

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

A. 510(k) Number:

k063243

B. Purpose for Submission:

New device

C. Measurand:

Troponin I

D. Type of Test:

Two-site sandwich immunoassay, quantitative

E. Applicant:

bioMerieux, Inc.

F. Proprietary and Established Names:

VIDAS® Troponin I Ultra

G. Regulatory Information:

1. Regulation section:

21 CFR 862.1215, Creatine phosphokinase/creatin kinase or isoenzymes test system

2. Classification:

Class II

3. Product code:

MMI (Immunoassay method, troponin subunit)

4. Panel:

Chemistry (75)

H. Intended Use:

1. Intended use(s):

See indications for use below.

2. Indication(s) for use:
VIDAS® Troponin I Ultra is an automated quantitative test for use on the VIDAS instruments for the determination of human cardiac troponin I in human serum or plasma (lithium heparin) using the ELFA (Enzyme-Linked Fluorescent Assay) technique. VIDAS Troponin I Ultra is intended to be used as an aid in diagnosis of myocardial infarction.
3. Special conditions for use statement(s):
For prescription use
4. Special instrument requirements:
VIDAS (k891385) and miniVIDAS (k923579)

I. Device Description:

Each VIDAS® Troponin I Ultra kit contains 60 tests. The kit is comprised of: 60 TNIU Reagent Strips, 60 Solid Phase Receptacles (SPR), TNIU controls (C1 and C2), TNIU calibrators (S1 and S2), TNIU Diluent, and one Master Lot Entry (MLE) Card.

The TNIU Reagent Strips consist of 10 wells covered with a labeled foil seal. Five of the wells contain either conjugate (alkaline phosphatase-labeled mouse monoclonal anti-cardiac troponin I antibody and preservative), wash buffer, or a cuvette with substrate (4-Methyl-umberlliferyl phosphate, dietholamine, and preservative). One well is designated for the sample and the remaining wells are empty.

The interior of the Solid Phase Receptacles (SPR) are coated with mouse monoclonal anti-cardiac troponin I antibody.

The TNIU controls (C1 and C2) are supplied with the kit as four, 2 mL vials of lyophilized human serum, troponin I, and preservative; 2 vials of C1 and 2 vials of C2.

The TNIU calibrators (S1 and S2) are supplied with the kit as four, 2 mL vials of lyophilized human serum, troponin I, and preservative; 2 vials of C1 and 2 vials of C2.

The TNIU diluent is read-to-use. It is supplied as one 2 mL vial and contains human serum with preservatives.

Human source material was tested and found negative for HIV-1/2, HBsAg, and HCV by FDA or European Union approved methods.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Dade Behring Dimension RxL CTNI immunoassay
Dade Behring Dimension CTNI calibrator

2. Predicate 510(k) number(s):
k010313
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	For the quantitative measurement of cardiac troponin I in human serum or plasma. Measurements of cardiac troponin I are used to aid in the diagnosis of acute myocardial infarction (AMI).	For the quantitative measurement of cardiac troponin I in human serum and plasma. Measurements of cardiac troponin I are used to aid in the diagnosis of acute myocardial infarction (AMI).
Sample type	Serum or plasma	Serum or plasma

Differences		
Item	Device	Predicate
Additional indication	None	Risk stratification of patients with acute coronary syndromes with respect to their relative risk of mortality
Reportable range	0.01 to 30 ng/mL	0.04 to 40 ng/mL
Sample volume	200 µL	50 µL

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

- Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline- Second Edition (CLSI EP5-A2)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP6-A)
- Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline (CLSI EP6-A)

L. Test Principle:

The VIDAS Troponin I Ultra (TNIU) Assay is one-step, sandwich enzyme-linked fluorescent immunoassay (ELFA) performed with an automated VIDAS or a miniVIDAS instrument. A pipette tip-like disposable device, the Solid Phase Receptacle (SPR), serves as the solid phase as well as a pipettor for the assay. Reagents for the assay are pre-dispensed in the sealed TNIU Reagent Strips.

All assay steps and assay temperatures are controlled by the instrument. The sample is transferred into the wells containing the conjugate (alkaline phosphatase-labeled

mouse monoclonal anti-cardiac troponin I antibody). The sample and conjugate mixture is cycled in and out of the SPR several times. Unbound sample is removed from the SPR during the wash step. During the detection step, the fluorescent substrate (4-Methyl-umberliferoyl phosphate) is cycled in and out of the SPR. The conjugate enzyme remaining in the SPR catalyzes the hydrolysis of the substrate into a fluorescent product 4-methylumbelliferone. Fluorescence is measured at 450 nm wavelength by the optical scanner in the instrument. The intensity of the fluorescence is directly proportional to the concentration of analyte present in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

The precision study was performed over a period of 10 days, 2 runs per day with 2 reagent lots and 3 test sites (n=240). The repeatability, inter-lot reproducibility, and inter-site reproducibility were calculated based on CLSI EP5-A2. Samples with TnI concentration at 4 different levels were tested (0.58, 3.55, 6.66, and 17.05 ng/mL). Repeatability ranged from 1.28-2.7% coefficient of variation (CV), inter-lot reproducibility ranged from 3.4-6.61% and inter-site reproducibility ranged from 3.74-7.86% CV.

A Limit of Quantitation (LoQ) study was performed as part of the same study to determine the lowest concentration of TnI that corresponded to a 10% CV. Four samples were tested in duplicate, 2 runs per day, for 10 days with 2 kit lots and across 3 testing sites (n=240). The LoQ was determined to be 0.11 ng/mL and corresponds to a coefficient of variation (CV) of approximately 10%. Three samples with values ranging from 0.05-0.08 ng/mL had CVs ranging from 13-18%. The results are shown in the table below.

Sample conc.	SD - inter-site	% CV - inter-site
0.05 µg/L	0.006	13.61
0.06	0.011	18.06
0.08	0.013	16.97
0.11	0.011	10.68
0.58	0.022	3.74
3.55	0.149	4.19
6.66	0.281	4.22
17.05	1.340	7.86

b. *Linearity/assay reportable range:*

The reportable range of the assay is 0.01 to 30 ng/mL.

The recovery across the range was evaluated by comparing the observed versus expected values obtained with the VIDAS TnI Ultra method. Two studies were performed, one evaluating the range from 0.02 to 32.4 ng/mL and the other evaluating the range from 0.03 to 0.68 ng/mL. In each case, a high plasma pool was created by spiking natural troponin antigen into normal plasma. A very low plasma pool was created by spiking a very low amount of the same antigen into normal plasma. The two pools were mixed in different proportions across the range of the assay. The observed results recovered in the range of 91-110% of the expected TnI values for test samples in the range of 3.66 to 32.4 ng/mL and 90-124% for test samples in the range of 0.06 to 0.68 ng/mL.

High dose hook effect was evaluated by testing normal human sera spiked with troponin I at high concentrations up to 1,000 ng/mL. No hook effect was observed with samples up to this level.

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

Traceability and Value Assignment:

The kit calibrators are traceable to reference calibrators that are prepared gravimetrically from NIST SRM 2921.

Stability: The shelf life of the product is stated to be 12 months when stored refrigerated at 2-8°C. Stability studies were performed to support these claims.

The calibrators and controls are lyophilized. After reconstitution, they are stable for up to 8 hours at 2-8°C or up to the expiration date of the kit when stored at -25±6°C. Calibrators and controls may be frozen and thawed up to 4 times.

The stability protocols and acceptance criteria were reviewed and found to be acceptable.

d. Detection limit:

Studies were performed following a protocol similar to CLSI EP17-A. A sample containing no troponin I was tested in duplicate using 2 kit lots over 15 assay runs. In all, 30 measurements (n=30) of the zero standard were performed. The Limit of Blank (LoB) was defined as the concentration corresponding to two standard deviations above the mean signal of the zero standard. The value is then converted to TnI concentration. Based on the sponsor's analysis limit of blank (LoB) was determined to be 0.0013 ng/mL.

The sponsor defined Limit of Detection (LoD) as the lowest signal that can be detected reliably. This value is then converted into TnI concentration. Two different samples with very low TnI concentration of approximately 0.006 to 0.003 ng/mL were tested with 2 kit lots. The limits of detection (LoD) were

determined to be 0.002 ng/mL and 0.008 ng/mL respectively. The sponsor chose 0.01 ng/mL as the LoD. The device reports results greater or equal to 0.01 ng/mL.

The Limit of Quantitation when defined as where the device achieves a coefficient of variation (CV) of approximately 10% is 0.11 ng/mL (see precision section 1. a. above).

e. Analytical specificity:

Evaluation of analytical specificity (cross-reactivity) was done by spiking each cross-reactant to target concentration into a troponin I negative serum. A control for each cross-reactant was prepared by spiking the samples with the same volume of the solvent used for reconstituting the cross-reactant. The cross-reactant test samples and the control samples were measured on the VIDAS TNIU and the cross-reactivity was calculated.

Cross-reactant	Concentration	% Cross-reactivity
Troponin-C (cardiac)	1000 ng/mL	<0.001
Troponin-T (cardiac human)	1000 ng/mL	0.2
Troponin-I (skeletal human)	1000 ng/mL	<0.001
Troponin-I (skeletal human)	1000 ng/mL	<0.001

The effect of potentially interfering endogenous substances (hemoglobin, bilirubin and triglycerides) was tested by spiking a samples containing approximately 0.4, 1, 2 and 4 ng/mL TnI with the appropriate concentration of the test substance and comparing the TnI recovery of the sample to that of a control sample. Hemoglobin up to 332 uM (2,178 mg/dL), bilirubin up to 510 uM (29 mg/dL), and triglycerides up to 30 g/L did not interfere with the test. Additionally, the device package insert recommends that samples that appear hemolyzed, icteric, or lipemic not use used and that, if possible, a new sample be collected.

The effect of potentially interfering common and prescription drugs was tested at concentrations in excess of 100 times the expected dose level in plasma. A list of these substances can be found in the package insert.

f. Assay cut-off:

The sponsor determined the cutoff to be 0.11 ng/mL based on the LoQ. (See precision section 1. 1. above)

2. Comparison studies:

a. Method comparison with predicate device:

Lithium heparin plasma samples (n=534) were assayed on the VIDAS TNIU and another commercially available TnI method. Samples ranged in value

from <0.01 to 19.02 ng/mL on the VIDAS TNIU method. The data were evaluated using Passing-Bablok regression (slope= 0.42, confidence interval 0.38-0.44) and the Pearson's correlation coefficient was calculated (0.97).

For the samples obtained from the US and French study sites, the concordance between the VIDAS TNIU method and a commercially available method is shown in the table below:

Times	0-6 hours after admission	4-12 hours after first collection
US Site Samples (n)	302	300
Concordance %	94.4%	95.3%
French Site Samples (n)	243	153
Concordance	87.2%	94.8%

b. Matrix comparison:

In order to demonstrate equivalence between serum and lithium heparin plasma TnI results, thirty-seven (37) sample pairs were evaluated. Both spiked and native samples were included in the study and sample values ranged in value from 0.04 to 38 ng/mL, which is slightly higher than the reportable range. Passing and Bablock regression analysis yielded the following equation with 95% confidence intervals:

$$\text{Serum (y)} = 0.95 [0.91; 0.97] \text{ Plasma (x)} - 0.01 [-0.09; 0.11]$$

The labeling recommends that the same collection tube type, serum or lithium heparinized plasma, should be used when performing serial sampling.

3. Clinical studies:

a. Clinical Sensitivity:

The clinical sensitivity and specificity studies were performed at two clinical sites, one in the United States (US) at a community hospital and one in France at a specialized cardiac hospital. For 16 weeks, assays were performed using samples from patients with chest pain and suspected myocardial infarction. The samples were collected from the patients within 6 hours following their admission, and then between 4 and 12 hours after the first sample collection.

At the US site a total of 602 samples from patients admitted to the emergency department (ED) were collected:

- Within 0-6 hours after admission, out of the 302 patients concerned, 36 were diagnosed as having myocardial infarction.

- Within 4-12 hours after the first sample collection, out of the 300 patients concerned who met the study inclusion criteria, 36 were diagnosed as having myocardial infarction.

The clinical sensitivity and specificity of VIDAS Troponin I Ultra was determined for a sample collected at the time of admission and the one subsequently collected, using the assay cutoff 0.11 ng/mL. The data are presented in the table below.

US Site

Times	0-6 hours after admission	4-12 hours after first collection
Samples (n)	302	300
Sensitivity %	69.44	97.22
95% Confidence interval	52.80 - 82.20	85.48-99.52
Specificity %	96.24	96.21
95% Confidence interval	93.14 - 97.97	93.09-97.95

At the French site a total of 396 samples from patients admitted to the Cardiology Intensive Care Unit were collected:

- Within 0-6 hours after admission, out of the 243 patients concerned, 116 were diagnosed as having myocardial infarction.
- Within 4-12 hours after the first sample collection, out of the 153 patients concerned who met the study inclusion criteria, 77 were diagnosed as having myocardial infarction.

The clinical sensitivity and specificity of VIDAS Troponin I Ultra was determined for a sample collected at the time of admission and the one subsequently collected using the assay cutoff of 0.11 ng/mL. The data are presented in the table below.

French site

Times	0-6 hours after admission	4-12 hours after first collection
Samples (n)	243	153
Sensitivity %	78.45	98.70
95% Confidence interval	69.93 – 85.07	92.82 – 99.78
Specificity %	90.55	92.11
95% Confidence interval	84.05 – 94.57	83.61 – 96.39

- b. *Clinical specificity:*
See Clinical Sensitivity section above.
 - c. Other clinical supportive data (when a. and b. are not applicable):
Not applicable.
4. Clinical cut-off:
See section 1.f. assay cutoff above.
 5. Expected values/Reference range:
In a study of 399 heparinized plasma samples from apparently healthy individuals in the United States, the upper limit of the 99th percentile for the method was determined to be 0.01 ng/mL.

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.