfer reagents through the analytical column. The analytical column contains aminophenylboronic acid bonded to a porous polymer support (gel). When the hemolysate passes through the column, the glycated component is retained by the complexing of its diol groups with the boronate. After the unretained non-glycated component elutes from the column, the glycated component is eluted from the column with a reagent that displaces it from the boronate. A spectrophotometric detector will measure the absorbance of the eluates at 413 ± 2 nm. The instrument can report out either the %HbA1c (NGSP) or the IFCC mmol/mol units.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision studies were performed at three different sites using three whole blood EDTA samples (low, normal, and abnormal) according to the CLSI EP5-A2 guideline. All samples were assayed twice a day in duplicates for over 20 days (N=80). Precision results are shown below:

Site 1:

	Level 1	Level 2	Level 3
Mean %HbA1c	5.70	7.06	10.96
Repeatability SD, (S_r)	0.07	0.06	0.09
Repeatability %CV = $(S_r/\text{mean}) \times 100$	1.24	0.79	0.78
Within-device precision SD, (S_T)	0.10	0.11	0.18
Within-device precision %CV = $(S_T/\text{mean}) \times 100$	1.84	1.58	1.62

Site 2:

	Level 1	Level 2	Level 3
Mean %HbA1c	5.71	7.08	10.88
Repeatability SD, (S_r)	0.05	0.06	0.09
Repeatability %CV = $(S_r/\text{mean}) \times 100$	0.85	0.79	0.85
Within-device precision SD, (S_T)	0.08	0.09	0.18
Within-device precision %CV = $(S_T/\text{mean}) \times 100$	1.47	1.20	1.62

Site 3:

	Level 1	Level 2	Level 3
Mean %HbA1c	5.85	7.06	11.03
Repeatability SD, (S_r)	0.10	0.04	0.10
Repeatability %CV = $(S_r/\text{mean}) \times 100$	1.68	0.57	0.92
Within-device precision SD, (S_T)	0.09	0.07	0.14
Within-device precision %CV = $(S_T/\text{mean}) \times 100$	1.55	1.04	1.27

Combined all sites:

	Level 1	Level 2	Level 3
Mean %HbA1c	5.76	7.07	10.96
Repeatability SD, (S_r)	0.07	0.05	0.09
Repeatability %CV = $(S_r/\text{mean}) \times 100$	1.26	0.72	0.85
Total precision SD, (S_T)	0.09	0.09	0.16
Total precision %CV = $(S_T/\text{mean}) \times 100$	1.62	1.28	1.50

b. *Linearity/assay reportable range:*

The sponsor conducted a linearity study according to the CLSI EP6-A guideline using EDTA whole blood samples. The linearity study used a high and a low patient pool to create additional intermediate levels of samples. A total of 7 samples with HbA1c concentrations ranging from 3.8% to 23.1% were tested in triplicate on the Premier Hb9210. The linear regression generated by plotting the expected values against the observed values was:

$$Y = 0.9823X - 0.2297, r^2 = 0.9958$$

The results of the study support the sponsor's claim that the assay is linear from 3.8 to 18.5% A1c. This assay has a claimed measuring range of 3.8 to 18.5% A1c.

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

Traceability:

The Premier Hb9210 method is traceable to the Diabetes Control and Complications Trial (DCCT) Method for Measurement of HbA1c. HbA1c values are reported according to the National Glycohemoglobin Standardization Program (NGSP) recommendations at the DCCT level.

The sponsor has documented traceability to the NGSP's recommended accuracy base for HbA1c by performing a direct comparison with a Secondary Reference Laboratory (SRL) using 40 fresh human specimens. An NGSP certification was provided with an expiration date of May 1, 2012. NGSP certification expires one year from the certification date and needs to be renewed annually.

Calibrators and control materials are commercially available and have been previously cleared in k936204 and k940143.

Samples stability:

A sample stability study using whole blood (and associated hemolysate) specimens at 3 different A1c concentrations were analyzed by the Premier Hb9210 method on day 0, then divided into aliquots stored at five different temperatures (37 ° C, 20-25 ° C, 2-6 ° C, -20 ° C, and -70 ° C). Hemolysates are made from the fresh whole blood sample with a 1:100 dilution with sample diluent. Sample stability study protocol and acceptance criteria has been provided and found to be adequate. Whole blood and hemolysate storage stability claims are listed in the table below:

Sample type	-70 ° C	-20 ° C	2-6 ° C	20-25 ° C	37 ° C
Whole blood	1 year	10 days	10 days	6 days	1 day
Hemolysate	1 year	10 days	7 days	1 day	1 day

The sponsor stated the following in their limitations in their labeling:

“Do not freeze/thaw samples more than once. Because the potential exists for thawing in a “frost-free” freezer, avoid storage of specimens in a frost-free freezer.”

d. Detection limit:

The detection limit is the lowest concentration that the assay can detect by linearity. See linearity study in M.1.b. above.

e. Analytical specificity:

i.) Studies were performed to assess common or known substances that could interfere with the Premier Hb9210. The interfering substances were evaluated in whole blood EDTA samples that contained two different concentrations of A1c (~6% and ~12%). Samples containing various concentrations of potential interferents were tested and the results compared to those obtained from control samples containing no potential interfering substances. The sponsor’s definition of non-significant interference is $\leq 10\%$ difference between the tested and the control samples.

The percent difference between the control sample and the sample spiked with the potential interfering substances was no greater than $\pm 10\%$ for concentrations at or below those listed in the following table.

Potential interfering substance	Concentration at which no significant interference ($\leq 10\%$) was observed
Acetylsalicylic acid(Aspirin)	≤ 90 mg/dL
Acetaldehyde	≤ 25 mg/dL
Bilirubin	≤ 20 mg/dL
Carbamylated Hgb	≤ 65 mg/dL
Triglyceride	≤ 3317 mg/dL
Sodium heparin	≤ 450 USP
EDTA	≤ 1440 mg/dL
Sodium fluoride	≤ 1157 mg/dL

ii.) To study the interference from labile A1c, three EDTA whole blood patients’ samples with A1c concentrations approximately at 5%, 7% and 11% were split into aliquots. These aliquots were supplemented by the addition of an aqueous glucose stock solution; up to 1500 mg/dL of glucose solution was tested. The samples were incubated for three hours at 37°C to facilitate formation of labile A1c. The samples were then run on the Premier Hb9210 in duplicate. The sponsor’s definition of non-significant interference is $\leq 5\%$ difference between the spiked and non-spiked

samples.

The sponsor concluded that labile A1c concentrations up to 1500 mg/dL do not interfere with the assay.

iii.) To study the interference at multiple variant concentrations for variants S, C, D, E, and F, patient samples with known concentrations of variant were mixed together with samples that did not have any variants in different proportions. All samples were tested using the Premier Hb9210 and a commercially available method that was free of interference from the variants. The sponsor's definition of non-significant interference is $\leq 7\%$ difference between the candidate method and the comparative method.

Based on the data, the sponsor claimed that no significant interference was observed for HbAS up to 35.8%, HbAC up to 34.8%, HbAD up to 28.9%, HbAE up to 16.9% and HbF up to 20.9%.

In the package insert the manufacturer has stated the following limitations:

Abnormal RBC survival- Correct HbA1c analysis depends on stable hemoglobin with typical lifespan. As with all HbA1c analytical methodologies, patients with shortened RBC life, such as occurs in hemolytic anemia, will exhibit decreased HbA1c values, with the decreased life span dependent upon the severity of the anemia and/or the presence of unstable hemoglobins like Hb SS, Hb CC, and Hb SC. Patients with extended red cell life such as polycythemia or after splenectomy, may exhibit increased HbA1c results. Iron deficiency anemia may yield falsely high results. GPP and/or fructosamine assays are recommended for these conditions.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison studies were performed according to the CLSI EP9-A2 guideline. 48 whole blood EDTA samples with % HbA1c ranging from 4.4% to 16.2 % were analyzed in singlet on both the Premier Hb9210 analyzer (candidate device) and the Ultra 2 analyzer (predicate device).

The linear regression correlation was calculated as follows:

$Y = 1.0069X - 0.1214, r^2 = 0.9962$ (X=predicate method, Y=candidate method)

95%CI of slope is 0.990 to 1.026

95%CI of intercept is -0.0316 to 0.2675

b. Matrix comparison:

Matrix comparison study was performed to evaluate different anticoagulants. 27 whole blood (venous) samples were collected in EDTA, Sodium heparin, and Sodium fluoride blood collection tubes. In addition, 20 matched capillary (fingersticks) samples were collected and compared to the venous EDTA whole blood samples. All samples were run in singlet on the Premier Hb 9210 system. The linear regressions results were summarized as follow:

For venous Sodium heparin samples vs. the EDTA whole blood samples:

$Y = 0.999X - 0.0057, r^2 = 0.9984, N=27$, sample range was 4.6-17.0%

For venous Sodium fluoride samples vs. the EDTA whole blood samples:

$Y = 1.0106X - 0.0885, r^2 = 0.9989, N=27$, sample range was 4.3-17.5%

For finger-sticks samples vs. the EDTA whole blood samples:

$Y = 0.9946X - 0.0358, r^2 = 0.9994, N=20$, sample range was 4.4- 12.7%

The sponsor claimed that whole blood samples from capillary (finger-stick) or EDTA venous samples are the recommended samples. In addition, anticoagulant tubes with sodium heparin or sodium fluoride are acceptable for use with the device.

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):

See 2.a. above

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The expected %HbA1c value for patients with diabetes will depend on physician discretion. The American Diabetes Association's (ADA) most recent Clinical Practice Recommendation of diabetes specifies a treatment goal of 7% or less and suggests additional action when the HbA1c level is above 8%*.

*American Diabetes Association, Standards of Medical Diabetes Care in Diabetes-2008, *Diabetes Care* (2008); 31 Suppl 1, S12.

N. Instrument Name:

Premier Hb9210 Instrument

O. System Descriptions:

1. Modes of Operation:

Batch mode - The automatic sample handling module is capable of running 210 samples automatically at a time, with one result produced in one minute.

2. Software:

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

Yes ____X____ or No _____

The sponsor referenced FDA's Guidance Document for software:

<http://www.fda.gov/cdrh/comp/guidance/1553.html>

Level of Concern: Moderate

3. Specimen Identification:

Samples are identified by automatic barcode read by the analyzer. The integrated auto sampler/sample transport is able to hold 210 samples (plus additional STAT samples are allowed throughout the run) to start a single batch run. The sample rack transport module is designed to hold a maximum of 21 racks (each linear rack holds 10 sample tubes).

4. Specimen Sampling and Handling:

There are 3 sample rack types: whole blood, hemolysate and anemic. Each rack has a unique identification letter and number with corresponding barcode. W for whole blood, H is for hemolysate, and A is for anemic. All racks hold standard 13x75 mm sample tubes with septum. Whole blood samples do not need to be re-mixed (either settled or mixed are both acceptable). Capillary fingersticks, EDTA whole blood, Sodium heparin whole blood, and Sodium fluoride whole blood are all acceptable sample types.

5. Calibration:

Calibration with two levels of whole blood calibrators must be carried out with each batch run and be accepted before calculations of controls and patients results. Calibrator materials are commercially available and have been cleared in k936204

6. Quality Control:

Two levels of quality control materials (whole blood) must be run with each batch. The QC materials are held in a 5-position QC wheel on the instrument. Control materials are commercially available and have been cleared in k940143.

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

1. A study to assess any potential carry-over of the Premier 9210 system was performed. Ten different samples with different concentrations of HbA1c were tested 4 separate times per day over a 5 day period. Multiple linear regression analyses and precision data were calculated for all the test results. The protocol and acceptance criteria were found to be adequate.
2. Packed red blood cells and anemic samples were evaluated to demonstrate that there is no effect from sample hemoglobin concentration on the results generated by the candidate assay. 3 levels of samples with different A1c concentrations (5%, 7%, and 9%) were tested. All the results generated were within 5% bias when compared to the same sample that had a normal hemoglobin concentration.

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.