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

A. 510(k) Number:

k053020

B. Purpose for Submission:

New Device

C. Measurand:

Troponin I

D. Type of Test:

Quantitative Chemiluminescence Immunoassay

E. Applicant:

Bayer HealthCare LLC

F. Proprietary and Established Names:

ADVIA Centaur® TnI-Ultra Assay
ADVIA Centaur® TnI-Ultra Calibrators

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):

   See indications for use statement below.

2. Indication(s) for use:

   The ADVIA Centaur® TnI-Ultra Method is for in vitro diagnostic use in the quantitative determination of cardiac Troponin I in human serum and heparizined and EDTA plasma. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction and in the risk stratification of patients with non-ST segment elevation acute coronary syndromes with respective to relative risk mortality, myocardial infarction or increased probability of ischemic events requiring urgent revascularization procedures.

   The ADVIA Centaur® TnI Calibrator is for the in vitro diagnostic use in the calibration of the TnI-Ultra assay on the ADVIA Centaur® system.

3. Special conditions for use statement(s):

   For prescription use only.

4. Special instrument requirements:

   ADVIA Centaur® System

I. Device Description:

The TnI-Ultra assay is comprised of three reagents: Binary Lite, Solid Phase and ancillary reagents. The TnI-Ultra also has an accompanying Master Curve Card that contains lot specific master curve calibration values. The Binary Lite reagent consists of polyclonal goat anti-cTnI antibody, two biotinylated monoclonal mouse anti-cTnI antibodies, stabilizers and preservatives. The TnI-Ultra assay includes 2 levels (low and high) lyophilized calibrators and barcode labels for the calibrators. All of the components listed above make up the TnI-Ultra assay ready pack.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Bayer ACS:180® cTnI Assay

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

   k980528 and k993309

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended use	Quantitative determination of cardiac troponin I (cTnI) in serum, heparinized or EDTA plasma using the ADVIA Centaur System. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction 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.	Quantitative determination of cardiac troponin I in serum or heparinized using Bayer Diagnostics ACS:180 (ADVIA Centaur) Automated Chemiluminscence Systems. Cardiac troponin I determinations aid in the diagnosis of acute myocardial infarction 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.
Assay Principle	Chemiluminescence Immunoassay	Same
Sample Volume	100 µL	100 µL
Calibrators	Hi and Low	Hi and Low

Differences		
Item	Device	Predicate
Sample Type	Serum and Heparized Plasma	Serum, Heparized Plasma and EDTA Plasma.
Instrument	ADVIA Centaur®	ACS:180®
Range	0.008 ng/mL to 50 ng/mL	0.07 ng/mL to 50 ng/mL

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

CLSI EP7A- Interference Testing in Clinical Chemistry

L. Test Principle:

The ADVIA Centaur TnI-Ultra assay is a three-site sandwich immunoassay that

utilizes direct chemiluminometric technology. The Binary Lite reagent includes a polyclonal goat anti-troponin I antibody labeled with acridinium ester and two biotinylated monoclonal anti-troponin I antibodies. The solid phase reagent is magnetic latex particles conjugated with streptavidin. The antibodies in the Binary Lite reagent bind to troponin I in the sample. The biotin contained in the immune complex then binds to the streptavidin-labeled magnetic particles. A direct relationship exists between the amount of troponin I present in the patient sample and the amount of relative light units (RLU) detected by the system.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Imprecision studies were conducted over a 20 day period on two instruments with commercially available control materials and patient pools. The following samples were run in duplicate in one run per day per system.

Level (ng/mL)	Sample Type	Within-Run CV%	Within-Run SD	Total CV%	Total SD
0.057	Patient Pool	5.3	0.003	7.4	0.0043
0.1	Control	3.2	0.0033	4.6	0.0047
0.24	Patient Pool	2.6	0.0062	3.5	0.0083
0.85	Control	1.6	0.0138	2.7	0.0265
3.91	Control	1.5	0.0604	2.8	0.1100
14.47	Control	1.5	0.2137	3.4	0.4926
37.8	Patient Pool	1.8	0.6866	3.5	1.3388
38.45	Patient Pool	1.9	0.736	3.1	1.205

To determine the functional sensitivity of the assay, a series of low serum pools was prepared by sequential dilution of a low sample with a negative serum pool and run on two instruments over a 20 day period. Recoveries for the low serum pools and controls from the two instruments were combined and the total % C.V. was calculated. The level for the 10% and 20% total CV was estimated to be 0.042 ng/mL and 0.022 ng/mL respectively. The upper 99^{th} percentile of normal distribution was found to be 0.044 ng/mL for serum (n=648).

The assay meets the guidelines from the European Society of Cardiologist and American College of Cardiology that the assay demonstrate an imprecision (total % CV) of 10% or less at the 99^{th} percentile of a normal reference population.

b. Linearity/assay reportable range:

To determine the high dose effect related with the ADVIA Centaur® TnI-Ultra Assay, high levels of troponin I antigen was spiked into negative serum pools. The reaction rates of the spiked samples were obtained from the ADVIA Centaur® TnI-Ultra Assay. There was no drop in rates for TnI concentrations up to 1000 ng/mL.

Serum samples with high troponin I concentrations were diluted with negative serum and obtained expected concentrations ranging from 0.724 ng/mL to 44.35 ng/mL. When compared to the expected value, the measured (observed) values of troponin I averaged 103% with a range of 91.6 to 113%. In addition, linearity was also studied in a high dose dilution recovery study. A high patient pool was created by diluting a patient sample (> 50ng/mL) with a negative patient sample. The observed concentrations ranged from 8.59 to 49.76 and the recoveries ranged from 96% to 100%. The linearity (from 8.59 to 49.76 ng/mL) equation for observed (y) and Theoretical (x) was y=0.999x - 0.42 with a R^2 of 0.999.

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

The ADVIA Centaur TnI-Ultra method is standardized to an internal standard manufactured using purified materials. Assigned values of the calibrators are traceable to this standard. The calibrator value is assigned through a two step process. The lyophilized calibrators are value assigned as zero to approximately 40 ng/mL. All future lots of calibrators will be value assigned against the master lot via nested testing procedures. The test lot and the master lot, together with previous lots, are value assigned through nested testing in the same run using ten replicates for each control level. The ADVIA Centaur system uses 2-point calibration of a master curve that is distributed with the reagent as a printed master curve card. The system uses the RLU's of the calibrators to adjust the master curve and this adjusted master curve is used for all calculations of patient sample and control doses. The sponsor suggests that calibration should occur with every new reagent lot and/or every 28 days within a lot.

Calibrators, after storage at the recommended storage condition are tested through the recommended shelf life. Shelf life was determined by analyzing calibrators throughout the time frame. The calibrators are assessed with dose determinations from the gold master curve as well as in its ability to calibrate an assay and recover appropriate control doses. The calibrators are stable for 10 months or until the expiration listed on the calibrator.

d. *Detection limit:*

The minimum detectable concentration (analytical sensitivity) was determined by running twenty replicated of a negative serum pool. The mean RLU's and SD from the negative serum pool were calculated. The concentration

corresponding to rate + 2xSD was determined to be 0.008 ng/mL. The analytical determination was calculated on a base pool by assaying in five replicates on the three instruments over four days using two lots.

Reagent Lot	Instrument	Mean RLU of zero std.	SD	Mean + 2xSD	Apparent doe (ng/mL)
1	1	1034	46	1126	0.0056
	2	1413	109	1631	0.0069
	3	1664	183	2030	0.0075
2	1	1575	65	1705	0.0553
	2	2065	224	2513	0.0185
	3	2272	156	2584	0.0038
			Grand mean		0.0079

e. Analytical specificity:

Potential cross reactants to troponin I were spiked into negative serum pool and tested for cross reactivity. Cardiac troponin T, troponin C, skeletal troponin I, actin, CK-MB and myoglobin 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 10% interference.

f. Assay cut-off:

See clinical cut-off

2. Comparison studies:

a. Method comparison with predicate device:

Correlation of the ACS:180 cTnI assay versus the ADVIA Centaur® TnI Ultra assay was evaluated with serum samples. Two sets of ranges were analyzed and calculated in order to capture medically relevant doses: 0.1 to approximately 35 ng/mL and 0.1 to approximately 4.0 ng/mL. The results were analyzed with the Passing-Bablok regression in addition to the least-squares regression method. The results for both ranged are summarized below.

Specimen type Regression method	Comparative System (x)	N	Regression Equation	Sample Range (ng/mL)
Serum Passing and Bablok	Bayer ADVIA Centaur®	346	1.10x-0.045	0.1 to 34.8
Linear Regression	Bayer ADVIA	346	1.26x- 0.52 r=0.975	0.1 to 34.8
Serum Passing and Bablok	Bayer ADVIA Centaur®	229	1.08x-0.02	0.1 to 4.0
Linear Regression	Bayer ADVIA Centaur®	229	1.04x + 0.04 r=0.946	0.1 to 4.0

Further comparison of clinical utility was done by comparing doses from ADVIA Centaur TnI-Ultra to the ACS:180 and the ADVIA Centaur cTnI using the WHO criteria cut-off of 0.9 ng/mL. The results for both are shown below.

ADVIA Centaur TnI- Ultra		ADVIA Centaur cTnI	
		< 0.9 ng/mL	≥ 0.9 ng/mL
	< 0.9 ng/mL	101	2
	≥ 0.9 ng/mL	7	261
	Concordance = 97.6%		
ADVIA Centaur TnI- Ultra		ACS:180 cTnI	
		< 0.9 ng/mL	≥ 0.9 ng/mL
	< 0.9 ng/mL	101	2
	≥ 0.9 ng/mL	20	236
	Concordance = 93.9%		

b. Matrix comparison:

Lithium heparin and serum sample pairs were assayed with the ADVIA Centaur® TnI-Ultra Assay. The linear regression equations are below:

y(Heparinized plasma)= 0.91x(serum) +0.67 ; r=0.964 and n=53.

Y(EDTA plasma)= 0.81x(serum) + 0.15 ; r=0.964 and n=31.

Evaluation of heparinized and EDTA plasma samples resulted in a mean 1% and 4% decrease in observed values, respectively, compared to serum. The labeling contains the instructions that plasma and serum samples from the same patient should not be used interchangeably with this test.

3. Clinical studies:

   a. Clinical Sensitivity:

   The clinical sensitivity based on the ACS:180 assay, to which this assay is equivalent, was determined to be 97.3%.

   b. Clinical specificity:

   The clinical specificity based on the ACS:180 assay, to which this assay is equivalent, was determined to be 97.0%.

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

   Not applicable.

4. Clinical cut-off:

   Using the definition of MI as described by the World Health Organization (WHO), evaluation of a population consisting of patients from multiple clinical sites was previously performed using the ACS:180 cTnI assay. The patient population which included both males and females consisted of 112 individuals who ruled-in for AMI and 166 individuals who ruled-out for AMI. Results from clinical data were analyzed based on Receiver Operating Characteristics (ROC) plots using the guidelines presented in CLSI document GP10-A. A 0.9 ng/mL diagnostic cutoff was determined.

5. Expected values/Reference range:

   The upper 99^{th} percentile of normal distribution was determined using 648 healthy individuals ranging from 17 to 91 years of age. The samples were assayed with the TnI-Ultra method and the troponin values were numerically ranked. The 99^{th} 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.