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

A. 510(k) Number:
K051433

B. Purpose for Submission:
New assay for I-STAT CREATINE KINASE MB (CK-MB) and change in indications for use for the i-STAT Cardiac Troponin I (cTnI) (k031739) to include use with whole blood instead of heparinized whole blood.

C. Measurand:
Creatine Kinase MB, Troponin I

D. Type of Test:
Quantitative/Electrochemical two site ELISA

E. Applicant:
I-STAT CORPORATION

F. Proprietary and Established Names:
I-STAT CREATINE KINASE MB (CK-MB)

G. Regulatory Information:

1. Regulation section:
   21CFR Sec- 862.1215-Creatine phosphokinase/creatine kinase or isoenzymes test system.
2. Classification:
   2
3. Product code:
   MYT - BIOSENSOR, IMMUNOASSAY, CPK OR ISOENZYMES
   MMI - IMMUNOASSAY METHOD, TROPONIN SUBUNIT
4. Panel:
   Chemistry (75)

H. Intended Use:

1. Intended use(s):
   See indications for use
2. Indication(s) for use:
   The i-STAT CK-MB test is an in vitro diagnostic test for the quantitative measurement of creatine kinase MB mass in whole blood or plasma samples. CK-MB measurements can be used as an aid in the diagnosis of myocardial infarction (MI), re-infarction, and the sizing of infarction. CK-MB measurements can also be used in monitoring reperfusion during thrombolytic therapy and perioperative myocardial infarction (poMI) after cardiac surgery.

   The i-STAT Cardiac Troponin I (cTnI) test is an in vitro diagnostic test for the quantitative measurement of cardiac troponin I in whole blood or plasma. Measurements of cardiac Troponin I are used in the diagnosis and treatment of myocardial infarction and as an aid in the risk stratification of patients with acute coronary syndromes with respect to their relative risk of mortality.

3. Special conditions for use statement(s):
   for prescription use
4. Special instrument requirements:
   i-STAT 1 Analyzer

I. Device Description:

The i-STAT CK-MB and cTnI tests are contained in single cartridges. In use, the user scans a bar-code and then places approximately 16 microliters of fresh whole blood in the cartridge. The cartridge is inserted into the thermally controlled i-STAT Analyzer, and all analytical steps are performed automatically. Patient and user information may be entered into the analyzer via a keypad during the automated analysis cycle. The CK-MB and cTnI test cartridges are assembled from plastic components that provide the conduits for fluid handling and house the sensor chips and heating elements necessary for temperature control and signal measurement.

Upon insertion of the cartridge into the analyzer, it performs several quality checks. The sample and enzyme-linked antibody conjugate are incubated for a predetermined period of time under temperature control. The sample is discarded and the substrate/wash solution is brought over the alkaline phosphatase captured on the CK-MB or cTnI sensor. The enzyme cleaves the substrate giving rise to an amperometric signal which the analyzer measures. The result is displayed and stored in memory for possible transfer via infra red to a printer or to electronic databases.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Biosite, Triage Cardiac Panel, i-STAT Cardiac Troponin I (cTnI)
2. Predicate 510(k) number(s):
   k030286, k031739
3. Comparison with predicate:

Characteristic	Triage CK-MB	i-STAT CK-MB
Assay methodology	Two-site ELISA	Two-site ELISA
Capture site	Heterogeneous	Heterogeneous
Capture antibodies	Monoclonal	Monoclonal
Enzyme label antibody	Polyclonal	Monoclonal
Enzyme label	Fluorescent dye	Alkaline phosphatase
Analysis sequence	Simultaneous capture/label	Simultaneous capture/label
Analysis time	16 minutes	5 minutes
Sample type	Whole blood or plasma	Whole blood or plasma
Enzyme detection	Fluorescent	Electrochemical
	i-STAT cTnI (k031739)	**New i-STAT cTnI**
Assay characteristics	Same	Same
Sample type	Heparinized whole blood or plasma	Whole blood or plasma

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

CLSI – EP09-A2: Method Comparison and Bias Estimation Using Patient Samples
CLSI – EP05-A2: Evaluation of Precision Performance of Clinical Chemistry Devices CLSI – EP07-A: Interference Testing in Clinical Chemistry
IEC – 61326: 2002 Electrical equipment for measurement, control and laboratory use-EMC requirements

L. Test Principle:

The **i-STAT CK-MB** test is an enzyme-linked immunosorbent assay (ELISA) with amperometric detection of the alkaline phosphatase enzyme signal, similar in principle to the i-STAT cTnI cartridge.

Antibodies specific to an epitope unique to the MB subunit, that therefore do not bind to CK-MM nor CK-BB, are patterned on the gold sensor via partial drop microprinitng of a carboxylated polystyrene latex microsphere suspension. The CK-MB capture antibodies are covalently bound to the microspheres prior to their deposition on the spheres. The gold sensor is situated on a silicon chip positioned in the microfluidic channel of the cartridge.

An alkaline phosphatase-CK-BB Fab conjugate is also printed on the silicon chip. This conjugate is formulated with antibody fragments that are specific to an epitope on the B subunit of creatine kinase, in a matrix of materials which aid in the stabilization of enzyme conjugate and aid in decreasing immunological interferences during the CK-MB assay. The specificity of the conjugate antibody to the B subunit allows this conjugate to recognize CK-MB and CK-BB but not CK-MM.

i-STAT cTnI Two Site Elisa. The analyte, cardiac Troponin I is captured by a probe impregnated with a monoclonal anti-cTnI antibody. The sample is discarded. The probe is treated with a second reagent composed of anti-cTnI polyclonal antibodies which are tagged with Alkaline Phosphatase. After washing, the sandwich complex is treated with a substrate which upon being cleaved by the captured alkaline phosphatase produces and electronic signal which is read by the i-STAT analyzer.

M. Performance Characteristics (if/when applicable):

i-STAT Cardiac Troponin I (cTnI) - subject of k031739 except for matrix studies below

1. <u>Analytical performance:</u>
   a. *Precision/Reproducibility:*
      An imprecision study involving twenty test events, three lots of i-STAT CK-MB test cartridges, seven i-STAT 1 analyzers and a single lot of control fluids was performed by hospital personnel at the clinical site. A second imprecision study was performed at i-STAT Canada Limited, Ottawa, by i-STAT personnel. Six different i-STAT 1 analyzers and the same cardiac marker control fluid lot were used in this study. In each event of these precision studies, different vials of three levels of controls were run in duplicate in each of three sub-lots of i-STAT CK-MB test cartridges. The hospital imprecision data was collected over a 23-day period while the study at i-STAT ran for 20 days.

The results of these studies are summarized below. The arithmetic mean of the total imprecision across all studies/sites is 10.5%, 10.4%, and 9.9% for level 1, 2 and 3 controls respectively.

Imprecision Estimated from 20-Event Control Fluid Studies

Site	Control Level	CK-MB mean ng/mL	Within Run %CV	Total within lot %CV	Total %CV
i-STAT Canada Limited, Ottawa Ontario	1	5.9	9.5	10.9	11.9
	2	25.8	9.4	9.4	10.4
	3	90.1	8.3	8.8	10.0
Utah Valley Regional Medical Center Provo, Utah	1	5.3	8.8	9.1	9.1
	2	22.2	8.2	10.2	10.3
	3	68.0	8.0	9.8	9.8

b. *Linearity/assay reportable range:*
up to 150 ng/mL

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
The calibration process in the factory is traceable to internal standards prepared using the recombinant CK-MB material recommended by the . American Association of Clinical Chemists (AACC) for the standardization of creatine kinase mass assays. The applicant uses a 6 level calibrator set in the factory with approximate values at: 0, 7, 20, 60, 125, 175 ng/mL

d. *Detection limit:*
lower limit of detection of 0.6 ng/mL.

e. *Analytical specificity:*
Tested for common medications and those commonly prescribed to patients with cardiovascular conditions. The levels of the potential interferents were set using the CLSI guideline EP7-A: Interference Testing in Clinical Chemistry, Approved Guideline.

Generic Name	Test Level uMol/L	Control (ng/ml)	CK-MB ng/ml	% change
Acetominophen	1660	14.1	15.1	6.6%
Acetylsalicylic Acid	3333	12.4	13.3	7.0%
Allopurinol	294	14.8	15.7	6.0%
Ampicillin	152	12.4	12.7	2.1%
Ascorbic Acid	227	14.8	15.8	6.8%
Atenolol	37.6	14.8	15.8	6.8%
Caffeine	308	15.0	15.7	4.3%
Captopril	23	12.4	12.7	2.6%
Chloramphenicol	155	14.8	15.9	7.2%
Diclofenac	169	14.8	15.9	7.4%

Generic Name	Test Level uMol/L	Control (ng/ml)	CK-MB ng/ml	% change
Digoxin	6.15	14.8	15.5	4.9%
Dopamine	5.87	14.1	13.9	-1.5%
Enalaprilat	0.86	14.8	15.9	7.6%
Erythromycin	81.6	15.0	14.6	-2.8%
Furosemide	181	15.0	15.4	2.5%
Ibuprofen	2425	15.0	15.0	-0.3%
Isorbide Dinitrate	636	12.4	12.5	0.8%
Methyldopa	71	15.0	16.2	8.2%
Nicotine	6.2	12.4	13.6	9.5%
Nifedipine	1156	12.4	13.0	4.5%
Phenytoin	198	15.0	15.4	2.5%
Propranolol	7.71	15.0	15.0	-0.1%
Salicylic Acid	4.34	12.4	12.7	1.9%
Sodium Heparin	90 U/mL	12.4	11.9	-4.0%
Theophylline	222	15.0	14.0	-6.8%
Verapamil	4.4	15.0	15.6	3.9%
Warfarin	64.9	15.0	15.0	0.1%

An important property of a CK-MB assay is its selectivity for the MB isoform of the creatine kinase enzyme. To demonstrate this selectivity, a plasma sample containing a low CK-MB level was measured pairwise using three different lots of CK-MB assay cartridges in the presence and absence of the other major isoforms of the CK enzyme.

CK isoform	Number of runs per condition	Mean CK-MB (ng/mL) With interferent	Mean CK-MB (ng/mL) without interferent
CK-BB 100 ng/mL	6	6.7 (0.6)*	7.1 (0.8)*
CK-MM 10000 ng/mL	6	7.3 (0.7)*	7.1 (0.6)*

* The number in parentheses is the standard deviation of the 6 cartridge results.

f. Assay cut-off:

Whole blood and plasma samples from 161 apparently healthy donors were assayed in duplicate using 3 different lots of i-STAT CK-MB cartridges. The 0 to 95% range of results spanned 0.0 ng/mL (µg/L) to 3.5 ng/mL (µg/L).

2. Comparison studies:

a. Method comparison with predicate device:

The test population at all three sites was comprised of patients in any hospital department (e.g., emergency department [ED], ICU, CCU, general ward) who presented with acute, severe, and prolonged chest pain. Testing was

performed by end-user level personnel. Operators included nurses, physicians, research technicians, and medical technologists. Analysis of the method comparison data was undertaken in accordance with recommendations set forth in the CLSI guideline EP9-A2: Method Comparison and Bias Estimation Using Patient Samples.

Method comparison data for i-STAT whole blood and plasma results versus AxSYM plasma result:
N - 263, slope = 1.01, intercept = -0.224, r = 0.993
Method comparison data for i-STAT whole blood and plasma results versus AxSYM plasma result for which [CK-MB] <20 ng/mL:
N = 234, slope = .0995, intercept = -0.053, r = 0.960

b. Matrix comparison:
Four 10 mL whole blood samples were drawn from 11 separate donors into untreated plastic vacutainers. Each sample was spiked with a concentrate containing both cTnI and CKMB. The 44 resulting samples were mixed and separated into a Li Heparin 5 mL vacutainer and an untreated 5 mL plastic vacutainer. These samples were allowed to incubate for 5 minutes. After the incubation, the 88 samples were run pairwise on a single lot of cTnI and CKMB assay cartridges using the i-STAT portable blood analyzer

Heparinized vs. Un-Heparinized CKMB:
y = 0.9385x + 3.7104, r2=0.975
Heparinized vs. Un-Heparinized cTnI:
y = 1.0341x + 0.1338, r2=0.9962

3. Clinical studies:
   a. Clinical Sensitivity:
   Not performed
   *b. Clinical specificity**:***
   Not performed
   c. Other clinical supportive data (when a. and b. are not applicable):

4. Clinical cut-off**:**
   Not performed
5. Expected values/Reference range:
   Whole blood and plasma samples from 161 apparently healthy donors were assayed in duplicate using 3 different lots of i-STAT CK-MB cartridges. The 0 to 95% range of results spanned 0.0 ng/mL (µg/L) to 3.5 ng/mL (µg/L).

N. Instrument Name:
i STAT 1 Analyzer - K001387

O. System Descriptions:

1. Modes of Operation:

   Single use cartridge

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:

   Bar code reader is incorporated into the system.

4. Specimen Sampling and Handling:

   Whole blood samples are applied directly into the sample well of the cartridge.

5. Calibration:

   Factory set

6. Quality Control:

   Quality control is material available. The reliability of the result is maintained through a combination of user testing and instrument self-checks. The self-checks occur with every cartridge run and verify performance of the analyzer and cartridge sub-systems. This includes checks on the individual sensor's performance, the integrity of the calibrant fluid, the response of the pressure and thermal transducers, and the flow of calibrant and sample within the cartridge. Any values that are statistically deviant from the factory-established expectation values would cause the test results to be suppressed.

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

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.