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

A. 510(k) Number:

k051968

B. Purpose for Submission:

Clearance to market a clinical analyzer with a creatinine electrode.

C. Measurand:

Creatinine

D. Type of Test:

Quantitative electrochemical

E. Applicant:

Radiometer Medical ApS

F. Proprietary and Established Names:

The ABL 837 Flex Analyzer

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1225: Creatinine test system.

2. Classification:

   Class II

3. Product code:

   CGL

4. Panel:

   (75) Chemistry

H. Intended Use:

1. Intended use(s):

   Please see indications for use.

2. Indication(s) for use:

   The ABL837 Flex Analyzer is intended for in vitro testing of samples of heparinized whole blood, plasma, and serum for the parameter Creatinine. Creatinine measurements measure the concentration of creatinine in blood. Creatinine measurements are used in the diagnosis and treatment of renal diseases and in monitoring renal dialysis.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   The ABL837 FLEX Analyzer

I. Device Description:

The ABL837 FLEX is an analyzer used as an in vitro diagnostic tool for measuring creatinine in whole blood, plasma, and serum. Users measure samples by injection into the instrument port. The device measures creatinine concentrations using two immobilized enzyme electrochemical sensors. One sensor responds to the total creatine and creatinine concentration in the patient sample, [creatine + creatinine]. The second only responds to the concentration of creatine, [creatine]. The instrument reports the difference of these two measurements as the concentration of creatinine, [creatinine].

J. Substantial Equivalence Information:

1. Predicate device name(s):
   i-STATA System Creatinine Test
   Roche Integra Creatinine plus version 2

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

   k973292
   k024098

3. Comparison with predicate:

Similarities		
Item	Device	Predicate(k973292)
Intended Use	Measurement of Creatinine	Same
Enzymes employed	Creatininase,creatinase, sacrosine oxidase	Same
Matix	Whole blood	Whole blood

Differences		
Item	Device	Predicate(k973292)
Detection Method	Electrochemical	Absorbance

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

CSLI EP5: "Evaluation of Precision Performance of Clinical Chemistry Devices"

CLSI EP9-A2 "Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline"

CLSI EP17-A: "Protocols for Determination of Limits of Detection and Limits of Quantitation"

L. Test Principle:

The measuring system is comprised of two electrodes. The first electrode contains the enzymes creatinase and sacrosin oxidase immobilized on the middle membrane of a three membrane diaphragm. Creatine from whole blood diffuses through the first membrane and decomposes to sarcosine, a reaction catalyzed by the creatinase trapped in the middle membrane. Sarcosine undergoes a second decomposition catalyzed by entrapped sarcosin oxidase to produce glycine, formaldehyde, and hydrogen peroxide. The hydrogen peroxide diffuses through the 3rd backing membrane into an electrolyte solution where it is oxidized to O_2 at a Pt electrode. The resulting current is proportional to the [creatine] in the patient sample.

The second electrode responds to both creatine and creatinine concentrations through the addition of creatininase to the middle enzyme-containing membrane. Creatininase catalyzes the conversion of creatinine to creatine which undergoes a subsequent creatinase catalyzed reaction to sarcosine. Sacrosine is converted to glycine by sarcosin oxidase with the production of H_2O_2. The hydrogen peroxide diffuses through the 3rd backing membrane where it is oxidized on a Pt electrode. Since the patient sample contains endogenous creatine which also produces H_2O_2 through sarcosin oxidase catalyzed decomposition, this electrode responds to the total concentration of creatine and creatinine, [creatine + creatinine].

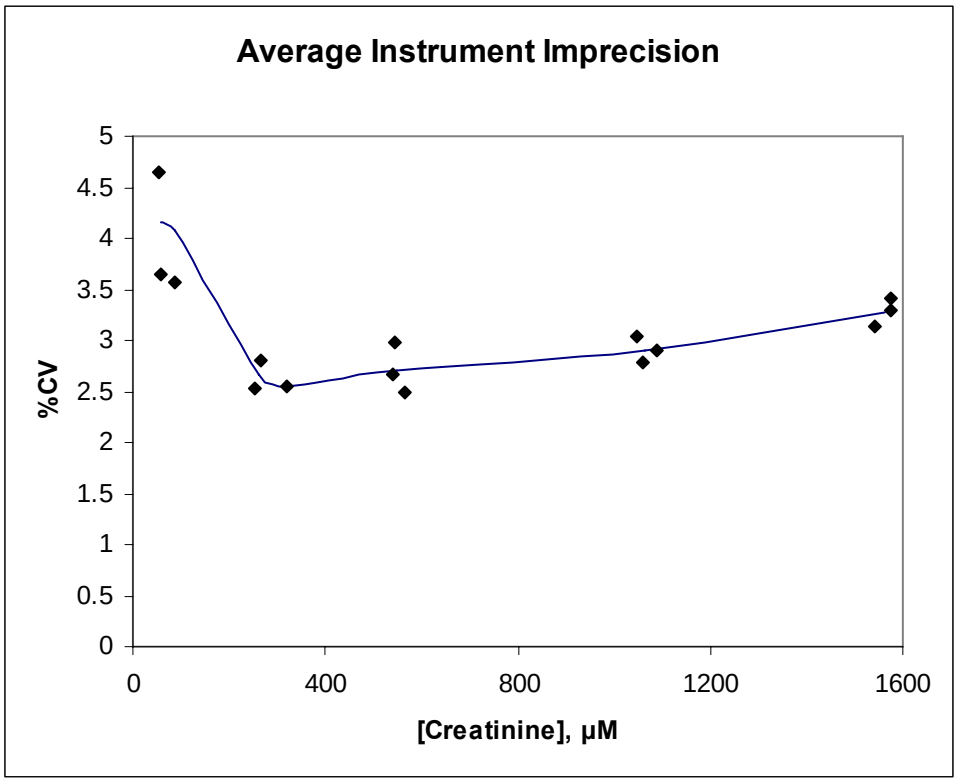
Creatinine concentrations are determined as a difference measurement between these two electrodes.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The company assessed the precision of their device on fresh whole blood using 5 different and freshly prepared creatinine concentrations. The company measured each concentration 5 times per day over 9 machines for a total of 45 measurements per day for each concentration, 624 measurements in total. Because creatinine samples were prepared each day during the 3 day evaluation period, the company assessed their precision on a total of 15 different concentration preparations of creatinine. The following is a graphical representation of the company's findings:



The company followed CSLI EP5 "Evaluation of Precision Performance of Clinical Chemistry Devices" in assessing the precision of their device using plasma. The company measured 3 different concentrations of creatinine in plasma in two separate runs of 2 measurements (four measurements/day) for 20 days. The company repeated this study on two different analyzers. Creatinine samples were created via spiking and kept frozen until measurement to prevent change in [creatinine] via the creatinine-creatine equilibrium. The following is a summary of the company's findings:

	Mean [Creatinine], mg/dL	Std. Deviation, mg/dL	Reproducibility/ Day-to-Day Imprecision %CV
Analyzer 1	0.71	0.015	2.18
	2.73	0.052	1.89
	6.42	0.14	2.19
Analyzer 2	0.72	0.02	2.32
	2.76	0.05	1.89
	6.50	0.15	2.25

The company further assessed the variability in their device by performing repeated measurements on three levels of quality control material. The company measured each level of material 3 times a day for 20 days on 10 different analyzers. As creatinine in the QC material was in equilibrium with creatine, the material was refrigerated but not frozen. The following is a summary of the company's findings:

Mean [Creatinine], mg/dL	Standard Deviation, mg/dL	Reproducibility/Day-to-Day Imprecision %CV
0.34	0.1	3.14
2.69	0.07	2.54
5.2	0.12	2.32

The data supplied by the company supports the precision claims made by the company in their product labeling.

b. Linearity/assay reportable range:

The company demonstrated the linearity of their proposed device by comparison to HPLC measurements. Because the proposed device determines [creatinine] – over the 0.3 – 20.4 mg/dL measurement range - indirectly through a difference measurement, the company first demonstrated the linearity of their device in the determination of creatinine against three background concentrations of creatine in serum. The company used HPLC as the comparator to independently assess the creatinine concentrations. After demonstrating the impact of varying creatine on creatinine measurements, the company demonstrated the linearity of proposed device vs. HPLC on serum and plasma samples. The company demonstrated the linearity of their proposed device on whole blood by comparison to measurements made on their device using plasma.

<u>ABL 837 versus HPLC on Serum</u>
Using a dialyzed serum pool, the company prepared test samples at seven different concentrations of creatinine. Creatinine concentrations for these samples were assigned as the mean of HPLC measurements. The company performed 3

measurements per day for 3 days across 9 analyzers at each creatinine concentration. A total of 492 measurements were reported. The company determined that the slope of their proposed device versus the reference method was 0.9935, the intercept was -0.007 mg/dL creatinine, and the r-squared value of the fit was 0.9989. Deviations from linearity were not judged to be statistically significant.

ABL 837 versus HPLC on Plasma

Using a dialyzed plasma pool, the company prepared test samples at seven different concentrations of creatinine. Creatinine concentrations for these samples were assigned as the mean of HPLC measurements. The company performed 3 measurements per day for 3 days across 9 analyzers at each creatinine concentration. A total of 184 measurements were reported. The company determined that the slope of their proposed device versus the reference method was 0.9772, the intercept was 0.019 mg/dL creatinine, and the r-squared value of the fit was 0.9994. Deviations from linearity were not judged to be statistically significant.

ABL 837 (whole blood) versus ABL 837 (plasma)

The company used split clinical samples, whole blood and plasma, to demonstrate the linearity of their proposed device using whole blood. The company compared the performance of their proposed device on whole blood to that of their proposed device measuring the matched plasma samples. Measurements of the plasma samples were treated as the reference values in this comparison. The company performed a total of 596 comparisons on clinical samples ranging in concentration from 0.46 to 23.16 mg/dL creatinine. Measurements were made in duplicate on both matrices. The company determined that the slope of their proposed device versus the reference method was 0.9888, the intercept was 0.045 mg/dL creatinine, and the r-squared value of the fit was 0.9989. Deviations from linearity were not judged to be statistically significant.

The company noted that their proposed device uses a pre-programmed, algorithmic transformation to convert the reported whole blood measurements to their plasma equivalent.

The data provide by the company supports their claim for linearity on whole blood over the concentration range of 0.28 – 20.36 mg/dL creatinine.

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

The company validated the claimed shelf life of their calibrators through accelerated aging studies. Calibrators were stored at different temperatures and withdrawn periodically for measurement. A total of 50 bottles for each level of calibrator were stored at varying temperatures. Withdrawn material was assayed using both the proposed device and a third party analyzer. The sponsor claims a 3 month shelf life for the calibrator solutions when stored at room temperature.

The company validated their claim for an "on-board" stability of their calibration using real-time data. The company provided data that demonstrated that their calibrators and device provided consistent results for the full 14 day period claimed in their product literature.

The company's cleaning solution contains creatinine and, as such, could change in performance due to the creatitine/creatine equilibrium. The company assessed the stability of their cleaning solutions through accelerated aging studies.

The company claims a 3 month shelf life for their cleaning solution when stored at room temperature.

d. Detection limit:

The company followed CLSI EP17 "Protocols for Determination of Limits of Detection and Limits of Quantitation" in assessing the lower measurement limit of their device. The company determined their limit of the blank, limit of detection, and limit of quantitation for their proposed device using serum. Serum was dialyzed to 0 mg/dL creatinine and creatine and then adjusted by spiking.

To determine the limit of the blank, the company spiked 0 mg/dLcreatinine serum to 0, 0.57, and 1.41 mg/dL creatine. The company measured these creatine samples 4 times at each concentration on 7 ABL837 analyzers over 2 days. From the mean and standard deviation of this set of measurements, the company determined that their limit of the blank was 0.04 mg/dL creatinine

To determine their limit of detection, the company assayed 0.11 mg/dL creatinine samples containing backgrounds of 0, 0.57, and 1.41 mg/dL creatine. Samples were measured 4 times over 2 days on 7 different ABL837 analyzers. Samples were kept at -20 °C and thawed before analysis. From the mean and standard deviation of this set of measurements, the company determined that their limit of detection was 0.06 mg/dL creatinine

The company determined the lower limit of quantitation, the lowest concentration where the device yielded clinically acceptable results, from an analysis of their total error and measurements on 0.11 and 0.28 mg/dL creatinine samples containing backgrounds of 0, 0.57, and 1.41 mg/dL creatine. As before, samples were measured 4 times over 2 days on 7 different ABL837 analyzers. Samples were kept at -20 °C and thawed before analysis. Both the 0.11 and 0.28 mg/dL creatinine measurements showed a consistent 0.02 mg/dL offset. The total error, defined by the company as the absolute bias plus twice the standard deviation, was 0.05 mg/dL, less than the limit of detection of 0.06 mg/dL.

The company opted to claim a lower limit for their device of 0.11 mg/dL. Based on the information supplied by the company, errors at this claimed lower limit will incur

a total error of approximately 40%. The sponsor's claimed measuring range is 0.3 - 20.4 mg/dL.

e. Analytical specificity:

The company followed CLSI EP-7A "Interference Testing in Clinical Chemistry, Approved Guideline" in assessing the impact of endogenous and exogenous chemicals on the performance of their device. Testing was performed on serum samples derived from one large pool derived from a single healthy donor. Serum samples were frozen and thawed immediately before use. Prior to measurement, 2 samples were thawed. The test sample was spiked to the target concentration with the interfering analyte. The control sample was spiked with an equal volume of saline. Measurements on both the sample with the interferant and the unadulterated control were conducted in triplicate.

The company set their maximum tolerated interference at an absolute change in concentration of 0.09 mg/dL. With their criteria, the company did not note any interference. The following is a summary of the company's findings:

Possible Inteferant	**[Interferant]**	**Mean [Creatinine]**	**Mean [Creatinine] with Interferant**	**%Difference**
Acetone	10 mM	67.73	66.97	-1.13
Acetylsalicylic acid	3.3 mM	75.23	76.10	1.15
Ampicillin	152 µM	71.97	72.43	0.65
Ascorbic acid	227µM	78.20	77.97	-0.30
Bleomycin	45 mg/L	71.90	72.00	0.14
Calcium Chloride	3 mM	80.23	79.97	-0.33
Cefoxitin	1.6 mM	70.17	70.20	0.05
Cephalexin	337 µM	69.50	68.63	-1.25
Cephalothin	759 µM	80.03	73.67	-7.96
Cephotaxime	671 µM	71.93	71.50	-0.60
Chlorpromazine	6.3 µM	73.93	72.73	-1.62
Creatine	200 µM	71.87	73.17	1.81
Dipyrone	50 mg/L	78.23	74.73	-4.47
Dobutamine	10 µg/L	78.20	75.60	-3.32
Dopamin	5.9 µM	74.03	74.73	0.95
Doxycycline	67.5 µM	75.37	83.00	10.13
Ethanol	86.8 mM	78.40	79.97	2.00
Gentisic acid	117 µM	77.13	73.63	-4.54
Glutamate	2 g/L	71.37	68.70	-3.74
Gluthation (oxidized, disulfide linked)	10 mg/L	74.20	74.50	0.40
Gluthation (reduced)	10 mg/L	72.30	72.80	0.69
Heparin (Li-salt)	80000 U/L	73.33	72.97	-0.50
Hepes	20 mM	74.40	73.70	-0.94

Possible Inteferant	[Interferant]	Mean [Creatinine]	Mean [Creatinine] with Interferant	%Difference
Ibuprofen	2.4 mM	71.97	72.47	0.69
Lidocaine hydrochloride	100 μM	73.30	71.60	-2.32
Lidocaine (free base)	100 μM	76.23	77.57	1.75
Lithium nitrate	3.2 mM	68.30	68.87	0.83
L-Proline	250 μM	72.50	74.60	2.90
Magnesium nitrate	3 mM	74.60	73.13	-1.97
Mercaptopurin	13.1 mM (saturated)	72.83	72.60	-0.32
Methyldopa	71 μM	80.33	78.83	-1.87
Metotrexate	2.0 mM	71.03	69.77	-1.78
a-Ketobutyric acid	5 mM	70.30	69.23	-1.52
Paracetamol (acetominophen)	1.7 mM	68.53	64.00	-6.61
Phenylbutazone	325 μM	66.13	62.70	-5.19
Rifampicin	78.1 μM	71.10	71.47	0.52
Sarcosine	1 μM	73.83	73.63	-0.27
Sodium hydrogen carbonate	40 mM	72.73	64.90	-10.77
Sodium hydrogen phosphate	2 mM	68.73	67.00	-2.52
Theophyllin	222 μM	67.00	66.57	-0.65
Theophyllin acetate	200 μM	79.63	78.63	-1.26
Uric acid	50 mM	66.20	63.77	-3.68
Cyclosporin	12 μM	80.03	82.50	3.08
Bilirubin	400 μM	57.10	56.93	-0.29
Hemoglobin (3.5% hemolyzed blood)	3.5% hemolysis	72.73	72.67	-0.09
Hemoglobin (10% hemolyzed blood)	10% hemolysis	65.50	67.37	2.85
Lipids (as Intralipid)	5% (v/v)	57.80	62.13	7.50
Lipids (as Intralipid)	2.5% (v/v)	67.33	68.77	2.13
Ammonia	1 mM	70.70	70.00	-0.99
Glucose	60 mM	75.13	72.53	-3.46
Urea	50 mM	72.43	71.83	-0.83
beta-Hydroxybutyrate	10 mM	80.57	80.03	-0.66
Lactic acid	30 mM	69.47	66.57	-4.17
Acetoacetate	10 mM	68.87	67.53	-1.94
Uric acid	3 mM	78.57	79.13	0.72
Pyruvate	3 mM	69.03	66.90	-3.09
pH 8.0	-	53.77	53.60	-0.31
pH 6.8	-	91.93	94.57	2.86
Thiocyanate	24 mM	69.97	70.67	1.00
Fluoride	50 mM	67.57	68.70	1.68

Possible Inteferant	[Interferant]	Mean [Creatinine]	Mean [Creatinine] with Interferant	%Difference
Citrate	50 mM	88.17	86.27	-2.16

The company assessed the impact of two drugs, L-Dopa and hydroxyurea, at 3 different concentrations of creatinine. The test sample was spiked to the target concentration with the interfering analyte. The control sample was spiked with an equal volume of saline. Measurements on both the sample with the interferant and the unadulterated control were conducted in triplicate. The company found the following:

Drug	Measured [Creatinine], md/dL without Interference	Measured [Creatinine], mg/dL With Interference	Δ[Creatinine], mg/dL	% Change
100 μM Hydroxyurea	0.75	0.79	0.04	5.30
	1.88	1.92	0.04	2.12
	6.23	6.31	-0.09	-1.45
20 μM L-Dopa	0.77	0.78	0.01	1.29
	1.93	1.95	0.02	1.03
	6.53	6.46	-0.07	-1.07

The company summarized these findings in their product documentation.

f. Assay cut-off:

Not applicable for a device of this type.

2. Comparison studies:

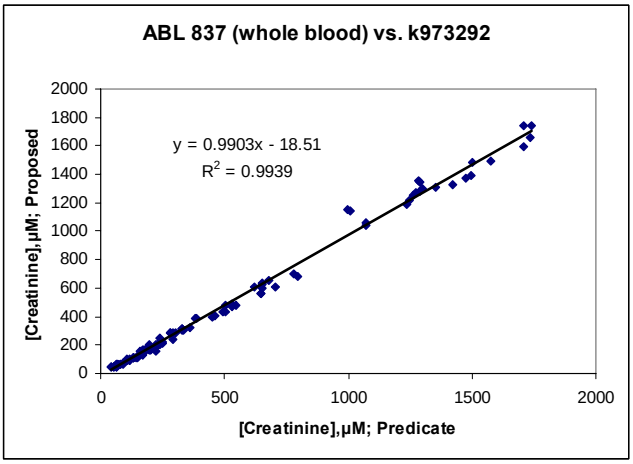
a. Method comparison with predicate device:

The company followed CLSI EP9-A2 "Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline" in demonstrating their equivalence to their predicate. The company supplied method comparisons on two matrix materials in demonstrating their equivalence to their predicates.

To demonstrate their equivalence to their predicate using whole blood, the company compared 55 heparinized whole blood samples taken from patients with kidney disease. Concentrations ranged in concentration from 0.50 to 19.69 mg/dL creatinine. The company made duplicate measurements on both their proposed device and their predicate (k973292).

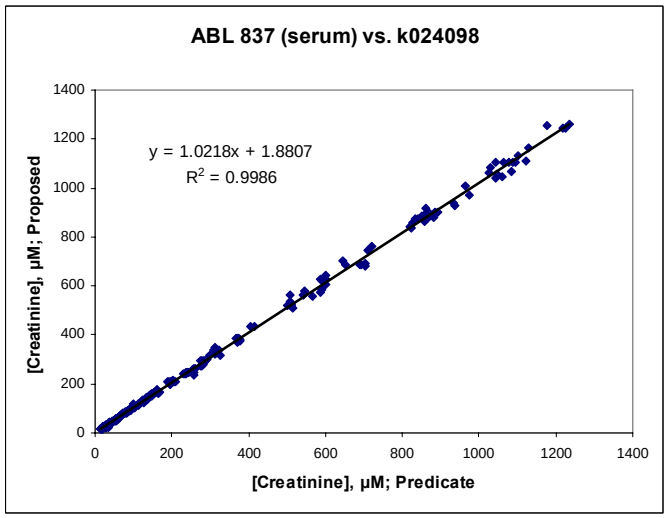
The company determined that the slope of their proposed device versus their whole

blood predicate was 0.9903, the intercept was -0.002 mg/dL creatinine, and the r-squared value of the fit was 0.9939. Deviations from linearity were not judged to be statistically significant. A graphical depiction of the company's findings is as follows:



The company performed an additional method comparison using a predicate device cleared for serum. The company demonstrated the equivalence of their device to this predicate using 104 clinical serum samples spanning a concentration range of 0.17 - 14.29 mg/dL creatinine. Measurements were made in duplicate on both the proposed device and the predicate (k024098).

The company determined that the slope of their proposed device versus their predicate was 1.0218, the intercept was 0.02 mg/dL creatinine, and the r-squared value of the fit was 0.9986. Deviations from linearity were not judged to be statistically significant. A graphical depiction of the company's findings is as follows:



The data supplied by the company supports their claim for equivalence to their on-market predicate.

b. Matrix comparison:

See method comparison above.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable for a device of this type.

b. Clinical specificity:

Not applicable for a device of this type.

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

Not applicable for a device of this type.

4. Clinical cut-off:

Not applicable for a device of this type.

5. Expected values/Reference range:

The company quoted the following reference ranges in their manual*:

Males: 0.6 – 1.2 mg/dL
Females: 0.5 – 1.1 mg/dL

*Tietz, NW, Logan NM. References ranges. In: Tietz NW, ed. "Fundamentals of Clinical Chemistry", 3rd Ed. Philadelphia, WB Saunders Company (1987).

N. Instrument Name:

ABL837 Flex

O. System Descriptions:

1. Modes of Operation:

The ABL837 Flex supports manual measurements of patient samples and automatic measurements of up to 3 patient samples. Automatic measurements are accomplished via bar coding on the patient samples. The required tests for the identified sample are retrieved from a networked server.

2. Software:

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

   Yes ___X____ or No _____

3. Specimen Identification:

   The ABL837 can accommodate up to 3 loaded samples simultaneously. Samples are identified via bar coding. Sample identification is carried with the data throughout the analysis. The software verification and validation information presented by the company supports their claims for this functionality.

4. Specimen Sampling and Handling:

   Patient samples are loaded onto the device using a previously cleared, gas tight syringe. Patient samples can be mixed within the syringe either manually or automatically by the analyzer. Mixing is accomplished via magnetic coupling to a mixing wire (stir bar) internal to the syringe. Samples are injected into the analyzer through a software trigger. No contact with the patient sample or syringe is required to transport the sample into the analyzer.

5. Calibration:

   Calibration of the instrument is accomplished manually or automatically through on-board timers and loaded calibrators. The unit automatically performs a 1 point calibration after 11 user measurements or if the instrument has idled for more than 30 minutes. The unit will automatically perform a 2 point calibration every hour for 4 hours after a reset. After this 4 hour period, the instrument automatically performs a 2 point calibration every 4 hours.

6. Quality Control:

   The instrument supports the use of 4 levels of loaded, always-ready control material. Measurements on a control can be made manually through the instrument interface. In addition, the instrument will automatically run quality control material according to a pre-programmed schedule. The schedule can be set and protected at the administrator level.

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

Not applicable to this submission.

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.