510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K222104

B Applicant

Siemens Healthcare Diagnostics Inc.

C Proprietary and Established Names

Atellica® CH Diazo Total Bilirubin (D_TBil)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
CIG	Class II	21 CFR 862.1110 - Bilirubin (Total Or Direct) Test System	CH - Clinical Chemistry

II Submission/Device Overview:

A Purpose for Submission:

New device

B Measurand:

Total bilirubin

C Type of Test:

Quantitative, photometric test

III Intended Use/Indications for Use:

A Intended Use(s):

See Indications for Use below.

B Indication(s) for Use:

The Atellica® CH Diazo Total Bilirubin (D_TBil) assay is for in vitro diagnostic use in the quantitative determination of total bilirubin in adults and children (non-neonates) in human serum and plasma using the Atellica® CH Analyzer. 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.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

D Special Instrument Requirements:

Atellica CH Analyzer

IV Device/System Characteristics:

A Device Description:

The Atellica® CH Diazo Total Bilirubin (D_TBil) assay consists of the following 2 packs:

Pack 1 (P1)	23.5 mL	Phosphate buffer (50mmol/L); NaCl (150mmol/L)
Pack 2 (P2)	8.8ml	2,4-Dicholoroaniline (5mmol/L); HCl (130mmol/L); Na-Nitrite (0.5mmol/L)

Materials required but not provided: Atellica CH Bilirubin Calibrator (BILI CAL).

B Principle of Operation:

The Atellica® CH Diazo Total Bilirubin (D_TBil) is an assay that uses 2,4-dichloroaniline (DCA). Direct bilirubin in the presence of diazotized DCA forms a red-colored azocompound in acidic solution that can be measured. A specific mixture of detergents enables the determination of total bilirubin. The detection wavelength is 545nm.

This assay requires 6.0 µL of sample for a single determination.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Dimension TBI Flex and DBI Flex Reagent Cartridges and TBI/DBI Calibrator

B Predicate 510(k) Number(s):

K060628

C Comparison with Predicate(s):

Device & Predicate Device(s):	K222104	K060628
Device Trade Name	Atellica® CH Diazo Total Bilirubin (D_TBil)	Dimension TBI Flex and DBI Flex Reagent Cartridges and TBI/DBI Calibrator
General Device Characteristic Similarities		
Intended Use/Indications For Use	Quantitative determination of total bilirubin in human serum and plasma. Measurement of total bilirubin is used in the diagnosis and treatment of liver, hemolytic, hematological, and metabolic disorders, including hepatitis and gall bladder block.	Same
Mode of Detection	Photometric (Diazo chemistry)	Same
Measuring Range	0.10 mg/dL – 25.0 mg/dL	Same
General Device Characteristic Differences		
Instrument Platform	Atellica CH Analyzer	Dimension® clinical chemistry system
Sample Matrix	Human serum and plasma (lithium heparin, sodium heparin, dipotassium EDTA)	Human serum and plasma (lithium heparin, EDTA)

VI Standards/Guidance Documents Referenced:

- Clinical and Laboratory Standards Institute (CLSI) EP05-A3 – Evaluation of Precision of Quantitative Measurement Procedures
- CLSI EP09c 3rd Edition – Measurement Procedure Comparison and Bias Estimation Using Patient Samples
- CLSI EP17-A2 – Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline –Second Edition
- CLSI EP06-2nd Edition – Evaluation of Linearity of Quantitative Measurement Procedures
- CLSI EP07-3rd Edition – Interference Testing in Clinical Chemistry
- CLSI EP37 1st Edition – Supplemental Tables for Interference Testing in Clinical Chemistry
- CLSI EP34 1st Edition – Establishing and Verifying an Extended Measuring Interval Through Specimen Dilution and Spiking
- CLSI EP28-A3c (Formerly C28-A3c) – Defining Establishing and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline –Third Edition
- CLSI EP32-R (Formerly X05-R) – Metrological Traceability and Its Implementation; A Report
- CLSI EP25-A (Replaces EP25-P) – Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline.

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision

Precision studies were conducted according to CLSI EP05-A3. Total precision was assessed in 2 runs (minimum 2 hours between each run), 2 replicates per run per day, over 20 days, for a total of 80 results per sample. Three spiked serum samples were tested using 3 reagent lots on one Atellica CH Analyzer. Repeatability and within-lab imprecision were calculated. Results were similar between reagent lots. The precision data from a representative reagent lot are summarized below.

Sample	Mean (mg/dL)	Repeatability		Within-lab (total)	
		SD (mg/dL)	%CV	SD (mg/dL)	%CV
Serum 1	1.02	0.015	1.5	0.034	3.3
Serum 2	13.40	0.053	0.4	0.140	1.0
Serum 3	22.39	0.067	0.3	0.189	0.8

Reproducibility

Testing was conducted according to CLSI EP05-A3. Reproducibility was assessed using 3 serum pool samples measured in 5 replicates, using 3 reagent lots, over 5 days, on 3 Atellica CH Analyzers, for a total of 225 replicates per sample. Repeatability, between-day, between-lot,

between-instrument, and reproducibility were calculated. The data for reproducibility studies are summarized below.

Sample	Mean (mg/dL)	Repeatability		Between-Day		Between-Lot		Between-Instrument		Reproducibility	
		SD (mg/dL)	% CV	SD (mg/dL)	% CV	SD (mg/dL)	% CV	SD (mg/dL)	% CV	SD (mg/dL)	% CV
Serum 1	1.03	0.012	1.2	0.009	0.9	0.013	1.3	0.011	1.1	0.023	2.2
Serum 2	13.24	0.037	0.3	0.062	0.5	0.028	0.2	0.047	0.4	0.091	0.7
Serum 3	22.14	0.057	0.3	0.106	0.5	0.053	0.2	0.063	0.3	0.146	0.7

2. Linearity:

Linearity studies were conducted according to CLSI-EP06 2nd Edition. A dilution series composed of 9 levels (0.04 - 27.91 mg/dL) was prepared by mixing different proportions of the high serum pool sample and the low serum pool sample. Four replicates for each sample were measured on the Atellica CH Analyzer using 3 reagent lots. The data was analyzed using a linear regression model as described in the guideline. The results support the claimed measuring range of 0.10 mg/dL – 25.0 mg/dL.

3. Analytical Specificity/Interference:

Interference studies were conducted according to the CLSI EP07 3rd Edition guideline. The effect of endogenous and exogenous substances on the D_TBil assay was evaluated using two human serum pools spiked to obtain bilirubin concentrations of ~1.0 mg/dL or ~14.0 mg/dL. Each sample was tested in 5 replicates. Testing used the paired-difference method of comparing a sample spiked with interferent to a sample spiked with control material (diluent used in the test sample). The sponsor considered interference to be non-significant if the difference between the samples with and without interferent are within 10.0%. The results of the interference studies are summarized below.

Interferent	Highest interferent concentration tested that showed no significant interference
Hemoglobin	1000 mg/dL
Triglyceride	1000 mg/dL
Acetaminophen	20 mg/dL
Acetylsalicylic acid	100 mg/dL
Ascorbic acid	5 mg/dL
Carbenicillin	3 mg/dL
Cholesterol	500 mg/dL
Cyanokit (Hydroxocobalamin)	40 µg/ml
Diazepam	20 µg/mL
Eltrombopag	25 µg/mL
Ethanol	800 mg/dL

Interferent	Highest interferent concentration tested that showed no significant interference
Ibuprofen	50 mg/dL
Immunoglobin G	5 g/dL
Levodopa	225 µg/mL
Phenazopyridine	80 µg/mL
Phloroglucinol	250 ng/mL
Rifampicin	6 mg/dL
Indican	1.5 mg/dL

4. Assay Reportable Range:

   The assay measuring interval is 0.10 to 25.00 mg/dL.

   The sponsor provided data to support that the measuring interval can be extended up to 50.00 mg/dL following manual or automated dilution.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

   The assay is traceable to SRM916 (NIST) Standard Reference Material.

6. Detection Limit:

   Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were validated based on the CLSI guideline EP17-A2.

   To calculate the LoB, four blank samples in replicates of five were tested using three reagent lots on one Atellica CH Analyzer over three days for a total of 60 measurements per reagent lot. LoB was determined using the 95% nonparametric percentile of the replicates for each of three reagent lots. The claimed LoB is 0.01 mg/dL.

   To calculate the LoD, two low native serum samples and two samples prepared from diluted serum pools were tested in replicates of five on one Atellica CH Analyzer using three reagent lots over three days for a total of 60 measurements per lot. The maximum observed LoD across the 3 lots tested was 0.02 mg/dL. The claimed LoD is 0.02 mg/dL.

   To calculate the LoQ, five low level total bilirubin sample pools targeted between 0.03 mg/dL and 0.17 mg/dL were tested in replicates of five on one Atellica CH Analyzer using three reagent lots over five days for a total of 125 determinations per lot. The maximum observed LoQ across all reagent lots was determined to be 0.04 mg/dL. The claimed LoQ is 0.1 mg/dL which is the lowest concentration that met the performance goal of less than 20% CV.

7. Assay Cut-Off:

   Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:
   A method comparison study was conducted in accordance with CLSI EP09c-A3 using 103 serum samples with 3 reagent lots on one Atellica CH Analyzer. Each serum sample was tested in duplicate. Results from the Atellica CH Diazo Total Bilirubin assay were compared to results using the predicate device. Results were analyzed using Deming regression. Only the first replicate result was used in the statistical analysis.

   The table below summarizes the data using serum samples from a representative lot:

N	Sample Range (mg/dL)	Intercept (mg/dL)	Slope	Correlation Coefficient (r)	Claimed Measuring Range (mg/dL)
103	0.14 -22.55	0.08	1.02	0.997	0.1-25.0

2. Matrix Comparison:
   A matrix comparison study was conducted according to CLSI EP09c-A3 using 1 reagent lot. Fifty-seven (57) matched serum and plasma (lithium heparin, sodium heparin, dipotassium EDTA) samples were assayed with one Atellica CH Analyzer in singlicate. Results were analyzed using Deming regression.

   The table below summarizes the matrix comparison data:

Analysis	Slope	Intercept (mg/dL)	Sample Range	N	r
Lithium heparin plasma vs. serum	0.98	0.05	0.24-22.61 mg/dL	57	0.997
Sodium heparin plasma vs serum	1.00	0.02	0.24-22.61 mg/dL	57	0.998
K2 EDTA plasma vs serum	0.99	0.03	0.24-22.61 mg/dL	57	0.998

   Results demonstrated equivalency between serum, lithium heparin plasma, sodium heparin plasma, and K2 EDTA plasma specimens.

C Clinical Studies:

1. Clinical Sensitivity:

   Not applicable.

2. Clinical Specificity:

   Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

   Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

The reference interval was verified by testing 21 serum samples (age range from 4 to 83) with the total bilirubin assay in accordance with CLSI EP28-A3c. Data support the pre-established reference interval of 0.3 - 1.2mg/dL (5.13 - 20.52 µmol/L)[1].

[1]Wu AHB, ed. Tietz Clinical Guide to Laboratory Tests. 4th ed. St. Louis, MO: Saunders; 2006:316.

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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