

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE**

A. 510(k) Number:

k103376

B. Purpose for Submission:

New device

C. Measurand:

Creatinine

D. Type of Test:

Enzymatic, colorimetric, quantitative

E. Applicant:

Seppim S.A.S.

F. Proprietary and Established Names:

ELITech Clinical Systems Creatinine PAP SL

ELITech Clinical Systems Elical 2

ELITech Clinical Systems Elitrol I and II

G. Regulatory Information:

Regulation	Classification	Product Code	Panel
21 CFR 862.1255 Creatinine Test system	Class II	JFY	Chemistry (75)
21 CFR 862.1150 Calibrator	Class II	JIX	Chemistry (75)
21 CFR 862.1660 Quality Control material (assayed and unassayed)	Class I, reserved	JJY	Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:

ELITech Clinical Systems Creatinine PAP SL reagent is for the quantitative in vitro diagnostic determination of creatinine in human serum and plasma on the Vital Scientific Selectra/Flexor Analyzers. It is not intended for use in Point of Care settings.

Creatinine measurements are used in the diagnosis and treatment of renal diseases, and in monitoring renal dialysis.

ELITech Clinical Systems ELICAL 2 is a multi-parametric calibrator for in vitro diagnostic use in the calibration of quantitative ELITech Clinical Systems methods on Vital Scientific Selectra Junior Analyzer and the Vital Scientific Flexor Junior Analyzers.

ELITech Clinical Systems ELITROL I is a multi-parametric control serum for in vitro diagnostic use in accuracy control of quantitative ELITech Clinical Systems methods on the Vital Scientific Selectra Junior Analyzer and the Vital Scientific Flexor Junior Analyzer.

ELITech Clinical Systems ELITROL II is a multi-parametric control serum for in vitro diagnostic use in accuracy control of quantitative ELITech Clinical Systems methods on the Vital Scientific Selectra Junior analyzer and the Vital Scientific Flexor Junior Analyzers.

3. Special conditions for use statement(s):

The test system is not for use in Point of Care settings

4. Special instrument requirements:

Performance was provided for the Vital Scientific Selectra Junior Analyzer which is also trademarked as the Vital Scientific Flexor Junior Analyzer.

I. Device Description:

The ELITech Clinical Systems Creatinine PAP SL reagent kit consists of two liquid ready to use reagents, "R1" and "R2". Reagent R1 contains: MOPS buffer (pH 7.50), EHSPT (N-Ethyl-N-2(-Hydroxy-3-Sulfopropyl)-*m*-Toluidine), Creatinase (microorganism), Sarcosine oxidase (microorganism), Ascorbate oxidase (vegetal).

Reagent R2 contains: MOPS buffer (pH 7.50), Amino-4-antipyrine (4-AAP), Creatininase (bacterial), Peroxidase (horseradish), and Sodium azide.

ELITech Clinical Systems ELICAL 2 is a lyophilized calibrator based on human serum containing added constituents.

ELITech Clinical Systems ELITROL I and II is a two level quality control product consisting of lyophilized human serum containing constituents at desired levels.

ELICAL2, ELITROL I and II are prepared exclusively from the blood of donors tested individually and found to be negative for HbsAg and to antibodies to HCV and HIV according to FDA-approved methods or methods in compliance with the European Directive 98/79/EC, Annex II, List A.

J. Substantial Equivalence Information:

Predicate device name(s) and K number(s):

Roche cobas c 111 Creatinine plus ver. 2 (k024098)

Roche Diagnostics Calibrator for Automated Systems (C.f.a.s) (k033501)

Roche Diagnostics Precinorm Universal and Precipath Universal Control Sera (k041227)

3. Comparison with predicate:

Similarities and Differences ELITECH Clinical Systems Creatinine PAP SL		
Item	Device	Predicate
Indications for use	Same	Creatinine measurements are used in the diagnosis and treatment of renal diseases, and in monitoring renal dialysis
Type of test	Same	Enzymatic colorimetric
Specimen	Serum and lithium heparin plasma	Serum, lithium heparin and EDTA plasma, urine
Standardization	Same	Traceable to ID-MS
Reportable range	0.28-22.30 mg/dL	0.06-30.5 mg/dL

Similarities and Differences ELITech Clinical Systems ELICAL 2		
Item	Device	Predicate
Intended use	Same	For in vitro diagnostic use

Similarities and Differences ELITech Clinical Systems ELICAL 2		
Item	Device	Predicate
		in the calibration of quantitative methods
Matrix	Same	Lyophilized calibrator based on human serum with constituents added as required to obtain desired component levels
Level	Same	Single level
Storage and stability	Same	Lyophilized: store at 2-8° C and protect from light until the expiry date. After reconstitution: 8 hrs between 15-25° C, 2 days between 2-8° C, 4 weeks between -25° to -15° C (freeze only once).

Similarities and Differences ELITech Clinical Systems ELITROL I and II		
Item	Device	Predicate
Intended use	Same	For in vitro diagnostic use in accuracy control of quantitative methods
Matrix	Same	Lyophilized calibrator based on human serum with constituents added as required to obtain desired component levels
Levels	Same	Two levels
Stability	Same	Lyophilized: store at 2-8° C and protect from light until the expiry date. After reconstitution: 12 hrs between 15-25° C, 5 days between 2-8° C, 4 weeks between -25° to -15° C (when frozen once).

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

Evaluation of precision performance of quantitative measurement methods; Approved guideline (CLSI EP5-A2)

Evaluation of the linearity of the measurement of quantitative procedures: a statistical approach, Approved guideline (CLSI EP6-A)

Interference Testing in Clinical Chemistry, Approved guideline (CLSI EP7-A2)

Method comparison and bias estimate using patient samples-Second Edition (CLSI EP9-A2)

Protocols for Determination of Limits of Detection and Limits of Quantitation; Approved Guideline (CLSI EP17-A)

L. Test Principle:

Creatininase hydrolyzes creatinine in the sample to creatine. Creatine is hydrolyzed by creatinase to sarcosine and urea. Sarcosine is then oxidized by sarcosine oxidase to produce hydrogen peroxide (H₂O₂). H₂O₂ reacts with 4-amino-antipyrine (4-AAP) and EHSPT (N-Ethyl-N-2(-Hydroxy-3-Sulfopropyl)-m-Toluidine) under the catalytic action of peroxidase to form a colored quinoneimine. The absorbance of the quinoneimine at 546 nm is proportional to the concentration of creatinine in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A precision study was performed by assaying three serum pools at varying concentrations over 20 operating days, on one Selectra Junior analyzer and with one lot of reagent. Assay runs were performed twice per day and each sample was tested in duplicate. Calibration was performed for each run. The results are summarized below.

Samples	n	Mean (mg/dL)	Within-run		Total	
			SD	CV(%)	SD	CV(%)
Serum pool 1	80	0.59	0.01	1.3%	0.02	3.2%
Serum pool 2	80	1.62	0.01	0.8%	0.03	1.6%
Serum pool 3	80	6.93	0.09	1.4%	0.19	2.8%

Another precision study was performed by assaying three serum pools and one control at varying concentrations over 10 operating days, on two Selectra Junior analyzers and with two lots of reagents. Assay runs were performed once per day and calibrated according to the device labeling. Each sample was tested in duplicate. The results are summarized below.

Samples	n	Mean (mg/dL)	Within-run		Total	
			SD	CV(%)	SD	CV(%)
Serum pool 1	40	0.58	0.01	2.3%	0.02	2.9 %
Serum pool 2	40	1.57	0.02	1.5 %	0.03	2.0 %
Serum pool 3	40	6.70	0.05	0.7 %	0.12	1.7 %
Control	40	3.74	0.02	0.7 %	0.06	1.6%

b. Linearity/assay reportable range:

A linearity study across the claimed assay range was performed by preparing samples from patient serum pools at a low creatinine concentration (0.28 mg/dL) and a high concentration (22.32 mg/dL). The low pool contained serum diluted with saline. The low and high pools were mixed in different proportions to create 9 dilutions. Eleven samples in all were assayed in triplicate

Data was analyzed using 1st, 2nd, and 3rd order least square regressions according to CLSI Protocol EP6-A. Based on the analysis the sponsor determined that first order regression was the best fit. The analysis of the first order regression yielded the following equation:

$$1^{\text{st}} \text{ order } y = 2.2x - 1.84$$

Additionally, the expected values were plotted against the observed values and a linear regression line was fitted with the following regression equation:

$$y = 0.9939x + 0.14, r^2 = 0.9999$$

Based on these results, the sponsor claims that the assay is linear from 0.28-22.30 mg/dL.

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

The calibrator material is purchased from a commercially available source. The creatinine in ELICAL 2 is traceable to ID-MS (Isotope dilution-Mass Spectrometry). Elical 2 calibrator is value assigned from an internal master lot of calibrator using three bottles of reconstituted Elical 2 calibrator evaluated in two runs on two Vital Scientific Flexor Junior Analyzers. The target value is the mean of the observed range of values and is listed on value sheet accompanying each lot of Elical 2. The sponsor claims the following

stability for Elical 2 after reconstitution: up to 8 hours when stored at 15-25° C, 2 days when stored at 2-8° C, and 4 weeks when stored at -25° to -15° C (freeze only one). The lyophilized material (unopened) is stable until the expiration date printed on the vial, 11 months when stored at 2-8° C.

Elitrol I and II control solutions are value assigned using two Vital Scientific Flexor Junior Analyzers. Each sample is tested in triplicate over several days. The target value of Level I and II are the median of the observed values range. After validation of the target value, a confidence range (high and low values) is calculated. The confidence range and target values are listed on the value sheet accompanying each lot of Elitrol I and II. The sponsor claims the following stability after reconstitution: up to 12 hrs between 15-25° C, 5 days between 2-8° C, 4 weeks between -25° to -15° C (when frozen once). The lyophilized material (unopened) is stable until the expiration date printed on the vial, 30 months when stored at 2-8° C.

d. Detection limit:

The sponsor states that the Limits of Blank (LoB), Detection (LoD) and Quantitation (LoQ) studies were conducted following CLSI EP17-A. The LoB study was performed by assaying 60 replicates of a blank sample in one assay run. The LoD was determined by assaying 15 replicates of four diluted patient pools with very low creatinine concentrations in one assay run. The LoQ was determined by assaying 15 replicates of four diluted patient pools with low creatinine concentrations (approximately 0.28 mg/dL) in one assay run. Each study was performed using one Selectra Junior analyzer and one lot of creatinine reagent.

The sponsor states that the limit of blank is 0.001 mg/dL and the limit of detection 0.0065 mg/dL, however the analyzer does not report creatinine values below the claimed limit of quantitation. The limit of quantitation based on the study described above is stated to be 0.28 mg/dL. Imprecision of the samples evaluated in the LoQ study ranged from 1.4-4.8% (CV%).

e. Analytical specificity:

Testing for interfering substances was based on CLSI EP-7A. Testing was performed on a minimum of five concentrations for each interfering substance. Two different clinically relevant concentrations of creatinine (1.58 and 6.67 mg/dL) were used for evaluation. Samples with increasing amounts of potential interferents were tested in triplicate and compared to the same sample without the interferent.

The sponsor defined non-significant interference as the highest level tested that does not cause >10% change between the tested samples and the control sample.

	Highest concentration tested that showing no significant interference (mg/dL) ($\leq 10\%$)
Triglyceride	3,198
Unconjugated Bilirubin	30
Conjugated Bilirubin	14.8
Hemoglobin	500
Glucose	550
Ascorbic Acid	20
Uric acid	24

A positive bias was observed with creatine ≥ 5 mg/dL.

Calcium dobesilate, Methyl-dopa and L-dopa cause falsely low results at therapeutic concentrations.

A summary of these results and interferences is found in the labeling.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The performance of the Creatinine PAP SL reagent on the Selectra Junior analyzer was compared with the Roche Creatinine plus v2 reagent on the cobas c111 analyzer. Study performed according to CLSI protocol EP9-A2 using 91 serum samples covering the measuring range with values from 0.3 to 20.30 mg/dL. The linear regression results are summarized below:

	Regression parameters	Confidence Interval 95%	
		Lower 95%	Upper 95%
Slope (b)	1.045	1.039	1.052
Intercept (a)	-0.01	-0.05	0.04

b. Matrix comparison:

To demonstrate comparable performance between serum and lithium heparin, the sponsor evaluated 36 matched serum and plasma sets ranging from 0.33 to

21.46 mg/dL on the Selectra Junior analyzer. The linear regression analysis resulted in a slope of 1.013 (95% CI 1.008-1.018), an intercept of 0.00 (95% CI -0.03 to 0.03), correlation coefficient of $r=1.000$

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:

In the labeling, the sponsor recommends that each laboratory should establish and maintain its own reference values. The data given are for information only.

REFERENCE VALUES

	Men	Women
Serum :	0.72 - 1.18	0.55 - 1.02 mg/dL
	64 - 104	49 - 90 $\mu\text{mol/L}$

Ceriotti, F., Reference Intervals for Serum Creatinine Concentrations: Assessment of Available Data for Global Application. Clin. Chem., (2008), 54, 559.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.