DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

July 28, 2017

ROCHE DIAGNOSTICS OPERATIONS
PATTY BATES
REGULATORY AFFAIRS PRINCIPAL
9115 HAGUE ROAD
INDIANAPOLIS, IN 46250

Re: K163633
Trade/Device Name: cobas HbA1c Test, cobas b 101 System
Regulation Number: 21 CFR 864.7470
Regulation Name: Glycosylated hemoglobin assay
Regulatory Class: II
Product Code: LCP, JJE
Dated: June 15, 2017
Received: June 16, 2017

Dear Patty Bates:

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. 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 Parts 801 and 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulations (21 CFR Parts 801 and 809), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638 2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. 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 http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Kellie B. Kelm -S

for Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology Devices
Office of In Vitro Diagnostics
and Radiological Health
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: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*

k163633

Device Name
cobas b 101 system
cobas HbA1c Test

Indications for Use *(Describe)*

cobas b 101 system: The cobas b 101 instrument is a multi-assay system designed to quantitatively analyze cobas reagent discs. The system is intended for professional, in vitro diagnostic use in a clinical laboratory setting or point-of-care (PoC) locations.

HbA1c test: The cobas HbA1c Test is an in vitro diagnostic test designed to quantitatively determine glycated hemoglobin (HbA1c) in human capillary and venous whole blood on the cobas b 101 instrument. The system is intended for professional use in a clinical laboratory setting or point-of-care (PoC) locations. Measurement of hemoglobin A1c is used to assess the level of control of a patient's diabetes and to monitor long term blood glucose control. Elevated levels of hemoglobin A1c indicate uncontrolled diabetes in a patient.

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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cobas b 101 system

510(k) Summary

k163633

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of 21 CFR 807.92.

In accordance with 21 CFR 807.87, Roche Diagnostics hereby submits official notification as required by Section 510(k) of the Federal Food, Drug and Cosmetics Act of our intention to market the device described in this Premarket Notification 510(k).

The purpose of this Traditional 510(k) Premarket Notification is to obtain FDA review and clearance for the **cobas b** 101 system and **cobas** HbA1c Test.

Submitter Name	Roche Diagnostics
Address	9115 Hague Road P.O. Box 50416 Indianapolis, IN 46250-0457
Contact	Patty Bates Phone: (317) 521-4572 FAX: (317) 521-2324 Email: patty.bates@roche.com Tracy Bush Phone: (317) 521-3723 FAX: (317) 521-2324 Email: tracy.bush@roche.com
Date Prepared	November 30 , 2016
Proprietary Name	**cobas** HbA1c Test **cobas b** 101 system
Common Name	Test system for HbA1c Discrete photometric chemistry analyzer for clinical use
Classification Name	Glycosylated hemoglobin assay – Class II Analyzer, chemistry (Photometric, discrete), for clinical use – Class I
Product Codes, Regulation Numbers	LCP, 21 CFR 864.7470 JJE, 21 CFR 862.2160
Predicate Devices	DCA Vantage

1. DEVICE DESCRIPTION

1.1. System: cobas b 101 system

The **cobas b** 101 system is a bench top analyzer which measures HbA1c. The system is fully automated, self-contained and utilizes a single use reagent disc. The system has the ability to measure capillary or venous whole blood samples. Sample is applied directly from the fingerstick or via a pipette when testing venous whole blood. The operator simply applies sample to the disc and places the disc in the instrument. There are no pre-analytics needed as the disc is self-filling by capillary forces. There is no intervention by the operator during measurement. At completion of the test, the instrument displays a quantitative result. No calculations or interpretation are required by the operator.

Calibration of the instrument is completed as part of the manufacturing process. Calibration information is contained on each disc and is read when the disc is loaded on the instrument. No calibration intervention is required by the operator.

An optional barcode scanner can be provided to read barcode information for patient identification. The barcode scanner uses LED as the light source. Results can be printed out by using an optional external printer.

A connection to a Data Management System is possible either via a USB interface to a local PC or via an Ethernet converted to a Laboratory Information Management System (LIMS). The communication protocol is defined according to the CLSI approved POCT1-A2 standard.

1.2. Reagent: cobas HbA1c Test

HbA1c (glycated hemoglobin) can be determined by using samples from capillary blood directly from the fingertip or from venous whole blood with heparin or EDTA (K_2 or K_3) anticoagulant. The blood sample is diluted and mixed with TRIS buffer to release hemoglobin from the erythrocytes. A fraction of the sample is conveyed into a reaction chamber where it is mixed with sodium lauryl sulfate (SLS). SLS is used to form the SLS-hemoglobin complex. The concentration of total hemoglobin is calculated by measuring SLS-hemoglobin complex with a wavelength of 525 nm. Hemoglobin A1c (HbA1c) in another fraction of the sample is first

denaturated by potassium ferricyanide and sucrose laurate. The denatured HbA1c bonds with HbA1c antibody on the latex particle. Latex agglutination inhibition reaction then occurs by reacting the agglutinator that has synthetic antigen which can bond with HbA1c antibody. The concentration of HbA1c is calculated by measuring the latex agglutination inhibition reaction with a wavelength of 625 nm. The % hemoglobin A1c value is measured using a ratio of concentrations of HbA1c to total hemoglobin.

2. INDICATIONS FOR USE

2.1. System: cobas b 101 system

The **cobas b** 101 instrument is a multi-assay system designed to quantitatively analyze **cobas** reagent discs. The system is intended for professional, in vitro diagnostic use in a clinical laboratory setting or point-of-care (PoC) locations.

2.2. Reagent: cobas HbA1c Test

The **cobas** HbA1c Test is an in vitro diagnostic test designed to quantitatively determine glycated hemoglobin (HbA1c) in capillary finger-stick or venous whole blood, collected in EDTA (K_2 or K_3) or lithium heparin tubes, on the **cobas b** 101 instrument. This test is intended for professional use in a clinical laboratory setting or point-of-care (PoC) locations. This test is not for screening or diagnosis of diabetes or neonatal use. Measurement of hemoglobin A1c is used to monitor long term blood glucose control in patients previously diagnosed with diabetes.

3. TECHNOLOGICAL CHARACTERISTICS

The following tables compare the **cobas b** 101 system with its predicate devices.

Candidate Device Name	Predicate Device Name	K-Number
cobas b 101 system and cobas HbA1c Test	DCA Vantage	K071466

Table 1: Instrument and Assay Comparison

Feature	Predicate Device: DCA Vantage (k071466)	Candidate Device: cobas b 101 system/cobas HbA1c Test
Instrument Intended Use	The DCA VantageTM is a semi-automated, benchtop system. It is designed to quantitatively measure the percent Hemoglobin A1c in blood and low concentrations of albumin in urine (microalbuinuria), creatinine in urine, and albumin/creatinine ratio in urine.	The **cobas b** 101 instrument is a multi-assay system designed to quantitatively analyze cobas reagent discs. The system is intended for professional, in vitro diagnostic use in a clinical laboratory setting or point-of-care (PoC) locations.
Assay Intended Use	This assay provides a convenient, quantitative method for measuring the percent concentration of hemoglobin A1c in blood.	The **cobas** HbA1c Test is an in vitro diagnostic test designed to quantitatively determine glycated hemoglobin (HbA1c) in capillary finger-stick or venous whole blood, collected in EDTA (K_2 or K_3) or lithium heparin tubes, on the **cobas b** 101 instrument. This test is intended for professional use in a clinical laboratory setting or point-of-care (PoC) locations. This test is not for screening or diagnosis of diabetes or neonatal use.
Assay Indications for Use	The measurement of hemoglobin A1c concentration is recommended for monitoring the long-term care of persons with diabetes.	Measurement of hemoglobin A1c is used to monitor long term blood glucose control in patients previously diagnosed with diabetes.
Assay Method	Latex agglutination - inhibition immunoassay	Same
Detection Method	photometry	Same
Applications/Test Time	6.5 minutes	<6 minutes
Test Platform	Single use	Same
Sample Type/Matrix	Whole blood: capillary and venous	Same
Sample Anticoagulants	EDTA, heparin, fluoride/oxalate, citrate	EDTA, lithium heparin
Sample Total Hemoglobin Range	7-24 g/dL	6-20 g/dL
Sample Application	Sample collected in capillary holder. Holder inserted into cartridge.	Sample collected directly to the disc or by transfer of sample using pipette or dropper.
Sample Volume	1 µL	2 µL
Reagent Test Principle	Monoclonal antibody agglutination reaction; intensity of light transmitted is measured by spectrophotometry.	Latex agglutination - inhibition immunoassay reaction to determine HbA1c by change of transmission of light; extent of light scatter is measured by spectrophotometry.

Feature	Predicate Device: DCA Vantage (k071466)	Candidate Device: cobas b 101 system/cobas HbA1c Test
Calibration Method	Calibration card for each reagent lot; no calibration by operator	Calibration information read from each reagent disc; no calibration by operator
Traceability/Standardization	IFCC, NGSP	Same
Reagent Stability	3 months at room temp	Store at 2-30 °C (36-86 °F) for 16 months
Operating Temperature Range	15-32 °C 61-88 °F	15-32 °C 59-90 °F
Measuring Range	2.5-14% HbA1c	4-12% HbA1c

4. NON-CLINICAL PERFORMANCE EVALUATION

The following internal performance data were provided in support of the substantial equivalence determination:

- Precision
- Linearity
- Hemoglobin Linearity
- Endogenous Interferences – Bilirubin/Lipemia/Glucose/Rheumatoid Factor
- Exogenous Interferences – Drugs
- Cross-reactivity – Carbamylated Hemoglobin, Acetylated Hemoglobin, Labile HbA1c, HbA0, HbA1a, HbA1b
- Hemoglobin Variants
- Stability

4.1. Precision

Internal precision of the **cobas** HbA1c Test was evaluated according to CLSI EP05-A3 on one **cobas** b 101 instrument with 2 **cobas** HbA1c Test disc lots and 1 **cobas** HbA1c Control lot. Two control samples and 8 K_2EDTA or K_3EDTA venous whole blood samples were measured over 21 days. The protocol consisted of measuring the sample material in duplicate in 2 runs per day

for 21 days producing n=84 results per sample. Samples and runs were randomized each day. Table 3 below summarizes the precision results.

Table 2: Internal Precision Data

			Repeatability		Between run		Between day		Total	
Sample	N	Mean (%)	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Sample 1	84	5.2	0.14	2.8	0.00	0.0	0.04	0.8	0.15	2.9
Sample 2	84	5.5	0.10	1.8	0.03	0.6	0.05	1.0	0.12	2.1
Sample 3	84	7.8	0.13	1.7	0.00	0.0	0.04	0.5	0.14	1.7
Sample 4	84	10.3	0.11	1.1	0.00	0.0	0.06	0.5	0.13	1.2
Sample 5	84	5.0	0.08	1.7	0.00	0.0	0.05	1.0	0.10	2.0
Sample 6	84	5.6	0.07	1.2	0.02	0.3	0.04	0.7	0.08	1.5
Sample 7	84	6.9	0.11	1.6	0.00	0.0	0.05	0.8	0.12	1.8
Sample 8	84	8.2	0.10	1.2	0.02	0.3	0.03	0.4	0.11	1.3
HbA1c Control Level 1	84	5.1	0.08	1.7	0.02	0.4	0.05	0.9	0.10	1.9
HbA1c Control Level 2	84	9.3	0.10	1.0	0.04	0.5	0.13	1.3	0.16	1.8

Note: SD of zero due to variance contributed by particular component was below stated significant figure.

External precision of the **cobas b** 101 HbA1c assay was performed according to CLSI EP05-A3 at 3 Point-of-Care sites. At each site, the samples were measured in duplicate 2x/day for 21 days for a total of n = 84 measurements. Six **cobas b** 101 instruments with 3 reagent disc lots were used in the study. Each PoC site assessed 2 reagent disc lots on 2 **cobas b** 101 instruments. Three lots of controls and 4 human sample pools were tested. The results are summarized in the table below.

Table 3: External Precision Data

				Repeatability		Between run		Between day		Total	
Sample	Site	N	Mean (%)	SD	% CV	SD	% CV	SD	% CV	SD	% CV
Sample 1	Site 1	168	5.3	0.06	1.2	0.04	0.9	0.04	0.7	0.09	1.6
	Site 2	168	5.2	0.07	1.4	0.00	0.0	0.05	0.9	0.09	1.7
	Site 3	168	5.1	0.08	1.5	0.03	0.6	0.02	0.3	0.09	1.7
	Combined	504	5.2	0.07	1.4	0.03	0.6	0.06	1.1	0.10	1.9
Sample 2	Site 1	168	5.4	0.07	1.3	0.03	0.5	0.06	1.2	0.10	1.8

				Repeatability		Between run		Between day		Total	
Sample	Site	N	Mean (%)	SD	% CV	SD	% CV	SD	% CV	SD	% CV
	Site 2	168	5.3	0.07	1.3	0.04	0.8	0.03	0.6	0.09	1.6
	Site 3	168	5.3	0.08	1.5	0.03	0.7	0.02	0.4	0.09	1.7
	Combined	504	5.3	0.07	1.4	0.04	0.7	0.06	1.1	0.10	1.9
Sample 3	Site 1	168	8.0	0.13	1.6	0.13	1.6	0.00	0.0	0.18	2.3
	Site 2	168	7.9	0.10	1.3	0.04	0.5	0.06	0.7	0.12	1.5
	Site 3	168	8.0	0.24	3.0	0.08	1.0	0.16	2.0	0.30	3.8
	Combined	504	8.0	0.17	2.1	0.09	1.1	0.11	1.3	0.22	2.7
Sample 4	Site 1	168	10.9	0.11	1.0	0.01	0.1	0.04	0.3	0.11	1.0
	Site 2	168	10.8	0.13	1.2	0.08	0.8	0.00	0.0	0.16	1.4
	Site 3	168	10.8	0.12	1.1	0.02	0.2	0.06	0.5	0.13	1.2
	Combined	504	10.8	0.12	1.1	0.05	0.5	0.06	0.6	0.14	1.3
Control Level 1	Site 1	168	5.2	0.10	2.0	0.09	1.8	0.17	3.2	0.22	4.2
	Site 2	168	5.1	0.09	1.8	0.05	1.0	0.17	3.4	0.20	4.0
	Site 3	168	5.2	0.13	2.5	0.00	0.0	0.07	1.3	0.14	2.8
	Combined	504	5.2	0.11	2.1	0.06	1.1	0.14	2.8	0.19	3.7
Control Level 2	Site 1	168	10.2	0.17	1.7	0.13	1.2	0.26	2.6	0.34	3.3
	Site 2	168	10.1	0.14	1.4	0.19	1.9	0.14	1.4	0.27	2.7
	Site 3	168	9.9	0.15	1.6	0.08	0.8	0.18	1.8	0.25	2.5
	Combined	504	10.1	0.16	1.5	0.14	1.4	0.23	2.3	0.31	3.1

4.2. Linearity/Assay Reportable Range

The linearity study was conducted to demonstrate that measurements across the claimed measuring range for the **cobas** HbA1c Test are linear. The study was performed according to CLSI guideline EP06-A.

The linearity study was performed on the **cobas b** 101 system by measuring 11 dilutions of a low (3.6% HbA1c) and high (12.9% HbA1c) K_2EDTA whole blood sample. The linearity data were analyzed with regards to linear, quadratic and cubic polynomials according to CLSI EP06-A. In a first step, a linearity check was performed with a first order (linear) regression and then with higher order models (quadratic and cubic). The coefficients obtained for the higher order models were then tested for significance. In the event that the coefficients obtained for the higher order

models were not significant, the data was considered linear. Otherwise, non-linearity was detected.

In the latter case, the higher order model must not deviate more than the acceptance criteria for the first order regression at the corresponding concentration values. Calculation of deviation from linearity was based on the third order model. The linearity results are in the table below:

Table 4: Linearity Results

Slope	Intercept	Pearson r	Claimed Measuring Range
0.996	-0.014	0.9961	4 – 12% HbA1c

4.3. Hemoglobin Linearity

The hemoglobin linearity study was conducted to assess the linearity of HbA1c measurements throughout the specified total hemoglobin concentration range of the **cobas** HbA1c Test.

One lot of reagent was utilized in this study. Four K_2EDTA and Li-Heparin venous whole blood samples across the HbA1c concentration range of approx. 4.5 - 14% HbA1c and a high total hemoglobin concentration of approx. 22g/dL were used. For each sample, a 10-level dilution series was prepared using NaCl as diluent.

Each sample and dilution level was tested in triplicate. The median of these 3 replicates was used for calculations. In addition to the calculated Hb-concentration, each dilution level sample was measured on the Sysmex KX-21 (FDA clearance k981761).

All results are within the acceptance criteria. The **cobas b** 101 measures HbA1c in presence of total hemoglobin concentrations between 6 – 20 g/dL.

4.4. Analytical Sensitivity

Please see linearity study.

4.5. Endogenous Interferences

4.5.1. Albumin/Bilirubin/Lipemia/Glucose/Rheumatoid Factor/ /Total Protein

The effect on quantitation of HbA1c in the presence of endogenous interfering substances was determined on the **cobas b** 101 system using the **cobas** HbA1c Test. The interference study was performed according to CLSI guideline EP07-A2. Sample pool material was K_2EDTA venous whole blood with a concentration of approximately 5.5 and > 9.0 % HbA1c.

For each interferent, a separate stock solution containing the potentially interfering material was prepared. All pools were prepared using K_2EDTA venous whole blood. Two HbA1c levels, one in the normal and another in the pathological range, were evaluated for each of the endogenous substances.

To achieve the target high concentration interferent pool (high sample pool), pooled whole blood was spiked with the interferent. Another pool (low sample pool), without interferent, was created by dilution of the pooled whole blood with the same volume of diluent as the high sample pool. This pool contains no interferent and serves as the reference pool for the testing. The high and low sample pools were mixed in different ratios to yield a dilution series with varying concentrations of the interferent.

There was no significant interference found up to the tested concentrations. The table below summarizes the results and claims for the endogenous substances.

Table 5: Potentially Interfering Endogenous Substances Results Summary

Endogenous Substance	Highest Level Tested with No Significant Interference	Labeling Claim: No significant interference up to
Albumin	77.5 g/L	60 g/L
Conjugated Bilirubin	85 mg/dL	60 mg/dL
Unconjugated Bilirubin	85 mg/dL	60 mg/dL
Lipemia / Intralipid	750 mg/dL	500 mg/dL
Lipemia / Native Triglycerides	694 mg/dL	500 mg/dL
Glucose	2800 mg/dL	2000 mg/dL
Rheumatoid Factor (RF)	1200 IU/mL	750 IU/mL
Total Protein	126 g/L	120 g/L

4.6. Exogenous Interferences – Drugs

The effect on quantitation of HbA1c in the presence of exogenous interfering substances was determined on the **cobas b** 101 system with the **cobas** HbA1c Test.
The table below lists the potential exogenous interferents and the concentrations tested:

Table 6: Potentially Interfering Drugs and Test Concentrations

Drug	Highest Level Tested with No Significant Interference (mg/L)
Acetyl Cysteine	1660
Ampicillin-Na	1000
Ascorbic acid	300
Cyclosporine	5
Cefoxitin	2500
Heparin	5000 U/L
Levodopa	20
Methyldopa +1,5	20
Metronidazole	200
Phenylbutazone	400
Doxycycline	50
Acetylsalycilic acid	1000
Rifampicin	60
Acetaminophen	200
Ibuprofen	500
Theophylline	100

The interference study was performed according to CLSI guideline EP07-A2. For each substance, a separate stock solution containing the potentially interfering drug was prepared. All pools were prepared using K_2EDTA venous whole blood. To achieve the target concentration drug pool, pooled whole blood was spiked with the drug. Another pool, without drug, was created by dilution of the pooled whole blood with the same volume of diluent as the high concentration drug pool. This pool contains no drug and serves as the reference pool for the testing. Each sample was tested in 5 replicates and the mean value used for the assessment. No interference was found at therapeutic concentrations using common drug panels.

4.7. Cross-Reactivity

4.7.1. Carbamylated Hemoglobin, Acetylated Hemoglobin and Labile HbA1c

The effect on quantitation of HbA1c in the presence of potential cross-reactants was determined on the **cobas b** 101 system with the **cobas** HbA1c Test. The study was performed according to CLSI guideline EP07-A2. Sample pool material was K_2EDTA venous whole blood with a concentration of approximately 5.5 and > 9.0 % HbA1c.

To prepare the carbamylated Hb high sample pool, sodium cyanate (final concentration is 3000 mg/dL) in isotonic saline is added to the whole blood sample. For the low sample pool, the same volume of isotonic saline (no sodium cyanate) is added to the whole blood sample.

To prepare the acetylated Hb high sample pool, acetylsalicylic acid in 75% Ethyl Alcohol (final concentration is 3000 mg/dL) is added to the whole blood sample. For the low sample pool, the same volume of 75% Ethyl Alcohol (no acetylsalicylic acid) is added to whole blood sample.

To prepare the labile HbA1c high sample pool, glucose in isotonic saline (final concentration is 3000 mg/dL) is added to the whole blood sample and incubated for one hour at 37°C. For the low sample pool, the same volume of isotonic saline (no glucose) is added to the whole blood sample.

For each interferent, a separate stock solution containing the potentially interfering cross-reactant was prepared. All pools were prepared using K_2EDTA venous whole blood. Two HbA1c levels, one in the normal and another in the pathological range, were evaluated for each of the cross-reactants.

To achieve the target high concentration cross-reactant pool (high sample pool), pooled whole blood was spiked with the cross-reactant. Another pool (low sample pool), without cross-reactant, was created by dilution of the pooled whole blood with the same volume of diluent as the high sample pool. This pool contains no cross-reactant and serves as the reference pool for the testing. The high and low sample pools were mixed in different ratios to yield a dilution series with varying concentrations of the cross-reactant. Each dilution level was tested in singlicate on 3 instruments and the median was used for calculations.

No relevant cross-reactivity was found up to the listed concentrations. The table below summarizes the results and claims for the hemoglobin derivative cross-reactants.

Table 7: Hemoglobin Derivative Cross-reactant Results and Claims

Cross-reactant	Highest Level Tested with No Significant Interference	Physiologically occurring concentration
Carbamylated Hb	3000 mg/dL	750 -1100 mg/dL
Acetylated Hb	3000 mg/dL	320 - 500 mg/dL
Labile HbA1c	3000 mg/dL	430 - 650 mg/dL

4.7.2. HbA0

A correlation analysis was performed. Correlation was determined between increasing amounts of hemoglobin (and hence HbA0) and the % relative bias of measured HbA1c using the **cobas b** 101 and the reference system **cobas** c 501. The HbA1c values were measured from approximately 60 K_2EDTA whole blood samples with **cobas b** 101 and **cobas** c 501 as the reference system. Total hemoglobin was measured with the reference system **cobas** c 501.

The relative bias between HbA1c results from **cobas b** 101 and **cobas** c 501 was calculated and plotted against the measured amounts of hemoglobin. A linear regression and the corresponding Pearson's correlation coefficient was calculated.

The data supports the claims that at physiologically occurring concentrations, no cross reactions with HbA0 were found.

4.7.3. HbA1a and HbA1b

A separate stock solution containing the potential cross-reactant HbA1a+b was prepared. This stock solution consisted of ~10.35 mg/ml HbA1a+b diluted in buffer. Ten dilutions of the stock were prepared at varying HbA1a+b concentrations. These samples were mixed with a normal and pathological K_2EDTA whole blood sample to create 11 K_2EDTA samples of varying HbA1a+b concentrations.

All K_2EDTA samples were measured in triplicate on the **cobas b** 101 instrument resulting in n=33 results per sample type (normal and pathological). The median value for each sample was used for calculation.

Because the instrument only reports the HbA1c concentrations and not the individual concentrations of A1c and total Hemoglobin, the expected HbA1c concentrations were calculated based on the c501 results for A1c and Hb total.

The results obtained met the predefined acceptance criteria. These results support the cross-reactivity claims in the labeling that at physiologically occurring concentrations, no cross reactions with HbA1a and HbA1b were found.

4.8. Hemoglobin Variants

Hemoglobin variant testing was conducted to determine if there is any significant interference with the major hemoglobin variants and the **cobas** HbA1c Test. Hemoglobin variants are structurally altered hemoglobin molecules with at least one amino acid exchange compared to the normal beta chain of hemoglobin. These changes are caused by mutations in the coding region of the globin genes which encode the protein part of hemoglobin. The most common hemoglobin variants are HbS, HbC, HbD and HbE. Moreover, in some conditions, the fetal hemoglobin HbF is elevated. Also, the erythrocytes of some patients (e.g. beta thalassemia minor) contain elevated levels of HbA2. It is crucial to ensure accurate HbA1c results from patients who are carriers of these variants.

Table 8: Hemoglobin Variant Samples

Variant Type	Number of Samples	% Variant
AS	20	29 – 41%
AC	20	28 – 36%
AD	20	36 – 42%
AE	20	20 – 27%
Elevated F	20	3 – 29%
Elevated A2	10	4.3 – 6.2%
Total	130	

Each sample was tested once in at least one run on 1 **cobas b** 101 instrument. A total of 130 samples were measured with a sample range of 4.35-11.58% HbA1c. Reference methods were

selected based on no interference for a particular variant. Results obtained were compared to those obtained with the reference methods. Mean values of triplicate measurements on the reference systems were used for comparison. Non-significant interference was defined as ≤ ± 10% difference between the candidate and reference methods.

The results obtained met the defined acceptance criteria for HbAS, HbAC, HbAD, HbAE and HbA2. HbF interference can be excluded up to an HbF concentration of 10%.

The sponsor has the following limitations in the labeling:

> Heterozygous presence of the most common hemoglobin variants (HbAS, HbAC, HbAD, HbAE, HbA2) does not interfere.
>
> Specimens containing high amounts of HbF (> 10 %) may result in lower than expected % HbA1c values (DCCT/NGSP).

4.9. Traceability

The **cobas** HbA1c Test has been standardized against the approved IFCC reference method for the measurement of hemoglobin A1c in human blood. The **cobas b** 101 instrument reports values in % hemoglobin A1c traceable to DCCT/NGSP by calculation. The **cobas b** 101 is certified with the National Glycohemoglobin Standardization Program (NGSP). The certification expires in one year. See NGSP website for current certification at http://www.ngsp.org.

4.10. Stability

The studies were performed according to CLSI guideline EP025-A. The **cobas** reagent disks can be stored at 2-30 °C for 16 months. The stability studies were found to be acceptable and support the claimed stability.

4.11. Expected Values

In 2016, the American Diabetes Association (ADA) recommended a reasonable A1c goal for many nonpregnant adults is < 7 % (53 mmol/mol). Providers might reasonably suggest more stringent A1C goals (such as 6.5 % (48 mmol/mol)) for selected individual patients if this can be achieved without significant hypoglycemia or other adverse effects of treatment. Appropriate patients might include those with short duration of diabetes, type 2 diabetes treated with lifestyle

or metformin only, long life expectancy, or no significant cardiovascular disease. Less stringent A1C goals (such as 8 % (64 mmol/mol)) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or longstanding diabetes in whom the general goal is difficult to attain despite diabetes self-management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin.

Source: American Diabetes Association. Standards of Medical Care in Diabetes-2016. Diabetes Care. 2016 Jan;39 Suppl. 1: S1-S112.

5. EXTERNAL (CLINICAL) TESTING

The following external performance data were provided in support of the substantial equivalence determination:

- Precision (see Section 4.1)
- Method Comparison to Reference Method
- Matrix Comparison – Anticoagulants

5.1. Method Comparison

5.1.1. Method Comparison versus Reference

Method Comparison of the **cobas b** 101 HbA1c assay was performed according to CLSI EP09-A3 at 3 Point of Care sites. Capillary whole blood and venous whole blood (EDTA (K_2) and Li-Heparin) from prospective blood sampling were measured on the **cobas b** 101 in singlicate. No contrived samples were tested. Venous EDTA (K_2) whole blood was measured on the Tosoh G8 HPLC Analyzer as the reference method. For capillary whole blood, the range tested was 4.3-11.6% HbA1c. For EDTA ($K_{2)}$ whole blood, the range tested was 4.4-11.4% HbA1c. For Lithium Heparin whole blood, the range tested was 4.3-11.6% HbA1c. The Passing Bablok regression results are listed in the tables below.

Table 9: Capillary

Site	N	Regression Line	Pearson's r
1	125	y = 1.00x-0.10	0.99
2	133	y = 1.00x-0.10	0.99
3	121	y = 1.00x-0.20	0.99

Table 10: EDTA K_2

Site	N	Regression Line	Pearson's r
1	125	y = 1.00x-0.20	0.99
2	133	y = 1.00x-0.20	0.99
3	121	y = 0.97x+0.04	0.99

Table 11: Lithium Heparin

Site	N	Regression Line	Pearson's r
1	125	y = 1.00x-0.20	0.99
2	130	y = 1.00x-0.20	0.99
3	117	y = 1.00x-0.20	0.99

5.2. Matrix Comparison

A matrix study was performed using EDTA (K_2) whole blood (reference) and EDTA (K_3) whole blood. Ninety one samples were collected and tested in singlicate on the **cobas b** 101. No samples were contrived. The Passing Bablok regression results are shown in the table below.

Table 12: cobas b101 EDTA (K_2) WB vs EDTA (K_3) WB

N	Regression Line	Pearson's r
91	y = 1.03x-0.00	0.99

6. SYSTEM DESCRIPTIONS

6.1. Modes of Operation:

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

Yes ____X____ or No _____

Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device using wireless transmission?

Yes _____ or No ___X__

6.2. Software

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

Yes _X__ or No

The applicant has provided documentation that indicates the device was designed and developed under good software life-cycle processes.

6.3. Specimen Identification

A barcode reader or keyboard may be used to enter patient information. Results are displayed on the screen and can be printed out by using an optional external printer.

6.4. Specimen Sampling and Handling

There are no pre-analytics needed. If a fingerstick is performed, the disc allows direct blood application straight from the fingertip to the disc. If a venous blood sample is drawn, the sample is transferred from the collection tube to the disc using a pipette or dropper. The disc is self-filling by capillary forces so that exact pipetting is not necessary. The test is completed in < 6 minutes.

6.5. Calibration

Calibration information is contained on each disc and is specific to each lot of reagent. The instrument automatically reads in the lot-specific calibration data from the barcode information printed on the **cobas** HbA1c Test disc. There is no calibration needed by the user.

6.6. Quality control

Two levels of controls are provided which are below and above the respective thresholds. Controls are used to check the system performance. The controls are liquid ready to use and include a dropper for easy application of the control liquid to the disc. The HbA1c control is a whole blood based matrix. Target ranges will be assigned per each control lot and checked with each disc lot. The mean value shall meet a defined target range to reflect a normal or pathologic value respectively based on cut-off points which are recommended e.g. by American Diabetes Association (ADA).

7. CLINICAL PERFORMANCE EVALUATION

Not applicable.

8. CONCLUSIONS

Based on the information provided in this submission, the **cobas b** 101 HbA1c system is substantially equivalent to the predicate device.