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

A. 510(k) Number:

k172783

B. Purpose for Submission:

New device

C. Measurand:

Cardiac troponin I (cTnI)

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Beckman Coulter, Inc.

F. Proprietary and Established Names:

Access hsTnI

G. Regulatory Information:

1. Regulation section:

   21 CFR 862.1215

2. Classification:

   Class II

3. Product code:

   MMI

4. Panel:

   Chemistry (75)

H. Intended Use:

1. Intended use(s):

   See indication(s) for use below.

2. Indication(s) for use:

   The Access hsTnI is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma using the UniCel DxI Access Immunoassay Systems to aid in the diagnosis of myocardial infarction (MI).

3. Special conditions for use statement(s):

   For prescription use only.

   For in vitro diagnostic use.

4. Special instrument requirements:

   Performance data below was collected on the Access UniCel DxI 800 Immunoassay System.

I. Device Description:

The Access hsTnI reagent packs contain specific reagents for the *in vitro* diagnostic measurement of cTnI including:

- R1a: Dynabeads paramagnetic particles coated with mouse monoclonal anti-human cTnI antibody suspended in TRIS buffered saline, with surfactant, bovine serum albumin (BSA), < 0.1% sodium azide, and 0.1% ProClin 300.
- R1b: 0.1 N NaOH.
- R1c: TRIS buffered saline, surfactant, protein (mouse), < 0.1% sodium azide, and 0.1% ProClin 300.
- R1d: Sheep monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein (bovine, sheep, mouse), < 0.1% sodium azide, and 0.25% ProClin 300.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Access AccuTnI+3 Reagent and Access AccuTnI+3 Calibrators for use on the Access 2 Immunoassay System

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

   k121214

3. Comparison with predicate:

Similarities and Differences		
Item	**Predicate Device Access AccuTnI+3 k121214**	**Candidate Device Access hsTnI**
Intended Use/ Indications for Use	Is a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of cardiac troponin I (cTnI) levels in human serum and plasma to aid in the diagnosis of myocardial infarction.	Same
Assay Principle	Chemiluminescent sandwich immunoassay	Same
Test System	Automated immunoassay instrument	Same
Sample Type	Serum and heparinized plasma	Same
Reagent Pack configuration	Reagents ready to use and separated in a single reagent pack	Same
Primary Reagent Materials	Solid phase magnetic particles, anti- cTnI antibodies	Dynabeads paramagnetic particles coated with mouse monoclonal anti-human cTnI antibody
Sample Volume	55µL	same
Specific Reagent Materials	Mouse monoclonal anti-human cTnI alkaline phosphatase conjugate, magnetic particles coated with mouse monoclonal anti- human cTnI	Sheep monoclonal anti-human cTnI alkaline phosphatase conjugate diluted in ACES buffered saline, with surfactant, BSA matrix, protein

Similarities and Differences		
Item	**Predicate Device Access AccuTnI+3 k121214**	**Candidate Device Access hsTnI**
		(bovine, sheep, mouse)
Immunoassay Instrument	Access 2 Immunoassay System	UniCel DxI 800 Access Immunoassay System
Analytical Measuring Range	0.02 ng/mL to 100 ng/mL (20 pg/mL to 100,000 pg/mL)	2.1 pg/mL to 27,027 pg/mL
Assay Protocol File (APF)	AccuTnI+3 APF with addition of the thermal algorithm	hsTnI APF with addition of the thermal algorithm

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

CLSI EP05-A3, Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline-Third Edition

CLSI EP06-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 EP17-A2, Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline – Second Edition

CLSI EP25-A, Evaluation of Stability of In Vitro Diagnostic Reagents; Approved Guideline

CLSI EP28-A3c, Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline – Third Edition

L. Test Principle:

The Access hsTnI is a two–site immunoenzymatic ("sandwich") assay. Monoclonal anti–cTnI antibody conjugated to alkaline phosphatase is added to a reaction vessel along with a surfactant–containing buffer and sample. After a short incubation, paramagnetic particles coated with monoclonal anti–cTnI antibody are added. The human cTnI binds to the anti–cTnI antibody on the solid phase, while the anti–cTnI antibody–alkaline phosphatase conjugate reacts with different antigenic sites on the cTnI molecules. 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 cTnI in the sample. The amount of analyte in the sample is determined from a stored, multi–point calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

The sponsor evaluated precision in several studies following the recommendations in CLSI EP05-A3.

Within-laboratory precision studies:

An internal study was conducted with five serum and five lithium heparin plasma sample pools with approximate TnI concentrations of 10, 20, 100, 5,000, and 20,000 pg/mL. Samples around the 99th percentile cut-off (i.e., 10, 20 pg/mL) were native sample pools, all others were spiked with native human cTnI. For the studies, the instruments were calibrated at 18°C, 24°C, and 30°C and subsequently each sample level was assayed in duplicate, in up to four runs per day, over 10 days at 18°C, 24°C, and 30°C (for a total of 9 different calibration temperature/run temperature conditions evaluated for each sample), using three reagent lots and three instruments for each calibration/run temperature condition (instrument and lot were confounded in this study) and one calibrator lot for the entire study. The total %CV estimates include the within-laboratory sources of variability (within-run, between-run, and between-day) as well as between-lot and between-instrument variability. The following data generated at one calibration/run temperature condition are representative of the results of all of the precision studies:

Sample	N	Mean (pg/mL)	Within-run		Between-Run		Between-Day		Within-Lab		Total	
			SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
Plasma 1	240	9.73	0.35	3.6%	0.20	2.1%	0.11	1.1%	0.42	4.3%	0.58	5.9%
Plasma 2	240	19.37	0.62	3.2%	0.26	1.4%	0.04	0.2%	0.67	3.5%	1.09	5.6%
Plasma 3	240	88.72	2.90	3.3%	2.66	3.0%	0.15	0.2%	3.94	4.4%	7.64	8.6%
Plasma 4	240	4989.95	170.11	3.4%	182.34	3.7%	0.84	0.0%	249.37	5.0%	479.96	9.6%
Plasma 5	240	17208.11	603.08	3.5%	323.44	1.9%	256.76	1.5%	730.92	4.2%	1031.91	6.0%
Serum 1	240	10.39	0.49	4.8%	0.23	2.2%	0.11	1.1%	0.56	5.4%	0.72	6.9%
Serum 2	240	12.24	0.55	4.5%	0.38	3.1%	0.10	0.8%	0.68	5.5%	0.78	6.4%
Serum 3	240	109.43	4.06	3.7%	1.77	1.6%	1.33	1.2%	4.62	4.2%	9.41	8.6%
Serum 4	240	4449.55	177.45	4.0%	53.31	1.2%	75.99	1.7%	200.27	4.5%	388.62	8.7%
Serum 5	240	18253.75	787.86	4.3%	167.84	0.9%	119.59	0.7%	814.37	4.5%	1299.56	7.1%

A second within-laboratory precision study was performed at one external site under normal laboratory conditions. Four commercial controls (QC), five lithium heparin plasma sample pools, and five serum sample pools were run in duplicate, two runs per day for 20 days. This study was performed using one reagent lot and one instrument. Results for this study are shown below:

Sample	N	Mean (pg/mL)	Between-Day		Between-Run		Within-Run (Repeatability)		Within-Laboratory (total)	
			SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)	SD (pg/mL)	CV (%)
Plasma 1	80	7.8	0.00	0.0	0.41	5.0	0.31	6.0	0.62	8.0
Plasma 2	80	13.0	0.47	3.7	0.38	2.9	0.41	3.2	0.73	5.6
Plasma 3	80	32.0	0.91	2.8	1.03	3.2	0.89	2.8	1.64	5.1
Plasma 4	80	106.8	2.23	2.1	0.00	0.0	3.59	3.4	4.22	4.0
Plasma 5	80	20268.0	286.00	1.4	413.00	2.0	805.00	4.0	949.00	4.7
Serum 1	80	7.9	0.00	0.0	0.41	5.3	0.31	4.0	0.52	6.6
Serum 2	79*	12.2	0.47	3.8	0.31	2.5	0.44	3.6	0.71	5.8
Serum 3	80	30.2	0.85	2.8	0.55	1.8	1.07	3.5	1.47	4.9
Serum 4	80	110.1	2.10	1.9	1.94	1.8	3.74	3.4	4.70	4.3
Serum 5	80	17831.0	347.00	1.9	527.00	3.0	652.00	3.7	908.00	5.1
QC1	80	25.6	0.99	3.9	0.64	2.5	0.99	3.9	1.54	6.0
QC2	80	61.8	2.43	3.9	1.42	2.3	1.56	2.5	3.22	5.2
QC3	80	1242.0	20.00	1.6	20.00	1.6	32.00	2.6	43.00	3.4
QC4	80	15415.0	324.00	2.1	292.00	1.9	598.00	3.9	740.00	4.8

*No result for one replicate due to insufficient quantity of sample

Reproducibility:

An external reproducibility study was performed at three sites. Four serum and four lithium heparin plasma sample pools as well as four quality control (QC) materials were run in duplicate, two runs per day, for five days, using one reagent lot and one calibrator lot and three instruments (one instrument per site). Calibration and run temperatures were based on ambient conditions at each site. Results for this study are shown below:

Sample	N	Mean pg/mL (SD)	Between site CV (SD)	Between Day CV (SD)	Between Run CV (SD)	Repeatability CV (SD)	Reproducibility CV
Plasma 1	60	12.3 (0.44)	0.9% (0.11)	1.2% (0.15)	1.9% (0.23)	2.6% (0.32)	3.6%
Plasma 2	60	30.8 (1.34)	1.9% (0.57)	0.0% (0.00)	2.4% (0.73)	3.1% (0.96)	4.3%
Plasma 3	60	106.1 (4.31)	2.7% (2.90)	0.7% (0.76)	1.0% (1.10)	2.7% (2.90)	4.1%
Plasma 4	60	19792.0 (805)	1.6% (309)	0.0% (0.00)	2.0% (401)	3.2% (626)	4.1%
Serum 1	60	11.6 (0.50)	1.5% (0.17)	0.0% (0.00)	1.8% (0.21)	3.7% (0.43)	4.3%
Serum 2	60	29.7 (1.42)	3.0% (0.88)	0.9% (0.28)	2.4% (0.72)	2.7% (0.79)	4.8%
Serum 3	60	110.6 (5.82)	4.1% (4.58)	0.3% (0.38)	1.3% (1.42)	3.0% (3.28)	5.3%
Serum 4	60	17681.0 (840)	1.9% (339)	2.3% (399)	2.6% (460)	2.6% (468)	4.7%
QC1	60	24.7 (1.73)	4.1% (1.02)	2.7% (0.66)	3.0% (0.73)	4.0% (0.99)	7.0%
QC2	59	63.4 (3.83)	2.6% (1.67)	4.1% (2.62)	2.9% (1.82)	2.1% (1.32)	6.1%
QC3	60	1273.0 (62)	2.6% (33)	3.1% (39)	1.7% (22)	2.1% (27)	4.9%
QC4	60	15362.0 (675)	0.0% (0.00)	1.9% (297)	2.2% (339)	3.3% (502)	4.4%

Field precision study:

The sponsor performed an in-house precision study to simulate the use of the device by the end user. This study was designed to incorporate different sources of variability that may be found in the field including: the simultaneous running of other assays; variability in test request type (e.g., panel, stat, and individual testing); variability of ambient temperatures. Three lithium heparin plasma and three serum samples with concentrations across the measuring range of the assay were assayed in randomized singlicates using three reagent lots on three UniCel DxI 800 instruments over three days for a total of 15 replicates per sample across all temperature conditions during a single day. During the course of a day, the ambient temperature in which the study was executed was cycled between 18°C and 28°C as described in the following table:

Time point	Ambient Temperature
1	23°C
2	20.5°C
3	18°C
4	23°C
5	25.5°C
6	28°C

A single calibration curve was generated at 23 ±2ºC on each instrument for this study. Results are shown below. Differences in the number of data points in the table were due to experimental design (automatic flex testing of high samples) and some replicates inadvertently not tested or not yielding results.

Instrument	Reagent Lot	Sample	N	Sample Mean (pg/mL)	Within-day		Between-day		Total	
					SD	CV	SD	CV	SD	CV
1	1	Plasma 1	89	9.02	0.75	8.3%	0.00	0.0%	0.75	8.3%
		Plasma 2	90	80.81	3.23	4.0%	1.50	1.9%	3.56	4.4%
		Plasma 3	180	12439.67	428.32	3.4%	76.20	0.6%	435.04	3.5%
		Serum 1	90	7.79	0.52	6.7%	0.00	0.0%	0.52	6.7%
		Serum 2	90	50.81	2.08	4.1%	1.92	3.8%	2.83	5.6%
		Serum 3	178	11440.96	428.97	3.7%	104.94	0.9%	441.62	3.9%
2	2	Plasma 1	90	8.64	0.60	7.0%	0.15	1.7%	0.62	7.2%
		Plasma 2	90	80.41	2.89	3.6%	0.00	0.0%	2.89	3.6%
		Plasma 3	182	12182.50	516.43	4.2%	0.06	0.0%	516.43	4.2%
		Serum 1	90	7.60	0.45	5.9%	0.05	0.7%	0.45	5.9%
		Serum 2	90	51.93	2.24	4.3%	1.75	3.4%	2.84	5.5%
		Serum 3	178	11254.04	486.16	4.3%	66.36	0.6%	490.67	4.4%

Instrument	Reagent Lot	Sample	N	Sample Mean (pg/mL)	Within-day		Between-day		Total	
					SD	CV	SD	CV	SD	CV
3	3	Plasma 1	90	8.62	0.58	6.7%	0.20	2.3%	0.61	7.1%
		Plasma 2	90	80.26	2.79	3.5%	0.73	0.9%	2.89	3.6%
		Plasma 3	182	12245.04	463.70	3.8%	199.44	1.6%	504.77	4.1%
		Serum 1	88	7.56	0.54	7.1%	0.14	1.8%	0.55	7.3%
		Serum 2	90	51.77	1.81	3.5%	1.48	2.9%	2.34	4.5%
		Serum 3	176	11317.71	482.52	4.3%	0.03	0.0%	482.52	4.3%

b. Linearity/assay reportable range:

Linearity was evaluated following the recommendations in CLSI EP06-A.

Study 1

Lithium heparin plasma and serum samples covering the upper range of the assay were used for the linearity determination. The low sample was a normal female sample. The high sample was prepared by spiking with native human antigen. Intermediate samples were prepared independently by using incrementally larger proportions of the high sample mixed with the low sample for a total of seven sample levels. The low sample was run in replicates of eight, and all other samples were run in replicates of four. All samples were run on one UniCel DxI 800 Immunoassay System per temperature, using one reagent lot and one calibrator lot at each of three temperature conditions (18 °C, 24 °C, and 30 °C). Test results did not deviate from linearity by more than 10%. Representative results for weighted linear regression are shown below:

Plasma:
y = 0.978x + 0.040 (range tested: 1.80 to 28070 pg/mL)

Serum:
y = 0.963x + 0.074 (range tested: 1.96 to 27302 pg/mL)

Study 2

Lithium heparin plasma and serum samples covering the low end of the assay range were used for the linearity determination. The low sample was a normal female sample. The high sample was prepared by spiking with native human antigen. Intermediate samples were prepared independently by using incrementally larger proportions of the high sample mixed with the low sample for a total of eight sample levels. The low sample was run in replicates of eight, and all other samples were run in replicates of four. All samples were run on one UniCel DxI 800 Immunoassay System per temperature, using one reagent lot and one calibrator lot at each of three temperature conditions (18 °C, 24 °C, and 30 °C). Test results did not deviate from linearity by more than 10%.

Representative results for weighted linear regression are shown below:

Plasma:
18°C: y = 1.058x – 0.074 (range tested: 1.25 to 94.86 pg/mL)

Serum:
30°C: y = 0.956x + 0.017 (range tested: 0.40 to 106.9 pg/mL)

These studies support the sponsor's measuring range claim of 2.1 pg/mL to 27,027 pg/mL.

Hook Effect

The sponsor demonstrated that there was no high dose hook effect from the concentration of the Access hsTnI S6 calibrator (~ 27,027 pg/mL) to 2,500,000 pg/mL.

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

Traceability

The sponsor's traceability scheme was reviewed and found acceptable. The Access hsTnI assay is traceable to a commercially available troponin method via value transference of true patient sample results.

Sample stability

To evaluate the stability of TnI in patient samples, at least 30 serum and 30 lithium heparin samples (ranging from 2 to 25,000 pg/mL) were tested using the Access hsTnI assay on the UniCel DxI800 instrument fresh (baseline) and at various time points after storage at room temperature (20-25°C), refrigerated (2-8°C), and frozen (-20°C). The studies support the following sample handling claims in the labeling:

- 4 hours at room temperature (15 to 25°C)
- 48 hours refrigerated (2-8°C)
- 3 days frozen (-20°C or colder)

d. *Detection limit:*

Limit of blank (LoB), limit of detection (LoD), and limit of quantitation (LoQ) studies were performed and analyzed following the recommendations in CLSI EP17-A2.

To estimate the LoB, four zero analyte samples (Access hsTnI S0 calibrator material) were measured in three runs with replicates of five using three reagent lots on each of three UniCel DxI 800 Access Immunoassay Systems at three calibration temperatures

(18°C, 24°C, 30°C) and three run temperatures (18°C, 24°C, 30°C). The LoB was calculated using a non-parametric approach. The sponsor claims that the LoB is 1.2 pg/mL.

To estimate the LoD, five native serum and five native lithium heparin low level samples were measured in two runs with replicates of five over five days, using three reagent lots and three UniCel DxI 800 Access Immunoassay Systems (one reagent lot for each instrument) at three calibration temperatures (18°C, 24°C, 30°C) and three run temperatures (18°C, 24°C, 30°C). The sponsor claims that the LoD is 2.1 pg/mL.

To estimate the LoQ, 13 native serum and 13 native lithium heparin samples were measured in two runs with replicates of five over five days, using three reagent lots and three UniCel DxI 800 Access Immunoassay Systems (one reagent lot for each instrument) at three calibration temperatures (18°C, 24°C, 30°C) and three run temperatures (18°C, 24°C, 30°C). The sponsor calculated the LoQ based on precision profile modeling. The sponsor claims a LoQ of 2.1 pg/mL at 20% CV within-laboratory imprecision, and a LoQ of 4.6 pg/mL at 10% CV within-laboratory imprecision. Based on regression analysis of the LoQ precision profiles, the sponsor also showed that the %CV at the 99th percentile upper reference limits was less than 10%. If a sample contains less than the LoQ for the assay, the UniCel DxI 800 instrument reports the result as less than that value, i.e. < 2.1 pg/mL.

These studies support the sponsor's claimed measuring range of 2.1 pg/mL to 27,027 pg/mL.

e. *Analytical specificity:*

Endogenous and exogenous interference was evaluated according to CLSI EP07-A2 by spiking lithium heparin and serum patient samples (~ 10 pg/mL and ~ 100 pg/mL TnI) with possible interferents. Concentrations of potential interferents were chosen according to recommendations in CLSI EP17-A2 or to be above therapeutic levels for drugs or above the reference intervals for endogenous interferents. Each spiked sample was tested in replicates of 12 on one UniCel DxI 800 instrument using three reagent pack lots and one calibrator lot. Results were compared to control samples without interferent. The sponsor considered a percent difference between test samples and control samples of greater than ± 10% for samples containing more than 11.5 pg/mL TnI and greater than ± 2.3 pg/mL for samples containing equal or less than 11.5 pg/mL TnI to be significant interference.

The highest concentrations of potentially interfering substances tested that showed non-significant interference are summarized in the table below:

Substance	Highest Concentration Tested Without Significant Interference
Acetaminophen	50 mg/dL
Acetylsalicylic Acid	65 mg/dL
Atenolol	1 mg/dL
Atorvastatin (Lipitor)	20 µg/mL
Conjugated Bilirubin	40 mg/dL
Unconjugated Bilirubin	20 mg/dL
Bivalirudin	42 µg/mL
Caffeine	10 mg/dL
Captopril	5 mg/dL
Cinnarizine	40 mg/dL
Clopidogrel	75 µg/mL
Cocaine	2 mg/dL
Cyclosporine	5 µg/mL
Digoxin	200 ng/mL
Dopamine	65 mg/dL
Fibrinogen	1000 mg/dL
Furosemide	40 mg/dL
Hemoglobin	400 mg/dL
Human Serum Albumin	6000 mg/dL
Ibuprofen	50 mg/dL
Intralipid	3000 mg/dL
Sodium Heparin	28.8 U/mL
Methyldopa	2.5 mg/dL
Nitrofurantoin	6.4 mg/dL
Nystatin	2 mg/dL
Phenobarbital	20 µg/mL
Rifampicin	60 µg/mL
Rosuvastatin (Crestor)	20 µg/mL
Tissue Plasminogen Activator (TPA)	5 µg/mL
Verapamil	16 mg/dL

In addition, the labeling includes the following limitations:

"Other potential interferences in the patient sample could be present and may cause erroneous results in immunoassays. Some examples that have been documented in literature include rheumatoid factor and fibrin. Carefully evaluate results if the sample is suspected of having these types of interferences."

"Endogenous alkaline phosphatase (ALP), exogenous ALP and proteins capable of binding to ALP may cause interference. Elevated ALP levels are commonly observed in patients with hepatobiliary disease and bone disease associated with increased osteoblastic activity. Alkaline phosphatase levels above 400 U/L may cause false positive results. In one study, a sample with cTnI concentration of approximately 8 pg/mL demonstrated an increase of 4 pg/mL when spiked with 800 U/L of alkaline phosphatase."

"Access hsTnI should not be used for patients taking asfotase alfa (i.e. Strensiq)."

HAMA

The sponsor provided results demonstrating that their formulation reduces the effects of HAMA interferents.

The labeling contains the following limitations:

"For assays employing antibodies, the possibility exists for interference by heterophile antibodies in the patient sample. Patients who have been regularly exposed to animals or have received immunotherapy or diagnostic procedures utilizing immunoglobulins or immunoglobulin fragments may produce human anti-animal antibodies, e.g., HAMA, that interfere with immunoassays. Additionally, other heterophile antibodies such as human anti-goat antibodies may be present in patient samples."

Troponin Autoantibodies

Troponin autoantibodies have been reported to be present in approximately 10-20% of patients presenting to the ER and may lead to falsely low troponin assay results and delay in treatment of acute coronary syndrome.[1,2] The Access hsTnI assay was designed to minimize interference from troponin autoantibodies and the sponsor conducted design verification activities to assess this.

[1]Park JY and Jaffe AS, Troponin Autoantibodies: From Assay Interferent to Mediator of Cardiotoxicity, *Clin Chem* 2017, 63(1):30-32.

[2]Nussinovitch U, Shoenfeld Y, Anti-troponin autoantibodies and the cardiovascular system, *Heart* 2010; 96(19):1518-1524.

Cross reactivity

To evaluate cross reactivity, the substances shown in the following table were added to lithium heparin plasma and serum patient samples at two TnI concentrations (~ 10 and ~ 100 pg/mL). Test results from samples spiked with the cross-reactant were compared to test results from samples without cross-reactant added. Samples were measured on three lots. The sponsor considered a percent difference between test samples and control samples of greater than ± 10% for samples containing more than 11.5 pg/mL TnI and

greater than ± 2.3 pg/mL for samples containing equal or less than 11.5 pg/mL TnI to show significant cross-reactivity. The sponsor did not observe significant cross-reactivity for the following substances at the concentrations listed below:

Substance	Concentration Added (ng/mL)
Actin	1,000
CK-MB	1,000
Myoglobin	1,000
Myosin	1,000
Cardiac troponin C	250
Skeletal troponin I	250
Tropomyosin	1,000
Cardiac Troponin T	125

f. Assay cut-off:

See section 4, Clinical cut-off, below.

2. Comparison studies:

a. Method comparison with predicate device:

A method comparison with the predicate device was not performed. Instead, accuracy was assessed in a clinical study (see section 3 "clinical studies" below).

Thermal Method Comparison

The Access hsTnI/UniCel DxI 800 test system employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. A thermal method comparison study was completed to evaluate the impact of temperature differences across the measuring range of the assay. At least 191 lithium heparin patient samples and 182 serum patient samples (containing ~2.1 to ~20,000 pg/mL troponin) were tested and evaluated using three reagent pack lots on four UniCel DxI 800 instruments at three calibration temperature conditions and at three different run temperature conditions: 18°C, 24°C, and 30°C. A Passing-Bablok regression analysis was performed comparing the concentrations from the three different run temperatures of the samples within a given calibration temperature. Results for a representative lot are shown below:

		Plasma			Serum		
Cal Temp	**Run Temperature (X vs Y)**	**n**	**Slope (95% CI)**	**Intercept**	**n**	**Slope (95% CI)**	**Intercept**
18 °C	18 °C v 24 °C	192	1.00 (0.99-1.01)	0.1 (-0.4-0.4)	185	1.01 (1.00-1.02)	-0.1 (-0.3-0.1)
	24 °C v 30 °C	193	1.02 (1.01-1.03)	0.1 (-0.2-0.3)	182	1.04 (1.02-1.06)	-0.2 (-0.4-0.0)
	18°C v 30 °C	194	1.03 (1.01-1.04)	0.1 (-0.1-0.5)	184	1.06 (1.04-1.08)	-0.3 (-0.7-0.1)
24 °C	18 °C v 24 °C	197	1.00 (0.99-1.01)	0.1 (-0.4-0.3)	189	1.01 (1.00-1.02)	-0.1 (-0.3-0.1)
	24 °C v 30 °C	197	1.02 (1.00-1.03)	0.2 (-0.1-0.4)	187	1.04 (1.03-1.06)	-0.2 (-0.4-0.0)
	18 °C v 30 °C	195	1.03 (1.01-1.04)	0.1 (-0.2-0.5)	187	1.06 (1.04-1.08)	-0.3 (-0.8-0.1)
30 °C	18 °C v 24 °C	194	1.00 (0.99-1.01)	0.3 (-0.1-0.5)	184	1.01 (1.00-1.02)	0.0 (-0.2-0.2)
	24 °C v 30 °C	194	1.01 (1.00-1.03)	0.2 (0.0-0.5)	184	1.04 (1.03-1.06)	-0.2 (-0.4-0.1)
	18 °C v 30 °C	194	1.02 (1.01-1.03)	0.4 (0.1-0.8)	185	1.06 (1.04-1.08)	-0.2 (-0.6-0.2)

The sponsor concluded that operation of the instrument across the labeled operating range of 18°C – 30°C does not impact analyte recovery for both lithium heparin plasma and serum sample types and included the following limitation in the labeling:

"Ambient laboratory temperature should be maintained between 18°C and 30°C (66.4°F and 86.0°F) while conducting patient sample testing. This assay employs an algorithm to correct for laboratory temperature fluctuations that could impact the accuracy of troponin test results. Up to 8% residual systematic bias may be observed when comparing patient results obtained at 18°C and 30°C (64.4°F and 86.0°F).

The results are similar when the calibration temperatures are compared across different run temperatures.

b. Matrix comparison:

Not applicable. The sponsor demonstrated the analytical and clinical performance of lithium heparin plasma and serum for use with the Access hsTnI assay on the UniCel DxI800 instrument.

3. Clinical studies:

a. Clinical Sensitivity:

A clinical study was performed to evaluate the clinical performance of the device at the different clinical cut-offs (see section 5 "Expected values/Reference range" below). A multicenter prospective study conducted in 2010-2011 enrolled 1929 patients from Emergency Departments presenting with chest pain or equivalent ischemic symptoms suggestive of Acute Coronary Syndromes. Final diagnoses were adjudicated by an independent panel of expert physicians using criteria consistent with the 2007 Universal Definition of Myocardial Infarction. Serial samples were collected from patients within 9 hours of admission to the Emergency Department (i.e., triage). The sample collection times were at time of admission (baseline), 1 to 3

hours, 3 to 6 hours, and 6 to 9 hours after admission to the Emergency Department. Investigators and adjudicators were blinded to the proposed device's results. Adjudicators were also blinded to site diagnoses. All results presented below were based on the adjudicated diagnoses. Lithium heparin and serum samples from 1854 patients were available for testing with the Access hsTnI assay on the DxI 800 Immunoassay System. Clinical performance was estimated at overall (male and female combined), male- and female-specific 99th percentile upper reference limit (URL) cut-offs, calculated as described in Section 5 "Expected values/Reference range" below. The results are summarized below:

Plasma:

Overall (99th percentile URL = 17.9 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	88.1% (89/101)	[80.2% - 93.7%]	88.5% (502/567)	[85.6% - 91.0%]
1-3 hours	94.1% (128/136)	[88.7% - 97.4%]	89.8% (981/1092)	[87.9% - 91.6%]
3-6 hours	94.1% (143/152)	[89.1% - 97.3%]	89.8% (1044/1163)	[87.9% - 91.5%]
6-9 hours	98.6% (70/71)	[92.4% - 100.0%]	85.1% (383/450)	[81.5% - 88.3%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	57.8% (89/154)	[49.6% - 65.7%]	97.7% (502/514)	[96.0% - 98.8%]
1-3 hours	53.6% (128/239)	[47.0% - 60.0%]	99.2% (981/989)	[98.4% - 99.7%]
3-6 hours	54.6% (143/262)	[48.3% - 60.7%]	99.1% (1044/1053)	[98.4% - 99.6%]
6-9 hours	51.1% (70/137)	[42.4% - 59.7%]	99.7% (383/384)	[98.6% - 100.0%]

Females (99th percentile URL = 14.9 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	83.3% (25/30)	[65.3% - 94.4%]	91.4% (234/256)	[87.3% - 94.5%]
1-3 hours	93.0% (40/43)	[80.9% - 98.5%]	91.6% (490/535)	[88.9% - 93.8%]
3-6 hours	96.0% (48/50)	[86.3% - 99.5%]	91.5% (509/556)	[88.9% - 93.7%]
6-9 hours	100.0% (22/22)	[84.6% - 100%]	88.0% (198/225)	[83.0% - 91.9%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	53.2% (25/47)	[38.1% - 67.9%]	97.9% (234/239)	[95.2% - 99.3%]
1-3 hours	47.1% (40/85)	[36.1% - 58.2%]	99.4% (490/493)	[98.2% - 99.9%]
3-6 hours	50.5% (48/95)	[40.1% - 60.9%]	99.6% (509/511)	[98.6% - 100.0%]
6-9 hours	44.9% (22/49)	[30.7% - 59.8%]	100.0% (198/198)	[98.2% - 100%]

Males (99th percentile URL = 19.8 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	88.7% (63/71)	[79.0% - 95.0%]	87.1% (271/311)	[82.9% - 90.7%]
1-3 hours	95.7% (89/93)	[89.4% - 98.8%]	88.0% (490/557)	[85.0% - 90.6%]
3-6 hours	94.1% (96/102)	[87.6% - 97.8%]	88.3% (536/607)	[85.5% - 90.8%]
6-9 hours	98.0% (48/49)	[89.1% - 99.9%]	81.3% (183/225)	[75.6% - 86.2%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	61.2% (63/103)	[51.1% - 70.6%]	97.1% (271/279)	[94.4% - 98.8%]
1-3 hours	57.1% (89/156)	[48.9% - 64.9%]	99.2% (490/494)	[97.9% - 99.8%]
3-6 hours	57.5% (96/167)	[49.6% - 65.1%]	98.9% (536/542)	[97.6% - 99.6%]
6-9 hours	53.3% (48/90)	[42.5% - 63.9%]	99.5% (183/184)	[97.0% - 100.0%]

Serum:

Overall (99th percentile URL = 18.1 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	87.3% (96/110)	[79.6% - 92.9%]	89.3% (534/598)	[86.5% - 91.7%]
1-3 hours	95.0% (134/141)	[90.0% - 98.0%]	90.0% (999/1110)	[88.1% - 91.7%]
3-6 hours	94.8% (147/155)	[90.1% - 97.7%]	89.5% (1074/1200)	[87.6% - 91.2%]
6-9 hours	97.1% (66/68)	[89.8% - 99.6%]	85.0% (398/468)	[81.5% - 88.2%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	60.0% (96/160)	[52.0% - 67.7%]	97.4% (534/548)	[95.8% - 98.6%]
1-3 hours	54.7% (134/245)	[48.2% - 61.0%]	99.3% (999/1006)	[98.6% - 99.7%]
3-6 hours	53.8% (147/273)	[47.7% - 59.9%]	99.3% (1074/1082)	[98.5% - 99.7%]
6-9 hours	48.5% (66/136)	[39.9% - 57.2%]	99.5% (398/400)	[98.2% - 99.9%]

Females (99th percentile URL = 13.6 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	82.8% (24/29)	[64.2% - 94.2%]	89.4% (237/265)	[85.1% - 92.9%]
1-3 hours	95.3% (41/43)	[84.2% - 99.4%]	90.8% (493/543)	[88.0% - 93.1%]
3-6 hours	96.1% (49/51)	[86.5% - 99.5%]	89.6% (519/579)	[86.9% - 92.0%]
6-9 hours	100.0% (20/20)	[83.2% - 100%]	86.0% (202/235)	[80.8% - 90.1%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	46.2% (24/52)	[32.2% - 60.5%]	97.9% (237/242)	[95.2% - 99.3%]
1-3 hours	45.1% (41/91)	[34.6% - 55.8%]	99.6% (493/495)	[98.5% - 100.0%]
3-6 hours	45.0% (49/109)	[35.4% - 54.8%]	99.6% (519/521)	[98.6% - 100.0%]
6-9 hours	37.7% (20/53)	[24.8% - 52.1%]	100.0% (202/202)	[98.2% - 100%]

Males (99th percentile URL = 19.8 pg/mL)

	Sensitivity		Specificity	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	86.4% (70/81)	[77.0% - 93.0%]	87.1% (290/333)	[83.0% - 90.5%]
1-3 hours	95.9% (94/98)	[89.9% - 98.9%]	87.8% (498/567)	[84.9% - 90.4%]
3-6 hours	95.2% (99/104)	[89.1% - 98.4%]	87.9% (546/621)	[85.1% - 90.4%]
6-9 hours	95.8% (46/48)	[85.7% - 99.5%]	82.0% (191/233)	[76.4% - 86.7%]

	Positive Predictive value (PPV)		Negative Predictive Value (NPV)	
Interval	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Baseline	61.9% (70/113)	[52.3% - 70.9%]	96.3% (290/301)	[93.6% - 98.2%]
1-3 hours	57.7% (94/163)	[49.7% - 65.4%]	99.2% (498/502)	[98.0% - 99.8%]
3-6 hours	56.9% (99/174)	[49.2% - 64.4%]	99.1% (546/551)	[97.9% - 99.7%]
6-9 hours	52.3% (46/88)	[41.4% - 63.0%]	99.0% (191/193)	[96.3% - 99.9%]

The following limitation is included in the labeling:

"Positive predictive values (PPV) demonstrated for female subjects using the established female 99th percentile URL values were lower than the PPV values obtained using the overall 99th percentile URL values. Using the lower female 99th percentile URLs may result in a higher proportion of positive test results for females that are non-MI. Taking into consideration the lower bound of the 95% CI, in the worst-case scenario (serum drawn at 6-9 hours after presentation) up to 75% of positive test results for females may be non-MI."

b. Clinical specificity:

See clinical sensitivity above.

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable.

4. Clinical cut-off**:**

Please see section 5 "Expected values/Reference range" below. Three cut-offs for this assay were determined based on the 99th percentile upper reference limit in apparently healthy adults.

5. Expected values/Reference range:

The sponsor conducted a multicenter prospective study to establish the 99th percentile upper reference limit (URL) in a population of apparently health adults with no known diseases of the cardiovascular system or other serious acute or chronic diseases or infections. The sponsor evaluated 1088 lithium heparin samples and 1085 serum samples from subjects enrolled at five geographically diverse locations. Both male and female subjects were included in the reference range study to determine the 99th percentile URL using a non-parametric empirical univariate distribution function. Results are as follows:

Population	**N**	**99th Percentile Upper Reference Limit in pg/mL (95% CI)**	
		Plasma	**Serum**
Females	593	14.9 (10.1 – 27.1)	13.6 (10.0 – 25.6)
Males	495	19.8 (15.9 – 38.4)	19.8 (15.4 – 44.8)
Overall (males and females combined)	1088	17.9 (14.7 – 27.1)	18.1 (14.3 – 25.6)

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable.

O. Conclusion:

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