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

A. 510(k) Number:

k060765

B. Purpose for Submission:

New 510(k)

C. Measurand:

Glucose in blood

D. Type of Test:

Quantitative, instrument read, whole blood glucose test

E. Applicant:

HemoCue AB

F. Proprietary and Established Names:

HemoCue Glucose 201 RT System

G. Regulatory Information:

1. Regulation section:
   862.1345, Glucose Dehydrogenase

2. Classification:

   Class II

3. Product code:
   LFR

4. Panel:

   75 (Chemistry)

H. Intended Use:

1. Intended use(s):

   See indications for use.

2. Indication(s) for use:

   The HemoCue Glucose 201 RT system is used for quantitative determination of glucose in whole blood supplementing the clinical evidence in the diagnosis and treatment of patients with diabetes. The HemoCue Glucose 201 RT system is for In Vitro Diagnostic use only. The HemoCue Glucose 201 RT Analyzer is only to be used with HemoCue Glucose 201 RT Microcuvettes. For professional use only.

3. Special conditions for use statement(s):

   The device is for in vitro diagnostic prescription use.

   The assay is intended for use in point-of-care settings and the appropriate studies were done. This claim, however, is not included in the Indications for Use statement.

4. Special instrument requirements:

   The microcuvettes and HemoCue 201 RT analyzer are not intended for use with other components. They are mutually exclusive.

I. Device Description:

The HemoCue Glucose 201 RT Analyzer is a portable device. The main parts are the cuvette holder (brings the microcuvette in correct measuring position), the optronic unit (a photometer which performs the measurement in the microcuvette) a display, a power adaptor and embedded software.

The single-use Microcuvette contains reagents deposited on its inner walls and serves both as a pipette and as a measuring cuvette. A blood sample of approximately 4 µL is drawn into the cavity by capillary action. The filled microcuvette is inserted into the HemoCue Analyzer. The measurement takes place in the analyzer in which the transmittance is measured and the absorbance and glucose level is calculated. The calibration of the analyzer is traceable to the ID (Isotope Dilution) GC-MS method. The HemoCue is factory calibrated and needs no further calibration. The reportable range is 12-560 mg/dL.

The instrument may be customized for use with or without plasma conversion of whole blood measurements. Plasma equivalents are determined by multiplying the whole blood reading by a factor of 1.1.
The sponsor indicates the device does not contain human source material.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   HemoCue Glucose 201 System

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

   k020935

3. Comparison with predicate:

   Both devices are for measurement of the same analyte in the same matrix, have the same intended use, and utilize similar test methodology. The microcuvettes and instrument are mutually exclusive. Both are for POC use, although not specifically identified in the Indications for Use statement.

   The reportable range of the candidate device has been expanded from 444 mg/dL to 560 mg/dL. Modifications have been made to the candidate device with regard to the chemical make-up of the microcuvette, storage requirements, dimensions, algorithm, and the software.

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

The sponsor referenced the following guidance document(s) or standards:

CLSI document EP9-A. Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline- Second Edition.

CLSI document EP5-A. Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline.

CLSI document EP7-A. Interference Testing in Clinical Chemistry; Approved Guideline.

CLSI document EP6-A. Evaluation of the Linearity of Quantitative Measurement Procedure: A Statistical Approach; Approved Guideline.

Guidance for Industry - Cybersecurity for Networked Medical Devices Containing Off-the-Shelf (OTS) Software issued January 14, 2005.

The sponsor did not indicate any deviation from these guidances.

L. Test Principle:

The chemical reaction in the cavity of the HemoCue Glucose 201 RT microcuvettes has two phases, hemolysis and the glucose reaction. The glucose reaction is a modified glucose dehydrogenase method in which a tetrazolium salt (MTT) is used to obtain a quantification of glucose in visible light. β-D-glucose is transformed to β-D-glucose using mutarotase. Glucose dehydrogenase acts as a catalyst for the oxidation of β-D-glucose, to form NADH, which in the presence of diaphorase produces a colored formazan with MTT. The measurement takes place in the analyzer in which the transmittance is measured and the absorbance and glucose level is calculated.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Studies were conducted according to CLSI EP-5A guidance "Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guidelines." One batch of Microcuvettes, 5 analyzers, 5 operators, and 3 levels of commercial control were used in the study. Each operator ran duplicate samples twice a day for 20 days. Four hundred samples were run at each level. Results of the studies are presented below.

HemoCue 201 RT Precision

Sample concentration, ng/mL	SD	CV%		SD	CV%
Within-Run			Total		
45	1.02	2.3		1.07	2.4
137	1.70	1.2		1.74	1.3
298	2.90	1.3		4.03	1.3

Precision was also established in POC studies. See the Method Comparison data in section M2, below.

b. Linearity/assay reportable range:

To verify linearity, the sponsor followed "Evaluation of the Linearity of Quantitative Analytical methods", CLSI Document EP6-A Vol. 21 No. 28. Five HemoCue 201 RT analyzers were used in the study. Four replicates per level were evaluated on each analyzer. Whole blood concentrations and plasma equivalent converted results (multiplied by 1.1) both appear linear. Samples were EDTA whole blood hemolysates spiked with Glucose to eleven different concentrations ranging from 10-600 mg/dL. Results of the study support the claimed reportable range (12-560 mg/dL).

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

No calibrators are required. The device is factory calibrated. Calibration is traceable to an ID-GCMS (Isotope Dilution- Gas Chromatography/Mass Spectrometry) system.

Users are instructed to follow local, state, and federal guidelines regarding quality control procedures.

A commercial control material is identified in the labeling, i.e., Eurotrol GlucoTrol-NG. This control was originally cleared during the review of k964053 under the name HemoCue GlucoTrol-NG.

The instrument contains electronic checks which validates that inputs from the LEDs are linear to the output signal of the detector. The sponsor states this indicates the electronics in the device are stable.

d. Detection limit:

The sponsor determined the lower limit of detection (LLD) for the HemoCue Glucose 201 RT system, defined as the lowest concentration which is measured by the analyzer with precision less than or equal to a 20 % CV. To establish this, EDTA samples were aged to concentrations down to 10 mg/dL and analyzed in replicates on multiple analyzers. A concentration of 12 mg/dL generated a 20% CV.

e. Analytical specificity:

The sponsor evaluated the potential for interference from different compounds, proteins and pH levels. The cross reactivity of the enzyme Glucose Dehydrogenase (GDH) with various types of sugar species was also evaluated. The accepted deviation between the test sample (containing the interfering substance) and the mean values for the reference sample (not having the interferents) was < 10%. Warnings are included in labeling for those with greater than 10% difference.

The sponsor states that they followed "Interference Testing in Clinical Chemistry", CLSI Document EP7-A vol. 22 No 27. The cross-reactivity of the sugar species was analyzed according to an internal procedure.

Five replicates were run on each of five HemoCue Glucose 201 RT analyzers. Results appear below:

Substance	**% Difference between spiked and non–spiked sample at a glucose level of 100 mg/dL**	**% Difference between spiked and non–spiked sample at a glucose level of 180 mg/dL**
Acetaminophen	0.38	0.50
EDTA 142 mg/dL	-2.0	-1.0
EDTA 731 mg/dL	-1.4	-1.8

Substance	% Difference between spiked and non–spiked sample at a glucose level of 100 mg/dL	% Difference between spiked and non–spiked sample at a glucose level of 180 mg/dL
Heparin	-0.39	-0.27
Heparin NaF	-1.55	-1.10
Potassium oxalate /Sodium fluoride	0.29	0.22
Ascorbic Acid	4.23	1.91
Bilirubin (conjugated)	4.03	1.74
Bilirubin (non-conjugated)	4.73	3.34
Dextran15 g/L	2.0	2.1
Dextran 30 g/L	3.0	3.4
Dextran 45 g/L	4.4	4.8
Dextran 60 g/L	6.3	10.1[1]
Dopamine	0.5	-0.4
Ephedrine	0.20	0.11
HbCO	2.19	2.08
HbO_2	7.5	4.0
Ibuprofen	1.43	0.00
Caffeine	0.48	0.22
Creatinine	-0.10	0.00
L-Dopa	-1.30	-0.34
MetHb 10 %	-4.5	-5.0
MetHb 17 %	-10.3[2]	-7.4
MetHb 26 %	-16.4[2]	-11.0[2]
MetHb 31 %	-19.7[2]	-12.5[2]
Methyldopa	0.00	-0.55
pH 6.3-6.8	-1.3	0.5
pH 8.5-9.1	-0.8	0.1
Salicylic Acid	1.63	0.92
Tetracycline	-0.41	-0.49
Cholesterol 6.4 mmol/L	-4.3	-
Cholesterol 7.6 mmol/L	-6.3	-
Cholesterol 8.7 mmol/L	-10.1[3]	-
Triglyceride 2.70 mmol/L	2.8	-
Triglyceride 5.07 mmol/L	7.3	-
Triglyceride 9.51 mmol/L	14.6[4]	-
Tolazamide	1.34	0.79
Tolbutamide	2.85	1.23
Urea	-0.29	-0.33
Uric Acid	0.10	0.50

[1] Dextran 60 g/L interfere > 10%. Limitation to 30 g/L

[2] MetHb >15 % interfere > 10%. Limitation to 15 %

[3] Cholesterol 8.7 mmol/L interfere > 10%. Limitation to 336 mg/dL

[4] Triglyceride >6.6 mmol/L interfere > 10%. Limitation to 584 mg/dL

f. Assay cut-off:
Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The accuracy of the HemoCue 201 RT system was studied at six locations in Sweden (including a study involving six untrained users at 3 at POC locations). A total of 460 samples were analyzed. A summary of the studies is presented below. (Note: For method comparison analysis, the first replicate of the HemoCue Glucose 201 RT is compared to the mean of the comparative method. The exception being the ID- GC/MS study, where only a single ID-GC/MS measurement was taken.)

Site	**Type of intended use site**	**Number of Operators**	**Number of samples**	**Type of samples**	**Comparative method**
A	Hospital Clinical Laboratory	1	136	Venous blood	ID GC-MS*
B	Hospital Clinical Laboratory	2	128	Venous blood	Modular Roche –Hexokinase
C	Hospital Clinical Laboratory	2	116	Venous blood	ARCHITECT ci8200 - Hexokinase
D	District health centre in primary care	1	26	Capillary blood	HemoCue Glucose 201
E	District health centre in primary care	2	26	Capillary blood	HemoCue Glucose 201
F	District health centre in primary care	3	28	Capillary blood	HemoCue Glucose 201

*ID-GC/MS stands for Isotope Dilution-Gas Chromatograph/Mass Spectrometer

Data collected during the study was also used to characterize precision. Portions of the analyses are presented here. Performance among all studies appears comparable.

Study A- Comparison to ID-GC/MS
Operators were provided with the HemoCue system and the instructions for use, in English, in order to evaluate readability of the labeling. Venous specimens were collected in EDTA tubes. All samples were analyzed in duplicate by the HemoCue and a single measurement was taken on the ID GC-MS reference method. After the study was completed the operators were given a questionnaire to evaluate the effectiveness of the

labeling. A copy of the questionnaire is included in the submission. Results from the questionnaire were favorable.

Study Results:

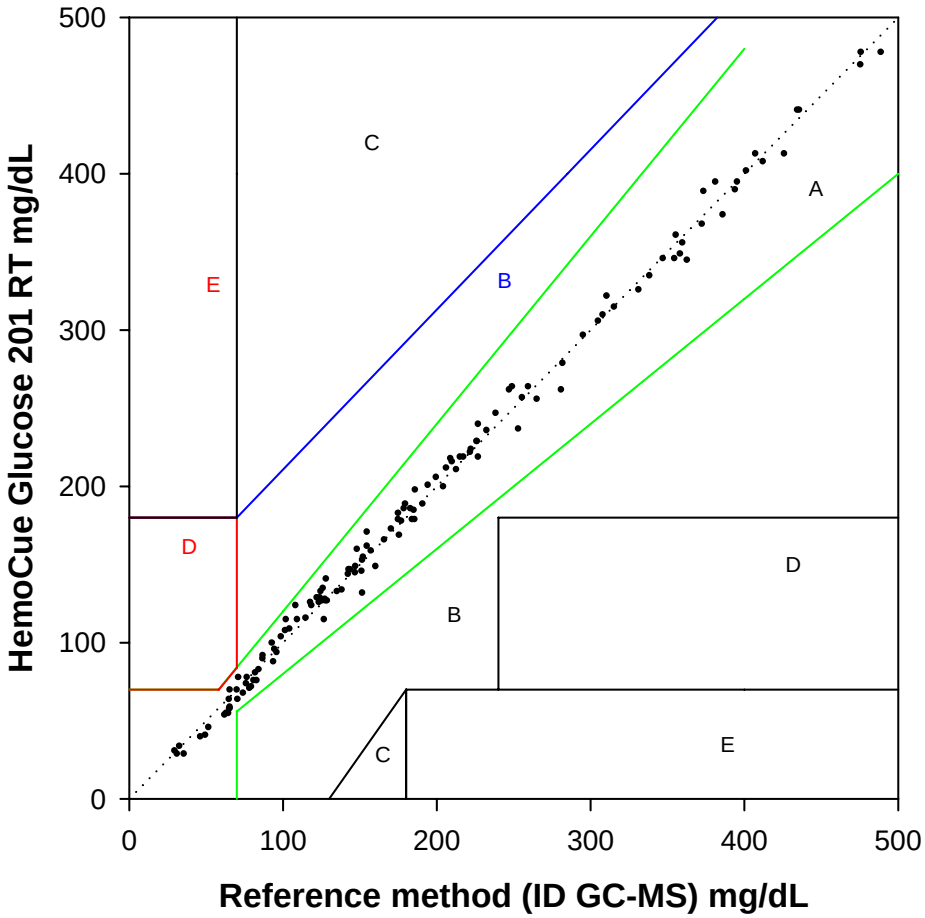
Total mean difference between Glucose 201RT system and the comparative method was 0.23 %.
R^2 = 0.996 for Glucose 201RT system individual results versus the comparative method.
Bias (Glucose 201 RT – Comparative method) was 0.4 mg/dL
The total standard deviation, SD, between duplicates was 3.1 mg/dL for the Glucose 201RT system.

HemoCue 201 vs. ID GC/MS

Error grid according to Clark et al.

for HemoCue Glucose 201 RT replicate 1 versus Comparative method, ID GC-MS, Linköping University Hospital, Linköping, Sweden

N=136



Precision- Sites A, B and C (Professional Users), Pooled

The results were divided into three groups; 0-200 mg/dL, 201-400 mg/dL and 401-500 mg/dL. The standard deviation for duplicate samples within each group were calculated according to the formula:

$SD = \sqrt{\frac{\sum d^2}{2n}}$ where *d* is the differences between two microcuvettes and *n* is the number of samples included in the calculation.

Group	Number of samples	SD
0-200 mg/dL	259	2.04
201-400 mg/dL	101	3.00
401-500 mg/dL	20	6.71

Sites D, E and F- POC Locations

Operators were provided with the test system and labeling. Operators did not receive training, coaching, prompting, or written or verbal instructions beyond the written test procedure.

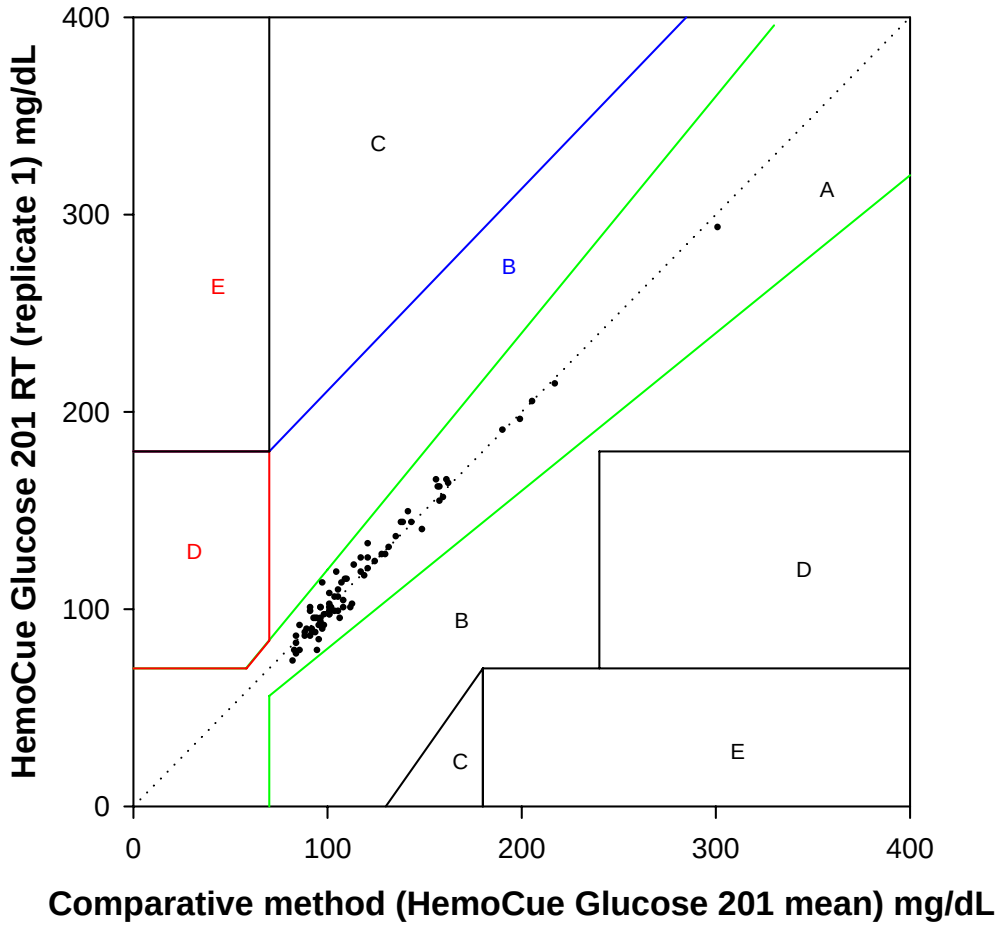
Finger stick samples were taken and tested on the HemoCue Glucose 201 RT system and compared to measurements from the predicate device, the HemoCue Glucose 201 system. All samples were analyzed in duplicate for both methods. The results from 80 samples at all three sites are combined for analysis. There was limited data above 180 mg/dL in these studies, i.e., 4 data points between 180 and 220 mg/dL and one at 300 mg/dL.

Study Results –pooled
Total mean difference between Glucose 201 RT and the comparative method was 0.88%
R^2=0.972 for HemoCue Glucose 201 RT individual results versus mean of Glucose 201 RT system.
Bias (Glucose 201 RT – Comparative method) was 1.03 mg/dL.
Calculated total error according to CLSI guidance EP21-A was –12.0 mg/dL to 12.3 mg/dL (95% confidence interval calculations).
Total standard deviation, SD, for duplicates was 3.71 mg/dL for the Glucose 201 RT system.

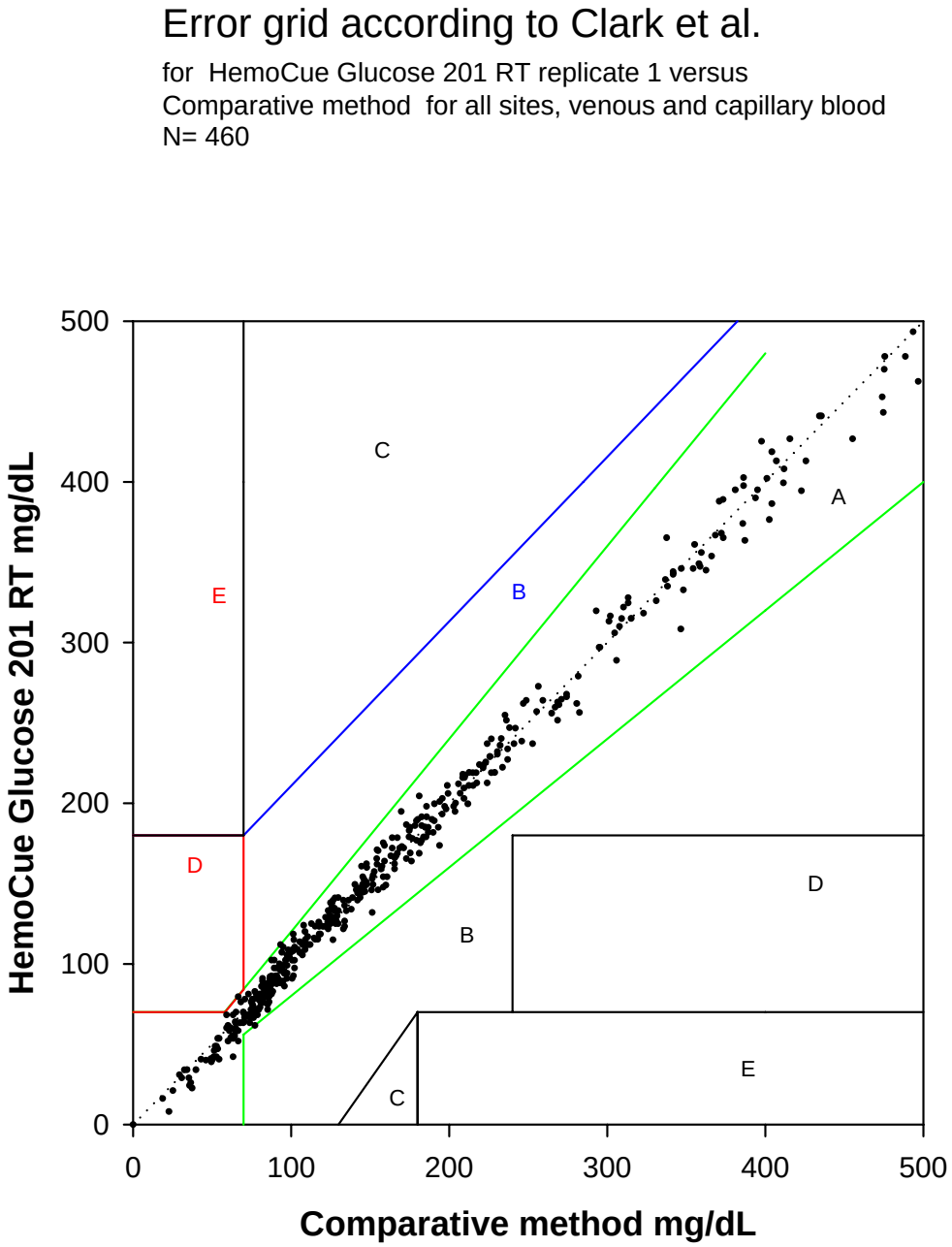
Precision estimates were NOT provided for these studies.

POC Method Comparison Data

Error grid according to Clark et al. for the
HemoCue Glucose 201 RT replicate 1 vs Comparative method
N=80, Three Point of Care sites



Combined Method Comparison Data Plotted on a Clarke Error Grid (460 samples)



b. Matrix comparison:

The sponsor demonstrated equivalence between capillary whole blood samples, arterial, and venous whole blood samples (EDTA, Heparin, Sodium oxalate, potassium oxalate). A minimum of 10 specimens of each sample type were drawn from multiple individuals, and the samples were spiked with glucose (in order to obtain glucose concentrations

spanning the reportable range). Each sample was analyzed by the HemoCue and a laboratory hexokinase method. Results among all matrices appear equivalent. Calculated differences between all data pairs were analyzed and are presented below.

Matrix Equivalence Study Results

Matrix	**Mean differences in Percent (Glucose 201 RT - Comparative)**
Capillary	0.3
Venous EDTA	-3.3
Venous NaHep	4.8
Venous KOx	7.4
Arterial	-4.5

Additionally, studies for venous EDTA and capillary blood were done during the method comparison studies. (See Section 2a above.) Anticoagulants (EDTA, heparin, and potassium oxalate) were also evaluated in the interference portion of the specificity studies. See section 1E above.

3. Clinical studies:

   a. Clinical Sensitivity:

   Not applicable. Clinical studies are not typically submitted for this device type and matrix.

   b. Clinical specificity:

   Not applicable. Clinical studies are not typically submitted for this device type and matrix.

   c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off:

   Not applicable. This is a quantitative test with reference ranges.

5. Expected values/Reference range:

   Fasting glucose values (reference interval): Plasma glucose, adults 74-106 mg/dL. This is consistent with the predicate's reference range.

N. Instrument Name:

HemoCue 201 RT

O. System Descriptions: (See Section 16.)

1. Modes of Operation:

   Photometric / Colorimetric

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 classified their device as a Moderate Level of Concern.

   The following sections are presented in the submission, and appear adequate:

   1. Software Description- A summary overview of the features that are controlled by the software and the intended software operating environment.
   2. Hazard Analysis- Tabular description of identified hardware and software hazards, including severity assessment and mitigations.
   3. Software Requirements Specification (SRS)- A summary of functional requirements for the software, e.g., interface, performance, or functional needs. The complete SRS is provided. (See page 163.)
   4. Architecture Design Chart
   5. Traceability Analysis
   6. Software Development Environment Description- A summary of the software development life cycle and the processes that are in place to manage the various life cycle activities, e.g., changes or adjustments to software after released into market.
   7. Verification and Validation Documentation- Verification means confirmation that specified requirements have been fulfilled. Validation is confirmation that specifications meet the needs of the user.
   8. Revision Level History- Revision history log, including release version numbers and dates.
   9. Unresolved Anomalies- The sponsor indicates there are ***no unresolved anomalies***.

3. Specimen Identification:

   Specimen information is manually entered by the operator.

4. Specimen Sampling and Handling:

   Whole blood capillary samples are the primary sample type used. Other anticoagulated venous whole blood samples are also acceptable, along with arterial samples.

5. Calibration:

   The instrument is calibrated at the manufacturer's site and is traceable to an ID/MS method. Using a series of calibrators, a standard curve is constructed which is lot specific. The calibration information is contained within the barcode which accompanies each reagent unit.

   Users do not calibrate the device.

6. Quality Control:

   The system utilizes external control materials. An FDA cleared control material is identified in the labeling. Additionally, the instrument contains electronic checks.

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.