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

A. 510(k) Number:

k171401

B. Purpose for Submission:

Modification of ELITech Clinical Systems BILIRUBIN TOTAL 4+1 and ELITech Clinical Systems BILIRUBIN DIRECT 4+1: changes to the reagent formula and analyzer test parameters.

C. Measurand:

Direct and Total Bilirubin

D. Type of Test:

Quantitative, colorimetric

E. Applicant:

ELITechGroup

F. Proprietary and Established Names:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1

ELITech Clinical Systems BILIRUBIN DIRECT 4+1

G. Regulatory Information:

Regulation section	Classification	Product code	Panel
21 CFR 862.1110, Bilirubin (total or direct) test system	II	CIG	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See Indications for use below.

2. Indication(s) for use:

   ELITech Clinical Systems BILIRUBIN TOTAL 4+1 is intended for the quantitative in vitro diagnostic determination of total bilirubin in human serum and plasma on ELITech Clinical Systems Selectra Pro Series Analyzers. Measurements of levels of bilirubin (direct or total), an organic compound formed during the normal and abnormal destruction of red blood cells, are used in the diagnosis and treatment of liver, hemolytic hematological, and metabolic disorders, including hepatitis and gall bladder block. It is not intended for use in Point of Care settings.

   ELITech Clinical Systems BILIRUBIN DIRECT 4+1 is intended for the quantitative in vitro diagnostic determination of direct bilirubin in human serum and plasma on ELITech Clinical Systems Selectra Pro Series Analyzers. Measurements of the levels of bilirubin (direct or total), an organic compound formed during the normal and abnormal destruction of red blood cells, are used in the diagnosis and treatment of liver, hemolytic hematological, and metabolic disorders, including hepatitis and gall bladder block. It is not intended for use in Point of Care settings.

3. Special conditions for use statement(s):

   For Prescription use only.

4. Special instrument requirements:

   Performance data was obtained on the Selectra ProM Analyzer.

I. Device Description:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1 is available as kit only. It consists of 2 reagents, "R1" and "R2". Reagent R1 contains sulfanilic acid 29 mmol/L, and cetrimide 29 mmol/L. Reagent R2 contains sodium nitrite 11 mmol/L.

ELITech Clinical Systems BILIRUBIN DIRECT 4+1 is available as kit only. It consists of 2 reagents, "R1" and "R2". Reagent R1 contains sulfanilic acid 29 mmol/L. Reagent R2 contains sodium nitrite 11 mmol/L.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   ABX Pentra Bilirubin, Total CP
   ABX Pentra Bilirubin, Direct CP

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

   k060325

3. Comparison with predicate:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1

Similarities /Differences		
Characteristics	Candidate Device ELITech Clinical Systems BILIRUBIN TOTAL 4+1	Predicate Device ABX Pentra Bilirubin, Total CP (k060325)
Intended Use	For quantitative in vitro diagnostic determination of total bilirubin in human serum and plasma.	Same
Sample Type	Serum, lithium heparin plasma	Same
Reagents	Liquid form, ready to use	Same
Assay Technology	Malloy-Evelyn modified. End point.	Photometric test using 2,4 dichloroaniline (DCA), and specific mixture of detergents
Assay Range	0.25 mg/dL to 25.00 mg/dL (4.3 to 427.6 µmol/L)	0.14 to 26.3 mg/dL (2.4 to 450.0 µmol/L)
Instrument	Selectra ProM Analyzer	ABX Pentra 400

ELITech Clinical Systems BILIRUBIN DIRECT 4+1

Similarities/Differences		
Characteristic	Candidate Device ELITech Clinical Systems BILIRUBIN DIRECT 4+1	Predicate Device ABX Pentra Bilirubin, Direct CP (k060325)
Intended Use	For the quantitative in vitro diagnostic determination of direct bilirubin in human serum and plasma.	Same
Sample Type	Serum, lithium heparin plasma	Same
Reagents	Liquid form, ready to use	Same
Assay Technology	Malloy-Evelyn modified. End point.	Photometric test using 2, 4 dichloroaniline (DCA), and specific mixture of detergents.
Assay Range	0.08 to 10.55 mg/dL (1.4 to 180.4 µmol/L)	0.04 to 6.79 mg/dL, post-dilution up to 33.0 mg/dL (0.69 to 116 µmol/L)
Instrument	Selectra ProM Analyzer	ABX Pentra 400

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

No standard or guidance documents were referenced.

L. Test Principle:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

Sulphanilic acid reacts with sodium nitrite to form diazotized sulphanilic acid. In the presence of accelerator (cetrimide), conjugated and unconjugated bilirubin react with diazotized sulphanilic acid to form azobilirubin. The increase of absorbance at 546 nm is proportional to the total bilirubin concentration.

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

Sulphanilic acid reacts with sodium nitrite to form diazotized sulphanilic acid. In the absence of accelerator (cetrimide), only conjugated bilirubin reacts with diazoted sulphanilic acid to form azobilirubin. The increase of absorbance at 546 nm is proportional to the direct bilirubin concentration.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. Precision/Reproducibility:

   Precision was evaluated using one serum control material, one human serum pool, and one spiked human serum pool sample. Within-run and total imprecision results were obtained by performing two runs per day, two measures per run, for 3 concentrations of samples on two instruments for twenty days. The results are presented in the table below:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1

Levels	n	Mean (mg/dL)	Within-run		Total	
			SD	CV%	SD	CV%
Level 1	80	1.15	0.02	1.8	0.06	5.0
Level 2	80	4.08	0.02	0.4	0.13	3.1
Level 3	80	14.61	0.08	0.5	0.43	2.9

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

Levels	n	Mean (mg/dL)	Within-run		Total	
			SD	CV%	SD	CV%
Level 1	80	0.36	0.01	3.8	0.02	5.2
Level 2	80	1.51	0.03	1.9	0.08	5.3
Level 3	80	3.99	0.04	0.9	0.19	4.7

b. *Linearity/assay reportable range:*

ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

The linearity of total bilirubin was studied by mixing a patient serum pool sample with a high bilirubin value (25.13 mg/dL) and a sample with low value (0.25 mg/dL) to obtain 11 levels with equidistant concentration, and then measuring the total bilirubin concentration of each of the 11 levels. All samples were assayed in triplicates. Data was analyzed using 1^{st}, 2^{nd} and 3^{rd} order least square regressions. A first order linear regression was generated as follows:

$$y = 1.1067x - 0.2378, r = 0.9994$$

The results of the study support the measuring range of 0.25 to 25.0 mg/dL.

A study evaluating the 1:5 auto-dilution used several spiked samples with total bilirubin concentrations between 32.80 to 115.66 mg/dL. The % recovery between the expected value and observed values were within 10% for samples with total bilirubin concentrations up to 60.00 mg/dL. Therefore the sponsor claimed that samples with total bilirubin concentration greater than the assay claimed measuring range and up to 60.00 mg/dL can be auto-diluted and assayed.

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

The linearity of direct bilirubin was studied by mixing a sample with high value (10.59 mg/dL) and a sample with low value (0.06 mg/dL) to obtain 11 levels with equidistant concentrations and then measuring the direct bilirubin concentration of each of the 11 levels. Data was analyzed using 1st, 2nd and 3rd order least square regressions. A first order linear regression was generated as follows:

$$y = 1.0943x - 0.2244, r = 0.9995$$

The results of the study support the measuring range of 0.08 to 10.55 mg/dL.

A study evaluating the 1:5 auto-dilution study using several spiked samples with direct bilirubin concentrations between 10.86 and 47.49 mg/dL. The % recovery between the expected value and observed values were within 10%. Therefore the sponsor claimed that sample with total bilirubin concentration greater than the assay claimed measuring range and up to 50.00 mg/dL can be auto-diluted and assayed.

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

Traceability:
The calibrator for the assay is ELITech Clinical Systems ELICAL 2 (cleared in k110780).

Controls recommended for the assay are ELITROL I and ELITROL II (cleared in k110780).

Stability:
An On-board stability study was performed for 30 days. Protocols and acceptance criteria for the stability study were reviewed and found acceptable. The study results support an on-board stability for 28 days for both total and direct bilirubin reagents.

A real time shelf-life stability study has been performed for 24 months at 2-8ºC. Protocols and acceptance criteria for the stability study were reviewed and found acceptable. The study supports a real time stability for both products at 24 months.

d. Detection limit:

The limits of blank (LoB), detection (LoD) and quantitation (LoQ) studies were conducted on two Selectra Pro Analyzers with two lots of reagents. The LoB was determined by analyzing a blank sample 60 times. LoD and LoQ studies each used 4 serum pools measured 15 times for both assays for a total of 60 measurements for each. The serum pools for LoD had concentrations approximately 4 times the LoB. LoQ was determined by analyzing 4 serum pools with analyte concentrations near the expected LoQ. Results are summarized below:

Assay	LoB	LoD	LoQ
Total bilirubin	0.01 mg/dL	0.04 mg/dL	0.15 mg/dL
Direct bilirubin	0.00 mg/dL	0.01 mg/dL	0.08 mg/dL

The ELITech Clinical Systems BILIRUBIN TOTAL 4+1 assay has a measuring range of 0.25 to 25.00 mg/dL.

The ELITech Clinical Systems BILIRUBIN DIRECT 4+1 assay has a measuring range of 0.08 to 10.55 mg/dL.

e. Analytical specificity:

Testing for interfering substances was performed on different concentrations for each interfering substances on both total and direct bilirubin assays. Samples with increasing amounts of triglycerides, hemoglobin, acetaminophen, acetylsalicylic, and ascorbic acid were tested in triplicates and compared to the same sample without the interfering substances. 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. Results are summarized in the tables below.

ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

The two levels of serum pool samples with a low and high concentrations of (1.0 and 15.0 mg/dL) of total bilirubin were tested and yielded the following results.

Substance Tested	Highest concentration tested showing non-significant interference (mg/dL)
Triglycerides	2100
Hemoglobin	500
Acetaminophen	30
Ascorbic acid	4
Acetylsalicylic acid	200

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

Two levels of serum pool samples with a low and high concentrations of (0.40 and 4.00 mg/dL) of direct bilirubin were tested and yielded the following results.

Substances tested	Highest concentration tested showing non-significant interference (mg/dL)
Triglycerides	2000
Hemoglobin	125
Acetaminophen	30
Ascorbic acid	0.5
Acetylsalicylic acid	200

Based on the interference study the following limitations are included in the labeling.

For ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

In very rare cases monoclonal gammapathies (multiple myeloma) in particular IgM type (Waldenstroms macroglobulinemia) can cause unreliable results.[1]

[1]Berth, M. & Delanghe, J. Protein precipitation as a possible important pitfall in the clinical chemistry analysis of blood samples containing monoclonal immunoglobulins: 2 case reports and a review of literature, Acta Clin Belg., (2004), 59, 263."

For ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

Ascorbic acid concentrations greater than 0.5 mg/dL cause falsely elevated total bilirubin results.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

A method comparison study was performed between the ELITech Clinical Systems BILIRUBIN TOTAL 4+1 reagents on a Selectra ProMAnalyzer and the ABX Pentra Total bilirubin reagent on an ABX Pentra analyzer. A total of 100 serum samples were tested including 10 contrived samples. The concentration range of samples tested was 0.32 to 23.02 mg/dL.
Regression analysis of the results yielded the following:

$y = 0.948x - 0.11$ $r^2 = 0.999$

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

A method comparison study was performed using the ELITech Clinical Systems BILIRUBIN DIRECT 4+1 reagent on Selectra Pro M Analyzer and the ABX Pentra Direct bilirubin reagent on an ABX Pentra analyzer. A total of 100 samples were tested including 10 contrived samples. The concentrations range of the samples tested was 0.09 to 10.52 mg/dL. Regression analysis of the results yielded the following:

$y = 0.926x - 0.03$ mg/dL $r^2 = 0.995$

b. Matrix comparison:

ELITech Clinical Systems BILIRUBIN TOTAL 4+1:

A matrix comparison study was performed by testing 40 paired serum and lithium heparin plasma samples using the ELITech Clinical Systems BILIRUBIN TOTAL 4+1 reagents on the Selectra Pro M Analyzer. Four out of the 40 samples were spiked. Samples range tested was 0.33 to 24.08 mg/dL. A result of the linear regression analysis is shown below:

$y = 0.985x + 0.03$ $r^2 = 0.997$

ELITech Clinical Systems BILIRUBIN DIRECT 4+1:

A sample matrix comparison study was performed by testing 40 paired serum and lithium heparin plasma samples using the ELITech Clinical Systems BILIRUBIN DIRECT 4+1 reagent on the Selectra Pro M Analyzer. Four of the 40 samples were spiked. Sample range tested was 0.09 to 7.78 mg/dL. A result of the linear regression analysis is shown below:

$y = 0.990x - 0.01$ $r^2 = 0.997$

The results of the matrix comparison study support the claim that serum and lithium heparin plasma samples can be used with these assays.

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:

   Total bilirubin: Serum, Plasma: Adults 0.2 to 1.12 mg/dL[2]

   Direct bilirubin: Serum, Plasma: <0.2 mg/dL[2]

   The above reference values are from:

   [2]Wu, H.B., General Clinical Tests. Tietz Clinical guide to laboratory tests, 4th Ed., (W.B. Saunders eds. Philadelphia USA), (2006), 172

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.