FEB 2 8 2013

510(k) Summary for COBAS INTEGRA Bilirubin Direct Gen.2

510(k) number k123965

Purpose of submission

Roche Diagnostics hereby submits this 510(k) to provide FDA with notification of intent to market a new device named COBAS INTEGRA Bilirubin Direct Gen.2 reagent.

This candidate device is a new reagent that was developed by Roche Diagnostics. The previous generation of reagent, COBAS INTEGRA Bilirubin Direct, was cleared in 510(k) k063543 and serves as the predicate device. The candidate and predicate devices use the same calibrator and controls. Only the reagents differ. This submission presents data to support clearance of this new reagent.

Measurand Direct Bilirubin

Type of test Quantitative diazo colorimetric method

Applicant Roche Diagnostics

Candidate device names

Proprietary name:
COBAS INTEGRA Bilirubin Direct Gen.2

Common name:
Bilirubin Direct Gen.2

Regulatory information

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

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510(k) Summary for COBAS INTEGRA Bilirubin Direct Gen.2, Continued

Intended use	In vitro test for the quantitative determination of direct bilirubin in human serum and plasma on COBAS INTEGRA systems.
Indications for use	COBAS INTEGRA Bilirubin Direct Gen.2 is an in vitro test for the quantitative determination of direct bilirubin in human serum and plasma on COBAS INTEGRA systems. Measurement of the levels of 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.
Special conditions for use	For prescription use only
Special instrument requirements	For use on the COBAS INTEGRA clinical chemistry analyzer
Candidate device description	COBAS INTEGRA Bilirubin Direct Gen.2 reagent provides quantitative measurement of the direct bilirubin that is present in a human serum or human plasma sample. Reagents are packaged in a cassette with two bottles labeled with their instrument positioning, R1 and SR. R1, or Reagent 1, contains Phosphoric acid 85 mmol/L, NaCL 50 mmol/L, and HEDTA 4.0 mmol/L at pH 1.9. SR, or Start Reagent, is a 3,5-dichlorophenyl diazonium salt at 1.5 mmol/L in acid buffer, pH 1.3.
Predicate device	Roche Diagnostics claims substantial equivalence to the COBAS INTEGRA Bilirubin Direct reagent that was cleared with the Special 510(k) k063543.

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Substantial equivalence - similarities

The following table compares the identical features of the candidate device to the predicate device that was cleared in 510(k) k063543.

Feature	Predicate Device: Bilirubin Direct	Candidate Device: Bilirubin Direct Gen.2
Sample Types	Serum and plasma	Same
Reference Method	Diazo colorimetric method	Same
Calibrator	Calibrator for automated systems (C.f.a.s.) and deionized water as the zero calibrator	Same
Calibration Stability	Recalibrate with each lot as and required following quality control procedures	Same
Calibration Mode	Linear regression	Same
Traceability	Standardized against the Doumas manual reference method	Same

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Substantial equivalence - differences

The following table compares the different features of the candidate device to the predicate device that was cleared in 510(k) k063543.

Feature	Predicate Device: Bilirubin Direct	Candidate Device: Bilirubin Direct Gen.2
Intended Use	COBAS INTEGRA Bilirubin Direct (BIL-D) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of the direct (conjugated) bilirubin concentration in serum and plasma.	In vitro test for the quantitative determination of direct bilirubin in human serum and plasma on COBAS INTEGRA systems.
Indications for Use	The cassette COBAS INTEGRA Bilirubin Direct (BIL-D) contains an in vitro diagnostic reagent system intended for use on COBAS INTEGRA systems for the quantitative determination of the direct (conjugated) bilirubin concentration in serum and plasma (test BIL-D, 0-049). Measurement of the levels of bilirubin, an organic compound formed during the normal and abnormal destruction of red blood cells, is used in the diagnosis of liver, hemolytic, hematological, and metabolic disorders, including hepatitis and gall bladder block.	COBAS INTEGRA Bilirubin Direct Gen.2 is an in vitro test for the quantitative determination of direct bilirubin in human serum and plasma on COBAS INTEGRA systems. Measurement of the levels of 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.
Permissible Anticoagulants	Li-heparin	Li-heparin K_2-EDTA K_3-EDTA
Instrument Platform	COBAS INTEGRA 400, 400 Plus, 700, and 800	COBAS INTEGRA 800

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Substantial equivalence - differences continued

Feature	Predicate Device: Bilirubin Direct	Candidate Device: Bilirubin Direct Gen.2
Reagent Composition	R1: Sulfanilic acid 35 mmol/L, Oxalic acid 40 mmol/L, HEDTA 4.0 mmol/L, and pH 1.2 R2: Sodium nitrite 3.9 mmol/L and pH 6.0 Sulfanilic acid reacts with sodium nitrite to form diazotized sulfanilic acid.	R1: Phosphoric acid 85 mmol/L, NaCL 50 mmol/L, HEDTA 4.0 mmol/L, and pH 1.9 SR: 3,5-DPD 1.5 mmol/L and pH 1.3
Reagent Shelf Life Stability	15-25 °C until expiration date	2-8 °C until expiration date
Reagent On-Board Stability	COBAS INTEGRA 700/800: 8 °C for 12 weeks COBAS INTEGRA 400/400 plus: 10-15 °C for 8 weeks	COBAS INTEGRA 800: 8 °C for 6 weeks
Controls	Precinorm U plus, Precipath U plus, Precinorm U, Precipath U	Precinorm U plus, Precipath U plus, PreciControl ClinChem Multi 1[A], PreciControl ClinChem Multi 2[A] [A]These two new controls were cleared for use with bilirubin direct with 510(k) # k102016.
Measuring Range	0.10 – 25 mg/dL	0.07 – 13.8 mg/dL
Expected Values	0 to 0.2 mg/dL	≤ 0.20 mg/dL
Lower Limits of Measure	LDL = 0.10 mg/dL	LoB = 0.05 mg/dL LoD = 0.07 mg/dL LoQ = 0.07 mg/dL

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Test principle

COBAS INTEGRA Bilirubin Direct Gen.2 measures direct bilirubin by employing the diazo colorimetric method. Conjugated bilirubin and δ-bilirubin (direct bilirubin) react directly with 3,5-dichlorophenyl diazonium salt in acid buffer to form the red-colored azobilirubin. The color intensity of the red azobilirubin formed is directly proportional to the direct bilirubin concentration. The color intensity is measured photometrically by a COBAS INTEGRA clinical chemistry analyzer.

Precision/ reproducibility

Precision was determined according to CLSI EP5-A2. The study included human sera samples (0.12, 3.76, and 13.2 mg/dL) and two serum-based control samples in two aliquots per run and two runs per day for 21 days.

Here are summaries of the repeatability and intermediate precision data.

Repeatability Summary

Specimen	PNU	PPU	Human Serum 1	Human Serum 2	Human Serum 3
Total Mean (mg/dL)	**0.75**	**1.9**	**0.12**	**3.8**	**13.2**
Within Run Imprecision SD (mg/dL)	0.01	0.01	0.01	0.01	0.04
Within Run Imprecision CV%	**1.2**	**0.6**	**7.4**	**0.4**	**0.3**
Min (mg/dL)	0.72	1.9	0.09	3.7	13.1
Max (mg/dL)	0.78	2.0	0.13	3.8	13.3

Intermediate Precision

Specimen	PNU	PPU	Human Serum 1	Human Serum 2	Human Serum 3
Total Mean (mg/dL)	**0.75**	**1.9**	**0.12**	**3.8**	**13.2**
Total Imprecision SD (mg/dL)	0.01	0.02	0.01	0.04	0.05
Total Imprecision CV%	**1.6**	**1.0**	**7.7**	**1.0**	**0.4**
Min (mg/dL)	0.72	1.9	0.09	3.7	13.1
Max (mg/dL)	0.78	2.0	0.13	3.8	13.3

Values that appear in bold type also appear in the labeling.

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Linearity/ assay reportable range

Linearity was assessed according to CLSI EP6-A with one batch of reagent, in one run, and with samples measured in triplicate. Two separate dilution series differing by sample type (serum and plasma) were prepared with thirteen levels each. Lithium-heparin was used to prepare the plasma sample series. The highest concentration samples exceed the desired measuring range. The highest concentration samples were created by taking low analyte native samples and spiking them with ditaurobilirubin.

Measuring Ranges that are Supported by the Linearity Data

	Plasma	Serum
Range tested (mg/dL)	0.01 – 19.5	0.02 – 19.4
Range found (mg/dL)	0.01 – 19.5	0.02 – 17.4
Recommended measuring range (mg/dL)	0.07 – 13.8	0.07 – 13.8

The quadratic model is significant for both sample types.

Linear Regression Equation for Serum
$y = 1.0000x - 0.0000$ $r^2 = 0.9944$

Linear Regression Equation for Plasma
$y = 1.0000x - 0.0000$ $r^2 = 0.9977$

Traceability, stability, and expected values

This method has been standardized against the manual test performance using the Doumas method.

The reagent has been evaluated for transport, shelf-life, open on-board, and calibration stability.

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Detection limit

LoB, LoD, and LoQ studies were performed based upon CLSI EP17-A2.

LoB Protocol: One blank sample was tested in n=5 with two analyzers with three reagent batches for two runs per day across three days.

LoD Protocol: Five low-analyte samples were measured in singlicate on two analyzers with three reagent batches for two runs per day across three days.

LoQ Protocol: A low-level sample set of nine was measured in singlicate, using three reagent batches on two analyzers for two runs per day across three days. The LoQ is determined based on precision at 20% CV.

The LoB, LoD, and LoQ claims represent the specifications for each.

LoB claim = 0.05 mg/dL
LoD claim = 0.07 mg/dL
LoQ claim = 0.07 mg/dL

Analytical specificity - interference from endogenous substances

The reagent was evaluated with two endogenous substances, hemoglobin and lipids, for potential interference with the measurement of direct bilirubin.

One pool of human serum was spiked with the interferent. A second pool of human serum contained none. The two pools were mixed in different ratios to yield a dilution series with varying concentrations of the interferent (from 0 to 10).

The endogenous interference data are summarized in the table. The labeling claims the specification, "No significant interference up to an H index of 25," and "No significant interference up to an L index of 750."

Endogenous Interference Summary Data

	no interference up to this concentration (mg/dl)
Lipemia low analyte	1098
Lipemia high analyte	1100
Hemolysis low analyte	35
Hemolysis high analyte	25

The lowest L index for which there is no significant interference is 1098.
The lowest H index for which there is no significant interference is 25.

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Analytical specificity - interference from common drugs

Eighteen commonly used drugs were added to native patient samples and examined for potential interference on measurement with COBAS INTEGRA Bilirubin Direct reagent.

Drug interference testing was performed with serum sample pools at two target concentrations of direct bilirubin, one at a low concentration of ~ 1.8 mg/dL and the second one at a high concentration of ~ 4.9 mg/dL.

Direct bilirubin concentration in all aliquots is measured in triplicate on the COBAS INTEGRA analyzer. The mean value among the triplicates for each aliquot is determined. From the mean values, the percent recovery to the initial value is calculated.

"Phenylbutazone causes falsely low bilirubin results." This statement appears in the labeling. The remaining 17 commonly used drugs produce no interference with BILD2 measurement.

	Drug	Highest Concentration Shown Not to Interfere with BILD2 (mg/L, except Heparin)
1	Acetylcystein	150
2	Ampicillin - Na	1000
3	Ascorbic acid	300
4	Ca - Dobesilate	200
5	Cyclosporine A	5
6	Cefoxitin	2500
7	Heparin - Na	5000 U
8	Intralipid	10000
9	Levodopa	20
10	Methyldopa + 1.5	20
11	Metronidazole	200
12	Doxycyclin	50
13	Acetylsalycilic acid	1000
14	Rifampicin	60
15	Acetaminophen	200
16	Ibubrofen	500
17	Theophylline	100

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Method comparison with predicate device

Direct bilirubin values for n=71 human sera samples were obtained using the candidate reagent (y-axis) to the predicate reagent (x-axis) on the COBAS INTEGRA 800 clinical chemistry analyzer. Samples ranged from 0.083 to 13.762 mg/dL and were tested in singlicate. The values were regressed using the Passing/Bablok model to produce the following equation. $R^2 = 0.9979$

$$y = 1.0490x + 0.0699 \text{ mg/dL}$$

Matrix comparison

Lithium-heparin, K_2-EDTA, and K_3-EDTA are permissible anticoagulants for use with this reagent because they do not interfere with recovery of direct bilirubin. 32 tubes were collected per anticoagulant. Plasma results were compared to serum results and percent recovery was determined.

Median Values for Anticoagulant Comparisons

anticoagulants	median recovery	median absolute deviation(mg/dL)
Li-Heparin (full)	102%	+0.02
Li-Heparin (half)		-0.05
K2-EDTA (full)	101%	+0.00
K2-EDTA (half)		-0.02
K3-EDTA (full)	100%	-0.00
K3-EDTA (half)		-0.03
Gel Separation Tube	104%	+0.02
Criteria	90 to 110%	<0.20

Comparisons were also regressed.

Serum vs. Li-heparin	P/B: y = 0.01 + 1.0179x,	r = 0.9988
Serum vs. K2-EDTA	P/B: y = -0.01 + 1.0120x,	r = 0.9988
Serum vs. K3-EDTA	P/B: y = -0.03 + 1.0095x,	r = 0.9988

Expected values/ reference range

Direct bilirubin ≤ 0.20 mg/dL

Balisteri WF, Shaw LM. Liver function. In: Tietz NW, ed. Fundamentals of Clinical Chemistry. 3rd ed. Philadelphia: WB Saunders 1987; 729-761.

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Conclusion	The submitted information in this premarket notification supports a substantial equivalence decision.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-002

February 28, 2013

Roche Diagnostics
c/o Susan Hollandbeck
Regulatory Affairs Consultant
9115 South Hague Road
Indianapolis, IN 46250

Re: k123965
Trade/Device Name: COBAS INTEGRA Bilirubin Direct Gen. 2 Reagent
Regulation Number: 21 CFR 862.1110
Regulation Name: Bilirubin (total or direct) test system
Regulatory Class: Class II
Product Code: CIG
Dated: December 21, 2012
Received: December 26, 2012

Dear Ms. Hollandbeck:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Parts 801 and 809), please contact the Office of *In Vitro* Diagnostics and Radiological Health at (301) 796-5450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Carol C. Benson -S FDA for

Courtney H. Lias, Ph.D.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (if known):
k123965

Device Name:
COBAS INTEGRA Bilirubin Direct Gen.2

Indications for Use:
COBAS INTEGRA Bilirubin Direct Gen.2 is an *in vitro* test for the quantitative determination of direct bilirubin in human serum and plasma on COBAS INTEGRA systems. Measurement of the levels of 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.

Prescription Use ___X___ And/Or Over the Counter Use ____.
(21 CFR Part 801 Subpart D) (21 CFR Part 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE; CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostics and Radiological Health (OIR)

Yung W. Chan -S

Division Sign-Off
Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) k123965