



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

**I Background Information:**

**A 510(k) Number**

K252393

**B Applicant**

Ortho-Clinical Diagnostics, Inc.

**C Proprietary and Established Names**

VITROS Immunodiagnostic Products hs Troponin I Reagent Pack

**D Regulatory Information**

Product Code(s)	Classification	Regulation Section	Panel
MMI	Class II	21 CFR 862.1215 - Creatine Phosphokinase/Creati ne Kinase or Isoenzymes Test System	CH - Clinical Chemistry

**II Submission/Device Overview:**

**A Purpose for Submission:**

New device

**B Measurand:**

Cardiac Troponin I (cTnI)

## **C Type of Test:**

Quantitative Immunoassay

## **III Intended Use/Indications for Use:**

### **A Intended Use(s):**

See Indications for Use below.

### **B Indication(s) for Use:**

For in vitro diagnostic use only.

For the quantitative measurement of cardiac troponin I (cTnI) in human plasma (heparin) using the VITROS 5600 Integrated System.

Cardiac troponin I is used to aid in the diagnosis of myocardial infarction (MI).

### **C Special Conditions for Use Statement(s):**

Rx - For Prescription Use Only

### **D Special Instrument Requirements:**

VITROS 5600 Integrated System

## **IV Device/System Characteristics:**

### **A Device Description:**

The VITROS Immunodiagnostic Products hs Troponin I Reagent Pack is performed on the VITROS 5600 Integrated System. Each reagent pack contains:

- 100 coated wells (biotin-BSA; streptavidin-mouse monoclonal anti-cTnI, 4 µg/mL).
- 8.2 mL assay reagent (buffer with horse serum, bovine gamma globulin, bovine serum albumin, and antimicrobial agent).
- 7.0 mL conjugate reagent (HRP-mouse monoclonal anti-cTnI, 5 µg/mL, in buffer with bovine serum albumin and antimicrobial agent).

The reagent pack includes the VITROS hs Troponin I Calibrators for calibration of the VITROS 5600 Integrated System.

The VITROS 5600 Integrated System reports cTnI results in units of ng/L or pg/mL.

Additional materials required but not provided with the product:

- VITROS Immunodiagnostic Products Signal Reagent
- VITROS Immunodiagnostic Products Universal Wash Reagent
- VITROS Immunodiagnostic Products Reagent Pack Storage Box with desiccant
- Quality control materials

## B Principle of Operation:

An immunoassay is performed using the components of the reagent pack in which cTnI present in the sample binds with a streptavidin-conjugated antibody and a horseradish peroxidase-labeled antibody conjugate. The antigen-antibody complex is captured to the surface of a well by biotin-BSA. A free-bound separation is effected to remove unbound antibodies by washing. The bound HRP conjugate is measured by a luminescent luminol reaction. The light signal is read by the instrument and is proportional to the concentration of cTnI.

## V Substantial Equivalence Information:

### A Predicate Device Name(s):

Vitros Troponin I ES Reagent Pack

### B Predicate 510(k) Number(s):

K062838

### C Comparison with Predicate(s):

Device & Predicate Device(s):	<u>K252393</u>	<u>K062838</u>
Device Trade Name	VITROS Immunodiagnostic Products hs Troponin I Reagent Pack	VITROS Immunodiagnostic Products Troponin I ES Reagent Pack
<b>General Device Characteristic Similarities</b>		
Intended Use/Indications For Use	To aid in the diagnosis of myocardial infarction.	Same
<b>General Device Characteristic Differences</b>		
Sample Type	Lithium heparin plasma	Serum and plasma (EDTA and lithium heparin)
Instrument(s)	VITROS 5600 Integrated System	VITROS Immunodiagnostic System ECi and ECiQ model analyzers
Measuring range	2.25 - 30,000 ng/L	12-80,000 ng/L
Biotin interference	No interference at up to 0.351 mg/dL	No interference at up to 0.00025 mg/dL

## VI Standards/Guidance Documents Referenced:

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

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

CLSI EP06 2<sup>nd</sup> Edition. Evaluation of the Linearity of Quantitative Measurement Procedure.

CLSI EP07. Interference Testing in Clinical Chemistry. 3rd ed.

CLSI EP37. Supplemental Tables for Interferent Testing in Clinical Chemistry – First Edition.

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

ISO 17511:2021. In vitro diagnostic medical devices - Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples.

## VII Performance Characteristics (if/when applicable):

### A Analytical Performance:

#### 1. Precision/Reproducibility:

Precision was evaluated consistent with the CLSI document EP05-A3. In the study, each of four patient plasma pools and two controls were tested in replicates of two per run, two runs per day over each of 20 days for a total of 80 measurements. The study was performed using each of three reagent lots on one VITROS 5600 Integrated System across a single calibration interval. The data were analyzed for within-run precision (repeatability) and within-device (with variance components of within-run, between-run, and between-day). Representative performance data is shown below.

Sample type	Mean conc. (ng/L)	Within-run		Within-device	
		SD	%CV	SD	%CV
Pooled patient samples	5.5	0.14	2.7	0.25	4.9
	11.7	0.31	2.7	0.57	4.9
	65.3	1.14	1.8	1.91	3.0
	309.2	3.42	1.1	9.15	3.0
Controls	14,090	262.7	1.9	415.8	3.0
	18,460	236.3	1.3	565.0	3.1

## 2. Linearity:

Linearity studies were performed in line with CLSI document EP06 2<sup>nd</sup> edition. For cTnI, the measurement procedure shows linearity for the interval from 2.25 to 30,000 ng/L, with deviations from linearity within +/- 10%.

Two studies were conducted. The first study used contrived samples (commercially available buffered human plasma that has been spiked with cTnI) that spanned the entire measuring interval using 11 levels with a minimum of 3 replicates for each level, the maximum observed % deviation from linearity was 4.2%. The second study used lithium heparin plasma patient samples and spanned the low end up to 4799 ng/L with 12 levels and a minimum of 5 replicates for each level, the maximum observed % deviation from linearity was 9.0%.

### Hook Effect

A commercially available buffered human plasma that has been stripped of troponin, and contains no measurable cTnI was spiked with cTnI (measured gravimetrically) to produce a fluid with a concentration of approximately 100,000 ng/L. This fluid was diluted with the human base matrix to produce a set of 10 samples covering the assay range from 0 ng/L up to approximately 100,000 ng/L. Samples were tested in triplicate and quality control samples were tested in singleton using one VITROS hs Troponin I assay lot in combination with one VITROS 5600 Integrated System. The sponsor demonstrated that there is no hook effect with the assay up to cTnI concentration of 100,000 ng/L.

## 3. Analytical Specificity/Interference:

The analytical specificity performance of the VITROS® Immunodiagnostic Products hs Troponin I Reagent Pack run on the VITROS 5600 Integrated System was established by conducting a cross-reactivity study and interference testing for endogenous and exogenous substances, consistent with CLSI EP07 and EP37.

### *Endogenous substances*

Interference from endogenous substances was assessed using two lithium heparin plasma samples with cTnI concentrations of approximately 10 ng/L and 350 ng/L. Each of the two samples was further divided into two aliquots for a control sample (with no added interferent) and test sample (with added interferent). The native concentrations of the substances were taken into account when calculations were made for spiking the substance. For screening, each sample was assayed in replicates of five using three lots of reagent packs on one instrument. For those substances that on initial screening were found to interfere, dose response testing was conducted to establish the concentration limit below which no significant interference is expected. The results are given in the table below: No significant interference, defined by the sponsor as within  $\pm 10\%$  difference in the mean for the test sample versus the mean of the control sample, was observed at the following concentrations.

<b>Substance</b>	<b>Highest concentration tested at which no significant interference is observed</b>
Bilirubin, conjugated	40 mg/dL
Bilirubin, unconjugated	40 mg/dL
Cholesterol	400 mg/dL
Fibrinogen	500 mg/dL
HAMA (human anti-mouse antibodies)	800 µg/L
Hemoglobin	750 mg/dL
Rheumatoid Factor	900 IU/mL
Total protein*	10.1 g/dL
Triglyceride	1500 mg/dL

\*Test results compared to a control sample with total protein concentration of 7.3 g/dL.

#### *Exogenous substances*

Interference from 64 exogenous substances (common prescription drugs, OTC medications and sample additives) was assessed using two lithium heparin plasma samples with cTnI concentrations of approximately 10 ng/L and 350 ng/L, as described above. No significant interference, defined by the sponsor as within  $\pm 10\%$  difference in the mean for the test sample versus the mean of the control sample was observed at the following concentrations.

<b>Substance</b>	<b>Highest concentration tested at which no significant interference is observed</b>
Acetaminophen	15.6 mg/dL
Acetylcysteine	15.0 mg/dL
Adrenaline (epinephrine)	20 µg/dL
Allopurinol	6.0 mg/dL
Alprazolam	0.0258 mg/dL
Ambroxol	63 µg/dL
Amlodipine besylate	0.0104 mg/dL
Amoxicillin	5.40 mg/dL
Ascorbic acid	5.25 mg/dL
Atorvastatin calcium	0.162 mg/dL
Benazepril HCl	0.044 mg/dL
Biotin	0.351 mg/dL
Bivalirudin	2.18 mg/dL
Caffeine	10.8 mg/dL
Carvedilol	43.2 µg/dL
Cefoxitin sodium	523 mg/dL
Ceftriaxone disodium hemi (heptahydrate)	100 mg/dL
Cephalexin sodium	13.4 mg/dL
Cinnarizine	108 µg/dL
Clopidogrel	2.4 µg/dL
Cocaine	0.6 mg/dL
Cotinine	0.24 mg/dL
Cyclosporine	0.18 mg/dL
Dextran	600 mg/dL

<b>Substance</b>	<b>Highest concentration tested at which no significant interference is observed</b>
Digoxin	0.0039 mg/dL
Diphenhydramine	0.0774 mg/dL
Dopamine	0.0621 mg/dL
Enalaprilat	0.0819 mg/dL
Enoxaparin (LMWH)	360 U/dL
Eptifibatide	1.44 mg/dL
Erythromycin	13.8 mg/dL
Ethanol	600 mg/dL
Fibrinogen	500 mg/dL
Fondaparinux	0.39 mg/dL
Furosemide	1.59 mg/dL
Heparin (Sodium), UFH	330 U/dL
Ibuprofen	21.9 mg/dL
Insulin	3.12 µg/dL
L-dopa (Levodopa)	0.75 mg/dL
Levothyroxine	0.0429 mg/dL
Lidocaine	1.5 mg/dL
Methylprednisolone	0.783 mg/dL
Metronidazole	12.3 mg/dL
Naproxen sodium	39.3 mg/dL
Nifedipine	0.0588 mg/dL
Nitrofurantoin	0.213 mg/dL
Nitroglycerin (Nitrostat)	1.2 µg/dL
Omeprazole	0.84 mg/dL
Oxycodone	0.0324 mg/dL
Oxytetracycline	1.2 mg/dL
Phenytoin	6.0 mg/dL
Propranolol HCl	0.115 mg/dL
Pseudoephedrine	0.330 mg/dL
Quinidine	1.5 mg/dL
Rifampicin (Rifampin)	4.8 mg/dL
Rivaroxaban	0.270 mg/dL
Salicylic acid	2.86 mg/dL
Sodium azide	17.5 mg/dL
Spirolactone	0.0555 mg/dL
Theophylline	6.0 mg/dL
tPA (alteplase) at 11.8 ng/L cTnI	0.6 mg/dL
tPA (alteplase) at 386 ng/L cTnI	0.3 mg/dL
Vancomycin hydrochloride	12.3 mg/dL
Verapamil	0.16 mg/dL
Vorapaxar	36 µg/dL
Warfarin sodium	8.0 mg/dL

Interference was observed in the presence of streptokinase (not commercially available in the United States):

Substance	Interferent concentration	cTnI conc.	Effect when above the concentration limit	%Interference
Streptokinase	37,500 U/dL	12.0 ng/L	Decreased cTnI results	-79%
	37,500 U/dL	390 ng/L	Decreased cTnI results	-65%

The following limitations are included in the labeling:

Dextran at therapeutic doses significantly interferes with this test. This test should not be used on patients taking Dextran. An alternate method not subject to Dextran interference should be used.

Heterophile as well as human anti-animal antibodies (most common human anti-mouse antibodies or HAMA) in serum or plasma of certain individuals are known to cause interference with immunoassays.<sup>1</sup> The anti-animal antibodies may be present in blood samples from individuals regularly exposed to animals or who have received preparations of mouse monoclonal antibodies for diagnosis or therapy. Results inconsistent with clinical observations indicate the need for additional testing.

Troponin autoantibodies have been reported to be present in approximately 10% to 20% of patients presenting to the emergency department (ED) and may lead to falsely low troponin assay results and delay in treatment of acute coronary syndrome.<sup>2,3</sup> Therefore, a test result that is inconsistent with the clinical picture and patient history should be interpreted with caution.

#### Cross-Reactivity

A study was conducted to quantify the level of cross-reactivity with the assay from certain structural similar substances. In the study, two test samples were prepared from plasma, containing no cTnI (i.e. immeasurable) and containing endogenous cTnI at approximately 10 ng/L. The cross-reactivity of the assay was evaluated by adding a potentially cross-reactive substance to each of the test samples. These samples were paired with two reference samples that were not spiked with cross-reactant and with the same cTnI concentration. Each sample was assayed in replicates of five using three lots and one instrument. The difference in results between test and reference sample was calculated for each of the two cTnI samples and analyzed for % cross-reactivity using the below equation. The results of the study found that there was no significant cross-reactivity of the substances at the concentrations tested.

$$\% \text{ Cross-reactivity} = \frac{(\text{Mean cTnI with cross-reactant} - \text{Mean cTnI with control})}{\text{Concentration of cross-reactant}} \times 100\%$$



Cross-Reactant	Concentration of Cross-Reactant, ng/L	% Cross-Reactivity
Actin (from Rabbit Muscle)	1,000,000	0.0%
Cardiac Troponin C (Recombinant)	1,000,000	0.0%
Cardiac Troponin T (Recombinant)	1,000,000	0.0%
CK-MB (Recombinant)	1,000,000	0.0%
Myoglobin (Recombinant)	1,000,000	0.0%
Myosin (Recombinant)	1,000,000	0.0%
Skeletal Troponin I	1,000,000	0.0%
Tropomyosin (from porcine muscle)	1,000,000	0.0%

The percent differences from this study are summarized below:

Substance	Mean Control (ng/L)	Mean with Interferent (ng/L)	Difference (ng/L)	Difference (%)
Actin (from Rabbit Muscle)	11.45	11.31	-0.14	-1.2%
Cardiac Troponin C (Recombinant)	11.45	25.34	13.89	121.4%
Cardiac Troponin T (Recombinant)	11.45	11.24	-0.21	-1.8%
CK-MB (Recombinant)	11.82	13.91	2.09	17.7%
Myoglobin (Recombinant)	11.82	11.46	-0.36	-3.1%
Myosin (Recombinant)	11.82	10.87	-0.95	-8.0%
Skeletal Troponin I	11.45	14.99	3.55	31.0%
Tropomyosin (from porcine muscle)	11.75	12.56	0.81	6.9%

An additional study was conducted to evaluate the interference from Cardiac Troponin C and the results are summarized below:

Cardiac Troponin C (ng/L)	Mean Control (ng/L)	Mean with Interferent (ng/L)	% Difference
20,000	10.37	10.69	3.1
40,000	10.37	11.73	13.1
60,000	10.37	12.27	18.3
80,000	10.37	11.87	14.5
1,000,000	11.45	25.34	121.4

4. Assay Reportable Range:

2.25 ng/L to 30,000 ng/L

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

The sponsor provided data to support that plasma samples may be stored for up to 8 hours at room temperature 15–30°C (59–86°F), and up to 11 months at  $\leq -20^{\circ}\text{C}$  with up to two freeze-thaw cycles.

The VITROS Immunodiagnostic Products hs Troponin I Reagent Pack is traceable to an internal standard.

6. Detection Limit:

*Limit of Blank (LoB)*

Testing was performed using four zero-analyte lithium heparin plasma samples tested with 10 replicates on two runs for five days. Testing was performed using three reagent lots and one instrument. 100 determinations were obtained for each sample. LoB was calculated non-parametrically. The largest estimate across all reagent lot-instrument combinations tested was 0.26 ng/L.

*Limit of Detection (LoD)*

Testing was performed using five lithium heparin plasma samples ranging from one to five times the estimated LoB tested with ten replicates on two runs for five days. Testing was performed using three reagent lots and one instrument. 100 determinations were obtained for each sample. The parametric approach described in EP17-A2 was followed to determine the LoD. The largest estimate across all reagent lot-instrument combinations tested was 0.43 ng/L.

*Limit of Quantitation (LoQ)*

Testing was performed using five lithium heparin plasma samples near and above the LOD tested with five replicates on one run for three days. Testing was performed using three reagent lots and one instrument. 75 determinations were obtained for each sample using each reagent lot. For each reagent lot-instrument combination, the within-laboratory precision for each sample, expressed as %CV, was plotted against the mean concentration obtained for each sample. LoQ was determined by the concentration where a power function model fit to the data equaled 20% CV. The largest estimate across all reagent lot-instrument combinations tested was 0.56 ng/L.

The sponsor claims a LoB of 0.26 ng/L, and LoD of 0.59 ng/L, and an LoQ of 2.25 ng/L.

7. Assay Cut-Off:

See clinical cut-off.

## 8. Carry-Over

A study was conducted to measure the risk of carryover. In the study, no increase in cTnI concentration was seen in low cTnI samples measured after samples spiked with 1,250,000 ng/L cTnI.

## **B Comparison Studies:**

### 1. Method Comparison with Predicate Device:

Not applicable.

### 2. Matrix Comparison:

Not applicable.

## **C Clinical Studies:**

### 1. Clinical Sensitivity:

A prospective, multicenter, blinded, non-interventional study was conducted to assess the diagnostic accuracy of the VITROS® Immunodiagnostic Products hs Troponin I Reagent Pack. The clinical study included 2145 patients 22 years and older (999 females and 1146 males) presenting with symptoms consistent with acute coronary syndrome across 24 emergency departments (ED) in the United States. For each patient enrolled into the study, lithium heparin plasma samples were collected by serial sampling multiple times over the course of their ED stay for determination of cTnI by the candidate device. These samples were stored frozen (-20°C) and sent to a laboratory for later testing. The sponsor provided evidence to support the sample handling and storage conditions of the clinical samples. All subjects were adjudicated by a panel of board-certified cardiologists who reviewed the subject's clinical presentation, medical history, relevant clinical data, and locally measured standard of care (SOC) troponin test. The adjudication outcome (MI or non-MI) was based on the Fourth Universal Definition of MI. The cTnI results were interpreted as positive for MI if plasma cTnI concentration were above the cut-off, and negative if less than or equal to the following cut-offs:

	Overall cut-off	Sex-specific cut-off
Male	11 ng/L	12 ng/L
Female		9 ng/L

The observed prevalence of MI in the study was 8.16% (6.21% female and 9.86% male). MI results were stratified by sex and analyzed for sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for each of the following intervals from time since presentation to the ED: 0-2 hours, ≥2-4 hours, ≥4-6 hours, and ≥6-11 hours. The results are summarized as follows:

Female using overall 11 ng/L cut-off									
Hours since presentation to ED	N	Sensitivity		Specificity		NPV		PPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
0–2 h	1042	87.10 (54/62)	76.55-93.31	91.63 (898/980)	89.73-93.21	99.12 (898/906)	98.27-99.55	39.71 (54/136)	31.87-48.10
≥2–4 h	858	91.80 (56/61)	82.21-96.45	90.21 (719/797)	87.95-92.09	99.31 (719/724)	98.39-99.70	41.79 (56/134)	33.78-50.26
≥4–6 h	508	95.24 (40/42)	84.21-98.68	86.48 (403/466)	83.08-89.29	99.51 (403/405)	98.22-99.86	38.83 (40/103)	29.99-48.49
≥6–11 h	541	93.55 (58/62)	84.55-97.46	86.01 (412/479)	82.62-88.83	99.04 (412/416)	97.55-99.63	46.40 (58/125)	37.90-55.12

Male using overall 11 ng/L cut-off									
Hours since presentation to ED	N	Sensitivity		Specificity		NPV		PPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
0–2 h	1214	84.87 (101/119)	77.35-90.21	82.10 (899/1095)	79.72-84.26	98.04 (899/917)	96.92-98.75	34.01 (101/297)	28.85-39.57
≥2–4 h	979	88.89 (88/99)	81.19-93.68	81.14 (714/880)	78.42-83.58	98.48 (714/725)	97.30-99.15	34.65 (88/254)	29.06-40.69
≥4–6 h	648	90.36 (75/83)	82.12-95.03	77.52 (438/565)	73.90-80.77	98.21 (438/446)	96.50-99.09	37.13 (75/202)	30.76-43.97
≥6–11 h	799	93.16 (109/117)	87.09-96.49	73.31 (500/682)	69.87-76.50	98.43 (500/508)	96.92-99.20	37.46 (109/291)	32.09-43.15

Female using sex-specific 9 ng/L cut-off									
Hours since presentation to ED	N	Sensitivity		Specificity		NPV		PPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
0–2 h	1042	88.71 (55/62)	78.48-94.42	90.31 (885/980)	88.29-92.00	99.22 (885/892)	98.39-99.62	36.67 (55/150)	29.38-44.62
≥2–4 h	858	95.08 (58/61)	86.51-98.31	88.58 (706/797)	86.19-90.61	99.58 (706/709)	98.76-99.86	38.93 (58/149)	31.47-46.94
≥4–6 h	508	97.62 (41/42)	87.68-99.58	84.98 (396/466)	81.45-87.94	99.75 (396/397)	98.59-99.96	36.94 (41/111)	28.54-46.21
≥6–11 h	541	96.77 (60/62)	88.98-99.11	84.76 (406/479)	81.27-87.70	99.51 (406/408)	98.23-99.87	45.11 (60/133)	36.91-53.59

Male using sex-specific 12 ng/L cut-off									
Hours since presentation to ED	N	Sensitivity		Specificity		NPV		PPV	
		%	95% CI	%	95% CI	%	95% CI	%	95% CI
0–2 h	1214	84.03 (100/119)	76.40-89.53	83.11 (910/1095)	80.77-85.21	97.95 (910/929)	96.83-98.69	35.09 (100/285)	29.78-40.79
≥2–4 h	979	88.89 (88/99)	81.19-93.68	81.48 (717/880)	78.78-83.91	98.49 (717/728)	97.31-99.15	35.06 (88/251)	29.42-41.15
≥4–6 h	648	89.16 (74/83)	80.66-94.19	78.41 (443/565)	74.83-81.60	98.01 (443/452)	96.26-98.95	37.76 (74/196)	31.27-44.72
≥6–11 h	799	93.16 (109/117)	87.09-96.49	75.07 (512/682)	71.69-78.17	98.46 (512/520)	96.99-99.22	39.07 (109/279)	33.53-44.90

The results were also stratified by sex and analyzed for the false negative rate per subject; where MI negative by the device is when the cTnI result was below the cutoff in each of the time intervals.

The sponsor provides the following information about the study in the labeling:

*False negative rate*

Using the sex-specific cut-off of 9 ng/L, the false negative rate for females was 3.2% (2/62). When using the overall cut-off of 11 ng/L, the false negative rate for females was 6.5% (4/62).

Using the sex-specific cut-off of 12 ng/L, the false negative rate for males was 8.0% (9/113). When using the overall cut-off of 11 ng/L, the false negative rate for males was 7.1% (8/113).

Serial blood samples for subjects in the VITROS hs Troponin I study were drawn no more than 11 hours after ED presentation; however, clinical information of the study subjects, including standard of care (SOC) troponin test results, were collected for the subjects' entire hospital stay. The standard of care (SOC) troponin tests were the tests used by each clinical study site and were reviewed by the adjudicators for the adjudicated diagnosis.

For 2 of the male false negative subjects, the earliest SOC troponin test results that exceeded the SOC troponin cutoff were from samples drawn more than 26 hours after the final VITROS hs Troponin I sample was collected. For 2 of the female false negative subjects, the earliest SOC troponin test results that exceeded the SOC cutoff were from samples drawn more than 17 hours after the final VITROS hs Troponin I sample was collected.

The sponsor provided the following information about the false positive rate observed in the study:

*False positive rate*

There are conditions other than MI that are known to cause acute or chronic myocardial injury and lead to elevated troponin values. The VITROS hs Troponin I clinical trial enrolled all subjects presenting to the emergency department with symptoms consistent with acute coronary syndrome. Some of these subjects had an acute or chronic condition other than MI. In the clinical trial, 15.79% (311/1970) of subjects without an MI diagnosis had at least one VITROS hs Troponin I test result above the overall 99th percentile cutoff on one or more serial draws. 91.96% (286/311) of these subjects were found to have decreased kidney function (eGFR < 60 mL/min/1.73m<sup>2</sup>, Stage 3 chronic kidney disease, or renal failure) or one or more of the following cardiac conditions: angina, atrial fibrillation, cardiomyopathy, coronary artery disease, heart failure or tachycardia (heart rate >100 BPM).

2. Clinical Specificity:

See Clinical Sensitivity section above.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):  
Not applicable.

#### **D Clinical Cut-Off:**

The cut-offs for this assay were determined based on the 99th percentile upper reference limit (URL) in apparently healthy adults. See Expected Values/Reference Range below (Section VII. E.) for the determination of the clinical cut-offs.

#### **E Expected Values/Reference Range:**

The VITROS Immunodiagnostic Products hs Troponin I Reagent Pack 99<sup>th</sup> percentile URLs were established from lithium heparin plasma of 952 apparently healthy adults, including 486 female and 466 male subjects. The subjects ranged in age from 22 to 91 years old, with 59% of the subjects  $\geq 50$  years of age. Subjects were excluded if they met any of the following criteria:

- History of kidney disease, diabetes, heart disease, cancer, lung disease, thyroid disease, or stroke
- High blood pressure, cholesterol, or triglycerides
- Muscle or skeletal injury or surgery in the last three months
- Current smoker
- Pregnant
- Additional exclusion criteria:
  - Hemoglobin A1c  $\geq 6.5\%$
  - NT-proBNP  $>125$  pg/mL for subjects  $<75$  years of age or  $>450$  pg/mL for subjects  $\geq 75$  years of age.
  - eGFR  $< 60$  mL/min

The 99<sup>th</sup> percentile URL values and respective 90% confidence intervals (CI), determined for females, males, and overall using the non-parametric statistical method, are shown in the table below.

Gender	Number of Subjects	99 <sup>th</sup> Percentile URL, ng/L (90%CI)
Female	486	9 (3.9 - 17.5)
Male	466	12 (8.8 - 20.9)
Overall	952	11 (8.2 - 14.3)

#### **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.