

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

A. 510(k) Number:

K132691

B. Purpose for Submission:

Addition of neonatal bilirubin assay to the ABL90 FLEX Analyzer

C. Measurand:

Neonatal Bilirubin

D. Type of Test:

Quantitative, Spectrophotometric

E. Applicant:

Radiometer Medical ApS

F. Proprietary and Established Names:

ABL90 FLEX

G. Regulatory Information:

Classification name	Regulation	Device Class	Product Code	Panel
Bilirubin in the neonate test system	862.1113	I, reserved	MQM	Chemistry (75)

H. Intended Use:

1. Intended use(s):

See Indication(s) for use.

2. Indication(s) for use:

The ABL90 FLEX analyzer is an in vitro diagnostic, portable, automated analyzer that quantitatively measures neonatal bilirubin in heparinised capillary whole blood. The ABL90 FLEX analyzer is intended for use by trained technologists, nurses, physicians and therapists. It is intended for use in a laboratory environment, near patient or point-of-care setting. These tests are only performed under a physician's order. Bilirubin measurements on the ABL90 FLEX analyzer are intended to aid in assessing the risk of kernicterus in neonates.

3. Special conditions for use statement(s):

For Prescription Use.

This test system is intended for Point-of-Care (POC) or clinical laboratory settings.

For neonatal use.

4. Special instrument requirements:

ABL90 FLEX Analyzer

I. Device Description:

Neonate Bilirubin (nBili) is a new test offered on the ABL90 FLEX Analyzer. The ABL90 FLEX Analyzer is a point of care and clinical laboratory instrument and has been previously cleared (k092686) for pH, pO₂, pCO₂, Sodium, Potassium, Calcium, Chloride, Glucose, Lactate, ctHb, sO₂, fO₂Hb, fCOHb, fMetHb, fHHb and fHbF. Enabling the nBili measurement is accomplished through software design changes introduced in software version 2.6 by adding the bilirubin calculation algorithm. No hardware or mechanical changes were needed.

J. Substantial Equivalence Information:

1. Predicate device name(s):

ABL800 FLEX

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

K050869

3. Comparison with predicate:

Similarities		
Item	Candidate Device: nBili on ABL 90 FLEX	Predicate Device: nBili on ABL800 FLEX (k050869)
Intended Use	The ABL90 FLEX analyzer is an in vitro diagnostic, portable, automated analyzer that quantitatively measures neonatal bilirubin in heparinised capillary whole blood. The ABL90 FLEX analyzer is intended for use by trained technologists, nurses, physicians and therapists. It is intended for use in a laboratory environment, near patient or point-of-care setting. These tests are only performed under a physician's order. Bilirubin measurements on the ABL90 FLEX analyzer are intended to aid in assessing the risk of kernicterus in neonates.	Same
Principle of Operation	Using spectrophotometric multi-component analysis through the instrument's existing CO-Oximetry module on a hemolyzed part of the sample.	Same
Test Principle	Optical	Same
Calibrations	2-point	Same

Differences		
Item	Candidate Device: nBili on ABL 90 FLEX	Predicate Device: nBili on ABL800 FLEX (k050869)
Intended use site	Laboratory and point-of-care.	Laboratory
Neonatal bilirubin measuring range	µmol/L: 218 - 6438 mg/dL: 1.26 – 37.93 mg/L: 126 – 3793	µmol/L: 1 - 1000 mg/dL: 0.0 – 58.5 mg/L: 0 - 585

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

CLSI EP5-A2, Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition.

CLSI EP6-A, Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.

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

CLSI EP9-A2, Method Comparison and Bias Estimation Using Patient Samples, 2002

CLSI EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline

ISO 14971:2007, Second edition 2007-03-01, Medical devices - Application of risk management to medical devices.

IEC 62304 First edition 2006-05, Medical device software - Software life cycle processes.

L. Test Principle:

Neonatal bilirubin measured in heparinized whole blood on the ABL90 FLEX analyzer using spectrophotometric multi-component analysis through the instrument's existing CO-Oximetry module on a hemolyzed part of the sample. This optical system of the ABL90 FLEX analyzer is designed to measure total hemoglobin and hemoglobin fractions as well as oxygen saturation.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Internal Testing

The internal precision study was performed as follows:

- A 20 day internal precision study was performed as specified in the CLSI Guideline EP5-A2 using one analyzer and three operators. Three levels of aqueous control solutions covering the device measuring range were analyzed in 2 runs per day with 2 replicates for each level. This generated within-run and total imprecision data for aqueous solutions of bilirubin. The results for both capillary and syringe mode are summarized below.
- An additional internal precision study was performed using freshly drawn whole blood, and freshly drawn cord blood, both spiked with bilirubin to obtain low, medium, and high bilirubin levels covering the device measuring range. All samples were adjusted to total hemoglobin (tHb) ~18g/dL and tonometered to 95 – 100% saturation to mimic neonate whole blood. All six levels of the prepared samples were analyzed in 5 runs with 5 replicates for each level. The results for both capillary and syringe mode are summarized below.

Bilirubin Syringe:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.05	2.4	0.07	3.2
Mid Control	80	7.4	0.11	1.5	0.14	1.9
High Control	80	30.9	0.45	1.4	0.57	1.8
Sample 1 Adult Blood	25	2.6	0.13	5.0	0.21	8.3
Sample 2 Adult Blood	25	7.4	0.09	1.2	0.15	2.1
Sample 3 Adult Blood	25	29.4	0.51	1.7	0.52	1.8
Sample 4 Cord Blood	25	2.4	0.12	4.9	0.18	7.4
Sample 5 Cord Blood	25	7.1	0.24	3.4	0.28	4.0
Sample 6 Cord Blood	25	29.9	0.21	0.7	0.26	0.9

Bilirubin Capillary:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.05	2.3	0.07	3.4
Mid Control	80	7.4	0.12	1.6	0.13	1.7
High Control	80	30.7	0.48	1.6	0.46	1.5
Sample 1 Adult Blood	25	2.3	0.15	6.7	0.18	7.7
Sample 2 Adult Blood	25	7.8	0.22	2.8	0.34	4.4
Sample 3 Adult Blood	25	30.2	0.73	2.4	0.80	2.6
Sample 4 Cord Blood	25	2.0	0.10	4.9	0.13	6.7
Sample 5 Cord Blood	25	7.0	0.19	2.7	0.24	3.4
Sample 6 Cord Blood	25	30.6	0.32	1.1	0.34	1.1

External Testing

The external precision study was performed at three Point-of-Care (POC) sites as follows:

- A 20 day external precision study was performed as specified in the CLSI Guideline EP5-A2 using one analyzer and three operators per site. Three levels of aqueous control solutions covering the device measuring range were analyzed in 2 runs per day with 2 replicates for each level. This generated within-run and total imprecision data for aqueous solutions of bilirubin. The results for both capillary and syringe mode are summarized below.
- An additional external precision study was performed using freshly drawn adult whole blood spiked with bilirubin to obtain low, medium, and high bilirubin levels covering the device measuring range. All samples were adjusted to tHb ~18g/dL and tonometered to 95 – 100% saturation to mimic neonate whole blood. Three levels of bilirubin were analyzed in 5 runs with 5 replicates for each level in one day. The results for both capillary and syringe mode are summarized below.

Site 1:

Bilirubin Syringe:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.05	2.4	0.08	4.1
Mid Control	80	7.3	0.05	0.7	0.09	1.3
High Control	80	30.3	0.09	0.3	0.50	1.6
Low Adult Blood	25	2.5	0.12	4.8	0.12	4.9
Mid Adult Blood	25	7.2	0.14	1.9	0.14	1.9
High Adult Blood	25	31.1	0.21	0.7	0.19	0.6

Bilirubin Capillary:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.04	1.8	0.08	3.7
Mid Control	80	7.3	0.06	0.8	0.10	1.3
High Control	80	30.2	0.19	0.6	0.49	1.6
Low Adult Blood	25	2.3	0.14	6.1	0.31	13.4
Mid Adult Blood	25	7.1	0.15	2.1	0.61	8.5
High Adult Blood	25	30.4	0.16	0.5	0.37	1.2

Site 2:

Bilirubin Syringe:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.2	0.06	2.9	0.11	4.9
Mid Control	80	7.6	0.07	0.9	0.13	1.6
High Control	80	31.6	0.28	0.9	0.41	1.3
Low Adult Blood	25	2.6	0.11	4.2	0.12	4.5
Mid Adult Blood	25	7.5	0.16	2.1	0.15	2.0
High Adult Blood	25	30.9	0.21	0.7	0.20	0.6

Bilirubin Capillary:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.2	0.05	2.3	0.08	3.6
Mid Control	80	7.5	0.10	1.4	0.13	1.7
High Control	80	31.3	0.38	1.2	0.40	1.3
Low Adult Blood	25	1.8	0.11	5.7	0.14	7.3
Mid Adult Blood	25	7.2	0.19	2.6	0.20	2.8
High Adult Blood	25	29.5	0.22	0.7	0.41	1.4

Site 3:

Bilirubin Syringe:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.06	2.8	0.10	4.8
Mid Control	80	7.3	0.06	0.9	0.11	1.5
High Control	80	30.4	0.20	0.7	0.27	0.9
Low Adult Blood	25	2.4	0.15	6.1	0.34	13.9
Mid Adult Blood	25	6.8	0.13	1.9	0.30	4.5
High Adult Blood	25	30.5	0.36	1.2	0.46	1.5

Bilirubin Capillary:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	80	2.1	0.05	2.3	0.09	4.2
Mid Control	80	7.3	0.09	1.2	0.11	1.5
High Control	80	30.3	0.37	1.2	0.34	1.1
Low Adult Blood	25	2.2	0.11	5.2	0.39	17.7
Mid Adult Blood	25	6.9	0.14	2.1	0.42	6.2
High Adult Blood	25	30.0	0.40	1.3	0.65	2.2

All 3 Sites Combined:

Bilirubin Syringe:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	240	2.1	0.06	2.7	0.10	4.6
Mid Control	240	7.4	0.06	0.8	0.11	1.5
High Control	240	30.7	0.20	0.7	0.40	1.3
Low Adult Blood	75	2.5	0.13	5.0	0.22	8.7
Mid Adult Blood	75	7.2	0.14	2.0	0.21	2.9
High Adult Blood	75	30.8	0.27	0.9	0.31	1.0

Bilirubin Capillary:

Sample	N	Mean (mg/dL)	Within Run		Total	
			SD	%CV	SD	%CV
Low Control	240	2.1	0.04	2.1	0.08	3.8
Mid Control	240	7.4	0.09	1.2	0.11	1.5
High Control	240	30.6	0.32	1.1	0.42	1.4
Low Adult Blood	75	2.1	0.12	5.7	0.30	14.0
Mid Adult Blood	75	7.1	0.16	2.3	0.44	6.3
High Adult Blood	75	30.0	0.28	0.9	0.49	1.6

b. Linearity/assay reportable range:

A linearity study was performed using a low concentration bilirubin sample, a high concentration bilirubin sample, and nine intermediate concentration bilirubin samples made by combining proportions of the low and high samples volumetrically. The high, low, and intermediate samples were run in replicates of four in one day. The data was analyzed in accordance with CLSI EP-6 with sample range tested from 0.9 to 40.3 mg/dL. The method is linear (first order) over the entire measuring range and yields the following linear regression results: $Y = 0.968X + 0.2984$, $R^2 = 0.9996$. These linearity results demonstrate the linearity of the device across the claimed measuring range of 1.6 – 37.9 mg/dL.

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

There is no unique calibration measurement for nBili. The concentration of total hemoglobin (ctHb) calibration curve is used in nBili measurements. The ctHb calibrator was previously cleared in k092686.

The ctHb calibrators are traceable to Hemoglobin Cyanide Standard purchased commercially, which is traceable to the NIST Reference materials.

d. Detection limit:

The limit of detection was determined in accordance with CLSI EP-17A. For the blank samples, whole cord blood specimens had the plasma fraction replaced with saline. In order to calculate the limit of detection (LOD), five whole blood samples, with bilirubin concentrations in the range of 0.5 to 2.0 mg/dL were each assessed in replicates of four on two instruments over a minimum of three days. The limit of blank (LOB) was calculated from these results using the 95th percentile of the ascending rank ordered values for each instrument. The mean LOB calculated from the two instruments was 0.82 mg/dL. The LOD was calculated as $LOD = LOB + C_p$ (Std Dev) and resulted in a mean LOD from the two instruments of 1.2 mg/dL. To determine LoQ, fourteen whole blood samples with bilirubin concentrations in the range of 0.35 to 2.45 mg/dL were each assessed in replicates of five on two instruments over a minimum of three days. LoQ was determined to be 1.2 mg/dL based on a mean %CV equal to or less than 20%.

The nbili measuring range is 1.6 – 37.9 mg/dL.

e. Analytical specificity:

Interference testing was performed by spiking the test matrix with cord blood samples to tHb ~18 g/dL and sO₂ close to 100% in order to mimic neonatal whole blood, then spiking these samples with interferents at the concentrations shown below. The interference has been tested at 2 levels of bilirubin, 5 mg/dL and 15 mg/dL. Sponsor defines non-significant interference as <10% bias between the spiked and unspiked samples. Sponsor defines significant interference to be ≥10% bias. The tables below summarize the interference testing results.

There was non-significant interference with Evans Blue, Intralipid, HbF, Hemolysis, and Triglyceride at the highest concentration indicated below: (Sponsor defines non-significant interference as $< \pm 10\%$)

Substances tested	Highest concentration tested with non-significant interference
Evans Blue	5 mg/L
Intralipid	1000 mg/dL
HbF	82%
Hemolysis	20% (equivalent to approximately 3000 mg/dL hemoglobin)
Triglyceride	500 mg/dL

Based on the initial screening interference testing, the following substances have the following interferences observed.

Fluorescein tested at 40 mg/L yielded a -309% bias at 5 mg/dL bilirubin level and a -111% bias at 15 mg/dL bilirubin. Patent Blue V tested at 10 mg/L yielded a -94% bias at 5 mg/dL bilirubin level and a -44% bias at 15 mg/dL bilirubin. Methylene Blue tested at 60 mg/L yielded a -449% bias at 5 mg/dL bilirubin level and a -120% bias at 15 mg/dL bilirubin. Cardio Green tested at 30 mg/L yielded a -82% bias at 5 mg/dL bilirubin level and a -36% bias at 15 mg/dL bilirubin. SHb tested at 10% yielded a 150% bias at 5 mg/dL bilirubin level and a 35% bias at 15 mg/dL bilirubin. Hydroxocobalamin Hydrochloride tested at 2 mg/L yielded a -15.8% bias at 5 mg/dL bilirubin level and a -85% bias at 15 mg/dL bilirubin. Cyanocobalamin tested at 2 mg/L yielded a -9% bias at 5 mg/dL bilirubin level and a -73% bias at 15 mg/dL bilirubin.

Since there was significant interference for Fluorescein, Patent Blue V, Methylene Blue, Cardio Green, SHb, Hydroxocobalamin Hydrochloride, and Cyanocobalamin based on an initial screening test. (Sponsor defines significant interference as $\geq \pm 10\%$) Sponsor performed a dose response interference test per CLSI EP7-A2 and determined the concentration at which the interfering substance does not interfere with the assay. The dose response test results are provided in the table below.

Interferents tested	Bilirubin concentration tested (mg/dL)	Concentration of interfering substance above which interference occurs
Fluorescein	5	1.5 mg/L
	15	4 mg/L
Patent Blue V	5	1.5 mg/L
	15	2.5 mg/L
Methylene Blue	5	0.75 mg/L
	15	2 mg/L
Cardio Green	5	3 mg/L
	15	10 mg/L
SHb	5	1.1%
	15	1.6%
Hydroxocobalamin Hydrochloride	5	0.19 g/L
	15	0.5 g/L
Cyanocobalamin	5	0.2 g/L
	15	0.7 g/L

pH interference was tested at levels from 6.8 to 7.9 and no significant interference was found.

In addition, Cyanmethemoglobin (HiCN) and Beta-carotene are known interferents with the assay because the spectra for HiCN and Beta-carotene overlap with the spectrum of bilirubin. Results from samples containing these substances should not be used. The sponsor has the following limitation listed in the label:

“Since the spectra for HiCN and Beta-carotene overlap with the spectrum of bilirubin, these are known interfering substances. Results from samples containing these substances should not be used.”

f. Assay cut-off: Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison study versus the predicate device (ABL835 analyzer) was conducted according to CLSI guideline “Method Comparison and Bias Estimation Using Patient Samples”, EP09-A2. The study was conducted for both capillary and syringe mode at three point-of-care sites and included a total of 224 samples for capillary mode and 210 samples for syringe mode spanning the entire measuring range. Freshly drawn whole blood neonate samples were tested on the predicate device first and the left over samples were tested on the candidate device. In order to cover the reportable range spiked blood samples were used. Spiked samples contributed no more than 20% of the total number of samples at each site for this

study. Site 1 used 8 spiked samples in both capillary and syringe testing. Site 2 and 3 used 9 spiked samples in both capillary and syringe testing. The linear regression results are summarized below:

Syringe mode:

Site	N	Slope (95% CI)	Intercept (95% CI) mg/dL	R ²	Sample range tested mg/dL
Site 1	74	0.9922 (0.964 – 1.020)	1.0207 (0.64 – 1.40)	0.9857	1.8 – 35.9
Site 2	51	1.0054 (0.980 – 1.031)	0.3744 (0.00 – 0.75)	0.9924	2.0 – 37.9
Site 3	85	0.9917 (0.969 – 1.014)	0.3623 (0.01 – 0.71)	0.9895	2.7 – 37.1
All sites combined	210	0.9903 (0.975 – 1.005)	0.6574 (0.44 – 0.88)	0.9878	1.8 – 37.9

Capillary mode:

Site	N	Slope (95% CI)	Intercept (95% CI) mg/dL	R ²	Sample range tested mg/dL
Site 1	77	0.9774 (0.950 – 1.005)	1.1199 (0.76 – 1.48)	0.9853	1.8 – 35.5
Site 2	56	0.9977 (0.974 – 1.021)	0.5358 (0.19 – 0.88)	0.9927	2.1 – 37.3
Site 3	91	0.9737 (0.948 – 0.999)	0.4862 (0.09 – 0.88)	0.9845	3.0 – 36.7
All sites combined	224	0.9760 (0.961 – 0.991)	0.7741 (0.55 – 1.00)	0.9861	1.8 – 37.3

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:

The reference ranges are as follows¹:

Age	Bilirubin
≤24 hrs, premature	103-205 µmol/L 1.0-8.0 mg/dL 10-80 mg/L
≤24 hrs, full-term	34-103 µmol/L 2.0-6.0 mg/dL 20-60 mg/L
≤48 hrs, premature	103-205 µmol/L 6-12 mg/dL 60-120 mg/L
≤48 hrs	103-171 µmol/L 6-10 mg/dL 60-100 mg/L
3-5 days, premature	171-239 µmol/L 10-14 mg/dL 100-140 mg/L
3-5 days, full-term	68-137 µmol/L 4-8 mg/dL 40-80 mg/L
>1 month	3.4-17 µmol/L 0.2-1.0 mg/dL 2-10 mg/L

Reference: ¹Tietz NW, Logan NM. Reference ranges. In: Tietz NW, ed. Fundamentals of clinical chemistry. 3rd ed. Philadelphia: WB Saunders Company, 1987: 944-75.

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.