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

A. 510(k) Number:

k170065

B. Purpose for Submission:

Addition of claim, for use in neonate serum and plasma

C. Measurand:

Total Bilirubin

D. Type of Test:

Quantitative colorimetric, vanadate oxidation

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

ADVIA® Chemistry Total Bilirubin_2 (TBIL_2)

G. Regulatory Information:

Product Code	Classification	Regulation	Panel
JFM	II	21 CFR §862.1110	Clinical Chemistry (75)
MQM	I, reserved	21 CFR §862.1113	

H. Intended Use:

1. Intended use(s):

   See indications for use statement below.

2. Indication(s) for use:

   For *in vitro* diagnostic use in the quantitative determination of total bilirubin in human serum and plasma of adults and neonates on the ADVIA® Chemistry systems.

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 total bilirubin measurement in newborn infants is intended to aid in indicating the risk of bilirubin encephalopathy (kernicterus).

3. Special conditions for use statement(s):

   This device is for prescription use only.

4. Special instrument requirements:

   Assay performance was demonstrated on the ADVIA® 1800 Chemistry Analyzer.

I. Device Description:

The ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) consists of two reagents that are liquid and ready to use. The reagents are packaged in wedges to be used directly on the ADVIA® Chemistry Systems.

Reagent 1 contains citrate buffer, pH 2.9 (0.1 M) and detergent. Reagent 2 contains phosphate buffer, pH 7.0 (10 mM) and 4 mM sodium metavanadate.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Abbott Laboratories Total Bilirubin

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

   k150510

3. Comparison with predicate:

Similarities		
Item	Candidate Device: ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) (k170065)	Predicate Device: Abbott Laboratories Total Bilirubin (k150510)
Intended use	For in vitro diagnostic use in the quantitative determination of total bilirubin in human serum and plasma of adults and neonates.	Same
Measurand	Total Bilirubin	Same
Sample Types	Serum and plasma from adults and neonates	Same

Similarities		
Item	Candidate Device: ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) (k170065)	Predicate Device: Abbott Laboratories Total Bilirubin (k150510)
Detection of Analyte	End-point colorimetric	Same
Reagent Form	Liquid, ready to use	Same

Differences		
Item	Candidate Device: ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) (k170065)	Predicate Device: Abbott Laboratories Total Bilirubin (k150510)
Assay Principle	The bilirubin is oxidized by vanadate at about pH 2.9 to produce biliverdin. In the presence of the detergent and the vanadate, both conjugated (direct) and unconjugated bilirubin are oxidized. This oxidation reaction causes the decrease in the optical density of the yellow color, which is specific to bilirubin. The decrease in optical density at 451/545 nm is proportional to the total bilirubin concentration in the sample.	Total (conjugated and unconjugated) bilirubin couples with a diazo reagent in the presence of a surfactant to form azobilirubin. The diazo reaction is accelerated by the addition of surfactant as a solubilizing agent. The increase in absorbance at 548 nm due to azobilirubin is directly proportional to the total bilirubin concentration.
Measurement Protocol	Vanadate oxidation method	Diazo colorimetric method
Reagent Composition	R1: Citrate buffer, pH 2.9 (0.1 mol/L); Detergent R2: Phosphate buffer, pH 7.0 (10 mmol/L); Sodium metavanadate (4 mmol/L)	R1: Surfactants (10.57%), HCl (6.563 g/L) R2: 2, 4-dichloroaniline (0.81 g/L), HCl (5.563 g/L), sodium nitrate (0.345 g/L), Surfactant (1.96%)
Measuring Range	0.15 - 35 mg/dL	0.3 - 25 mg/dL
Expected values	Age: 0-1 day: <8.0 mg/dL 1-2 days: <12.0 mg/dL 3-5 days: <16.0 mg/dL >5 days – 60 years: 0.3-1.2 mg/dL* 60 – 90 years: 0.2-1.1 mg/dL >90 years: 0.2-0.9 mg/dL *Ages >5 days to <29 days are neonates and >29 days to 60 years are children and adults.	<u>Premature Newborn</u> <24 hours: <8.0 mg/dL <48 hours: <12.0 mg/dL 3 to 5 days: <15.0 mg/dL 7 days: <15.0 mg/dL <u>Full Term Newborn</u> <24 hours: <6.0 mg/dL <48 hours: <10.0 mg/dL 3 to 5 days: <12.0 mg/dL 7 days: <10.0 mg/dL <u>Adults</u>: 0.3 – 1.2 mg/dL

Differences		
Item	Candidate Device: ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) (k170065)	Predicate Device: Abbott Laboratories Total Bilirubin (k150510)
Instrument	ADVIA® Chemistry 1800 System	ARCHITECT c8000 System

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

CLSI EP05-A2. Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline; Second Edition.

CLSI EP06-A. Evaluation of the Linearity of Quantitative Analytical Measurement Procedure: A Statistical Approach, Approved Guideline.

CLSI EP07-A2. Interference Testing in Clinical Chemistry, Approved Guideline, Second Edition.

CLSI EP09-A3. Measurement Procedure Comparison and Bias Estimation Using Patient Samples, Approved Guideline, Third Edition.

CLSI EP 17-A2. Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline; Second Edition.

CLSI EP28-A3c. Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory, Approved Guideline, Third Edition.

L. Test Principle:

The ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) method is based on a chemical oxidation method using vanadate as an oxidizing agent. The bilirubin is oxidized by vanadate at about pH 2.9 to produce biliverdin. In the presence of the detergent and the vanadate, both conjugated (direct) and unconjugated bilirubin are oxidized. This oxidation reaction causes the decrease in the optical density of the yellow color, which is specific to bilirubin. The decrease in optical density at 451/545 nm is proportional to the total bilirubin concentration in the sample. The concentration is measured as an endpoint reaction.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) was previously established in k063845.

b. *Linearity/assay reportable range:*

Linearity was evaluated according to CLSI EP06-A. A high serum pool was prepared by spiking human serum with unconjugated bilirubin at a known concentration. A low serum pool was prepared by dilution of human serum with saline. Dilutions were prepared by mixing different proportions of the high and low serum pools to create nine (9) samples (0, 5, 9.9, 14.8, 19.8, 24.7, 29.6, 34.5, and 39.2 mg/dL), which spanned the assay range. Samples were assayed in triplicate and the mean result was compared to the expected values determined by the dilution scheme. Linear regression analysis of the mean observed concentration and expected values is summarized in the table below.

Slope	y- intercept	r
0.999	0.0510	0.999

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

The ADVIA® Chemistry Calibrator, traceable to the AACC reference method (Doumas), was previously cleared in k030169.

d. *Detection limit:*

Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) were determined in accordance with CLSI EP17-A2. The LoB, LoD, and LoQ for bilirubin were determined by running replicate measurements on blank and low level analyte serum samples using three reagent lots, one calibrator lot, one system, and one operator across multiple days.

LoB was determined by running 4 blank samples in 5 replicates over 3 days (for a total of 60 replicates per lot). LoD and LoQ were determined by testing 4 low analyte samples in 20 replicates over 3 days. LoB and LoD were calculated nonparametrically. The limit of quantitation (LoQ) was calculated for each reagent lot with the maximum LoQ across all reagent lots taken as the LoQ for the assay. The results are summarized in the table below.

LoB	LoD	LoQ
0.02 mg/dL	0.06 mg/dL	0.08 mg/dL

The measuring range of the assay is 0.15 - 35.1 mg/dL and is supported by the linearity and detection limit studies.

e. *Analytical specificity:*

Interference testing of ascorbic acid and triglycerides for ADVIA® Chemistry Total Bilirubin 2 (TBIL_2) was established in k063845. Interferences typically seen in

neonates were evaluated according to CLSI EP7-A2 using one reagent lot and one calibrator lot.

Interference from cyanokit and 3 endogenous compounds was evaluated using native serum samples with low (~ 1 mg/dL) and high (~10 mg/dL) bilirubin levels. Bilirubin samples were prepared by spiking a native serum pool with approximately 1 mg/dL or 10 mg/dL bilirubin. Test samples were prepared by spiking each drug or endogenous substance (at least five concentrations per interferent) into the low and high bilirubin samples. Test samples were assayed in triplicate and the mean concentration of bilirubin for each interferent concentration was compared to control samples containing no interferent. The sponsor defined significant interference as greater than or equal to 10% difference between the test and control samples.

Potentially Interfering Substance	Highest concentration of interferent tested that did not show significant interference
Indican	10 mg/dL
Cyanokit	40 µg/mL
Fetal Hemoglobin	1000 mg/dL
Hemoglobin A	1000 mg/dL

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison study was performed in accordance with CLSI EP09-A3. The levels of total bilirubin were measured using the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) and a legally marketed comparator method with an assay measuring range of 0.146 - 35.1 mg/dL.

One hundred and nineteen (119) serum samples from neonates with ages of 5 hours to 8 days were tested. The range of samples tested was 0.8 - 26.6 mg/dL and included five spiked samples. Data were analyzed using a weighted Deming linear regression.

N	119
Slope	1.06
y-intercept	-0.24
Correlation coefficient (r)	0.990

Bias at the medical decision levels (MDLs) were calculated from the linear regression equation. MDL concentrations (bias) are as follows: 1.0 mg/dL (-0.2 mg/dL), 8.0 mg/dL (0.2 mg/dL), 13.0 mg/dL (0.5 mg/dL), and 17.0 mg/dL (0.8 mg/dL).

b. Matrix comparison:

Matrix equivalency for neonate patient samples was not evaluated. In k063845, commutability between serum and lithium heparin plasma was evaluated using adult samples.

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:

The reference interval for the ADVIA® Chemistry Total Bilirubin_2 (TBIL_2) is outlined in the literature reference: *Wu AHB. Tietz Clinical Guide to Laboratory Tests, 4th edition, Saunders Elsevier, St. Louis, MO: 2006:172*. Verification of the described reference range was completed in accordance with CLSI EP28-A3c with a minimum of 20 samples for each age category listed. Each age group was analyzed separately with data summarized in the table below. The reference range verification study supports the use of the literature reference interval.

Age Range	Acceptable Range
0-1 day	<8.0 mg/dL
1-2 days	<12 mg/dL
3-5 days	<16.0 mg/dL
>5 days – 60 years	0.3-1.2 mg/dL
60-90 years	0.2-1.1 mg/dL
>90 years	0.2-0.9 mg/dL

In addition, the clinical interpretation of the risk for hyperbilirubinemia in neonates is supported by the following literature reference: *Subcommittee on Hyperbilirubinemia. Subcommittee on Hyperbilirubinemia. Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics 2004; 114: 297-3 16*. This reference indicated high risk for developing clinically significant hyperbilirubinemia in term and near-term newborns as summarized in the table below.

Age	Total Bilirubin
24 hours	≥ 8.0 mg/dL
48 hours	≥13.0 mg/dL
84 hours	≥17.0 mg/dL

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.