EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR COBAS INTEGRA 800 TINA-QUANT HbA1C Dx. GEN.2 ASSAY
DECISION SUMMARY

A. 510(k) Number: k121291

B. Purpose for Submission: Clearance of new assay

C. Measurand: Whole Blood Glycated Hemoglobin (HbA1c)

D. Type of Test: Quantitative turbidimetric inhibition immunoassay

E. Applicant: Roche Diagnostics Corporation.

F. Proprietary and Established Names: COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay

G. Regulatory Information:

FDA identifies this type of device as:

A Hemoglobin A1c Test system is a device used to measure the percent concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for development of diabetes mellitus.

1. New Regulation Number:

   21 CFR 862.1373

2. Classification:

   Class II

3. Product code:

   PDJ

4. Panel:

   Chemistry (75)

H. Intended Use:

1. Intended use(s):

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 COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay is an in vitro diagnostics reagent system intended for quantitative determination of mmol/mol hemoglobin A1c (IFCC) and % hemoglobin A1c (DCCT/NGSP) in hemolysate or whole blood on the Roche COBAS INTEGRA 800 clinical chemistry analyzer.

2. Indication(s) for use:

Same as intended use.

3. Special conditions for use statement(s):

This device has significant negative interference with fetal hemoglobin (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF including those with known Hereditary Persistence of Fetal Hemoglobin.

Glycated HbF is not detected by the assay as it does not contain the β-chain that characterizes HbA1c. However, HbF is measured in the total Hb assay and as a consequence, specimens containing high amounts of HbF (>7%) may result in lower than expected mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP).

Hemoglobin A1c should not be used to diagnose diabetes mellitus in patients with a hemoglobinopathy but normal red cell turnover (e.g. sickle cell trait)

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

Hemoglobin A1c should not be used to diagnose diabetes mellitus in patients with hereditary spherocytosis, malignancies or severe chronic hepatic and renal disease.

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.

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

For prescription use only.

4. Special instrument requirements:

   All performance data was conducted using the Cobas Integra 800 Analyzer

I. Device Description:

The COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay consists of two working reagents (R1 and R2) and an Hemolyzing reagent. The R1 reagent consists of antibody reagent, MES buffer: 0.025 mol/L; TRIS buffer: 0.015mol/L, ph6.2; HbA1c antibody (bovine serum): ≥0.5 mg/ml; stabilizers; preservatives (liquid). R2 reagent (Polyhapten reagent) consists of MES buffer: 0.025 mol/L; TRIS buffer: 0.015 mol/L, ph 6.2, HbA1c polyhapten: ≥ 8µg/mL; stabilizers; preservatives (liquid)

The Roche Tina-quant Hemoglobin A1c Gen. 2 consists of two application types: The Whole Blood application uses an automated on-board sample pretreatment with hemolyzing reagent. The Hemolysate application consists of a manual pretreatment step which is performed using the hemolyzing reagent before the sample is placed on the analyzer.

Calibrators (Roche Cfas HbA1c) and controls (Roche PreciControl HbA1c norm and path) are recommended for use with this device. The calibrators and controls were previously cleared under 510(k) numbers k052101 and k103099 respectively.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   No predicate device exists for this intended use

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

   Not applicable

3. Comparison with predicate:

   Not applicable

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

CLSI EP05-A2 Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline – 2nd edition

L. Test Principle:

Anticoagulated whole blood is hemolyzed prior to determination of HbA1c by a turbidimetric inhibition immunoassay (TINIA). Liberated hemoglobin (Hb) in the

hemolyzed sample is converted to a derivative having a characteristic absorption spectrum and measured biochromatically. The instrument calculates the %HbA1c from the HbA1c/Hb ratio according to a user selected protocol.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   A precision study was performed by testing 4 levels of HbA1c in anticoagulated venous whole blood patient samples at the following targeted HbA1c values: 5%, 6.5%, 8% and 10% (Samples 1-4). Precision was evaluated using 3 reagent lots and 3 COBAS INTEGRA 800 analyzers. Additionally, 2 controls (PreciControl HbA1c norm and path - Samples 5, 6), were evaluated in this precision study. 2 aliquots per sample were run twice a day (singlicate) for 21 days. For each sample, there were 756 measurements (252 measurements per analyzer). Results are shown below:

Hemolysate Application: Cobas Integra 800 analyzer #1

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.16%	0.04	0.8	0.04	0.7	0.04	0.8	0.00	0.0	0.06	1.3
Sample2 6.49%	0.04	0.6	0.04	0.7	0.03	0.4	0.00	0.1	0.06	1.0
Sample3 7.73%	0.05	0.6	0.05	0.6	0.03	0.4	0.00	0.1	0.07	0.9
Sample4 11.76%	0.05	0.4	0.04	0.4	0.03	0.3	0.04	0.4	0.08	0.8
Sample5 5.40%	0.04	0.7	0.04	0.7	0.03	0.5	0.01	0.1	0.06	1.2
Sample6 9.51%	0.04	0.4	0.05	0.5	0.03	0.3	0.02	0.2	0.07	0.8

Hemolysate Application: Cobas Integra 800 analyzer #2

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.16%	0.03	0.6	0.02	0.5	0.03	0.6	0.00	0.0	0.05	0.9
Sample2 6.47%	0.04	0.6	0.03	0.4	0.04	0.6	0.00	0.0	0.06	1.0
Sample3 7.27%	0.05	0.6	0.03	0.4	0.04	0.6	0.01	0.2	0.07	0.9
Sample4 11.84%	0.05	0.5	0.03	0.3	0.09	0.8	0.05	0.4	0.12	1.0
Sample5 5.384%	0.03	0.6	0.04	0.8	0.03	0.7	0.00	0.0	0.06	1.2
Sample6 9.56%	0.04	0.5	0.03	0.4	0.04	0.5	0.04	0.5	0.09	0.9

Hemolysate Application: Cobas Integra 800 analyzer #3

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.22%	0.04	0.7	0.03	0.5	0.04	0.7	0.00	0.0	0.06	1.1
Sample2 6.56%	0.06	0.9	0.02	0.2	0.05	0.8	0.00	0.0	0.08	1.2
Sample3 7.81%	0.06	0.7	0.06	0.7	0.06	0.8	0.01	0.1	0.10	1.3
Sample4 11.91%	0.08	0.6	0.03	0.2	0.09	0.8	0.08	0.6	0.15	1.2
Sample5 5.46%	0.05	0.9	0.04	0.7	0.04	0.8	0.00	0.0	0.07	1.3
Sample6 9.63%	0.06	0.6	0.03	0.3	0.08	0.8	0.03	0.3	0.11	1.1

Hemolysate Application: Cobas Integra 800 analyzers (combined)

Mean	Repeatability		Between Run		Between Day		Between Lot		Between - Instrument		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.18%	0.04	0.7	0.03	0.5	0.04	0.7	0.00	0.0	0.04	0.7	0.07	1.3
Sample2 6.50%	0.06	0.9	0.02	0.2	0.04	0.6	0.00	0.0	0.05	0.7	0.08	1.3
Sample3 7.75%	0.06	0.7	0.06	0.7	0.05	0.6	0.01	0.1	0.05	0.6	0.09	1.2
Sample4 11.85%	0.08	0.6	0.03	0.2	0.08	0.7	0.06	0.5	0.06	0.6	0.12	1.2
Sample5 5.41%	0.05	0.9	0.04	0.7	0.04	0.7	0.00	0.0	0.04	0.7	0.07	1.4
Sample6 9.55%	0.06	0.6	0.03	0.3	0.05	0.6	0.03	0.4	0.06	0.7	0.11	1.1

The between-analyzer and between–lot precision was equal to or less than 1.4% for concentrations in the range of 5.2% to 11.9% HbA1c in the Hemolysate application.

Whole Blood Application: Cobas Integra 800 Analyzer #1

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.27%	0.04	0.7	0.01	0.1	0.03	0.6	0.00	0.0	0.05	1.0
Sample2 6.53%	0.04	0.6	0.02	0.3	0.04	0.6	0.00	0.0	0.06	0.9
Sample3 8.14%	0.09	1.0	0.00	0.0	0.05	0.6	0.00	0.0	0.1	1.2
Sample4 11.97%	0.07	0.6	0.05	0.4	0.07	0.6	0.02	0.2	0.11	0.9
Sample5 5.644%	0.03	0.6	0.02	0.4	0.04	0.7	0.00	0.1	0.06	1.0
Sample6 10.34%	0.04	0.4	0.02	0.2	0.06	0.5	0.00	0.0	0.07	0.7

Whole Blood Application: Cobas Integra 800 Analyzer#2

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.19%	0.05	0.9	0.03	0.5	0.04	0.7	0.04	0.7	0.08	1.4
Sample2 6.56%	0.05	0.8	0.03	0.4	0.03	0.4	0.04	0.7	0.08	1.2
Sample3 8.03%	0.06	0.7	0.03	0.3	0.04	0.5	0.05	0.6	0.09	1.1
Sample4 12.08%	0.08	0.7	0.05	0.4	0.03	0.2	0.05	0.4	0.11	0.9
Sample5 5.5544%	0.04	0.7	0.04	0.8	0.03	0.4	0.05	0.9	0.08	1.5
Sample6 10.36%	0.05	0.5	0.04	0.4	0.05	0.5	0.03	0.3	0.09	0.9

Whole Blood Application: Cobas Integra 800 Analyzer #3

Mean	Repeatability		Between Run		Between Day		Between Lot		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.30%	0.04	0.8	0.03	0.6	0.02	0.4	0.01	0.1	0.06	1.1
Sample2 6.675%	0.05	0.8	0.04	0.7	0.03	0.4	0.02	0.3	0.07	1.1
Sample3 8.16%	0.04	0.5	0.05	0.6	0.03	0.4	0.05	0.6	0.08	1.1
Sample4 12.22%	0.08	0.7	0.07	0.5	0.04	0.3	0.14	1.2	0.18	1.5
Sample5 5.466%	0.04	0.7	0.04	0.6	0.03	0.5	0.00	0.1	0.06	1.1
Sample6 10.48%	0.05	0.5	0.05	0.5	0.04	0.4	0.10	1.0	0.13	1.3

Whole Blood Application: Cobas Integra Analyzer (combined)

Mean	Repeatability		Between Run		Between Day		Between Lot		Between Instrument		Total	
HbA1c	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Sample1 5.25%	0.04	0.8	0.02	0.4	0.03	0.6	0.02	0.4	0.05	1.0	0.08	1.5
Sample2 6.63%	0.05	0.7	0.03	0.5	0.03	0.5	0.03	0.4	0.06	0.9	0.09	1.4
Sample3 8.11%	0.06	0.8	0.03	0.3	0.04	0.5	0.04	0.5	0.07	0.8	0.11	1.4
Sample4 12.09%	0.08	0.7	0.06	0.5	0.05	0.4	0.09	0.7	0.12	1.0	0.18	1.5
Sample5 5.624%	0.04	0.7	0.04	0.6	0.03	0.6	0.03	0.5	0.05	0.9	0.09	1.5
Sample6 10.39%	0.05	0.5	0.04	0.4	0.05	0.5	0.06	0.6	0.07	0.6	0.12	1.2

The between-analyzer and between-lot precision was equal to or less than 1.5% for concentrations in the range of 5.3% to 12.1% HbA1cIn the Whole Blood application.

b. Linearity/assay reportable range:

Linearity was previously evaluated for this assay under k072714. The reportable range for this device is 4.2-20.1% HbA1c (DCCT/NGSP); 23-196 mmol/mol HbA1c (IFCC).

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

Traceability

The assigned HbA1c and total hemoglobin values of the COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay 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 derived result of the ratio (%) from the NGSP correlation is calculated from the individual quantitative results for total hemoglobin and 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 equivalents units (mmol/mol).

Calibrator and Control materials:
Value assignment for calibrators (Roche Cfas HbA1c) and controls (Roche PreciControl HbA1c norm and path) that are recommended for use with this device were previously reviewed under submissions k052101 and k103099, respectively.

Stability
Stability protocols and acceptance criteria for calibrators (Roche Cfas HbA1c) and controls (Roche PreciControl HbA1c norm and path) that are recommended for use with this device were previously reviewed under submissions k052101 and k103099, respectively.

d. Detection limit:

The Limit of Blank and Limit of Detection were previously established in k110313

e. Analytical specificity:

i.) Endogenous Interference
Studies were performed to assess common or known substances that could interfere with the COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 test system using the hemolysate application. Pooled whole blood was spiked with interferent and hemolyzed with Tina Quant HbA1c Gen. 2 hemolyzing reagent. The same whole blood pool, without interferent, was equally hemolyzed. The interfering substances were evaluated at two HbA1c levels (~6.5 and ~8.9% HbA1c). Serial dilutions were performed and samples were analyzed to establish at which point the interferent may affect the assay. Significant interference was defined as the % recovery of $\geq \pm$ 7% of the expected 100% recovery. Results showed that no significant interference was observed with the following substances up to the stated concentrations below:

Potential Interferent	Range tested	Highest Concentration in which no significant interference was observed
Lipemia (Intralipid)	0-2000mg/dL	800 mg/dL
Conjugated Bilirubin	0-66 mg/dL	60 mg/dL
Unconjugated bilirubin	0-66 mg/dL	60 mg/dL
Rheumatoid Factor	0-1200 IU/mL	750 IU/mL
Glucose	0-2000 mg/dL	1000 mg/dL
Total Protein	0-24.5g/dL	21 g/dL

ii.) Drug Interference:

Drug interferences were evaluated using the hemolysate application. Two HbA1c concentrations of pooled whole blood (~6.5% and ~8.5%) were spiked with the . potential interferent and hemolyzed with the Tina Quant HbA1c hemolyzing reagent. Percent HbA1c values were compared to the same sample with no potential interferent present. Significant interference was considered present if the % recovery of HbA1c exceeded ± 7% of the expected 100% recovery. Results showed that no significant interference was observed with the following substances up to the stated concentrations below:

Acetylcystein	150 mg/dL
Ampicillin-Na	1000 mg/dL
Ascorbic Acid	300 mg/dL
Cefoxitin	2500 mg/dL
Heparin	5000 U/L
Levodopa	20 mg/dL
Methyldopa	20 mg/dL
Metronidazole	200 mg/dL
Doxycyclin	50 mg/dL
Acetylsalicylic Acid	1000 mg/dL
Rifampicin	60 mg/L
Cyclosporine	5 mg/L
Acetaminophen	200 mg/L
Ibuprofen	500 mg/L
Theophylline	100 mg/L
Phenylbutazone	400 mg/L

iii.) Cross Reactivity with Hemoglobin Derivatives:

Potential interference from HbA0, HbA1a+b , Acetylated Hb, Carbamylated Hb, Glycated Albumin, and Labile HbA1c were evaluated using the hemolysate application. Two HbA1c concentrations of pooled whole blood

(~6.5% and~ 8.0%) were spiked with the prepared potential interferent, (HbA0: 12mg/mL, HbA1a+b: 0.16mg/mL, acetylated Hb: 0.2 mg/mL, Carbamylated Hb: 0.2 mg/mL and glycated albumin: 1mg/mL) and hemolyzed with the Tina Quant HbA1c hemolyzing reagent. The % HbA1c values were compared to the same sample with no potential interferent present. Ten replicates of each sample pool and different mixing ratios of the pools were analyzed on the Roche COBAS Integra 800 analyzer. Significant interference was considered present if the % recovery of HbA1c exceeded ± 7% of the expected 100% recovery. The sponsor states that there were no cross reactions at physiologically occurring concentrations with HbA0, HbA1a, HbA1b, acetylated hemoglobin, carbamylated hemoglobin, glycated albumin and labile HbA1c.

iv.) Hemoglobin Variant Interference:

A hemoglobin variant interference study was performed using a total of 110 samples known to contain Hemoglobin variants S,C, E, D, A2 and F. Testing of the samples was performed in singlicate on the COBAS Integra 800 analyzer and compared to results obtained by a reference method that has been demonstrated to be free from the hemoglobin interference being tested. The following is a table of samples that were measured:

Hemoglobin Variant	Number of Samples	% Content of Variant in sample	mMol/mol HbA1c
HbS	20	31-42% S	30-100
HbC	20	36-42% C	26-104
HbE	20	27-33% E	38-81
HbD	20	37-42% D	30-96
HbF	20	2-30% F	30-90
HbA2	10	4-7% A2	30-70

Hemoglobin Variant Results Summary

	Percent Relative Bias from Reference Method at Low and High Concentrations of HbA1c Samples	
Hb Variant	~6.0 % HbA1c	~9.0 % HbA1c
C	-2.09	-3.34
S	4.64	4.02
E	0.47	-4.29
D	-2.57	-0.86
A2	1.19	-6.58
F	Bias exceeds -7% when HbF content exceeds + 7% (see below for additional discussion on HbF)	

The results show there is no significant interference for HbS (≤42%), HbC

(≤42%), HbE (≤33%), HbD (≤42%), HbA2 (≤7%).

The results show there is significant interference due to the presence of HbF in the sample. The extent of interference is directly proportional to the amount of HbF contained within the sample. The labeling states that, "Specimens containing high amounts of HbF (>7%) may result in lower than expected mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP). No significant interference is observed among specimens tested that contain <7% HbF. A negative bias with HbF is directly proportional in magnitude to the %HbF content. For example, significant interference that produces a negative bias of 7% was observed with specimens containing 7% HbF."

In addition, the device labeling contains the following prominent boxed warning:

"This device has significant negative interference with fetal hemoglobin (HbF). HbA1c results are invalid for patients with abnormal amounts of HbF including those with known Hereditary Persistence of Fetal Hemoglobin. Refer to the Limitations-interference section of this package insert for details."

The device contains the following additional warnings:

"Whenever it is suspected that the presence of an Hb variant (e.g. HbSS, HbCC or HBSC) affects the correlation between the HbA1c value and glycemic control, HbA1c must not be used for the diagnosis of diabetes mellitus."

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The method comparison study was conducted using the whole blood application and the hemolysate application. 141 variant-free samples ranging from 4.7% to 12.2% HbA1c were evaluated using the candidate COBAS INTEGRA 800 Tina-quant HbA1cDx Gen. 2 method. Samples were tested in singlicate over a 3 day period. The results were compared to testing performed at a secondary NGSP reference laboratory using a cleared HPLC-based HbA1c assay. The distribution of samples spanned the measuring interval (with a concentration of samples around the clinical decision points) as follows:

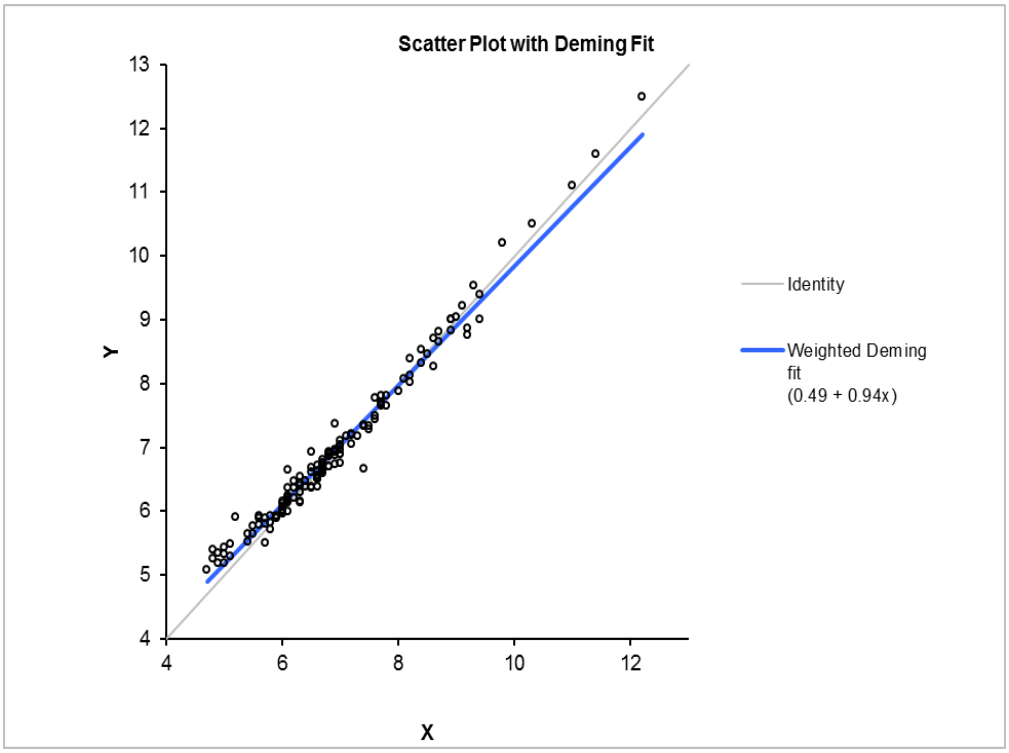
Hemoglobin A1c level	Number of samples	%samples tested
≤ 5%	5	3.5%
5 – 6%	21	14.9%
6 – 6.5%	28	19.9%
6.5 – 7%	33	23.4%
7 – 8%	27	19.1%
8 – 9%	15	10.6%
> 9%	12	8.5%
Total samples	141	100%

Bias between Candidate and NGSP methods

Hemolysate Application
Deming (weighted) and Passing- Bablok regression analyses were performed for the Tina-quant HbA1c Gen.2 (hemolysate application) versus the reference method.

Summary of results are as follows:

	y-intercept	Slope
Deming	0.493 95% CI: 0.267 to 0.719	0.936 95% CI: 0.903 to 0.969
Passing-Bablok	0.500 95% CI: 0.270 to 0.686	0.934 95% C: 0.906 to 0.967



The following biases between Tina-quant HbA1c Gen.2 (hemolysate application) versus the reference method were observed:

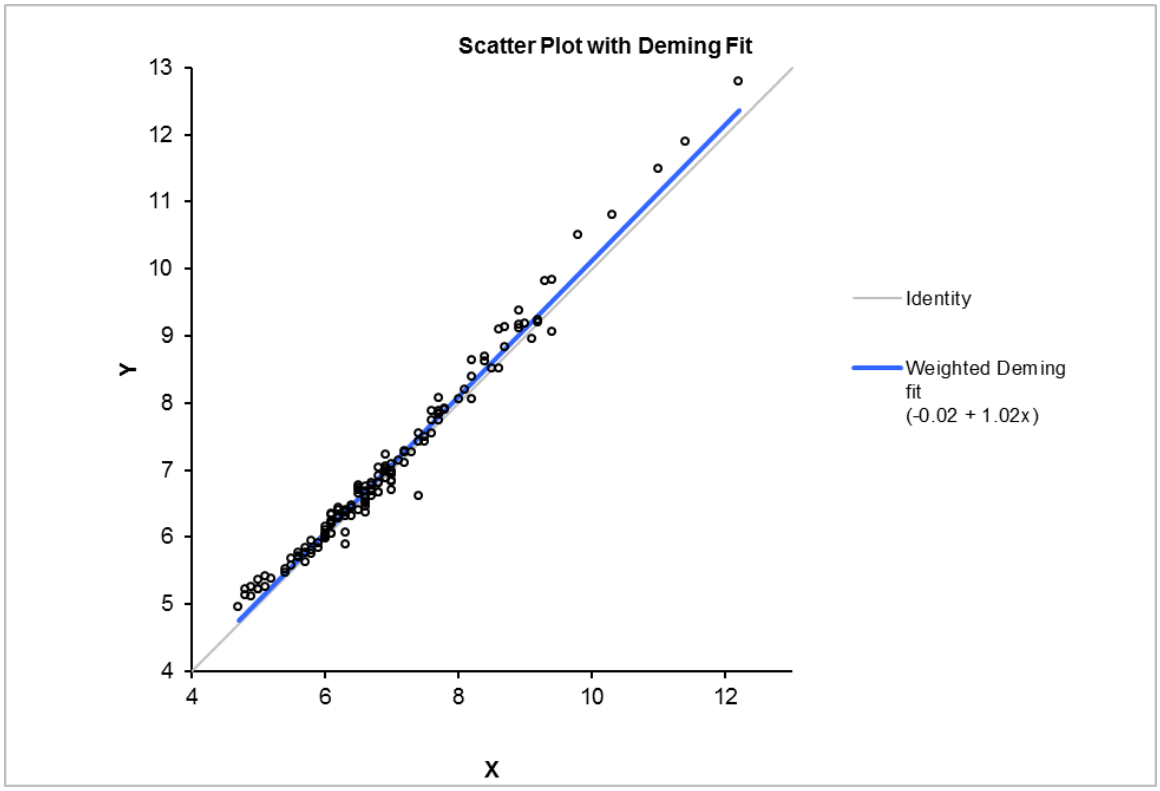
Decision Level	Bias	%Bias
5.0	0.173	3.46%
6.5	0.077	1.18%
8.0	-0.019	-0.23%

Whole Blood Application

Deming (weighted) and Passing- Bablok regression analyses were performed for the Tina-quant HbA1c Gen.2 (whole blood application) versus the reference method.

Summary of results are as follows:

	y-intercept	Slope
Deming	-0.015 95% CI: -0.241 to 0.211	1.015 95% CI: 0.982 to 1.049
Passing-Bablok	0.012 95% CI: -0.206 to 0.209	1.011 95% C: 0.981 to 1.043



The following biases between Tina-quant HbA1c Gen.2 (whole blood application) versus NGSP Tosoh HPLC (Reference Method) were observed:

Decision Level	Bias	%Bias
5.0	0.061	1.22%
6.5	0.084	1.29%
8.0	0.107	1.34%

Total Error Near the Cutoff

Using the results of bias estimation (%Bias) in the method comparison study and precision estimates in the reproducibility study, Total Error (TE) three concentrations: (5.2%, 6.5% and 8.0%) was calculated as follows: %TE =|%Bias| + 1.96 *%CV*(1+%Bias). The results are presented in the tables below.

Hemolysate application

Decision Level	%Bias	%CV	%TE
5.2	3.08%	1.3%	5.7%
6.5	1.18%	1.3%	3.8%
8.0	-0.23%	1.2%	2.6%

Whole blood application

Decision Level	%Bias	%CV	%TE
5.2	1.21%	1.5%	4.2%
6.5	1.29%	1.4%	4.1%
8.0	1.34%	1.4%	4.1%

b. *Matrix comparison*

Acceptable sample types for both the hemolysate and whole blood applications include Li-Heparin, K2-EDTA, K3-EDTA, KF/Na_2-EDTA, Na-Heparin, NaF/K-Oxalate and NaF/Na2-EDTA. Matrix equivalence was previously established in k110313 and k102914.

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):

The sponsor cited scientific literature and references to current clinical practice guidelines as clinical justification for the use of HbA1c as a

acceptable marker for diagnosing diabetes. The available literature was reviewed and found to be adequate to support this new diagnostic claim.

4. Clinical cut-off**:**

   Not applicable

5. Expected values/Reference range:

   Protocol 1 (acc. to IFCC): 20-42 mmol/mol HbA1c

   Protocol 2 (acc. to DCCT/NGSP): 4.0-6.0 % HbA1c

   HbA1c levels higher than the upper end of this reference range are an indication of hyperglycemia during the preceding 2 to 3 months or longer. According to the recommendations of the American Diabetes Association values above 48 mmol/mol HbA1c (IFCC) or 6.5 % HbA1c (DCCT/NGSP) are suitable for the diagnosis of diabetes mellitus. Patients with HbA1c values in the range of 39-46 mmol/mol HbA1c (IFCC) or 5.7-6.4 % HbA1c (DCCT/NGSP) may be at a risk of developing diabetes. [1, 2]

   HbA1c levels may reach 195 mmol/mol (IFCC) or 20 % (DCCT/NGSP) or higher in poorly controlled diabetes. Therapeutic action is suggested at levels above 64 mmol/mol HbA1c (IFCC) or 8 % HbA1c (DCCT/NGSP). Diabetes patients with HbA1c levels below 53 mmol/mol HbA1c (IFCC) or 7 % HbA1c (DCCT/NGSP) meet the goal of the American Diabetes Association.[3, 4]

   HbA1c levels below the established reference range may indicate recent episodes of hypoglycemia, the presence of Hb variants, or shortened lifetime of erythrocytes.

   Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

[1]International Expert Committee Report on the Role of the A1C Assay in the Diagnosis of Diabetes. Diabetes Care 2009; 32(7):1327-1334

[2]Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2010; 33(1):62-69.

[3]Sacks BW, Bruns DE, Goldstein DE, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Clin Chem 2002;48:436-472.

[4]American Diabetes Association. Standards of Medical Care for patients with diabetes mellitus. Diabetes Care [Suppl.] 1995;18(1):8-15.

N. Proposed Labeling:

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

O. Other Supportive Instrument Characteristics Data Not Covered In The "Performance Characteristics" Section above:

None

P. Risks to Health:

The risks to health for a device of this type are related to the consequences of decisions made based on false positive and false negative results.

The consequences of a false positive result include unnecessary work up and evaluation for confirmation of disease. The inconvenience of undergoing such unnecessary testing and the mental anxiety of possibly having a serious disease such as diabetes may not be insignificant. The consequence of a falsely elevated HbA1c in the pre-diabetes stage (HbA1c 5.7-6.4%) may lead to unwarranted clinical follow-up with blood and urine testing and unnecessary anxiety.

The consequences of false negative results are more substantial. If no other testing is performed a false negative result could lead to a missed diagnosis of diabetes and the missed opportunity to begin appropriate evaluation/work-up and treatment. Such a missed opportunity could expose the patient to the potential for progression to hyperglycemic emergencies, such as diabetic ketoacidosis.

Q. Benefit/Risk Analysis:

In 2010, the American Diabetes Association (ADA) recommended the use of HbA1C to diagnose diabetes in addition to fasting plasma glucose (FPG) and oral glucose tolerance testing (OGTT). FPG and OGTT are effective for the diagnosis of diabetes mellitus, have been used for decades, and are well tolerated. However, both are less convenient than HbA1c testing since patients must fast prior to having blood drawn for FPG levels and OGTT requires patients to fast prior to testing and to drink a glucose solution within 5 minutes. Patients must then wait 2 hours to have blood drawn. HbA1c is a more chronic vs. acute marker of dysglycemia. The benefits of using HbA1c to diagnose diabetes include:

- Greater convenience since fasting is not required
- Evidence to suggest greater pre-analytical stability
- Less day-to-day variation during periods of stress and illness compared to blood glucose measurements.

As stated above, the risk of this device is related to false positive and false negative test results. When used in the appropriate patient population, the risks of using HbA1c levels for diagnosis of diabetes can be mitigated as follows.

The labeling should specifically warn against the use of this device to diagnose diabetes as follows:

- HbA1c should not be used to diagnose diabetes during pregnancy. It 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.
- The test should not be used for patients with:
  - Hemoglobinopathies
  - Abnormal red cell turnover
  - Iron deficiency
  - Hemolytic anemia
  - Severe chronic hepatic and renal disease
  - Other conditions such as hereditary spherocytosis, or malignancies.

In addition:

- The device must have and maintain certification by an acceptable certifying glycohemoglobin standardization organization.
- Performance of the device must be adequate with respect to precision, accuracy, linearity and interference, including the following:
  - Device precision should be evaluated using whole blood samples with concentrations near 5.0%, 6.5% 8.0% and 12% HbA1c. Testing should evaluate precision over a minimum of 20 days using at least 3 lots of the device and 3 instruments as applicable.
  - Performance testing of device accuracy should include a minimum of 120 samples whose concentrations challenge clinical decision points and show little to no bias versus the reference method.
  - The device should demonstrate a total error less than or equal to 6%.
  - Performance testing should show that there is little to no interference from common hemoglobin variants to include Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2 and Hemoglobin S.
- Warnings in the labeling should address interference from Hemoglobin F, and other hemoglobin variants with low frequency in the population.

Care should be taken when interpreting any HbA1c result from patients with Hb variants. The presence in the specimen of abnormal hemoglobin variants might affect the half-life of the red cells or the in vivo glycation rates. In these cases even analytically correct results do not reflect the same level of glycemic control that would be expected in patients with normal hemoglobin. Whenever the presence of an Hb variant (e.g. HbSS, HbCC, or HbSC) is suspected, HbA1c must not be used for the diagnosis of diabetes mellitus.

The benefits of the HbA1c assay for diagnosis outweigh the risks. The ability to more rapidly diagnose diabetes is particularly beneficial and HbA1c is widely familiar to clinicians as a marker of glycemic control. The identified risks posed by this device are adequately mitigated.

R. Conclusion:

The petition for Evaluation of Automatic Class III Designation for this device is accepted. The device is classified as Class II under regulation 21 CFR 862.1373with special controls. The device is classified under the following:

Product Code: PDJ

Device Type: Hemoglobin A1C test system

Class: II (Special Controls)

Regulation: 21CFR 862.1373

(a) *Identification*. A hemoglobin A1c test system is a device used to measure the percent concentration of hemoglobin A1c in blood. Measurement of hemoglobin A1c is used as an aid in the diagnosis of diabetes mellitus and as an aid in the identification of patients at risk for developing diabetes mellitus.

(b) *Classification*. Class II (special controls). Hemoglobin A1c test systems must comply with the following special controls:

1) The device must have initial and annual standardization verification by a certifying glycohemoglobin standardization organization deemed acceptable by FDA.

2) The premarket notification submission must include performance testing to evaluate precision, accuracy, linearity and interference, including the following:

    i) Performance testing of device precision must, at a minimum, use blood samples with concentrations near 5.0%, 6.5%, 8.0% and 12% hemoglobin A1c. This testing must evaluate precision over a minimum of 20 days using at least 3 lots of the device and 3 instruments, as applicable.
    ii) Performance testing of device accuracy must include a minimum of 120 blood samples that span the measuring interval of the new device and compare results of the new device to results of the standardized test method. Results must demonstrate little or no bias versus the standardized method.
    iii) Total error of the new device must be evaluated using single measurements by the new device compared to results of the

standardized test method, and this evaluation must demonstrate a total error less than or equal to 6%.

iv) Performance testing must demonstrate that there is little to no interference from common hemoglobin variants, including Hemoglobin C, Hemoglobin D, Hemoglobin E, Hemoglobin A2 and Hemoglobin S.

3) When assay interference from Hemoglobin F or interference with other hemoglobin variants with low frequency in the population is observed, a warning statement must be placed in a black box and must appear in all labeling material for these devices describing the interference and any affected populations.