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

A. 510(k) Number:

k121985

B. Purpose for Submission:

Modification of a previously cleared total bilirubin assay (k060574) – reduced sample size from 4.0 uL to 2.6 uL.

C. Measurand:

Total Bilirubin

D. Type of Test:

Quantitative, enzymatic, colorimetric assay

E. Applicant:

Abbott Laboratories

F. Proprietary and Established Names:

ARCHITECT Total Bilirubin

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CIG	Class II	21 CFR §862.1110, Bilirubin (total or direct) test system	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indications for use below.

2. Indication(s) for use:

   The ARCHITECT Total Bilirubin assay is used for the quantitation of total bilirubin in human serum or plasma on the ARCHITECT c8000 system. Measurement of total bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis and treatment of liver, hemolytic hematological and metabolic disorders, including hepatitis and gall bladder block.

   A bilirubin (total and unbound) in the neonate test system is a device intended to measure the levels of bilirubin (total and unbound) in the blood (serum) of newborn infants to aid in indicating the risk of bilirubin encephalopathy (kernicterus).

3. Special conditions for use statement(s):

   For prescription use only

4. Special instrument requirements:

   Abbott ARCHITECT c8000

I. Device Description:

The total bilirubin reagent kit is packaged as two liquid, ready-to-use reagents, R1 and R2. The following reactive ingredients are presented in the following table:

	Reactive Ingredients	Concentration
R1	Surfactants	4.51%
	HCl	8.204 g/L
R2	2,4 – dichloroaniline	0.81 g/L
	HCl	5.563 g/L
	Sodium Nitrite	0.345 g/L
	Surfactant	1.96%

This device is the same as the device cleared previously in the Abbott Total Bilirubin assay (k060574). The only claimed change to the device is the sample volume (4.0µL to 2.6 µL).

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Abbott Total Bilirubin

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

   k060574

3. Comparison with predicate:

Similarities and Differences

Characteristic	Predicate device: Abbott Total Bilirubin (k060574)	Candidate device: ARCHITECT Total Bilirubin
Intended Use	The Total Bilirubin assay is used for the quantitative analysis of total bilirubin in human serum or plasma of adults and neonates	Same
Test Method	Coupling with the diazo reagent in the presence of a surfactant to form azobilirubin and detection at 548 nm.	Same
Detection of Analyte	End-point colorimetric	Same
Calibration Curve Type	3 point curve	Same
Specimen Type	Serum or plasma	Same
Patient population	Adults and Neonates	Same
Platform	ARCHITECT c8000 Analyzer	Same
Measuring Interval	0.1 to 25.0 mg/dL	Same
Sample size	4.0 µL	2.6 µL

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

CLSI documents:

Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A3)

Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A2)

Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach (EP6-A)

Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A2)

Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A2)

Protocols for Determination of Limits of Detection and Limits of Quantitation (EP17-A)

L. Test Principle:

The total bilirubin assay is a quantitative colorimetric measurement of total bilirubin in human (adult and neonates) serum or plasma. Total (conjugated and unconjugated) bilirubin couples with the diazo reagent in the presence of a surfactant to form azobilirubin. The increase in absorbance at 548 nm due to azobilirubin is directly proportional to the total bilirubin concentration.

M. Performance Characteristics (if/when applicable):

1. <u>Analytical performance:</u>

a. Precision/Reproducibility:

Precision was performed for 20 days using one lot of reagent, one lot of calibrators, and one lot of controls following guidance outlined in CLSI EP5-A2. All testing was performed on the ARCHITECT c8000. Four control levels (level 1, level 2, level 3, and level 4) were tested in replicates of two, in two runs per day for 20 days (N=80). Results are summarized in the following table:

20 day precision for serum controls

Matrix	Level	N	Mean (mg/dl)	Within-run		Between-run		Total precision	
				SD	%CV	SD	%CV	SD	%CV
Serum Controls	1	80	0.75	0.01	1.23	0.00	0.43	0.01	1.96
	2	80	4.11	0.02	0.48	0.03	0.76	0.06	1.43
	3	80	5.86	0.03	0.43	0.02	0.41	0.07	1.20
	4	80	15.70	0.05	0.31	0.08	0.52	0.16	1.00

An additional 5 day precision study was performed using patient samples, with one lot of reagent, one lot of calibrators, and one lot of controls. All testing was preformed on the Architect c8000. Three levels of serum concentrations were tested in replicates of five for five days (N=50). Results are summarized in the following table:

Matrix	Level	N	Mean	Total SD	Total % CV
Serum	1	50	0.89	0.027	3.0
	2	50	9.52	0.159	1.7
	3	50	22.14	0.219	1.0

b. Linearity/assay reportable range:

A linearity study was performed following guidance from CLSI EP6-A. Nine samples were prepared by diluting a high patient sample with a low patient sample to obtain concentrations that span the entire claimed measuring range. Each serum sample was tested in replicates of four using one lot of reagent on the ARCHITECT c8000 instrument. The concentrations of samples tested spanned the claimed measuring range 0.1 to 25 mg/dL. Three linearity studies were conducted with the following components of total bilirubin: 75% Conjugated and 25% Unconjugated, 50% Conjugated and 50% Unconjugated, 25% Conjugated and 75% Unconjugated. The observed values were plotted against the expected values and an appropriate line fitted by standard linear regression. The following is a representative summary of results from these studies:

	Serum
Correlation (r)	1.00
Slope	0.98
Intercept	0.06

The linearity data support the sponsor's claim that the measuring range for serum is 0.1 - 25 mg/dL

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

Calibrators were previously cleared- See k060574 for traceability, stability, and expected value information.

d. Detection limit:

The sponsor conducted a Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) study following the CLSI EP-17A guideline. The LoB was determined using three ARCHITECT instruments (N=60 per instrument) using three blank samples. This study was conducted over one day. LoD and LoQ study was performed on two ARCHITECT c8000 Systems in 5 runs over 3 days with several low samples. LoQ is defined as

the value obtained with ≤ 20% CV. The following is a summary of results:

Device	Reportable range	LoB	LoD	LoQ
Total Bilirubin	0.1 – 25 mg/dL	0.01 mg/dL	0.05 mg/dL	0.07 mg/dL

These detection limit studies support the claimed measuring range 0.1 – 25 mg/dL.

e. Analytical specificity:

A study of common interferents was conducted. Solutions of human serum albumin were spiked with two levels of bilirubin (a high normal total bilirubin and an abnormal high total bilirubin). These two solutions were spiked with varying levels of interferent. The spiked samples were tested in seven replicates and these results were compared to seven replicates of a reference sample (without spiked interferent). Interference was evaluated at two medical decision points for total bilirubin. The percent recovery was determined by dividing the mean result of replicates for each interferent level by the mean result of the replicates for the reference sample. The sponsor's acceptance criteria was set at ± 10% or ± 0.3 mg/dL difference between the interferent results and the reference results, whichever is greater (The acceptance criteria of ≤ 10% or ± 0.3 mg/dL is applied using the ≤10% criteria first. If the percentage is > 10%, the observed vs. target values must be within 0.3mg/dL). The following is a summary of results:

Intralipid at concentrations > 750 mg/dL have been shown to interfere with the measurement of Total Bilirubin at the target concentration of 1.2744 mg/dL. Indican concentrations > 0.175 mmol/L have been shown to interfere with Total Bilirubin target concentrations at 1.3241 mg/dL. Hemoglobin tested up to 2000 mg/dL do not interfere with the total bilirubin assay.

Other interferences from medications or endogenous substances may affect results and the sponsor refers user to the literature for more information in the labeling.

Literature cited: Young, D.S. *Effects of Preanalytical Variables on Clinical Laboratory Tests*, 2nd ed. Washington DC: AACC Press; 1997:3-85

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was conducted using 138 adult serum samples ranging from 0.11 to 23.96 mg/dL. All samples were tested on the Architect c8000 System and the candidate device was compared against the predicate device. The following table provides a summary of the regression analysis:

Adult Sample comparison:

Sample type	N	Range (mg/dL)	Slope	Intercept	Correlation Coefficient
Serum	138	0.11 – 23.96	0.98	0.07	0.9991

In addition, 54 neonate serum samples ranging from 0.94 to 19.05 mg/dL were compared using the candidate device evaluated on the Architect c8000 System against another FDA cleared device (Roche total bilirubin on Hitachi 717). The following table provides a summary of the regression analysis:

Neonatal Sample comparison:

Sample type	N	Range (mg/dL)	Slope	Intercept	Correlation Coefficient
Serum	54	0.94 – 19.05	0.99	0.32	0.9967

b. Matrix comparison:

Thirty subjects' total bilirubin results using glass serum tube (control) were compared to plastic K2 EDTA, Lithium heparin with and without a gel barrer, and sodium heparin tubes. All the results generated from the plastic tubes (SST tube, lithium heparin, sodium heparin, and plasma lithium heparin with gel separator) had less than 10% differences when compared to the glass tube (control). Total bilirubin concentrations tested range from 0.1 to 25 mg/dL. Passing-Bablok regression analysis results are summarized below:

			Passing-Bablok			
			Slope		Intercept	
Tube Type	**N**	**Corr Coef**	**Slope**	**95% CI**	**Intercept**	**95% CI**
Serum Separator Tube (SST)	30	0.9999	1.00	(0.99, 1.01)	0.01	(0.00, 0.02)
K2 EDTA Plasma Tube (non gel)	30	0.9995	1.05	(1.02, 1.07)	-0.01	(-0.10, 0.00)
Lithium Heparin Plasma Tube (non gel)	30	0.9998	1.00	(0.99, 1.01)	0.01	(-0.01, 0.01)
Lithium Heparin Plasma Tube (Plasma Separator Tube PST) with gel	30	0.9999	1.00	(1.00, 1.00)	0.00	(-0.00, 0.01)
Sodium Heparin Plasma Tube (non gel)	30	0.9999	1.00	(0.99, 1.00)	0.00	(0.00, 0.01)

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:

Adult Range: A reference range confirmation study was performed following guidance from CLSI C28-A3 using 26 samples. The study confirms with a 95% confidence interval an adult reference range of 0.2 to 1.2 mg/dL.

The expected values for the neonates are based on the literature*

Reference Range	Premature Newborn: < 24 Hours < 8.0 < 48 Hours < 12.0 3 to 5 Days < 15.0 7 Days < 15.0 Full Term Newborn: < 24 Hours < 6.0 < 48 Hours < 10.0 3 to 5 Days < 12.0 7 Days < 10.0 Adult: 0.2 to 1.2 mg/dL

The following reference was cited: *American Academy on Pediatrics Subcommittee on Hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004; 114(1):297-316.

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.