510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY AND INSTRUMENT COMBINATION TEMPLATE

A. 510(k) Number:

k110277

B. Purpose for Submission:

Addition of Neonatal Bilirubin to a previously cleared RapidPoint® 405 System under k002738

C. Measurand:

Neonatal Bilirubin

D. Type of Test:

Quantitative, Spectrophotometric

E. Applicant:

Siemens Healthcare Diagnostics

F. Proprietary and Established Names:

RAPIDPoint® 405 System Neonatal Bilirubin (nBili) Test

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1113 –Bilirubin in the neonate test system

2. Classification:

   Class I, reserved

3. Product code:

   MQM

4. Panel:

   Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indication(s) for use below.

2. Indication(s) for use:

   The Rapidpoint 405 system is intended for in vitro diagnostic use and is designed to provide the determination in whole blood for the following parameters:

   Partial Pressure of Carbon dioxide
   Partial pressure of oxygen
   pH
   Sodium
   Potassium
   Ionized calcium
   Chloride
   Glucose
   Total hemoglobin and fractions: fO2Hb, fCOHb, fMetHb, fHHb
   Neonatal bilirubin

   This test system is intended for use in point of care or lab settings

   The following list includes the **Indications for Use** information for each analyte measured on the Rapidpoint 405 System**:**

   pCO_2, $p0_2$, pH. Measurements of blood gases (pCO2, p02) and blood pH are used in the diagnosis and treatment of life-threatening acid-base disturbances.

   Neonate Bilirubin. 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).

   Sodium. Sodium measurements obtained by this device are used in the diagnosis and treatment of aldosteronism (excessive secretion of the hormone aldosterone), diabetes insipidus (chronic excretion of large amounts of dilute urine, accompanied by extreme thirst), adrenal hypertension, Addison's disease (caused by destruction of the adrenal glands), dehydration, inappropriate antidiuretic hormone secretion, or other diseases involving electrolyte imbalance.

   Potassium. Potassium measurements obtained by this device are used to monitor

electrolyte balance in the diagnosis and treatment of diseases conditions characterized by low or high blood potassium levels.

Chloride. Chloride measurements are used in the diagnosis and treatment of electrolyte and metabolic disorders such as cystic fibrosis and diabetic acidosis.

Ionized calcium. Calcium measurements are used in the diagnosis and treatment of parathyroid disease, a variety of bone diseases, chronic renal disease and tetany (intermittent muscular contractions or spasms).

Glucose. Glucose measurements are used in the diagnosis and treatment of carbohydrate metabolism disorders including diabetes mellitus, neonatal hypoglycemia, and idiopathic hypoglycemia, and of pancreatic islet cell carcinoma.

Total hemoglobin. Total hemoglobin measurements are used to determine the hemoglobin content of human blood.

Oxyhemoglobin. Oxyhemoglobin measurements are used to measure the hemoglobin content of whole blood for the detection of anemia.

Carboxyhemoglobin. Carboxyhemoglobin measurements are used to determine the carboxyhemoglobin (the compound formed when hemoglobin is exposed to carbon monoxide) content of human blood as an aid in the diagnosis of carbon monoxide poisoning.

Sulfhemoglobin. Sulfhemoglobin measurements are used to determine the sulfhemoglobin (a compound of sulfur and hemoglobin) content of human blood as an aid in the diagnosis of sulfhemoglobinemia (presence of sulfhemoglobin in the blood due to drug administration or exposure to a poison).

3. Special conditions for use statement(s):

   For Prescription use.

   It is also intended for Point-of-Care (POC) or clinical laboratory settings.

   For neonatal use.

4. Special instrument requirements:

   Siemens RAPIDPoint 405, software version 3.7 or higher

I. Device Description:

Neonate Bilirubin (nBili) is a new parameter offered on the RAPIDPoint 405 (RP405) blood gas system. The RP405 system is a point of care and clinical laboratory testing blood gas

analyzer and has been previously cleared (k002738) for pCO_2, pO_2, pH, Sodium, Potassium, Calcium, Chloride, Glucose, fO2Hb, fCOHb, fMetHb, fHHb. Enabling the nBili measurement is accomplished through software design changes introduced in Software Version 3.7. No hardware or mechanical changes were needed.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Neonate Bilirubin on RAPIDLab® models 1245 and 1265

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

   k073537

3. Comparison with predicate:

Reagent Similarities and Differences		
Item	Candidate Device: nBili on RAPIDPoint 405 (k110277)	Predicate Device: nBili on RAPIDLab models 1245 and 1265 (k073537)
Intended Use and indications for use	In vitro diagnostic test for the determination of total neonatal bilirubin (nBili) concentration in the whole blood of newborn infants. Measurement of nBili aids in assessing the risk of kernicterus. Intended for use in point of care or clinical laboratory settings.	Same
Principle of Operation	Blood Gas Analyzer	Same
Test Principle	Optical	Same
Measured Parameter	Total Bilirubin	Same
Parameter Nomenclature	nBili	Same
Technology	Automated co-oximetry using spectral analysis from on-board visible absorption spectrophotometer	Same
Specimen type	Neonatal whole blood	Same
Expected Value	Age Value ≤ 1 day Premature < 8.0 mg/dL Full-term < 6.0 mg/dL 1-2 days Premature < 12.0 mg/dL Full-term < 8.0 mg/dL Age Value	Same

Reagent Similarities and Differences		
Item	Candidate Device: nBili on RAPIDPoint 405 (k110277)	Predicate Device: nBili on RAPIDLab models 1245 and 1265 (k073537)
	3-5days Premature < 16.0 mg/dL Full-term < 12.0 mg/dL > 5 days Premature < 2.0 mg/dL Full-term < 0.2-1.0 mg/dL	
Reported Output	nBili	Same
Reporting Range	2.1-30.0 mg/dL	Same
Calibration	2-point calibration using automated on-board reagent	Same
Main Test Steps	Collect sample, insert device into sample leur, and select "Start"	Same

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

Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices - Guidance for Industry and FDA Staff

Format for Traditional and Abbreviated 510(k)s - Guidance for Industry and FDA Staff

CLSI EP17-A, 'Protocols for Determination of Limits of Detection and Limits of Quantitation'

CLSI EP6-A, 'Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach'

CLSI EP5-A2, 'Evaluation of Precision Performance of Quantitative Measurement Methods'

CLSI EP9-A2, 'Method Comparison and Bias Estimation Using Patient Samples'

L. Test Principle:

The RAPIDPoint 405 system uses multiple wavelength spectrophotometry (CO-oximetry) to measure the transmission of light through a sample of neonate whole blood to determine concentrations of hemoglobin derivatives and bilirubin. The RAPIDPoint 405 system aspirates the whole blood sample at the sample port and then transfers the sample to the CO-ox sample chamber. As the sample flows through an optical chamber, the CO-ox optics head directs light through the sample and to a polychromator that measures the intensity of transmitted light at different wavelengths. Iterative least squares analysis is used to determine raw bilirubin values. Raw values are then corrected for hematocrit to produce nBili results.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Quality control precision was performed by using three levels of RapidQC® Complete (quality control materials) and one level of Calibration Verification Material (CVM®). For all of the quality control precision testing, six RP405 instruments were used at one internal site. There were a total of 5 different operators who performed the testing during the study. The test protocol used was adopted from CLSI document EP5-A2, 'Evaluation of Precision Performance of Quantitative Measurement Methods'. One lot of each aqueous control material was used throughout the study. The three levels of ampoule Complete QC along with CVM level 1 were run in duplicate, twice per day, per level on each instrument for a minimum of 20 days. Each "run" of duplicate results was spaced at least 2 hours apart from each other. The repeatability and within laboratory precision for each control product and level were calculated and compared with internal precision guidelines. All data was included in the analysis. The results were as follows:

Level	N	Mean (mg/dL)	Total SD (mg/dL)	% Total CV
RapidQC Control Material Level 1	516	20.4	0.80	3.9
RapidQC Control Material Level 2	516	10.6	0.54	5.1
RapidQC Control Material Level 3	517	5.0	0.26	5.2
Calibrator Verification Material	514	24.1	0.79	3.3

Additionally, reproducibility was performed using whole blood specimens from in-house donors collected in lithium heparin green top tubes. Whole blood specimens were fully oxygenated, altered to tHb levels of 12-22 g/dL and spiked with bilirubin concentrations between 3-25 mg/dL. Prepared samples were run on RP405 in syringe and capillary modes. Each run had a single target bilirubin level at three different tHb levels in triplicate. Runs were performed for nBili levels across the measuring range (3, 5, 12, 16, 20, 23, and 25 mg/dL). Five operators participated in this study. The precision results are summarized as follows:

The results in the syringe mode were as follows:

Target nBili Level (mg/dL)	N	Mean	Within-Run SD (mg/dL)	% Within-run CV	Total Analytical Error (mg/dL)
3	53	3.6	0.32	9.0	1.29
5	108	5.1	0.36	7.0	1.20
8	54	8.2	0.29	3.6	1.39
12	108	11.6	0.46	4.0	1.23
16	54	15.1	.047	3.1	1.28
20	108	19.9	0.48	2.4	1.56
23	54	23.1	0.48	2.1	1.30
25	54	24.2	0.48	2.0	1.40

The results in the capillary mode were as follows:

Target nBili Level (mg/dL)	N	Mean	Within-Run SD (mg/dL)	% Within-run CV	Total Analytical Error (mg/dL)
3	53	3.5	0.53	15.3	1.26
5	108	5.0	0.44	8.7	1.56
8	54	8.0	0.53	6.7	1.30
12	105	11.1	0.49	4.4	1.36
16	54	15.0	0.39	2.6	1.43
20	108	19.5	0.53	2.7	1.71
23	54	23.5	0.63	2.7	2.08
25	54	23.9	0.52	2.2	2.10

Point-Of-Care reproducibility was performed on the quality control material using 3 typical POC intended use operators over the course of 20 days. It was performed at three sites on three levels of QC materials and one level of Calibration Verification Material tested in quadruplicate. The precision (within run and total) results are summarized as follows:

The results were as follows for the manual quality control:

Analyte	Control	Target	Site	N	Mean (mg/dL)	WR SD (mg/dL)	WR CV (%)	Betw Day SD (mg/dL)	Betw Day CV (%)	Total SD (mg/dL)	Total CV (%)
nBili	361902	20.3	1	23	20.61	0.5	2.6	0.2	0.8	0.6	2.7
			2	23	20.55	0.4	2.1	0.4	1.9	0.6	2.8
			3	20	20.39	0.4	1.8	0.3	1.4	0.5	2.2
			All	**66**	**20.52**	**0.5**	**2.4**	**0.2**	**1.0**	**0.5**	**2.6**
	362902	10.5	1	23	10.67	0.2	1.8	0.2	1.4	0.2	2.3
			2	25	10.72	0.2	1.5	0.3	2.9	0.3	3.3
			3	20	10.31	0.4	3.5	0.2	1.7	0.4	3.9
			All	**68**	**10.58**	**0.2**	**2.3**	**0.3**	**2.4**	**0.4**	**3.7**
	363902	5.0	1	24	4.98	0.1	1.6	0.2	4.8	0.3	5.1
			2	23	5.26	0.1	2.7	0.2	3.9	0.2	4.8
			3	21	4.57	0.2	4.5	0.2	4.7	0.3	6.5
			All	**68**	**4.95**	**0.2**	**3.1**	**0.2**	**4.7**	**0.5**	**9.6**

b. *Linearity/assay reportable range:*
The measuring range of this device is 2.1-30 mg/dL. Linearity by dilution was performed using whole blood from a single donor that was split into two pools: one pool was altered to a bilirubin concentration of ~40 mg/dL and the other pool was left unaltered (0.5-1.5 mg/dL). Nine sample pools were created by using various portions of each pool to span the measuring range (2-30 mg/dL). Each pool was run in random order on one RP405 analyzer in syringe mode in replicates of four in one day. The data was analyzed in accordance with CLSI EP-6. The data was fit to linear, quadratic, and cubic models and the linear model was found to have the best mathematical fit. The linear regression generated is Y=-0.558+ 1.05x, R=0.999. Samples range tested from 2.0 to 41.7 mg/dL.

These results demonstrate the linearity of the device across the claimed measuring range of 2-30 mg/dL.

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

There is no unique calibration measurement for nBili. The tHb calibration curve is used in nBili measurements. The calibrator for tHb was cleared in k031560.

d. *Detection limit:*

The limit of detection was determined in accordance with CLSI EP-17A. Whole blood was collected from eleven donors. For the blank samples, blood was left

unaltered and exposed to light for a minimum of five hours. Low level samples were altered to have bilirubin concentrations in the range of 0.6 to 2.0 mg. The samples were each assessed in replicates of 6-12 over three days on four RP405 instruments in syringe mode for a total of 90 blank and 78 low level samples each.. The limit of blank (LOB) was calculated from these results using the 95_{th} percentile of the ascending rank ordered values for each instrument. The LOD was calculated to be 0.5 mg/dL. LoQ is determined to be 2.1 mg/dL based on a 13% CV.

The nbili measuring range is 2.1 – 30 mg/dL.

e. Analytical specificity:

Interference testing was performed on four RP405 instruments using fully oxygenated whole blood that was prepared to have 17 g/dL tHb and either 3 mg/dL or 20 mg/dL unconjugated bilirubin. The samples were split and spiked with either the potential interferent or an equivalent volume of diluent and run on the RP405 system in syringe mode. Each run had a control and test sample in triplicate and three runs of each interferent were performed. Bias was calculated for each substance tested (bias= mean test-mean control) as was the interference (% interference = bias/mean control *100).

For each substance tested, the bias was calculated (bias = (mean test – mean control)) as well as the percent of interference (% effect of interference = (bias / mean control)*100). A substance was defined as a significant interferent if the bias (mean nBili test value – mean nBili control value) exceeds a calculated limit. Any compound that resulted in greater than 13% bias when tested at 5 mg/dL or 10% bias when tested at 20 mg/dL was considered an interferent. Hemolysis, Indocyanine Green, Lipid, Beta Carotene (at 0.22 mg/dL) and high and low pH do not interfere with the measurement of nBili on RP405. Evans Blue, Fluorescein, Methylene Blue, Sulfan Blue, and Cyanmethemoglobin are all interfering substances. The results of the interference testing are as follows:

Potential Interfering Substance	Level Tested	% Effect of Interference at nBili = 5mg/dl	% Effect of Interference at nBili = 20mg/dL	Substance Interferes?
Lipid	5% in plasma (4980 mg/dL)	-8.4	-1.7	No
Abnormal low pH	6.96	-10.4	-2.9	No
Abnormal high pH	7.67	7.7	2.0	No
Indocyanine Green	5 mg/L	8.2	1.3	No
Beta-carotene	0.22 mg/dL	0.6	2.2	No
Evans Blue	5 mg/L	-23.4	-4.4	Yes
Sulfan Blue	10 mg/L	147.0	57.1	Yes
Methylene Blue	50 mg/L	-100.0	-65.7	Yes
CyanMet Hb	10%	54.0	118.6	Yes
Fluorescein	4.2 nmol/mL	-20.9	-5.1	Yes
Hydroxocobalamin	0.3 mg/mL	-9.5	-5.2	No

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed at an internal site. Whole blood umbilical cord samples were obtained and the samples were spiked with unconjugated bilirubin at concentrations that span the measuring range. The samples were run on the RP405 and the RL1265 analyzer in both the syringe and capillary modes in single replicate. There were three operators that performed the study and there were a total of 43 samples. Deming regression was performed on each individual observation from the RP405 and RL1265 to determine the slope and intercept. The results yielded a linear regression of $y = 0.975x + 0.391$ with an r^2 of 0.996 using a range of nBili data from 2.3 to 29.0 mg/dL.

In addition, the sponsor also performed a method comparison at three external clinical sites using at least three typical point of care operators testing a minimum of 40 unadulterated neonatal whole blood clinical specimens per site and 5 samples at sites

2 and 3 that were spiked using commercially available unconjugated bilirubin to expand the range of the samples. The highest naturally occurring RL1265 nBili value measured at the external clinical trials was 23.9 mg/dL. As a surrogate for rare naturally occurring high nBili samples, supplemental spiked cord blood was used to demonstrate the full reportable range. Umbilical cord blood was used as it mimics neonate samples because, unlike adult blood, cord whole blood contains native fetal hemoglobin and neonate cells. Deming regression was performed on each individual observation from the RP405 and RL1265 to determine the slope and intercept.

The Deming regression correlation results of the method comparison studies for the three external sites (1-3) and the internal site (4) and the combination of these (all) are summarized as follows:

Trial Site	Sample Size (N)	Deming Orthogonal Slope	95% Confidence Interval of Slope	Deming Orthogonal Intercept	95% Confidence Interval of Intercept	Std Error of the Estimate (Sy.x)	Coeff of Determ. (r^2)	Corr Coeff (r)	Minimum RL12x5 Value, mg/dL	Maximum RL12x5 Value, mg/dL
1	48	0.93	0.85 – 1.02	0.54	(-0.28) - 1.37	1.02	0.920	0.959	2.6	20.5
2	55	0.96	0.91 – 1.02	-0.27	(-0.92) - 0.37	1.33	0.959	0.979	2.1	28.4
3	56	0.96	0.90 - 1.03	-0.26	(-0.98) - 0.46	1.27	0.941	0.970	2.6	28.7
4	43	0.97	0.95 - 1.00	0.39	0.06 - 0.73	0.54	0.996	0.998	2.3	29.0
All	202	0.98	0.95 - 1.00	-0.12	(-0.43) - 0.20	1.16	0.966	0.983	2.1	29.0

b. Matrix comparison:

Not Applicable

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:

Reference ranges for the assay are based on literature reference and are shown in the following table:

Age	mg/dL
Premature Infants	
≤1 day	<8.0
1–2 days	<12.0
3–5 days	<16.0
Full Term Infants	
≤1 day	<6.0
1–2 days	<8.0
3–5 days	<12.0

Tietz NW. *Fundamentals of Clinical Chemistry*. Philadelphia, PA: Saunders; 1986

N. Instrument Name:

RAPIDPoint 405

O. System Descriptions:

1. Modes of Operation:

   Neonatal Bilirubin (nBili) is a new parameter offered on the Rapidpoint 405 (RP405) blood gas system. The RP405 system is a point of care and laboratory testing blood gas analyzer and currently measures a variety of parameters that have been previously cleared under k002738 and k020616. With the planned release of software version 3.7, the ability to measure nBili will be added to the system.

2. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes____X___ or No_____

3. Specimen Identification:

Samples are identified through barcode.

4. Specimen Sampling and Handling:

   User can analyze samples using the sample collection devices and whole blood is collected in a heparanized syringe or capillary.

5. Calibration:

   The tHb calibrator has been previously cleared in k031560. There is no unique calibration measurement for nBili. The tHb calibration curve is used in nBili measurements. The targeted calibration points for tHb are:

   •Calibration Point: 0 g/dL

   •Slope Point: 15 g/dL

6. Quality Control:

   There quality control material is the RapidQC® Complete external controls cleared in k970956 control materials required for nBili.

   The nBili QC is dependent on tHb QC. If tHb or any of the four CO-ox fractions (*F*O_2Hb, *F*COHb, *F*MetHb, and *F* HHb) fail or miss QC, nBili is also marked QC Failed or QC Missed. If nBili fails or misses QC, tHb and the other CO-ox fractions are not affected

P. Other Supportive Instrument Performance Characteristics Data Not Covered In The "Performance Characteristics" Section above:

Not applicable

Q. Proposed Labeling:

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

R. Conclusion:

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