

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

A. 510(k) Number:

k052503

B. Purpose for Submission:

New device

C. Measurand:

Troponin I

D. Type of Test:

Quantitative, two-site sandwich immunoassay

E. Applicant:

Bayer HealthCare

F. Proprietary and Established Names:

Troponin I Ultra Assay and Calibrator for the ADVIA IMS® System

G. Regulatory Information:

1. Regulation section:
21 CFR 862.1215, Immunoassay method, troponin subunit
21 CFR 862.1150, Calibrator, Secondary
2. Classification:

Class II
3. Product code:

MMI, JIT
4. Panel:

(75) Chemistry

H. Intended Use:

1. Intended use(s):

The ADVIA IMS[®] Troponin I Ultra (TnI-Ultra) method is for *in vitro* diagnostic use to quantitatively measure the cardiac troponin I in human serum and plasma (lithium heparin). When used in conjunction with other clinical data such as presenting symptoms and diagnostic procedures, measurements of cardiac troponin I aid in the diagnosis of acute myocardial infarction (AMI) and in the risk stratification of patients with non-ST segment-elevation, acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.

The ADVIA IMS[®] TnI-Ultra Calibrator is for the *in vitro* diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA IMS[®] system

2. Indication(s) for use:

See Intended Use above.

3. Special conditions for use statement(s):

Prescription Use only

4. Special instrument requirements:

ADVIA IMS[®] System

I. Device Description:

ADVIA IMS[®] TnI Ultra reagent pack is supplied as: Reagent 1 (R1) containing mouse monoclonal anti-troponin I conjugate, bovine serum albumin, sodium azide, buffer, surfactant and preservative; Reagent 2 (R2) containing polyclonal goat anti-troponin I alkaline phosphatase (ALP) conjugate, bovine serum albumin, sodium azide, buffer, surfactant and preservative.

ADVIA IMS[®] TnI-Ultra Calibrator is supplied as 6 vials of Calibrator with levels 1-6. Level 1 contains bovine serum albumin, sodium azide, buffer and preservatives. Levels 2-6 contain bovine serum albumin, troponin I, sodium azide, buffer and preservatives.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Bayer ACS:180 cTnI Assay

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

k980528

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Quantitative determination of cardiac troponin I in serum or lithium heparin serum	Same
Indications for Use	For in vitro diagnostic use to quantitatively measure the cardiac Troponin I in human serum and plasma (lithium heparin). When used in conjunction with other clinical data such as presenting symptoms and diagnostic procedures, measurements of cardiac Troponin I aid in the diagnosis of acute myocardial infarction (AMI) and in the risk stratification of patients with non-ST segment-elevation, acute coronary syndromes with respect to relative risk of mortality, myocardial infarction, or increased probability of ischemic events requiring urgent revascularization procedures.	Same
Assay principle	Chemiluminescence immunoassay	Same
Sample type	Human serum and heparinized plasma	Same

Differences		
Item	Device	Predicate
Measuring range	0.01 to 50 ng/mL	0.10 to 50 ng/mL
Expected values	AMI cutoff ≥ 1.5 ng/mL Normal < 0.04 ng/mL	AMI cutoff ≥ 1.5 ng/mL Normal < 0.07 ng/mL
Hook effect	No high dose hook effect up to 1200 ng/mL	No high dose hook effect up to 1000 ng/mL

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

CLSI H18-A2, CLSI C28-A, CLSI EP5-A, CLSI EP9-A, CLSI EP7-P

L. Test Principle:

The ADVIA IMS[®] Troponin I Ultra (TnI-Ultra) assay is a heterogenous sandwich immunoassay using magnetic separation. Reagent 1 (R1) contains a fluoresceinated monoclonal antibody to troponin I and Reagent 2 (R2) contains a polyclonal antibody to troponin I conjugated to the enzyme alkaline phosphatase (ALP). The sandwich complex formed by the analyte and the antibody conjugates is captured by the magnetic particles so that the troponin I concentration in the sample can be measured in terms of enzyme activity. The enzyme substrate used for this assay is a dioxetane phosphate derivative, which is dephosphorylated by ALP resulting in photon emission. Luminescence is measured by a photomultiplier tube. The dose response curve is proportional to the analyte concentration in the sample.

M. Performance Characteristics (if/when applicable):**1. Analytical performance:****a. *Precision/Reproducibility:***

Imprecision was evaluated in a protocol similar to CLSI EP5-A. Studies were performed over a 10-day period on two instruments with serum pools and Bayer Cardiac Control materials. The protocol consisted of five replicates of each control or pool and one run per day per system.

Samples	N	Mean (ng/mL)	Within Run SD	Within Run CV (%)	Total SD	Total CV (%)
Control Level 1	50	1.55	0.02	1.2	0.09	5.7
Control Level 2	50	14.06	0.08	0.6	0.32	2.2
Control Level 3	50	32.93	0.53	1.6	0.90	2.7
Pool Level A	49	0.04	0.002	5.1	0.002	5.8
Pool Level B	49	0.21	0.01	2.9	0.01	5.4
Pool Level C	50	9.05	0.10	1.1	0.24	2.7
Pool Level D	50	38.69	0.59	1.5	0.94	2.4

To determine the functional sensitivity of the assay, a series of low serum pools was prepared by sequential dilutions of a low sample with a negative serum pool and run on two instruments over a ten day period. Recoveries for the low serum pools from the two instruments were combined and the total CV was calculated. The level for the 10% total CV was estimated to be 0.03 ng/mL. The upper 99th percentile of normal distribution was found to be 0.04 ng/mL for serum (n = 337).

The assay meets the guidelines from the European Society of Cardiology and American College of Cardiology that the 99th percentile of a reference group is used as the cutoff for increased troponin levels and that the assay should have the imprecision (total CV) at the 99th percentile cutoff of 10% or less.

b. Linearity/assay reportable range:

To determine the high dose hook effect, high levels of troponin I antigen were spiked into negative serum pool. The reaction rates of the spiked samples were obtained from the ADVIA IMS. There was no drop in rates for TnI concentrations up to 1200 ng/mL.

Serum samples with high troponin I concentrations were mixed in various proportions with serum samples containing low levels of troponin I with expected concentrations ranging from 0.01 to 36.2 ng/mL. When compared to the expected value, the measured (observed) values of troponin I averaged 103% with a range of 98.9 to 108.8%. Linearity was also evaluated by spiking troponin I in the calibrator serum base. These pools were then mixed in various proportions to prepare five levels with expected concentrations ranging from 0.2 to 50 ng/mL and tested on two ADVIA IMS systems. When compared to the expected value, the measured (observed) values averaged 100.5% with a range of 96 to 106%.

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

The ADVIA IMS[®] TnI-Ultra method is traceable to an internal standard manufactured using purified material. Assigned values of the calibrators are traceable to this standardization. The calibrator value is assigned through a two step process. The Master Lot value is assigned via serum sample correlation between the ADVIA IMS TnI and the ACS:180 TnI assays. The assigned calibrator values are based on in-house and external clinical trial correlation data. The future lots are value assigned through a nested testing protocol.

Calibrators, after storage at the recommended storage condition are tested through the recommended shelf life. Data from calibrators stored at stress temperatures are utilized to ensure lot to lot consistency and provide information for product stability during shipping. The ADVIA IMS[®] TnI-Ultra Calibrator is stable at $\leq 20^{\circ}\text{C}$ until the expiration date on the vial. Thawed calibrators should be stored at 2-8°C for up to 7 days. Aliquots can be stored frozen for up to 30 days.

d. Detection limit:

The minimum detectable concentration (MDC) was determined by running 20 replicates of a serum pool from normal donors. The mean rate and standard

deviation from the normal serum pool were calculated. The concentrations corresponding to mean rate +2 times S.D. was determined to be 0.01 ng/mL.

e. Analytical specificity:

Potential cross reactants to troponin I were spiked into serum pools and tested for cross-reactivity. Cardiac troponin T, troponin C and skeletal troponin I all showed negligible cross-reactivity. Serum pools spiked with hemoglobin up to 500 mg/dL, triglyceride up to 1000 mg/dL, bilirubin up to 20 mg/dL and albumin up to 6500 mg/dL showed less than 5% interference.

f. Assay cut-off:

See clinical cutoff

2. Comparison studies:

a. Method comparison with predicate device:

Correlation was evaluated with serum samples tested on the ACS:180 vs. ADVIA IMS and the ADVIA Centaur vs. the ADVIA IMS troponin I assays using a protocol similar to CLSI EP9-A.

	n	Regression equation	R	S _{y,x}	Range of analyte concentration
y = ADVIA IMS, x = ACS:180	97	0.90x + 0.43	0.954	2.64	0.01-49.6 ng/mL
y = ADVIA IMS, x = ADVIA Centaur	146	0.981x + 0.20	0.953	1.91	0.01-37.8 ng/mL

b. Matrix comparison:

Lithium heparin and serum sample pairs were assayed with the ADVIA IMS[®] TnI-Ultra assay. The linear regression equation is: y (Heparinized plasma) = 0.8908 x (serum) + 0.2327; R = 0.993, n = 45, with values ranging from 0.03 to 19.4 ng/mL. The dose recoveries for the plasma samples were about 11% lower than the corresponding serum samples. The labeling contains the instructions that plasma samples showed an 11% reduction in dose compared to serum samples and to not use heparinized plasma and serum samples from the same patient interchangeable with this test.

3. Clinical studies:

a. Clinical Sensitivity:

The clinical sensitivity based on the ACS:180 assay (k980528), to which this assay is equivalent, was determined to be 94.6 %.

b. Clinical specificity:

The clinical specificity based on the ACS:180 assay(k980528), to which this assay is equivalent, was determined to be 98.8 %. See k

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

4. Clinical cut-off:

The upper 99th percentile of normal distribution was determined using 337 serum samples from donors with no known cardiovascular diseases. The samples were assayed with the TnI-Ultra method and the troponin values were numerically ranked. The 99th percentile was found to be 0.04 ng/mL.

The AMI Troponin I cut-off value is based on the data for the ACS:180 troponin I assay (k980528) to which the ADVIA IMS TnI-Ultra method is equivalent. Evaluation of a population of patients from multiple clinical sites was performed. The patient population which included both females and males consisted of 112 individuals who ruled-in for AMI and 166 patients who ruled-out for AMI. Patient results were analyzed using Cumulative Distribution Analysis (CDA). The diagnostic cutoff for AMI patients was determined to be 1.5 ng/mL.

5. Expected values/Reference range:

The upper 99th percentile of normal distribution was determined using 337 serum samples from donors with no known cardiovascular diseases. The samples were assayed with the TnI-Ultra method and the troponin values were numerically ranked. The 99th percentile was found to be 0.04 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.