

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

A. 510(k) Number:

k071474

B. Purpose for Submission:

New device

C. Measurand:

Myeloperoxidase

D. Type of Test:

Quantitative, Enzyme Immunoassay

E. Applicant:

Dade Behring, Inc.

F. Proprietary and Established Names:

Dimension MPO Flex reagent cartridge

Dimension MPO Calibrator

Dimension MPO Control

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
NTV (Myeloperoxidase, Immunoassay, System, Test)	II	21 CFR 866.5600	82 (immunology)
JIT (Calibrator, secondary)	II	21 CFR 862.1150	75 (chemistry)
JJX (Quality Control Material)	I	21 CFR 862.1660	75 (chemistry)

H. Intended Use:

1. Intended use(s):

See indications for use statement below.

2. Indication(s) for use:

MPO Flex® reagent cartridge:

The MPO method is an *in vitro* diagnostic test for the quantitative measurement of myeloperoxidase (MPO) in human plasma on the Dimension® clinical chemistry system with the heterogeneous immunoassay module. Myeloperoxidase measurements may be used in conjunction with clinical history, ECG, and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.

MPO Calibrator:

The MPO Calibrator is an *in vitro* diagnostic product intended to be used to calibrate the Myeloperoxidase (MPO) method on the Dimension® clinical chemistry system with the heterogeneous immunoassay module.

MPO Control:

The myeloperoxidase control is an *in vitro* diagnostic product intended for use as an assayed quality control product to monitor the performance of the Myeloperoxidase (MPO) method on the Dimension® clinical chemistry system with the heterogeneous immunoassay module.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

Siemens Dimension® RxL

I. Device Description:

MPO Reagent:

The MPO reagent contains 4 flex cartridges per carton. Reagents are contained in 8 segregated wells in a plastic cartridge. Wells 1 and 2 contain the liquid mouse monoclonal conjugate preparation. Wells 3 and 4 contain a tablet of chromium dioxide linked mouse monoclonal. Wells 5 and 6 contain a CPRG substrate reagent. Well 7

contains a diluent for the CPRG tablet. Well 8 contains a diluent for the chromium dioxide tablet.

MPO Calibrator:

The MPO calibrators contain ten 2.0 mL vials (2 vials per 5 levels) of calibrators. The MPO Calibrator is a frozen bovine albumin based product containing human myeloperoxidase, stabilizers and preservatives in a synthetic matrix.

The sponsor states that all donors of human serum supplied with the kit have been tested and found negative for hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV1 and HIV2) and hepatitis C virus.

MPO Control:

The MPO Controls contain twelve 2.0 mL vials (6 vials per 2 levels) of controls. The MPO control is a frozen bovine albumin based product containing human myeloperoxidase, stabilizers and preservatives in a synthetic matrix.

The sponsor states that all donors of human serum supplied with the kit have been tested and found negative for hepatitis B surface antigen (HBsAg) and antibodies to human immunodeficiency virus (HIV1 and HIV2) and hepatitis C virus.

J. Substantial Equivalence Information:

Item	Predicate - PrognostiX MPO	Dimension® MPO
Intended Use	The <i>CardioMPO</i> Reagent Kit is an enzyme immunoassay intended for the quantitative determination of myeloperoxidase in human plasma, to be used in conjunction with clinical history, ECG and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.	The MPO method is an <i>in vitro</i> diagnostic test for the quantitative measurement of myeloperoxidase (MPO) in human plasma on the Dimension® clinical chemistry system with the heterogeneous immunoassay module. Myeloperoxidase measurements may be used in conjunction with clinical history, ECG, and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.
Assay Type	Sandwich enzyme immunoassay	Sandwich enzyme immunoassay
Reportable Range	13 to 5000 pmol/L	20 to 5000 pmol/L

Item	Predicate - PrognostiX MPO	Dimension® MPO
Hook Effect	No high dose effect up to 800,000 pmol/L	No high dose effect up to 800,000 pmol/L
Clinical study results	Odds ratio increases from 1.0 to a max. of 3.3 across 4 quartiles	Odds ratio increases from 1.0 to a max. of 2.3 across 4 quartiles
Expected Values	≤ 539 pmol/L	<20 - 633 pmol/L
Antibody	PrognostiX polyclonal rabbit and goat monoclonal	Dade Behring mouse monoclonal
Calibration Interval	Calibration curve using six levels updated for each run.	Calibration curve updated for each lot, using five levels every 30 days with the same reagent lot.
Sample Volume	5 uL	30 uL
Sample	Lithium Heparin Plasma	EDTA, Li or Na heparin plasma
Controls	3 levels; human MPO in lithium heparin plasma	2 levels; human MPO in BSA

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

STANDARDS	
Title and Reference Number	
Stability Testing of In Vitro Diagnostic Reagents (13640)	
Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP09-A2)	
Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)	
Medical devices – Application of risk management to medical devices (14971:2000)	
Medical Devices - Symbols to be used with medical device labels, labeling and information to be supplied (15223)	
Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline-Second Edition (EP5-A2)	

GUIDANCE		
Document Title	Office	Web Page
User Fees and Refunds for Premarket Notification Submissions (510(k)s) – Guidance for Industry and FDA Staff	CDRH	http://www.fda.gov/cdrh/mdufma/guidance/1511.html
Guidance for Industry and FDA Staff - Use of Symbols on Labels and	CDRH	http://www.fda.gov/cdrh/ocd/guidance/4444.html

in Labeling of In Vitro Diagnostic Devices Intended for Professional Use		
Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable - Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff	CDRH	http://www.fda.gov/cdrh/oivd/guidance/1588.html

L. Test Principle:

The Dimension MPO reagent kit is a one step enzyme immunoassay based on the “sandwich” principle. The sample is incubated with chromium dioxide particles coated with mouse monoclonal antibodies specific for MPO, and conjugate reagent (B-galactosidase labeled mouse monoclonal antibodies specific for MPO). A particle/MPO/conjugate forms during the incubation period. Unbound conjugate is removed by magnetic separation and washing. The sandwich bound B-galactosidase is combined with the chromogenic substrate chlorophenol red-B-D-galactopyranoside (CPRG). Hydrolysis of CPRG releases a chromophore (CPR). The concentration of MPO present in the patient sample is directly proportional to the rate of color change due to formation of CPR measured at 577 nm.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

A precision study was conducted based on a modified version of a 20 day ANOVA protocol (EP5-A2) using 3 levels of plasma pools (low, mid and high) and 2 control levels with 7 reagent lots at three sites. Samples 1, 2, 3, 5, 6 and 8 were conducted at the sponsor’s internal site. Samples 4, 7, 9 and 10 were conducted at two external sites. Samples 8-10 below were tested using one lot with two plasma pools run in triplicate at three sites over twenty days. The compiled table below shows the results from both studies and a multi-site ANOVA summary.

Plasma Pool Low											
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Multi-Site ANOVA Summary Stats
Mean:	400.5	485.9	441.7	464.5	538.9	426.1	494.1	559.1	525.0	540.6	542.0
SD_R:	8.5	11.9	11.5	11.0	21.5	13.3	10.9	16.2	9.8	14.9	13.9
%CV_R:	2.1	2.4	2.6	2.4	4.0	3.1	2.2	2.9	1.9	2.8	2.7
SD_T:	13.6	14.1	14.0	11.3	22.3	14.7	17.2	24.2	21.3	22.4	27.9
%CV_T:	3.4	2.9	3.2	2.4	4.1	3.4	3.5	4.3	4.1	4.2	5.1

Plasma Pool Mid											
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Multi-Site ANOVA Summary Stats
Mean:	1318	1469	1463	1529	1450	1307	1465	803.8	775.2	782.0	787.0
SD_R:	31.9	30.2	32.9	59.1	35.9	46	43.6	17.2	19.0	16.0	17.5
%CV_R:	2.4	2.1	2.2	3.9	2.5	3.5	3.0	2.1	2.5	2.1	2.2
SD_T:	48.5	44.5	49.9	59.1	38.5	50.8	53.3	25.0	28.4	28.5	30.6
%CV_T:	3.7	3.0	3.4	3.9	2.7	3.9	3.6	3.1	3.7	3.7	3.9

Plasma Pool High					
	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5
Mean:	2608	2831	2728	2846	2639
SD_R:	65.7	67.4	49.4	68.2	76.2
%CV_R:	2.5	2.4	1.8	2.4	2.9
SD_T:	109.4	82.4	74.9	76.1	89.6
%CV_T:	4.2	2.9	2.7	2.7	3.4

Dim MPO QC Lev 1						
	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Multi-Site ANOVA Summary Stats
Mean:	416.5	428.4	465.4	443.7	454.2	454.0
SD_R:	11.9	16.3	12.7	17.6	16.9	15.9
%CV_R:	2.9	3.8	2.7	4.0	3.7	3.5
SD_T:	15.7	20.4	16.1	22.4	21.8	22.8
%CV_T:	3.8	4.8	3.5	5.1	4.8	5.0

Dim MPO QC Lev 2						
	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Multi-Site ANOVA Summary Stats
Mean:	3455	3644	2584.2	2556.1	2556.8	2569.0
SD_R:	122.3	121.0	61.3	59.9	49.3	57.1
%CV_R:	3.5	3.3	2.4	2.3	1.9	2.2
SD_T:	125.1	131.6	80.0	94.6	111.0	104.5
%CV_T:	3.6	3.6	3.1	3.7	4.3	4.1

Notes:
1. SD _R and %CV _R are estimates of repeatability
2. SD _T and %CV _T are estimates of within-lab precision
3. Different plasma pools were made for different studies. They were targeted for similar analyte concentrations but had different means. As such, precision estimates may be compared across the studies but the mean values would be expected to vary.

b. *Linearity/assay reportable range:*

Linearity was assessed in a recovery study according to CLSI EP6-A: *Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*. A 7-level dilution series (concentrations shown below) run in replicates of five were prepared by mixing low and high patient samples. A linear regression equation was conducted for expected results versus observed results. The resulting linear regression equation is $y=1.018x - 1.833$ with a R^2 of .999. The results of the recovery study shown below and the functional sensitivity study shown in section d. below support the sponsor claimed range of 20 to 5000 pmol/L.

Sample #	Expected (pmol/L)	Observed Mean (pmol/L)	% Recovery
1 (Low)	26	26	
2	892	848	95.0
3	1759	1783	101.4
4	2574	2636	102.4
5	3440	3550	103.2
6	4307	4432	102.9
7 (High)	5122	5122	

The sponsor also conducted a hook effect study to assess samples above the range of the test. Samples were prepared by spiking purified human MPO into a normal human plasma base. The concentrations were verified by making a dilution with human pooled plasma of known low analyte concentration so that the expected value would fall within the MPO assay range. The samples were tested to determine if high samples would give erroneous results. The MPO assay upper range is 5000 pmol/L. Samples whose signals either exceed the upper assay range limit or cause the instruments protected feature are flagged as “Above Assay Range”. Based on the results from the study and the additional features of the instrument, the sponsor reports that there was no observed hook effect for samples up to 800,000 pmol/L.

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

Traceability

No reference standard is available for myeloperoxidase. An anchor pool was prepared from patient reference samples which consisted of native analyte in human serum. A master pool was derived from the anchor pool which is a 5-level liquid working standard of purified analyte in BSA. The initial master pool is assigned from the anchor pool during a patient sample method comparison spanning the assay range. All subsequent master pools are assigned using a set protocol on multiple instruments. The working calibrator materials are assigned values based on the master pool using a set protocol on multiple instruments.

The two MPO controls have the same formulation and approximate values as the MPO calibrator levels 2 and 4 (500 and 3000 pmol/L) and are made from independent production runs.

Stability

The sponsor conducted a closed vial calibrator/control stability study in which 3 lots of five levels (approx. 0, 500, 1000, 3000, 5375 pmol/L) of calibrators (stored at -20 C) were tested in replicates at time increments between 0 and 13 months. The study results support the sponsor's calibrator/control stability claim of 13 months.

The sponsor conducted an open vial stability study in which 2 vials of each level were assayed in triplicate for 15 days. The open vial results were compared with an unopened vial for 15 days. The study results support the sponsor's calibrator/control stability claim of 14 days when stored at 2-8 C°.

The sponsor conducted a sample stability study to determine the specimen types and the temperature required for sample storage. 20 EDTA plasma samples (10 collected in house and 10 from a blood bank) and 20 lithium heparin plasma samples (10 collected in house and 10 from a blood bank) were frozen at -20 C. Calibration was conducted daily and the samples were tested in replicates of 5 at day 0, month 1, month 3 and month 6 with the MPO reagent. The results support the sponsor's 6 month sample stability claim when frozen at -20° C.

The sponsor conducted a further sample stability study to determine the number of storage days for a sample if stored at 4° C. Ten paired EDTA and Lithium Heparin samples were stored at 4° C and were run in triplicate with the reagent. The results support the sponsor's 6 day sample stability claim when stored at 4° C.

The sponsor conducted a freeze-thaw stability study to determine the number of times a sample containing myeloperoxidase could be thawed. The paired lithium heparin and EDTA plasma samples from the anticoagulant study in the matrix comparison section 2b below were assayed fresh and then frozen at -70°C. The samples were thawed, assayed in replicates of five and then refrozen. The results support the sponsor's freeze thaw statement within the package insert of "MPO levels in EDTA and heparinized plasma have been shown to be stable through three freeze/thaw cycles."

d. Detection limit:

The sponsor conducted a limit of the blank study according to CLSI EP17 in which calibrator 1 (0 pmol/L) was assayed 20 consecutive times. The limit of the blank is 13 pmol/L which is the mean value (n=20) plus two standard deviations of the level 1 (0 pmol/L) MPO Calibrator.

The sponsor conducted a functional sensitivity study (one run per testing day for 20 days). Four separate studies (3 in-house sites and 1 external site) were conducted with five human plasma pools with low MPO concentrations. The within-lab precision versus the mean MPO concentration was plotted. The functional sensitivity estimate for each study was read as the MPO concentration giving a 20% CV within-lab precision. The results per site ranged from 7 pmol/L to 16 pmol/L which support the sponsor's functional sensitivity claim of 20% CV at 20 pmol/L.

e. Analytical specificity:

The sponsor conducted an interference study according to CLSI EP7-A2. Bias was defined as the difference in the results between the control sample (without the interferent) and the test sample (contains the interferent) expressed in percent. The sponsor's acceptance criterion was that a bias exceeding 10% was considered as significant interference. Myeloperoxidase samples with concentrations between 481 and 2000 pmol/L were tested for bilirubin (conjugated and non-conjugated), lipemia and hemoglobin. The results showed no significant interference for hemoglobin up to 1000 mg/dL, bilirubin (conjugated and non-conjugated) up to 60 mg/dL and lipemia (Intralipid) up to 3000 mg/dL

Cross reactivity was studied using potentially cross-reacting substances commercially purchased. The substances were spiked into samples containing 0 and approximately 1500-2000 pmol/L myeloperoxidase. Percent cross-reactivity was defined as (Mean Test Result - Mean Control Result)/Cross Reactant Compound Concentration in pmol/L *100. The cross-reactivity was less than 0.15% for all cross reactants except Eosinophil Peroxidase which was 0.43%. The results for the cross-reactivity studies are shown in the tables below

Test Sample: DM MPO Calibrator Level 1 (0 pmol/L)						
	[Test Substance]		Mean [MPO]		Bias	X- Reactivity
Substance	nmol/L	pmol/L	Control	Test	(pmol/L)	(%)
α-1 Antitrypsin	1250	1,250,000	-4.8	-5.7	-0.9	0.00
C-reactive protein	550	550,000	-4.8	-5.3	-0.5	0.00
Lysozyme	4500	4,500,000	-4.8	1.8	6.6	0.00
Immunoglobulin A	400	400,000	-5.8	-5.5	0.3	0.00
Elastase	2500	2,500,000	-5.0	499.2	504.2	0.02
Eosinophil peroxidase	922	922,000	2.3	3960.5	3958.2	0.43
Lactoperoxidase	800	800,000	-4.8	-5.1	-0.3	0.00
Lactoferrin	800	800,000	-4.8	-1.7	3.1	0.00
COX1	900	900,000	-4.1	-2.5	1.6	0.00
COX2	900	900,000	-2.7	-2.5	0.2	0.00
Thyroid peroxidase	600	600,000	-3.4	284.7	288.1	0.05
Troponin I	2150	2,150,000	-3.1	6.2	9.3	0.00

Test Sample: Sodium Heparin Human Plasma Pool (~1800 pmol/L)						
	[Test Substance]		Mean [MPO]		Bias	X-Reactivity
Substance	(nmol/L)	(pmol/L)	Control	Test	(pmol/L)	(%)
α -1 Antitrypsin	1250	1,250,000	1815.2	1831.1	15.9	0.00
C-reactive protein	550	550,000	1815.2	1834.0	18.8	0.00
Lysozyme	4500	4,500,000	1815.2	1869.9	54.7	0.00
Immunoglobulin A	400	400,000	1840.3	1763.8	-76.5	-0.02
Elastase	2500	2,500,000	1837.0	2113.5	276.5	0.01
Eosinophil peroxidase	922	922,000	1809.6	3436.5	1626.9	0.18
Lactoperoxidase	800	800,000	1815.2	1694.6	-120.6	-0.02
Lactoferrin	800	800,000	1815.2	1790.7	-24.5	0.00
COX1	900	900,000	1868.7	1762.7	-106.0	-0.01
COX2	900	900,000	1541.4	1457.9	-83.5	-0.01
Thyroid peroxidase	600	600,000	1884.5	2010.0	125.5	0.02
Troponin I	2150	2,150,000	1859.1	1899.7	40.6	0.00

An extensive list of other compounds was evaluated for interference and was found to have no significant interference. The list can be found in the package insert.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

The sponsor conducted a method comparison study according to CLSI EP9-A2. One hundred and thirty-nine lithium heparin samples ranging from 154 to 4869 pmol/L were analyzed using the Dimension MPO on the Dimension RxL and the Prognostix MPO assay. The Passing-Bablok linear regression results are shown in the table below.

Slope	Intercept (pmol/L)	Correlation Coefficient	N
1.03 (95%CI: 0.97 to 1.12)	91.8 (95% CI: -10.0 to 180.6)	0.88	139

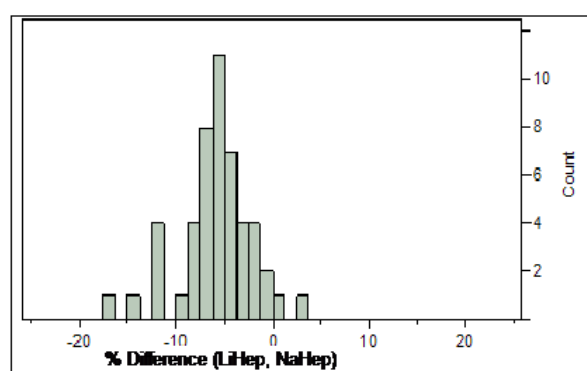
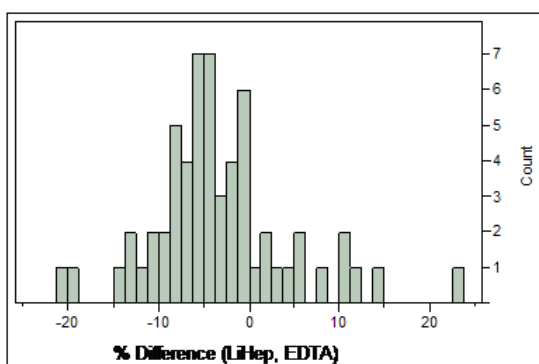
b. Matrix comparison:

The sponsor conducted a matrix comparison study to evaluate the effects of EDTA

and Sodium Heparin samples with the Dimension MPO assay. The Passing-Bablok linear regression (x=Li heparin values) results are shown in the table below.

Comparative Specimen	Slope	Intercept (pmol/L)	Correlation Coefficient	Range (pmol/L)	N
Lithium Heparin vs. EDTA	1.01	-19.3	0.997	165-3812	59
Lithium Heparin vs. Sodium Heparin	0.96	-7.2	0.999	167-3401	49

The frequencies for the % differences ranged from < -20% to > 20% as shown in the plots below.



3. Clinical studies:

a. *Clinical Sensitivity:*

Not applicable

b. *Clinical specificity:*

Not applicable.

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

A clinical study was conducted which included 400 EDTA samples collected from patients presenting to the Emergency Department or acutely to outpatient facilities with chest pain or equivalent symptoms suggestive of Acute Coronary Syndrome (ACS). Approximately 85% of the patient population presented within 24 hours of the onset of symptoms. On electrocardiogram (ECG), 15.5% of patients had ST

segment elevation; 6.75% of patients had ST segment depression; 33% had one of the following: new Q-waves, old Q-waves, or non-specific T wave abnormality; and 44.75% had none of the aforementioned changes on ECG. Patients were assessed for major adverse cardiac events (MACE) which includes myocardial infarction, recurrent ischemia associated with ECG changes, recurrent ischemia requiring hospitalization or revascularization, and death. Incidence of MACE was assessed by a review of medical records and/or medical database searches. Patients were excluded: if the chest pain was due to trauma or if they were apparently healthy individuals. The demographics of the patients are shown in the table below.

MPO Quartiles and Selected Demographics by Quartile

Variable	N*	Quartile (Range of MPO in pM)			
		Q1 (94-581)	Q2 (582-894)	Q3 (895-1657)	Q4 (1658-5000)
Mean Age (years)	400	54	54	57	59
WBC (x 10 ⁹ /L)	386	6.76	8.09	9.05	12.09
Male Sex	400	59%	61%	55%	55%
Caucasian	400	42%	41%	50%	52%
HX Diabetes	400	28%	33%	27%	41%
HX Hypertension	400	65%	73%	68%	69%
HX Hyperlipidemia	400	37%	36%	36%	39%
Current Smoker	400	38%	39%	39%	32%
Prior MI	400	21%	28%	23%	19%
Prior PCI	400	14%	14%	13%	12%
Prior CABG	400	5%	7%	8%	12%
HX CHF	400	6%	11%	14%	21%

*Number of patients from whom data was available; Q1=99 patients, Q3 =101 patients, Q2 & Q4=100 patients

Odds ratios were determined using univariate and multivariate logistic regression models. Each MPO quartile was compared versus MPO quartile 1 for the outcomes of MACE at the 30 day and 180 day intervals post-presentation. The multivariate analysis included the following variables in addition to MPO: age, sex, race, history of hypertension, history of hyperlipidemia, smoking status, history of diabetes, white blood cell count (WBC), and the following cardiac markers: Dimension[®] troponin I (CTNI), NTproBNP (PBNP) and hsCRP (CCRP). Results of the univariate and multivariate analysis are displayed in the following two tables below.

Univariate Analysis (N=400)

Analysis	Odds ratio (Confidence Interval)	p-value
30 days		
MPO Q2 vs. Q1	1.36 (0.55-3.40)	0.827
MPO Q3 vs. Q1	2.63 (1.14-6.06)	0.024
MPO Q4 vs. Q1	4.29 (1.91-9.61)	0.000

180 days		
MPO Q2 vs. Q1	0.99 (0.41-2.40)	0.799
MPO Q3 vs. Q1	2.10 (0.95-4.63)	0.066
MPO Q4 vs. Q1	4.12 (1.95-8.73)	0.000

Multivariate Analysis (N=386; 14 patients excluded due to missing WBC)

Analysis	Odds ratio (Confidence Interval)	p-value
30 days		
MPO Q2 vs. Q1	1.41 (0.51-3.89)	0.510
MPO Q3 vs. Q1	3.03 (1.19-7.76)	0.021
MPO Q4 vs. Q1	4.31 (1.62-11.50)	0.004
Age	1.01 (0.98-1.03)	0.684
Sex	2.69 (1.40-5.16)	0.003
History of hypertension	1.07 (0.53-2.19)	0.843
History of hyperlipidemia	3.40 (1.80-6.44)	0.000
Smoking status	0.92 (0.49-1.74)	0.796
History of diabetes	0.99 (0.52-1.87)	0.970
White blood cell count	1.06 (1.00-1.13)	0.044
CTNI	1.37 (1.09-1.74)	0.008
PNBP	1.00 (1.00-1.00)	0.606
CCRP	0.99 (0.98-1.00)	0.072
180 days		
MPO Q2 vs. Q1	0.98 (0.37-2.56)	0.960
MPO Q3 vs. Q1	2.21 (0.93-5.26)	0.073
MPO Q4 vs. Q1	3.66 (1.50-8.94)	0.004
Age	1.01 (0.99-1.03)	0.421
Sex	2.19 (1.19-4.03)	0.011
History of hypertension	0.98 (0.50-1.91)	0.943
History of hyperlipidemia	2.24 (1.23-4.09)	0.009
Smoking status	0.79 (0.43-1.46)	0.455
History of diabetes	0.70 (0.39-1.28)	0.251
White blood cell count	1.04 (0.99-1.10)	0.117
CTNI	1.32 (1.05-1.66)	0.016
PNBP	1.00 (1.00-1.00)	0.928
CCRP	1.00 (0.99-1.00)	0.321

Logistic-regression models were used to calculate odds ratios and 95th percentile confidence intervals. Odds ratios (shown below) were calculated for MPO separately and after adjustment for age, gender, Troponin I, NT-proBNP, C-reactive protein, white blood cell count, ST-segment depression, history of hypertension, history of hypercholesterolemia, history of diabetes, and smoking status. In each analysis the first quartile served as the reference group for calculation of odds ratio.

MACE at 30 Days

	Q1*	Q2	Q3	Q4
MPO (pmol/L)	94-581	582-894	895-1657	1658-5000
Odds Ratio	1.00	1.36	2.63	4.29
95% CI	NA	0.55-3.40	1.14-6.06	1.91-9.61
Adjusted Odds Ratio	1.00	1.41	3.03	4.31
95% CI	NA	0.51-3.89	1.19-7.76	1.62-11.50

MACE at 6 Months

	Q1*	Q2	Q3	Q4
MPO (pmol/L)	94-581	582-894	895-1657	1658-5000
Odds Ratio	1.00	0.99	2.10	4.12
95% CI	NA	0.41-2.40	0.95-4.63	1.95-8.73
Adjusted Odds Ratio	1.00	0.98	2.21	3.66
95% CI	NA	0.37-2.56	0.93-5.26	1.50-8.94

ROC analysis was conducted to determine if MPO is a significant predictor of the ROC curve (or area under the curve (AUC) after adjustment for covariates such as race, gender, hyperlipidemia, CRP and troponin (chart shown below). MPO did not have a statistically significant added effect over Troponin I, which could be due to competing effect of MPO and Troponin I or simply a difference in their biological variation.

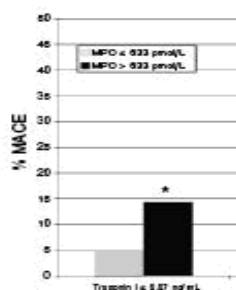
ROC Curve Results for Predictive Probability of Covariates With and Without Addition of MPO			
Model†	0 days	30 days	180 days
Race	0.62 (AUC)	0.61 (AUC)	0.62 (AUC)
Race & MPO	0.72 (AUC)	0.71 (AUC)	0.71 (AUC)
Difference (95% CI)	-0.10 (-0.15 to -0.04)	-0.10 (-0.15 to -0.04)	-0.09 (-0.14 to -0.04)
p-value	0.0010	0.0011	0.0004
Sex	0.59 (AUC)	0.60 (AUC)	0.59 (AUC)
Sex & MPO	0.73 (AUC)	0.74 (AUC)	0.73 (AUC)
Difference (95% CI)	-0.14 (-0.21 to -0.07)	-0.14 (-0.20 to -0.08)	-0.14 (-0.20 to -0.08)
p-value	<0.0001	<0.0001	<0.0001

hsCRP	0.51 (AUC)	0.51 (AUC)	0.54 (AUC)
hsCRP & MPO	0.69 (AUC)	0.68 (AUC)	0.68 (AUC)
Difference (95% CI)	-0.17 (-0.26 to -0.09)	-0.17 (-0.26 to -0.08)	-0.14 (-0.22 to -0.06)
p-value	0.0001	0.0002	0.0003
Hyperlipidemia	0.63 (AUC)	0.64 (AUC)	0.62 (AUC)
Hyperlipidemia & MPO	0.73 (AUC)	0.73 (AUC)	0.71 (AUC)
Difference (95% CI)	-0.10 (-0.15 to -0.04)	-0.09 (-0.14 to -0.04)	-0.09 (-0.14 to -0.04)
p-value	0.0004	0.0003	0.0003

†Values for covariate and covariate & MPO correspond to area under the ROC curve (AUC)

Further analysis of the clinical data was made by stratifying patients using the upper limit of the MPO reference interval (633 pmol/L) and Dimension Troponin I at the 99th percentile (0.07 ng/mL). The analysis shows that patients at risk for MACE within 30 and 180 days were identified significantly more often for MPO>633 pmol/L than for MPO ≤633 pmol/L when Troponin ≤0.07 ng/mL.

Improved Stratification for MACE When Dimension Troponin I is 0.07 ng/mL.⁺



* p = 0.008 vs. MPO ≤ 633 pmol/L. One sided p values were calculated using Fisher's Exact test

⁺ Data shown represents incidence of MACE at 30 days; incidence of MACE at 180 days was similar

The results showed that MPO is a significant predictor of MACE at 30 days and at 6 months and supports a substantial equivalence decision.

4. Clinical cut-off:

Not applicable.

5. Expected values/Reference range:

The sponsor conducted a reference range study using EDTA samples per CLSI protocol C28-A2 *How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline—Second Edition*. The sponsor selected the lower, one-sided 95% region of results obtained with the assay in a healthy population as the Dimension® MPO reference interval.

The sponsor includes the following in the labeling:

“In a study of 286 EDTA plasma samples from apparently healthy individuals, the reference interval encompassing the lower 95% region for the Dimension® MPO method was as follows:

<u>N</u>	<u>Range encompassing the lower 95% region</u>
286	51–633 pmol/L

Each laboratory should establish its own expected values for MPO as performed on the Dimension® system.”

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.