510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
DEVICE ONLY TEMPLATE

A. 510(k) Number:
K031604

B. Analyte:
1,5-anhydroglucitol

C. Type of Test:
Quantitative

D. Applicant:
Tomen America Inc.

E. Proprietary and Established Names:
GlycoMark™

F. Regulatory Information:

1. Regulation section:
   21 CFR 864.7470
2. Classification:
   Class II
3. Product Code:
   NOZ
4. Panel:
   81

G. Intended Use:

1. Intended use(s):
   The GlycoMark™ test provides quantitative measurement of 1,5-anhydroglucitol (15AG) in serum or plasma. The test is for professional use, and is indicated for the intermediate term monitoring of glycemic control in people with diabetes.
2. Indication(s) for use:
   The GlycoMark™ test provides quantitative measurement of 1,5-anhydroglucitol (15AG) in serum or plasma. The test is for professional use, and is indicated for the intermediate term monitoring of glycemic control in people with diabetes.
3. Special condition for use statement(s):
   None
4. Special instrument Requirements:
   Roche Hitachi 917 or other appropriate open systems

H. Device Description:
GlycoMark™ is an enzymatic method consisting of a two-reagent test kit (Reagent 1 and Reagent 2) and is to be used with a fully automated chemistry analyzer. The test system also includes a calibration standard and a two-level control set, both of which are purchased separately.

Reagent 1 is the pretreatment reagent (1 bottle, 20 mL) and contains the following: 4-aminoantipyrine, glucokinase, adenosine triphosphate, phosphoenol pyruvate, sodium azide, various buffers, water, and BSA.

Reagent 2 is the coloring reagent (1 bottle, 10 mL) and contains the following: pyranose oxidase, peroxidase, N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline sodium dehydrate, sodium chloride, sodium azide, various buffers, and water.

The calibration standard contains 15AG, sodium azide, sodium chloride, and water. It is supplied in 3 vials, 5 mL each.

The control set contains a low and high control made up of 15AG and sodium azide. The low control has approximately 4.0-5.5 µg/mL 15AG, and the high control has approximately 13.0-16.0 µg/mL 15AG. Each control level is supplied in 3 vials, 2 mL each.

I. Substantial Equivalence Information:

1. Predicate device name(s):
   Tina-Quant A1C Assay
2. Predicate K number(s):
   K934070
3. Comparison with predicate:

Similarities		
Item	**Device**	**Predicate**
Indications for Use	Used in the management and treatment of diabetes, for monitoring glycemic control	Used in the management and treatment of diabetes, for monitoring glycemic control
Differences		
Item	**Device**	**Predicate**
Intended Use	Quantitative measurement of 15AG in serum or plasma	Quantitative measurement of the percent of glycated hemoglobin in whole blood
Methodology	Colorimetric assay	Turbidimetric inhibition immunoassay

J. Standard/Guidance Document Referenced (if applicable):
Not applicable

K. Test Principle:
The method uses the enzyme pyranose oxidase (PROD) to oxidize the 2nd position hydroxyl group of 15AG and to detect the generated hydrogen peroxide by colorimetry using peroxidase (POD). As PROD reacts with glucose, the sample is pretreated by enzyme reaction using glucokinase (GK). Glucose is converted into glucose-6-phosphate (G-6-P), a species non-reactive with PROD. To drive the reaction to completion, an adenosine triphosphate (ATP)-regenerating system

consisting of pyruvate kinase (PK) and phosphoenol pyruvate (PEP) is utilized. As ATP is converted to adenosine diphosphate (ADP), PK, in the presence of PEP, catalyzes the phosphorylation of ADP back to ATP. Following the conversion of glucose to G-6-P, the assay is rendered specific for 15AG.

L. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Within-assay: Twenty (20) replicates of the GlycoMark™ controls (low and high) were assayed according to standard procedure. Mean, standard deviation, and percent coefficient of variation (%CV) were calculated for each control solution. The within-assay precision ranged from approximately 1.3 to 3.8 %CV.

Between-assay (day-to-day): Two (2) replicates of each of the GlycoMark™ controls and two serum pools were assayed twice daily with one lot of reagents according to standard procedure for a total of 10 days. Mean, standard deviation, and percent coefficient of variation (%CV) for each sample over the entire 10 day set were calculated from their respective daily standard calibrations. The %CVs ranged from approximately 0.8% to 3.8%.

b. Linearity/assay reportable range:

Linearity was evaluated in a series of experiments using spiked samples. The concentrations of 15AG in the samples ranged from 0 µIU/mL to 113 µIU/mL. The samples were tested in quadruplicate with GlycoMark™, and the averaged obtained result was compared to the expected result by linear regression. The data indicated that GlycoMark™ is linear to at least 110 µg/mL 15AG.

c. Traceability (controls, calibrators, or method):

Calibration of the assay was established with a Master Reference preparation. A Working Reference preparation was assigned off of the Master Reference preparation and adjusted, as necessary, to be within 1% of the Master Reference. New batches of the 50 µg/mL calibrator are compared in multiple assays on a Hitachi analyzer to the Working Reference, and must be within 5% of the Working Reference. Similarly, new batches of controls are assigned off of the Working Reference in multiple assays on a Hitachi analyzer. Control ranges are established based on the assay results.

d. Detection limit:

Twenty-one (21) replicates of a saline reagent blank were analyzed as unknowns in one assay run. The analytical sensitivity is estimated to be 0.2 µg/mL, and this is defined as the mean 15AG concentration plus one standard deviation.

e. Analytical specificity:

To evaluate the effect of interfering substances, fresh serum was collected from apparently healthy individuals and pooled. The pool was then aliquoted, spiked with specified concentrations of

interfering substances, and quantified in triplicate determinations in the GlycoMark™ assay using one lot of kit reagents. Percent recoveries for aliquots containing interferent were calculated by comparison to control samples containing no added interferences.

The data showed that GlycoMark™ is unaffected by hemoglobin up to 125 mg/dL, triglycerides up to 1153 mg/dL, and bilirubin up to 53 mg/dL. GlycoMark™ results were also unaffected by the following substances at their noted concentrations: glucose- 1000 mg/dL; maltose- 500 mg/dL; ascorbic acid- 25 mg/dL; uric acid- 20 mg/dL; creatinine- 10 mg/dL; urea- 20 mg/dL.

f. Assay cut-off:
See Detection limit above.

2. Comparison studies:
   a. Method comparison with predicate device:
   A prospective, longitudinal study was performed with seventy-seven (77) patients with diabetes (both type 1 and type 2). The patients exhibited suboptimal glycemic control (A1C level greater than or equal to 7%) at study entry, and these patients were monitored for eight weeks following initiation or modification of anti-hyperglycemic treatments. Measurements for GlycoMark™, A1C, fructosamine, and glucose were performed every two weeks for the first four weeks (Visits 1-3) and then at Week 8 (Visit 4). Correlations of the markers were determined by association between variables (Spearman's non-parametric analysis). GlycoMark™ 15AG showed a high association with A1C and fructosamine.

   Additionally, concordance of time-dependent changes of GlycoMark™ 15AG values with A1C was determined. "Concordance" was defined as either increases in 15AG values with corresponding decreases in A1C values, or, conversely, decreases in 15AG values with corresponding increases in A1C values. 89.6% of the patients (69 of 77) displayed concordance in changes of GlycoMark™ and A1C values with time.

   b. Matrix comparison:
   To assess the potential matrix effect of EDTA plasma on 15AG measurements, blood collections were obtained from 10 healthy volunteers, and then processed to serum and EDTA plasma in parallel. The samples were then randomly tested in the GlycoMark™ assay. The mean serum 15AG was 24.0 µg/mL and the mean plasma 15AG was 23.6 µg/mL, with a percent difference of -1.3%.

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:
   A study was done with a presumptively normal population in order to determine GlycoMark™ reference ranges for 15AG. The study included serum samples from 82 males between the ages of 18 and 39, 82 females between the ages of 19 and 39, and 30 males and 30 females of age 40 or greater, for a total of 224 individuals. Ethnic backgrounds included African Americans, Caucasians, Asians, and Hispanics. The data did not demonstrate differences in ages, but there were gender differences. The following table provides the male and female ranges, based on nonparametric 5^{th}-95^{th} percentiles.

	Mean (SD) µg/mL 15AG	Reference Interval µg/mL 15AG
Males	22.5 (5.8)	10.7-32.0
Females	17.7 (6.2)	6.8-29.3

M. Conclusion:

GlycoMark™ has the same indication as A1C assay in that they are both used in the management and treatment of diabetes and for monitoring glycemic control. The technological characteristics, on the other hand, differ. (Question 5)

The new method uses the enzyme pyranose oxidase to oxidize the 2^{nd} position hydroxyl group of 15AG and to detect the generated hydrogen peroxide by colorimetry using peroxidase. The predicate is based on turbidimetric inhibition and involves antigen-antibody reactions. However, the characteristics of the new device could not affect safety or effectiveness because colorimetry is a well-established scientific method.

Additionally, the method comparison data provided demonstrated equivalence between the GlycoMark™ and the A1C. Other analytical data and manufacturing information provided were adequate as well. Therefore, I recommend a substantial equivalence determination for the GlycoMark™.

I also recommend a substantial equivalence determination for the calibrators (21 CFR 862.1150, 75JIS, class II) and controls (21 CFR 862.1660, 75JJX, class I), which will be sold separately.