510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K240927

B Applicant

Beckman Coulter, Inc

C Proprietary and Established Names

Access Thyroglobulin

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
MSW	Class II	21 CFR 866.6010 - Tumor-Associated Antigen Immunological Test System	IM - Immunology

II Submission/Device Overview:

A Purpose for Submission:

Modification of previously cleared device – the change of substrate for the assay on the Dxl 9000 Access Immunoassay Analyzer

B Measurand:

Thyroglobulin (Tg)

C Type of Test:

Quantitative, Chemiluminescent Immunoassay

III Intended Use/Indications for Use:

A Intended Use(s):

Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human serum and plasma using the Access Immunoassay Systems. This device is intended to aid in monitoring for the presence of persistent or recurrent/metastatic disease in patients who have differentiated thyroid cancer (DTC) and have had thyroid surgery (with or without ablative therapy), and who lack serum thyroglobulin antibodies.

B Indication(s) for Use:

Same as Indended Use

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only
For In Vitro Diagnostic Use Only

The Instruction for Use of the device contains the following warnings:

The presence of serum autoantibodies to thyroglobulin (TgAb) can interfere with assays for thyroglobulin (Tg). Therefore, sera which contain TgAb, even at very low levels, should not be tested for Tg.

The concentration of thyroglobulin in a given specimen determined with assays from different manufacturers can vary due to differences in assay methods and reagent specificity. The results reported by the laboratory to the physician must include the identity of the Tg assay used. Values obtained with different assay methods cannot be used interchangeably. If, in the course of monitoring a patient, the assay method used for determining Tg levels serially is changed, additional sequential testing should be carried out to confirm baseline values.

D Special Instrument Requirements:

DxI 9000 Access Immunoassay Analyzer (K221225)

IV Device/System Characteristics:

A Device Description:

Each Access Thyroglobulin reagent kit contains two reagent packs (50 tests/pack). Each pack contains the following:

- R1a (3.25 mL): Dynabeads paramagnetic particles coated with streptavidin and coupled to biotinylated mouse monoclonal antithyroglobulin antibodies in TRIS buffer with protein (bovine) and preservatives

- R1b (3.10 mL): Mouse monoclonal anti-thyroglobulin-alkaline phosphatase (bovine) conjugate in a TRIS buffer with protein (bovine, murine) and preservatives
- R1c (3.10 mL): HEPES buffer with protein (bovine, murine) and preservatives

Materials needed but not supplied:

- Access Thyroglobulin Calibrators: Six levels (0, 1.0, 10, 100, 250, and 500 ng/mL)
- Quality Control Materials: commercial control material
- Substrate: Lumi-Phos PRO
- Unicel DxI Wash Buffer II
- Access Thyroglobulin Sample Diluent (optional)

The modification of the Access Thyroglobulin is to replace substrate (Lumi-Phos 530) of the Access Thyroglobulin with a new substrate (Lumi-Phos PRO) on the DxI 9000 Access Immunoassay Analyzer.

B Principle of Operation:

The Access Thyroglobulin assay is a simultaneous one-step immunoenzymatic ("sandwich") assay. A sample is added to a reaction vessel with four biotinylated anti-thyroglobulin antibodies coated on streptavidin paramagnetic particles, and monoclonal anti-thyroglobulin antibody alkaline phosphatase conjugate. The thyroglobulin in the sample binds to the biotinylated antibodies on the solid phase, while the conjugate antibody reacts with a different antigenic site on the thyroglobulin molecule. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional to the concentration of thyroglobulin in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve.

V Substantial Equivalence Information:

A Predicate Device Name(s):

Access Thyroglobulin

B Predicate 510(k) Number(s):

K220972
K241423

C Comparison with Predicate(s):

Device & Predicate Device(s):	K240927 (Candidate)	K241423 (Predicate)	K220972 (Predicate)
Device Trade Name	Access Thyroglobulin	Access Thyroglobulin	Access Thyroglobulin
General Device Characteristic Similarities			
Intended Use/ Indications for Use	Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human serum and plasma using the Access Immunoassay Systems. This device is intended to aid in monitoring for the presence of persistent or recurrent/metastatic disease in patients who have differentiated thyroid cancer (DTC) and have had thyroid surgery (with or without ablative therapy), and who lack serum thyroglobulin antibodies.	Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human plasma using the Access Immunoassay Systems. This device is intended to aid in monitoring for the presence of persistent or recurrent/metastatic disease in patients who have differentiated thyroid cancer (DTC) and have had thyroid surgery (with or without ablative therapy), and who lack serum thyroglobulin antibodies.	Access Thyroglobulin assay is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of thyroglobulin levels in human serum using the Access Immunoassay Systems. This device is intended to aid in monitoring for the presence of persistent or recurrent/metastatic disease in patients who have differentiated thyroid cancer (DTC) and have had thyroid surgery (with or without ablative therapy), and who lack serum thyroglobulin antibodies.
Analyte	Thyroglobulin	Same	Same
Technology	Chemiluminescent	Same	Same
Method	Automated	Same	Same
Antibodies	Mouse monoclonal antibodies	Same	Same
Assay Architecture	Biotinylated mouse monoclonal anti-thyroglobulin antibodies pre-coupled to paramagnetic particles coated with streptavidin.	Same	Same
Assay Throughput	~42 minutes	Same	Same
Measuring Range	0.1 – 500 ng/mL	Same	Same

General Device Characteristic Differences			
Sample Matrix	Serum and Plasma (heparin)	Plasma (heparin)	Serum
Sample Volume	45 µL	40 µL	
Substrate	Lumi-Phos PRO substrate	Access Substrate (Lumi-Phos 530)	
Instrument	DxI 9000 Access Immunoassay Analyzer	Access 2 Immunoassay Analyzer	

VI Standards/Guidance Documents Referenced:

The following Clinical and Laboratory Standards Institute (CLSI) guideline was used:

- CLSI EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline – Third Edition
- CLSI EP06-2nd Edition-: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline
- CLSI EP09c 3rd Edition: Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Third Edition
- CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

Precision testing was performed in accordance with CLSI guideline EP05-A3.

a) With-in Laboratory Precision:

The within-laboratory precision was evaluated using three reagent lots and three DxI 9000 Access Immunoassay Analyzers. Six levels of human serum samples in a minimum of two replicates per run, two runs per day for 20 days, resulting in a minimum of 80 datapoints for each sample per reagent lot per instrument. The data were analyzed for repeatability (within-run), between-run, between-day, and within-laboratory precision. The mean (ng/mL), standard deviation (SD) (ng/mL) and percent coefficient of variation (%CV) were calculated for each sample. The representative data of within-laboratory precision using one lot of reagents on one instrument are summarized in the table below.

Sample	Mean (ng/mL)	N	Within-Run		Between-Run		Between-Day		Within-Laboratory	
			SD	% CV	SD	% CV	SD	% CV	SD	% CV
1	0.3	88	0.02	5.4	0.01	4.7	0.01	4.4	0.02	8.4
2	5.5	88	0.26	4.7	0.26	4.7	0.09	1.6	0.38	6.8
3	22	88	0.95	4.4	0.88	4.1	0.41	1.9	1.36	6.3
4	111	80	2.22	2.0	0.64	0.6	1.47	1.3	2.74	2.5
5	376	80	8.91	2.4	5.04	1.3	9.06	2.4	13.67	3.6
6	417	80	8.82	2.1	6.25	1.5	10.13	2.4	14.82	3.6

b) Lot-to-Lot Precision

The lot-to-lot precision of Lumi-Phos PRO Substrate was assessed in K223921.

The lot-to-lot precision of the modified Access Thyroglobulin reagent was evaluated using three reagent lots on the DxI 9000 Access Immunoassay Analyzer. Serum samples at different concentrations were tested in five replicates per run, one run per day over five days, resulting N=75 datapoints per sample on one instrument. The same study was also performed on two additional instruments. The data were analyzed for within-run, between-day, and between-lot, and total precision. Across three instruments, the CV% for reagent lot-to-lot imprecision is ≤ 6.6% for all samples tested.

c) Instrument-to-Instrument Precision:

The study was performed by testing six serum samples at different concentrations on three DxI 9000 Access Immunoassay Analyzers. Each sample was tested in five replicates per run, one run per day over five days, resulting in minimum N=75 datapoints using one lot of reagents. The same study was also performed on two additional reagent lots. The representative data of instrument-to-instrument reproducibility are summarized in the table below on one representative reagent lot are summarized in the table below.

Sample	Mean (ng/mL)	N	Within-Run		Between-Day		Between-Instrument		Total	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV
1	0.34	75	0.02	5.9	0.02	4.5	0.00	0.0	0.03	7.4
2	6.2	75	0.20	3.2	0.09	1.5	0.18	2.9	0.28	4.6
3	21	75	0.82	3.9	0.49	2.3	0.69	3.3	1.18	5.7
4	109	75	2.98	2.7	1.62	1.5	0.92	0.8	3.51	3.2
5	370	75	11.84	3.2	6.37	1.7	13.31	3.6	18.92	5.1
6	402	75	10.18	2.5	13.09	3.3	16.94	4.2	23.70	5.9

2. Linearity:

A linearity study of the modified Access Thyroglobulin assay on the DxI 9000 Access Immunoassay Analyzer was performed in accordance with CLSI EP06-Ed2. Three linearity dilution series were prepared by mixing High and Low native serum samples. The first dilution series included seven dilution samples covering the range of 0.03 – 14.76 ng/mL.

The second dilution series included eight dilution samples covering the range of 0.03 – 87.52 ng/mL. The third dilution series included seven dilution samples covering the range of 0.03 – 642.23 ng/mL. For all three-dilution series, the lowest samples were tested in replicates of eight, while all other samples were tested in replicates of four on one DxI 9000 Access Immunoassay Analyzer using one modified Access Thyroglobulin reagent lot. For each level, the mean of the measured values, predicted value and the percent deviation from linearity were calculated. The data sets from the three series were also combined for a single linearity analysis. The results are summarized in the tables below.

Dilution Range (ng/mL)	Slope (95% CI)	Intercept (95% CI)	R2	% Deviation from Linearity
0.03 – 14.76	0.948 (0.937, 0.958)	0.002 (-0.001, 0.004)	0.998	-3.8 – 5.5
0.03 – 87.52	1.003 (0.991, 1.015)	-0.000 (-0.002, 0.002)	0.998	-3.1 – 1.8
0.03 – 642.23	0.977 (0.969, 0.986)	0.001 (-0.001, 0.002)	0.999	-3.2 – 2.3
All Combined (0.03 – 642.23)	0.976 (0.969, 0.983)	0.001 (-0.001, 0.002)	1.000	-6.6 – 4.1

The data support the linearity interval from 0.03 to 642.23 ng/mL with the % deviations from linearity within ±10%. The study results support the linearity of the claimed analytical measuring interval (AMI): 0.1 – 500 ng/mL.

3. Analytical Specificity/Interference:

   Refer to K220972

4. Assay Reportable Range:

   The assay reportable range for the Access Thyroglobulin is the same as the claimed AMI: 0.1–500 ng/mL.

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

   a) Traceability:

   The traceability was established in K002905. There is no change to the traceability of the modified Access Thyroglobulin.

   b) Stability:

   The Access Thyroglobulin Reagent kit and the Lumi-Phos PRO substrate are packaged separately. Access Thyroglobulin Reagent kit stability was established in K220972. The proposed change is to replace the substrate (Lumi-Phos 530) with a new substrate (Lumi-Phos PRO) for the assay run on DxI 9000 Access Immunoassay Analyzer. The shelf-life

claims and on-board stability claims of Lumi-Phos PRO substrate were established in K221225.

6. Detection Limit:

The Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) of the modified Access Thyroglobulin on the DxI 9000 Access Immunoassay Analyzer were determined based on the CLSI guideline EP17-A2.

a) LoB:

The LoB was determined by testing five thyroglobulin-depleted individual native serum samples using two modified Access Thyroglobulin reagent lots on two DxI 9000 Access Immunoassay Analyzers. Samples were run in five replicates per run, one run per day, for three days on one DxI 9000 Access Immunoassay Analyzer, resulting in 75 replicates for each reagent lot on each instrument. LoB was defined as the value corresponding to the 95th percentile of the rank position of the distribution of values. This resulted in the LoB value of 0.01 ng/mL for each of two reagent lots. The claimed LoB for the modified Access Thyroglobulin on the DxI 9000 Access Immunoassay Analyzer is 0.03 ng/mL.

b) LoD:

The LoD was determined by testing six native serum specimens comprised of an individual native serum sample and five pools of native serum samples using two modified Access Thyroglobulin reagent lots on two DxI Access 9000 Immunoassay Analyzers. Samples were run a minimum of eight replicates per run, one run per day, for five days for each reagent lot on each DxI 9000 Access Immunoassay Analyzer. The LoD was calculated for each reagent lot based on LoB + "SD multiplied by the 95th percentile of the standard normal distribution" per CLSI EP17-A2. The claimed LoD for the modified Access Thyroglobulin assay on the DxI 9000 Access Immunoassay Analyzer is 0.05 ng/mL.

c) LoQ:

The LoQ was determined by testing 10 native serum specimens comprised of two individual native serum samples and eight pools of native serum samples using two modified Access Thyroglobulin reagent lots on two DxI 9000 Access Immunoassay Analyzers. Samples were run a minimum of nine replicates per run, one run per day, for five days for each reagent lot on each DxI 9000 Access Immunoassay Analyzer. The estimated LoQ of the modified Access Thyroglobulin was set to be the Thyroglobulin concentration which met the within-laboratory imprecision of 20%CV. The claimed LoQ for the modified Access Thyroglobulin assay on the DxI 9000 Access Immunoassay Analyzer is 0.1 ng/mL.

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

CLSI guideline EP09c, 3rd Edition was followed to compare the modified Access Thyroglobulin assay on the DxI 9000 Access Immunoassay Analyzer to the predicate device, the Access Thyroglobulin assay on the Access 2 Immunoassay Analyzer. Samples falling within the analytical measuring interval of both assays were evaluated. A total of 187 serum samples (185 were native individual serum samples, two samples were native serum samples supplemented with purified human Thyroglobulin antigen) were tested with four modified Access Thyroglobulin reagent pack lots on four DxI 9000 Access Immunoassay Analyzers (candidate), and four Access Thyroglobulin reagent pack lots on four Access 2 Immunoassay Analyzers (predicate). The comparison between paired measurements was analyzed using Passing-Bablok method by fitting the observed modified Access Thyroglobulin on the DxI 9000 Access Immunoassay Analyzer (y) into a linear regression model, with the observed value from the predicate (x). The results are summarized in the following table:

N	Range of Observations (ng/mL)	Slope [95% CI]	Intercept [95% CI]	Correlation Coefficient (r)
187	0.350 – 472.628	0.996 (0.991 to 1.001)	0.004 (-0.029 to 0.021)	0.999

2. Matrix Comparison:

Refer to K241423

C Clinical Studies:

Refer to K002905

D Clinical Cut-Off:

Refer to K002905

E Expected Values/Reference Range:

Refer to K220972

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.