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

**A. 510(k) Number:**

k160571

**B. Purpose for Submission:**

New Device

**C. Measurand:**

Whole blood Glycosylated Hemoglobin (HbA1c)

**D. Type of Test:**

Quantitative turbidimetric inhibition immunoassay

**E. Applicant:**

Roche Diagnostics Operations

**F. Proprietary and Established Names:**

cobas c 513 Analyzer

cobas c 513 Tina-quant HbA1cDx Gen.3 Assay

**G. Regulatory Information:**

| Product Code | Classification | Regulation Section | Panel |
|---|---|---|---|
| PDJ | Class II | 21 CFR 862.1373 | Chemistry, 75 |
| JJE | Class I | 21 CFR 862.2160 | Chemistry, 75 |

**H. Intended Use:**

1. Intended use(s):

   See Indications for use below

2. Indication(s) for use:

   The cobas c 513 clinical chemistry analyzer is a fully automated, standalone clinical

chemistry analyzer intended for the in-vitro quantitative determination of analytes in body fluids.

The Tina-quant Hemoglobin A1cDx Gen.3 assay is intended for use as an aid in diagnosis of diabetes and as an aid in identifying patients who may be at risk for developing diabetes. It 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/Hitachi cobas c 513 clinical chemistry analyzer. HbA1c determinations are useful for monitoring of long-term blood glucose control in individuals with diabetes mellitus.

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.
   - For diagnostic purposes, mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP) should be used in conjunction with information from other diagnostic procedures and clinical evaluations.
   - The test is designed only for accurate and precise measurement of mmol/mol HbA1c (IFCC) and % HbA1c (DCCT/NGSP). The individual results for total Hb and HbA1c concentration should not be reported.
   - 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).
   - As a matter of principle, care must be taken when interpreting any HbA1c result from patients with Hb variants. Abnormal hemoglobins 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.26 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.
   - 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)
   - Any cause of shortened erythrocyte survival or decrease in mean erythrocyte age will reduce exposure of erythrocytes to glucose with a consequent decrease in mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP), even though the time-averaged blood glucose level may be elevated. Causes of shortened erythrocyte lifetime might be hemolytic anemia or other hemolytic diseases, homozygous sickle cell trait, pregnancy, recent significant or chronic blood loss, etc. Similarly, recent blood transfusions can alter the mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP). Caution should be used when interpreting the HbA1c results from patients with these conditions. HbA1c must not be used for the diagnosis of diabetes mellitus in the presence of such conditions.
   - Hemoglobin A1c should not be used to diagnose diabetes mellitus in patients with hereditary spherocytosis, malignancies or severe chronic hepatic and renal disease.

- 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.
- mmol/mol HbA1c values (IFCC) and % HbA1c values (DCCT/NGSP) are not suitable for 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:

   Roche cobas c 513 Analyzer

## I. Device Description:

The cobas c 513 Tina-quant HbA1cDx Gen.3 consists of two working reagents (R1 and R2) and a 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; detergents and preservatives (liquid). Anticoagulated whole blood is hemolyzed either manually or automatically prior to determination of HbAlc by a turbidimetric inhibition immunoassay.

The cobas c 513 Tina-Quant assay consists of two separate applications that are specific to the sample types, whole blood and hemolysate. The Whole Blood Application differs from the Hemolysate Application in the hemolyzing step. For the Whole Blood Application, whole blood samples are placed on the analyzer. Hemolysis occurs onboard the analyzer. For the Hemolysate Application, hemolyzed samples are placed on the analyzer. Hemolysis occurs manually before placing the samples onboard the analyzer. The two applications yield the same results.

Calibrators (Roche C.f.a.s. 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):

   COBAS INTEGRA 800 Tina-quant HbA1cDx Gen.2 assay

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

   k121291

3. Comparison with predicate:

| Similarities | | |
|---|---|---|
| **Item** | **Candidate Device (Tina-quant Hemoglobin A1cDx Gen 3 assay)** | **Predicate Device (Tina-quant HbA1cDx Gen.2 assay, k121291)** |
| Intended Use | 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. | Same |
| Test Principle | Quantitative turbidimetric inhibition immunoassay | Same |
| Calibrator | C.f.a.s. HbA1c | Same |
| Controls | PreciControl HbA1c norm and path | Same |
| Reagent Stability | Unopened:<br>2-8ºC until expiration date<br><br>On-board in use:<br>2-8ºC for 28 days | Same |
| Reporting Units | % HbA1c NGSP/DCCT and mmol/mol IFCC | Same |
| Antibody | Polyclonal anti-HbA1c from sheep blood | Same |
| Traceability | The assigned HbA1c and total hemoglobin values are certified with the National Glycohemoglobin Standardization Program (NGSP). The NGSP certification expires in one year. | Same |

| Differences | | |
|---|---|---|
| **Item** | **Candidate Device (Tina-quant Hemoglobin A1cDx Gen 3 assay)** | **Predicate Device (Tina-quant HbA1cDx Gen.2 assay, k121291** |
| Instrument Platform | cobas c 513 | COBAS Integra 800 |
| Measuring Range | Hemoglobin:<br>4-40 g/dL (2.48-24.8 mmol/L)<br><br>HbA1c:<br>0.3-1.93 g/dL (0.186 – 1.2 mmol/L)<br><br>This corresponds to a measuring range of 23‑146 mmol/mol HbA1c (IFCC) and 4.2‑15.5 % HbA1c (DCCT/NGSP) at a typical hemoglobin concentration of 8.2 mmol/L. | Hemoglobin:<br>4‑35 g/dL (2.48 – 21.7 mmol/L)<br><br>HbA1c:<br>0.3‑3.4 g/dL (0.186 – 2.11 mmol/L)<br><br>This corresponds to a measuring range of 23‑258 mmol/mol HbA1c (IFCC) and 4.3‑24.8 % HbA1c (DCCT/NGSP) at a typical hemoglobin concentration of 13.2 g/dL. |
| Sample Types | Anticoagulated whole blood or hemolysate<br>Acceptable anticoagulants for both the hemolysate and whole blood applications include:<br>Li-Heparin<br>K2-EDTA<br>K3-EDTA<br>NaF/K-Oxalate | Anticoagulated whole blood or hemolysate<br>Acceptable anticoagulants for both the hemolysate and whole blood applications include:<br>Li-Heparin<br>K2-EDTA<br>K3-EDTA<br>Na-Heparin<br>NaF/K-Oxalate<br>NaF/Na2-EDTA |

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

- CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods
- CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures
- CLSI EP17-A2: Evaluation of Detection Capability of Clinical Laboratory Measurement Procedures
- IEC 61010-2-101:2015 Safety requirements for electrical equipment for measurement, control and laboratory use - Part 2-101: Particular requirements for in vitro diagnostic (IVD) medical equipment

## L. Test Principle:

HbA1c determination is based on the turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood. Glycohemoglobin in the sample reacts with anti-HbA1c to form soluble antigen-antibody complexes. Polyhaptens react with excess anti-HbA1c to form an insoluble antibody-polyhapten complex which can be measured turbidimetrically. The instrument calculates the %HbA1c from the HbA1c/Hb ratio according to a user selected protocol.

This method uses tetradecyltrimethylammonium bromide (TTAB) as the detergent in the hemolyzing reagent to eliminate interference from leukocytes (TTAB does not lyse leukocytes). Sample pretreatment to remove labile HbA1c is not necessary.

## M. Performance Characteristics (if/when applicable):

1. Analytical performance:

*a. Precision/Reproducibility:*

Precision was performed in Accordance with CLSI Guideline EP5-A2 to evaluate repeatability (within-run precision) and intermediate precision of within-laboratory precision (total precision). Two aliquots of each sample were measured once each in two runs per day for 21 days on three cobas c 513 analyzers using 3 reagent lots per system. Eight total samples were evaluated in each run: two controls, PreciControl HbA1c norm and path, and 7 human samples with approximate HbA1c concentrations of 5%, 6.5%, 7.0%, 8.0%, 10.5%, 12% and 14%. All testing was completed within one calibration cycle for each analyzer on both anticoagulated ($K_2$-EDTA) venous whole blood and hemolysate applications. Samples were randomized in each run and mean, repeatability and intermediate precision as CV and SD values, and the upper 95% confidence interval for SD and CV values were calculated. Results are summarized below.

Hemolysate Application: cobas c 513 Analyzer #1

| **Mean** | **Repeatability** | | **Between Run** | | **Between Day** | | **Between Lot** | | **Total** | |
|---|---|---|---|---|---|---|---|---|---|---|
| %HbA1c | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.59% | 0.02 | 0.5 | 0.02 | 0.4 | 0.02 | 0.4 | 0.02 | 0.3 | 0.04 | 0.8 |
| Human2, 6.18% | 0.03 | 0.4 | 0.00 | 0.0 | 0.02 | 0.4 | 0.02 | 0.4 | 0.04 | 0.7 |
| Human3, 6.97% | 0.03 | 0.4 | 0.01 | 0.1 | 0.02 | 0.4 | 0.03 | 0.5 | 0.05 | 0.7 |
| Human4, 8.05% | 0.03 | 0.3 | 0.02 | 0.2 | 0.03 | 0.3 | 0.06 | 0.7 | 0.07 | 0.9 |
| Human5, 10.3% | 0.04 | 0.4 | 0.01 | 0.1 | 0.03 | 0.3 | 0.05 | 0.5 | 0.08 | 0.7 |

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human6, 11.8% | 0.05 | 0.5 | 0.05 | 0.4 | 0.05 | 0.4 | 0.07 | 0.6 | 0.11 | 0.9 |
| Human7, 13.9% | 0.05 | 0.5 | 0.03 | 0.2 | 0.06 | 0.4 | 0.00 | 0.0 | 0.09 | 0.7 |
| Preci Norm, 5.40% | 0.02 | 0.4 | 0.01 | 0.1 | 0.02 | 0.4 | 0.01 | 0.2 | 0.03 | 0.6 |
| Preci Path, 10.4% | 0.04 | 0.4 | 0.00 | 0.0 | 0.04 | 0.4 | 0.06 | 0.6 | 0.08 | 0.8 |

Hemolysate Application: cobas c 513 Analyzer#2

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.67% | 0.02 | 0.5 | 0.02 | 0.5 | 0.02 | 0.4 | 0.01 | 0.3 | 0.04 | 0.02 |
| Human2, 6.26% | 0.03 | 0.4 | 0.01 | 0.1 | 0.03 | 0.4 | 0.02 | 0.4 | 0.05 | 0.03 |
| Human3, 7.06% | 0.03 | 0.4 | 0.00 | 0.0 | 0.03 | 0.4 | 0.03 | 0.4 | 0.05 | 0.03 |
| Human4, 8.14% | 0.03 | 0.3 | 0.00 | 0.0 | 0.03 | 0.4 | 0.04 | 0.4 | 0.06 | 0.03 |
| Human5, 10.4% | 0.04 | 0.4 | 0.01 | 0.1 | 0.04 | 0.4 | 0.05 | 0.5 | 0.08 | 0.04 |
| Human6, 12.0% | 0.05 | 0.5 | 0.04 | 0.3 | 0.06 | 0.5 | 0.11 | 0.9 | 0.15 | 1.3 |
| Human7, 13.8% | 0.06 | 0.5 | 0.04 | 0.3 | 0.04 | 0.3 | 0.07 | 0.5 | 0.10 | 0.05 |
| Preci Norm, 5.46% | 0.02 | 0.4 | 0.01 | 0.2 | 0.02 | 0.4 | 0.02 | 0.4 | 0.04 | 0.03 |
| Preci Path, 10.5% | 0.04 | 0.4 | 0.02 | 0.2 | 0.04 | 0.4 | 0.05 | 0.5 | 0.08 | 0.04 |

Hemolysate Application: cobas c 513 Analyzer#3

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.63% | 0.02 | 0.5 | 0.03 | 0.7 | 0.01 | 0.3 | 0.03 | 0.6 | 0.05 | 1.1 |
| Human2, 6.23% | 0.03 | 0.4 | 0.02 | 0.3 | 0.02 | 0.3 | 0.03 | 0.5 | 0.05 | 0.8 |
| Human3, 7.03% | 0.03 | 0.4 | 0.03 | 0.4 | 0.02 | 0.2 | 0.04 | 0.6 | 0.06 | 0.9 |

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human4, 8.11% | 0.03 | 0.4 | 0.02 | 0.2 | 0.03 | 0.4 | 0.07 | 0.8 | 0.08 | 1.0 |
| Human5, 10.4% | 0.04 | 0.4 | 0.02 | 0.2 | 0.03 | 0.3 | 0.09 | 0.9 | 0.11 | 1.1 |
| Human6, 11.9% | 0.06 | 0.5 | 0.03 | 0.2 | 0.04 | 0.4 | 0.09 | 0.7 | 0.12 | 1.0 |
| Human7, 13.8% | 0.06 | 0.4 | 0.05 | 0.3 | 0.04 | 0.3 | 0.09 | 0.7 | 0.13 | 0.9 |
| Preci Norm, 5.45% | 0.02 | 0.4 | 0.02 | 0.4 | 0.02 | 0.3 | 0.03 | 0.5 | 0.04 | 0.8 |
| Preci Path, 10.4% | 0.04 | 0.4 | 0.03 | 0.2 | 0.03 | 0.3 | 0.09 | 0.9 | 0.11 | 1.1 |

Hemolysate Application: All 3 analyzers (combined)

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Between Instrument | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.63% | 0.02 | 0.5 | 0.03 | 0.6 | 0.02 | 0.4 | 0.02 | 0.4 | 0.04 | 0.9 | 0.06 | 1.3 |
| Human2, 6.23% | 0.03 | 0.4 | 0.01 | 0.2 | 0.02 | 0.4 | 0.03 | 0.4 | 0.04 | 0.7 | 0.06 | 1.0 |
| Human3, 7.03% | 0.03 | 0.4 | 0.02 | 0.2 | 0.02 | 0.3 | 0.04 | 0.5 | 0.05 | 0.7 | 0.07 | 1.0 |
| Human4, 8.11% | 0.03 | 0.4 | 0.01 | 0.2 | 0.03 | 0.4 | 0.06 | 0.7 | 0.04 | 0.5 | 0.08 | 1.0 |
| Human5, 10.4% | 0.04 | 0.4 | 0.02 | 0.2 | 0.04 | 0.3 | 0.07 | 0.7 | 0.03 | 0.3 | 0.10 | 0.9 |
| Human 6 11.9% | 0.06 | 0.5 | 0.04 | 0.3 | 0.05 | 0.5 | 0.09 | 0.7 | 0.09 | 0.7 | 0.15 | 1.3 |
| Human7, 13.8% | 0.06 | 0.4 | 0.04 | 0.3 | 0.05 | 0.4 | 0.07 | 0.5 | 0.02 | 0.1 | 0.11 | 0.8 |
| Preci Norm, 5.45% | 0.02 | 0.4 | 0.01 | 0.3 | 0.02 | 0.4 | 0.02 | 0.4 | 0.04 | 0.8 | 00.06 | 1.1 |
| Preci Path, 10.4% | 0.04 | 0.4 | 0.01 | 0.1 | 0.04 | 0.4 | 0.07 | 0.7 | 0.03 | 0.3 | 0.10 | 0.9 |

Whole Blood Application: cobas c 513 Analyzer #1

| **Mean** | **Repeatability** | | **Between Run** | | **Between Day** | | **Between Lot** | | **Total** | |
|---|---|---|---|---|---|---|---|---|---|---|
| %HbA1c | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.54% | 0.03 | 0.6 | 0.02 | 0.5 | 0.01 | 0.3 | 0.07 | 1.5 | 0.08 | 1.7 |
| Human2, 6.21% | 0.02 | 0.4 | 0.01 | 0.1 | 0.02 | 0.3 | 0.01 | 0.2 | 0.03 | 0.6 |
| Human3, 6.97% | 0.03 | 0.4 | 0.01 | 0.2 | 0.02 | 0.3 | 0.01 | 0.2 | 0.04 | 0.6 |
| Human4, 8.10% | 0.04 | 0.5 | 0.01 | 0.1 | 0.03 | 0.4 | 0.04 | 0.5 | 0.06 | 0.8 |
| Human5, 10.5% | 0.04 | 0.4 | 0.04 | 0.4 | 0.01 | 0.1 | 0.09 | 0.8 | 0.10 | 1.0 |
| Human6, 11.8% | 0.05 | 0.4 | 0.04 | 0.4 | 0.08 | 0.6 | 0.10 | 0.8 | 0.14 | 1.2 |
| Human7, 13.9% | 0.06 | 0.5 | 0.06 | 0.4 | 0.05 | 0.4 | 0.06 | 0.4 | 0.12 | 0.8 |
| Preci Norm, 5.4% | 0.03 | 0.5 | 0.01 | 0.2 | 0.02 | 0.4 | 0.03 | 0.5 | 0.05 | 0.8 |
| Preci Path, 10.6% | 0.04 | 0.4 | 0.04 | 0.4 | 0.03 | 0.3 | 0.08 | 0.8 | 0.10 | 1.0 |

Whole Blood Application: cobas c 513 Analyzer #2

| **Mean** | **Repeatability** | | **Between Run** | | **Between Day** | | **Between Lot** | | **Total** | |
|---|---|---|---|---|---|---|---|---|---|---|
| %HbA1c | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.64% | 0.03 | 0.6 | 0.03 | 0.7 | 0.01 | 0.2 | 0.02 | 0.4 | 0.05 | 1.0 |
| Human2, 6.29% | 0.03 | 0.4 | 0.01 | 0.2 | 0.02 | 0.3 | 0.02 | 0.3 | 0.04 | 0.6 |
| Human3, 7.05% | 0.03 | 0.5 | 0.03 | 0.5 | 0.01 | 0.1 | 0.02 | 0.2 | 0.05 | 0.7 |
| Human4, 8.17% | 0.04 | 0.5 | 0.03 | 0.4 | 0.02 | 0.3 | 0.05 | 0.6 | 0.07 | 0.9 |
| Human5, 10.5% | 0.05 | 0.5 | 0.03 | 0.3 | 0.02 | 0.2 | 0.07 | 0.6 | 0.09 | 0.8 |
| Human6, 12.1% | 0.07 | 0.6 | 0.04 | 0.3 | 0.07 | 0.6 | 0.15 | 1.3 | 0.19 | 1.5 |
| Human7, 13.9% | 0.06 | 0.4 | 0.05 | 0.3 | 0.08 | 0.6 | 0.13 | 0.9 | 0.17 | 1.2 |
| Preci Norm, 5.51% | 0.03 | 0.5 | 0.02 | 0.4 | 0.01 | 0.2 | 0.01 | 0.2 | 0.04 | 0.7 |
| Preci Path, 10.6% | 0.05 | 0.5 | 0.04 | 0.4 | 0.01 | 0.1 | 0.07 | 0.6 | 0.09 | 0.9 |

Whole Blood Application: cobas c 513 Analyzer #3

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.61% | 0.03 | 0.7 | 0.02 | 0.4 | 0.02 | 0.3 | 0.01 | 0.2 | 0.04 | 0.9 |
| Human2, 6.27% | 0.03 | 0.4 | 0.02 | 0.3 | 0.01 | 0.2 | 0.04 | 0.6 | 0.05 | 0.8 |
| Human3, 7.04% | 0.04 | 0.5 | 0.02 | 0.3 | 0.01 | 0.2 | 0.04 | 0.6 | 0.06 | 0.9 |
| Human4, 8.21% | 0.04 | 0.5 | 0.04 | 0.4 | 0.01 | 0.1 | 0.09 | 1.1 | 0.10 | 1.2 |
| Human5, 10.6% | 0.04 | 0.4 | 0.04 | 0.4 | 0.00 | 0.0 | 0.13 | 1.2 | 0.14 | 1.3 |
| Human6, 12.0% | 0.06 | 0.5 | 0.05 | 0.4 | 0.05 | 0.04 | 0.07 | 0.6 | 0.11 | 0.9 |
| Human7, 13.8% | 0.07 | 0.5 | 0.03 | 0.2 | 0.04 | 0.3 | 0.27 | 2.0 | 0.28 | 2.1 |
| Preci Norm, 5.48% | 0.03 | 0.5 | 0.01 | 0.2 | 0.01 | 0.3 | 0.01 | 0.3 | 0.04 | 0.7 |
| Preci Path, 10.7% | 0.05 | 0.5 | 0.06 | 0.6 | 0.00 | 0.0 | 0.13 | 1.2 | 0.15 | 1.4 |

Whole Blood Application: All 3 analyzers (combined)

| Mean %HbA1c | Repeatability | | Between Run | | Between Day | | Between Lot | | Between Instrument | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV | SD | %CV |
| Human1, 4.60% | 0.03 | 0.6 | 0.02 | 0.5 | 0.01 | 0.3 | 0.04 | 0.9 | 0.04 | 1.0 | 0.07 | 1.6 |
| Human2, 6.26% | 0.03 | 0.4 | 0.01 | 0.2 | 0.02 | 0.3 | 0.02 | 0.4 | 0.04 | 0.6 | 0.06 | 0.9 |
| Human3, 7.02% | 0.03 | 0.5 | 0.02 | 0.4 | 0.02 | 0.2 | 0.03 | 0.4 | 0.04 | 0.5 | 0.06 | 0.9 |
| Human4, 8.16% | 0.04 | 0.5 | 0.03 | 0.3 | 0.02 | 0.3 | 0.06 | 0.8 | 0.04 | 0.5 | 0.09 | 1.1 |
| Human5, 10.5% | 0.04 | 0.4 | 0.04 | 0.4 | 0.01 | 0.1 | 0.10 | 0.9 | 0.00 | 0.0 | 0.11 | 1.1 |
| Human 6 12.0% | 0.06 | 0.5 | 0.04 | 0.3 | 0.07 | 0.6 | 0.11 | 0.9 | 0.11 | 0.9 | 0.19 | 1.5 |
| Human7, 13.9% | 0.06 | 0.5 | 0.05 | 0.3 | 0.06 | 0.4 | 0.18 | 1.3 | 0.00 | 0.0 | 0.20 | 1.5 |
| Preci Norm, 5.47% | 0.03 | 0.5 | 0.01 | 0.3 | 0.02 | 0.3 | 0.02 | 0.3 | 0.04 | 0.8 | 0.06 | 1.1 |
| Preci Path, 10.6% | 0.05 | 0.5 | 0.05 | 0.5 | 0.1 | 0.1 | 0.09 | 0.9 | 0.00 | 0.0 | 0.12 | 1.1 |

*b. Linearity/assay reportable range:*

A linearity study was conducted according to CLSI EP06-A using two separate dilution series consisting of at least 11 levels that were prepared using human hemolysate sample pools with varying concentrations of either HbA1c or Hb to cover entire measuring range of the assay. Samples were measured in triplicate and data analysis as performed separately for each sample. The sponsor performed first order linear regression.

The linear regression statistics are as follows:

Hb: Intercept= 0.051, slope=0.983, $r^2$=0.9998

HbA1c: Intercept= 0.002, slope=0.972, $r^2$=0.9980

The claimed measuring ranges are:

Hb: 4-40 g/dL (2.48 – 24.8 mmol/L)

HbA1c: 0.3 – 1.96 g/dL (0.186 – 1.20 mmol/L)

The linearity results support the claims that the assay is linear across the reportable measuring range of 4.2-15.5 % HbA1c (DCCT/NGSP) which corresponds to a measuring range of 23-146 mmol/mol HbA1c (IFCC) at a typical hemoglobin concentration of 8.2 mmol/L.

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

Traceability

The assigned HbA1c and total hemoglobin values of the cobas c 513 Tina-quant Hemoglobin A1c Gen.3 assay is certified with the National Glycohemoglobin Standardization Program (NGSP). 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 C.f.a.s HbA1c) and controls (Roche PreciControl HbA1c norm and PreciControl HbA1c path) that are recommended for

use with this device were previously reviewed under 510(k) numbers k052101 and k103099 respectively.

Stability:

Stability data for calibrators (Roche C.f.a.s. HbA1c) and controls (Roche PreciControl HbA1c norm and PreciControl HbA1c path) were previously reviewed and found acceptable under 510(k) numbers k052101 and k103099, respectively.

*d. Detection limit:*

Limits of blank and detection were determined according to EP17-A2. For determination of Limit of Blank (LoB) one analyte free sample was measured with three lots in 10-fold determination. Six runs distributed over ≥ 3 days using one cobas c 513 analyzer were performed. In total, 60 measurements were obtained per lot. LoB was defined by the sponsor as the 95th percentile of the 60 measured values. In their design (n=60) the 95th percentile was the average of the 57th and 58th value.

For determination of the Limit of detection (LoD), five unique human samples were diluted with hemolyzing reagent to achieve low-analyte concentrations. They were measured with three reagent lots in two-fold determination. Six runs distributed over ≥ three days on one c 513 analyzer were performed. In total, 60 measurements were obtained per lot. The sponsor defined LoD as the concentration, at which there was 95% probability that a sample contains analyte.

The detection limits are summarized in the table below:

| | Limit of Blank | Limit of Detection |
|---|---|---|
| Hb | 0.50 g/dL (0.31 mmol/L) | 1.00 g/dL (0.62 mmol/L) |
| HbA1c | 0.19 g/dL (0.12 mmol/L) | 0.29 g/dL (0.18 mmol/L) |
| % HbA1c (based on a typical Hb concentration of 13.2 g/dL or 8.2 mmol/L) | 2.27 % | 2.41% |

*e. Analytical specificity:*

Endogenous Interferences:

Studies were performed to assess common or known substances that may interfere with the cobas c 513 Tina-quant HbA1cDx Gen.3 Assay. Pooled whole blood samples with two HbA1c levels (~6.2% and ~10.7% HbA1c, respectively) were spiked with the maximum level of the six interferents in separate preparations, resulting in 12 spiked samples. These samples were then hemolyzed with Tinaquant HbA1c Hemolyzing Reagent. Another pool, without interferent, was equally hemolyzed. A minimum of a 10-level dilution series was then created for each of the 12 spiked samples by using the interferent free pool as the diluting reagent. The twelve dilution series was tested in ten replicates for % HbA1c using the Hemolysate

Application only.
Samples were analyzed in replicates of ten on the cobas c 513 Tina-quant HbA1cDx Gen.3 and the results were compared to the results from the reference sample (aliquot with no interfering substance). The comparison was evaluated as a percent deviation. The sponsor defines significant interference as ≥±7% deviation of a measurement from the reference sample (aliquot with no interfering substance) in terms of % HbA1c.

Endogenous Interference

| **Interferent** | **Maximum Concentration Tested without significant Interference** |
|---|---|
| Lipemia | 600 mg/dL |
| Bilirubin | 66 mg/dL |
| Ditaurobilirubin | 66 mg/dL |
| Glucose | 2000 mg/dL |
| Rheumatoid Factor | 1200 IU/mL |
| Total Protein | 28 g/dL |

Drug interference:

Drug interferences were evaluated by using a panel of commonly used drugs was added to native patient samples and examined for potential effect on % HbA1c determination with the Hemolysate Application. Drug interference testing was performed with hemolysate samples at 2 different HbA1c levels (~6% and 8% HbA1c). Each drug was added in two defined concentrations with concentration 1 being several times (typically 5 times) the maximum daily dosage and concentration 2 being the maximum daily dosage level. Samples were measured in ten replicates using the cobas c 513 system. Samples were analyzed on the cobas c 513 Tina-quant HbA1cDx Gen.3 and the values obtained with the test samples were compared to the reference value (HbA1c sample with no drug added) and the deviation from the reference was calculated. .

Significant interference was defined by the sponsor as > ±7% deviation from the reference sample (aliquot with no interfering substance). Results demonstrated no significant interference was observed with the following substances up to the stated concentrations in the following table:

| Drug | Highest concentration in which no significant interference was observed (mg/L) |
|---|---|
| N-Acetylcysteine | 1660 |
| Ampicillin-Na | 1000 |
| Ascorbic acid | 300 |
| Cefoxitin | 2500 |
| Heparin | 5000 U/L |
| Levodopa | 20 |
| Methyldopa | 20 |
| Metronidazole | 200 |
| Doxycyclin | 50 |
| Acetylsalicylic acid | 1000 |
| Rifampicin | 60 |
| Cyclosporin | 16.6 |
| Phenylbutazone | 400 |
| Acetaminophen | 200 |
| Ibuprofen | 500 |
| Theophylline | 100 |

Cross Reactivity with Hemoglobin Derivatives:

Cross reactivity studies were performed to determine if the Tina-quant Hemoglobin A1cDx Gen.3 assay demonstrates cross-reactivity from HbA0, HbA1a+b, Acetylated Hb, Carbamylated Hb, glycated albumin and Labile HbA1c using the hemolysate application. Two HbA1c concentrations of pooled whole blood (~6.5% and ~9% HbA1c) were spiked with the potential interferent and each sample was analyzed in replicates of ten. The sponsor defined no significant interference as $\leq \pm 7\%$ deviation between the test sample (containing interferent) and the reference sample (aliquot with no interfering substance) at both % HbA1c levels tested. The highest concentration at which no significant interference was observed are listed below:

- HbA0: 120 g/dL
- HbA1a+b: 0.96 g/dL
- Acetylated Hb: 2 g/dL
- Carbamylated Hb: 2 g/dL
- Glycated Albumin: 10 g/dL
- Labile HbA1c: 1500 mg/dL

The labeling states that no cross reactions with HbA0, HbA1a, HbA1b, acetylated hemoglobin, carbamylated hemoglobin, glycated albumin and labile HbA1c were found for the anti-HbA1c antibodies used in this kit.

Hemoglobin Variants

Hemoglobin variant testing was conducted to determine if there was any significant interference with any of the major hemoglobin variants and the Tina-quant Hemoglobin A1cDx Gen.3 assay. Testing of the samples was performed in singlicate on the cobas c 513 analyzer using the hemolysate application 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** | **Variant Concentration Range (%)** | **Range of %HbA1c Concentration** |
|---|---|---|---|
| HbS | 20 | 31 – 42% S | 5.0 – 14.4 |
| HbC | 20 | 36 – 42% C | 4.7 – 13.0 |
| HbE | 20 | 27 – 33% E | 5.0 – 9.7 |
| HbD | 20 | 37 – 42% D | 5.0 – 10.9 |
| HbF | 20 | 2 – 30% F | 5.8 – 10.1 |
| HbA2 | 10 | 4 – 7% A2 | 5 – 10 |

Hemoglobin Variant Results Summary:

| **Hb Variant** | **Percent Relative Bias from Reference Method at Low and High Concentrations of HbA1c Samples** | | | |
|---|---|---|---|---|
| | ~6.0 % HbA1c | | ~9.0 % HbA1c | |
| | Relative % Difference | Range | Relative % Difference | Range (%) |
| HbC | -2.0% | -3.5 - (-1.3) | 1.2% | -1.2 - 2.5 |
| HbD | -1.3% | -4.0 - 1.79 | -1.3% | -4.79 - 2.45 |
| HbE | -1.5% | -1.9 - 0.8 | -2.3% | -2.4 - (-0.3) |
| HbS | -1.8% | -4.5 - (-0.2) | 0.7% | -0.9 - 2.5 |

| Hb Variant | Percent Relative Bias from Reference Method at Low and High Concentrations of HbA1c Samples | | | |
|---|---|---|---|---|
| | ~6.0 % HbA1c | | ~9.0 % HbA1c | |
| HbA2 | -1.6% | -4.1 – 3.4 | 2.7% | -0.3 – 3.0 |
| HbF | Specimens containing high amounts of HbF (> 7 %) may yield lower than expected HbA1c values. | | | |

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 heterozygous presence of the most common hemoglobin variants (HbAS, HbAC, HbAD, HbAE) does not interfere with this assay.

Glycated HbF is not detected as it does not contain the glycated 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)

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 method sheet for details.

The device label also contains the following additional warning:

As a matter of principle, care must be taken when interpreting any HbA1c result from patients with Hb variants. Abnormal hemoglobins 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 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:*
A method comparison study was performed to compare the sample results from the Tina-quant HbA1c Gen.3 on the cobas c 513 to testing performed at a secondary NGSP reference laboratory using a cleared HPLC-based HbA1c assay (Tosoh G8-

HPLC method). One hundred and fifty-four (154) samples were tested using the whole blood application, and one hundred and fifty-five (155) samples were tested using the hemolysate application. Samples were tested over a 3 day period with one lot of reagent on one cobas c 513 analyzer. The samples were distributed across the claimed measuring range of the assay (4.8 %-15.3% HbA1c as measured by comparator method) with concentrations around the clinical decision points as follows in the tables below:

Whole Blood (Venous) Application

| Hemoglobin A1c Level | Number of Samples Tested | % of Samples Tested |
|---|---|---|
| ≤ 5% | 6 | 3.9% |
| 5 – 6% | 26 | 16.9% |
| 6 – 6.5% | 30 | 19.5% |
| 6.5 – 7% | 36 | 23.4% |
| 7– 8% | 25 | 16.2% |
| 8– 9 % | 14 | 9.1% |
| > 9% | 17 | 11.0% |
| Total | 154 | 100.0% |

Hemolysate Application:

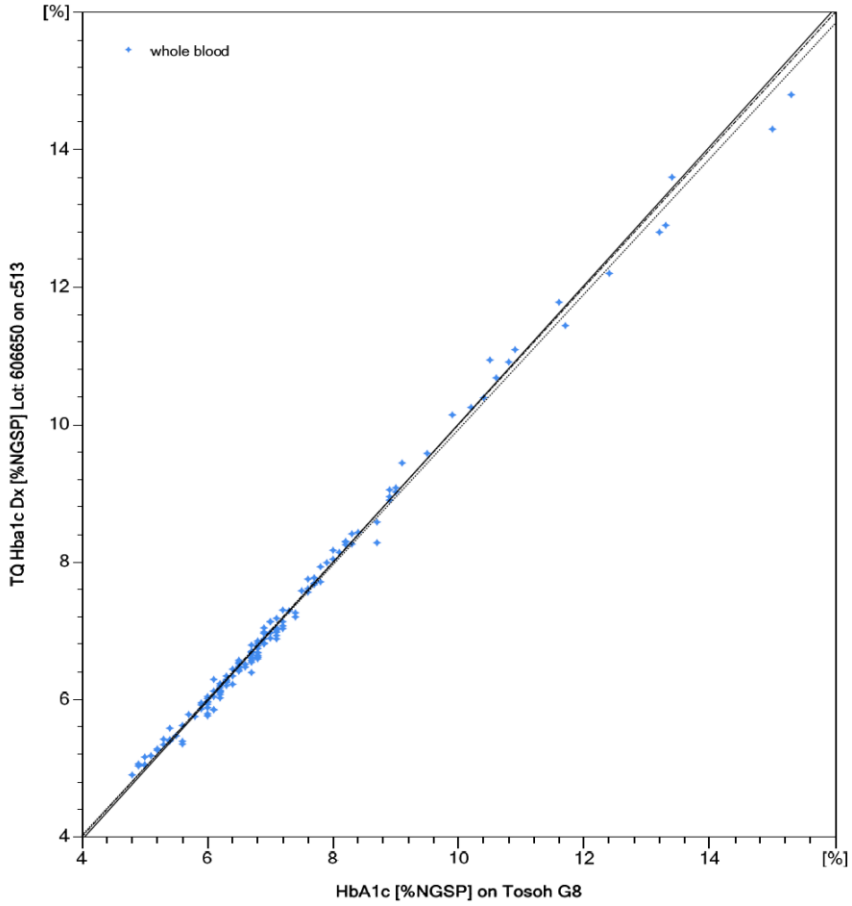
| Hemoglobin A1c Level | Number of Samples Tested | % of Samples Tested |
|---|---|---|
| ≤ 5% | 6 | 3.9% |
| 5 – 6% | 25 | 16.1% |
| 6 – 6.5% | 30 | 19.4% |
| 6.5 – 7% | 36 | 23.2% |
| 7– 8% | 25 | 16.1% |
| 8– 9 % | 14 | 9.0% |
| > 9% | 19 | 12.3% |
| Total | 155 | 100.0% |

The samples were measured by the secondary NGSP reference laboratory using a Tosoh G8 HPLC system (X axis) and by the Roche Tina-quant HbA1c Gen.3 test system (Y axis). Deming (weighted) and Passing-Bablok regression analyses were performed for the Tina-quant HbA1c Gen. 3 (whole blood application) versus the reference method. The summary of results is below.

Whole (Venous) Blood Application:

| | y-intercept | Slope |
|---|---|---|
| Deming | 0.0805<br>95% CI: -0.0112 to 0.172 | 0.985<br>95% CI: 0.973 to 0.997 |
| Passing-Bablok | -0.0808<br>95% CI: -0.229 to 0.0796 | 1.009<br>95% CI: 0.9985 to 1.031 |

Whole (Venous) Blood Application Scatter Plot: Tosoh G8 HPLC system (X axis) vs. Roche Tina-quant HbA1c Gen.3 test system (Y axis)

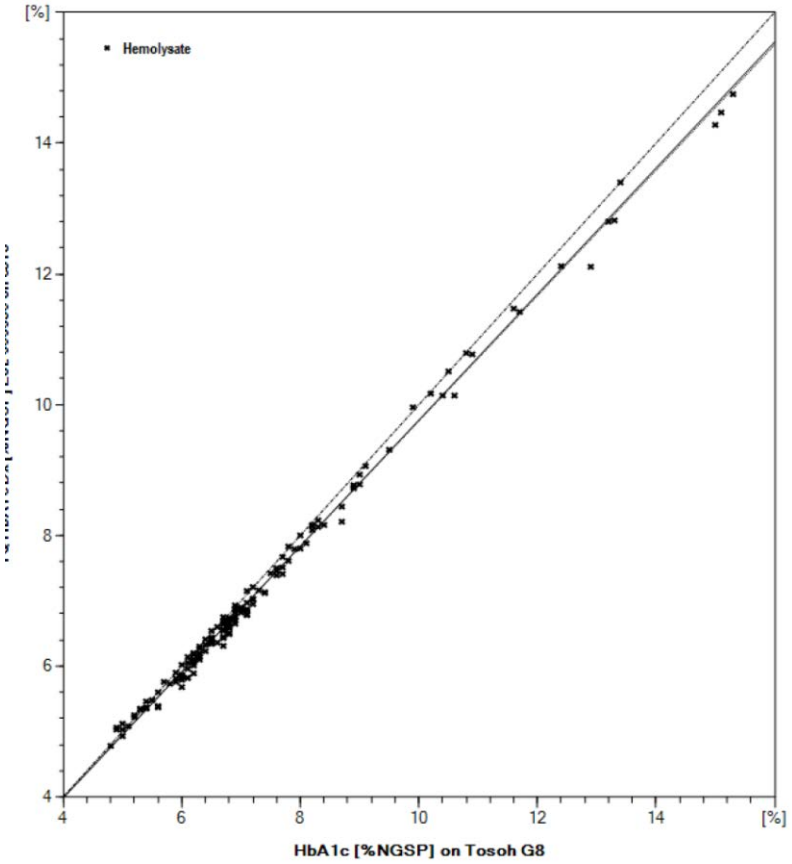



Hemolysate Application:

Summary of results are as follows (Hemolysate Application):

| | y-intercept | Slope |
|---|---|---|
| Deming | 0.166<br>95% CI: 0.0926 to 0.239 | 0.959<br>95% CI: 0.949 to 0.968 |
| Passing-Bablok | 0.128<br>95% CI: 0.00868 to 0.230 | 0.964<br>95% CI: 0.940 to 0.975 |

Hemolysate Application Scatter Plot: Tosoh G8 HPLC system (X axis) vs. Roche Tina-quant HbA1c Gen.3 test system (Y axis)




The following biases were observed between the Cobac c 513 and the reference method:

Whole (Venous) Blood Application:

| %HbA1c Decision Level | Bias (% HbA1c) | Relative Bias (%) |
|---|---|---|
| 5.0% | -0.0358 | -0.7 |
| 6.5% | -0.0223 | -0.3 |
| 8.0% | -0.00874 | -0.1 |
| 12.0% | 0.0273 | -0.2 |

Hemolysate Application:

| %HbA1c Decision Level | Bias (% HbA1c) | Relative Bias (%) |
|---|---|---|
| 5.0% | -0.0536 | -1.1 |
| 6.5% | -0.108 | -1.7 |
| 8.0% | -0.163 | -2.0 |
| 12.0% | -0.308 | -2.6 |

*Total Error Near the Cutoff*

Using the results of bias estimation (%Bias) in the method comparison study and precision in the reproducibility study, Total Error (TE) four concentrations: (5.0%, 6.5% , 8.0% and 12.0%) was calculated as follows: %TE =|%Bias| + 1.96 *%CV*(1+%Bias). The results are presented in the following tables:

Total Error: Whole (Venous) Blood

| Decision Level | \|%Bias\| | %CV | %TE |
|---|---|---|---|
| 5.0 | 0.7 | 1.6 | 3.9 |
| 6.5 | 0.3 | 0.9 | 2.1 |
| 8.0 | 0.1 | 1.1 | 2.3 |
| 12.0% | 0.2 | 1.5 | 3.1 |

Total Error: Hemolysate

| Decision Level | \|%Bias\| | %CV | %TE |
|---|---|---|---|
| 5.0 | 1.1 | 1.3 | 3.7 |
| 6.5 | 1.7 | 1.0 | 3.7 |
| 8.0 | 2.0 | 1.0 | 4.0 |
| 12.0% | 2.6 | 1.3 | 5.2 |

*b. Matrix comparison:*

A matrix comparison study was performed to evaluate the effects of different anticoagulants on analyte recovery. At least 40 samples of each sample type and at least 40 half-filled tubes of each sample type were evaluated. The half-filled (double concentrated) and filled sample tubes were from one donor. Samples covered the measuring range. The hemolysate application was used for these measurements. The following anticoagulants were used and the following regression results obtained:

$K_2$-EDTA whole blood vs K3-EDTA: $y=0.974x +0.172$; $r^2=0.9881$

$K_2$-EDTA whole blood vs Li Heparin: $y=1.027x-0.130$; $r^2=0.9841$

$K_2$-EDTA whole blood vs NaF/Potassium oxalate: y=1.020x-0.0865; $r^2$=0.9860

The labeling states that the only acceptable anticoagulants are Li‑heparin, $K_2$‑EDTA, $K_3$‑EDTA and Fluoride/potassium oxalate.

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:

   The labeling states the following:

   Protocol 1 (ratio definition for mmol/mol HbA1c, according to IFCC): 20‑42 mmol/mol HbA1c

   Protocol 2 (ratio definition for % HbA1c, according 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.[1,2] 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 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 (IFCC) or 7 % (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]American Diabetes Association. Standards of Medical Care in Diabetes for patients with Diabetes mellitus. Diabetes Care [Supplement 1] 2012 S11-S63.

[4]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.

**N. Instrument Name:**

cobas c 513 Analyzer

**O. System Descriptions:**

1. Modes of Operation:

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

   Yes _____ or No ___x_____

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

   Yes _____ or No ___x_____

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

3. Specimen Identification:

   Sample identification is by barcode.

4. Specimen Sampling and Handling:
   Whole blood samples are obtained using collection devices with the following anticoagulants: Li‑heparin, K2‑EDTA, K3‑EDTA and Fluoride/potassium oxalate. The labeling states that only anticoagulated whole venous blood or hemolysate can be used with this assay.

5. Calibration:
   Both Hb and HbA1c assays must be calibrated in parallel using Roche C.f.a.s. HbA1c calibrators (previously cleared in k052101). A 2 point calibration is recommended for Hb and a full calibration is recommended for HbA1c. In addition, a full calibration is recommended after 29 days during shelf life, after reagent lot change and as required following quality control procedures

6. Quality Control:
   Quality control of the Tina-quant Hemoglobin A1cDx Gen.3 assay can be conducted using commercially available Roche control materials (PreciControl HbA1c norm and PreciControl HbA1c path; these were previously cleared in k103099).

   The labeling states the following: "The control intervals and limits should be adapted to each laboratory's individual requirements. Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

   Follow the applicable government regulations and local guidelines for quality control."

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

None

**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.