

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

A. 510(k) Number:

k051564

B. Purpose for Submission:

New Device

C. Measurand:

C-reactive protein

D. Type of Test:

Quantitative

E. Applicant:

Olympus

F. Proprietary and Established Names:

OLYMPUS CRP Latex reagent

OLYMPUS CRP Latex Calibrator Normal Set

OLYMPUS CRP Latex Calibrator Highly Sensitive Set

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5270 C-reactive protein immunological test system

21 CFR 862.1150 Calibrator

2. Classification:

Class II

3. Product code:

NQD, cardiac c-reactive protein, antigen, antiserum, and control
JIT, calibrator, secondary

4. Panel:

82 Immunology
75 Chemistry

H. Intended Use:

1. Intended use(s):

See indications for use statement below.

2. Indication(s) for use:

Olympus System Reagent and calibrators for the quantitative determination of C-Reactive Protein in human serum and plasma on OLYMPUS Analyzers.
Measurement of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. Measurements may also be used as an aid in the identification of individuals at risk of future cardiovascular disease. High sensitivity CRP (hsCRP) measurements, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, maybe useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

OLYMPUS AU400/AU400E, AU600/AU600E, AU2700 and AU5400 Clinical Chemistry Analyzers.

I. Device Description:

The Olympus CRP Latex reagent is an in vitro diagnostic device that consists of ready to use buffer and latex particles coated with rabbit anti-CRP antibodies. Depending on the application used (different instrument settings), two measuring ranges are available: Normal application (CRP Concentrations ranging between 1.0-480 mg/L) and Highly Sensitive (Cardiac/ Neonatal) Application- (CRP concentrations ranging between 0.2- 160 mg/L).

The CRP Latex Calibrator set (both normal and highly sensitive) is a five level calibrator set. The Olympus CRP Calibrator is a liquid human serum based product assayed for levels of C-reactive protein. Constituent values are adjusted where necessary by the addition of analytical grade serum proteins.

Each human serum donor used in the preparation of the calibrator material was tested by a FDA approved method for the presence of the antibody to HIV-1/2 and HCV as well as for hepatitis B surface antigen and was not repeatedly reactive.

J. Substantial Equivalence Information:

1. Predicate device name(s):

OLYMPUS CRP Latex Immunoturbidimetric Reagent

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

k041668

3. Comparison with predicate:

Similarities		
Item	Device	Predicate
Intended Use	Olympus System Reagent and calibrators for the quantitative determination of C-Reactive Protein on OLYMPUS Analyzers. Measurements of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. Measurements may also be used as an aid in the identification of individuals at risk of future cardiovascular disease. High sensitivity CRP (hsCRP) measurements, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, maybe useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary syndromes.	Olympus System Reagent and calibrators for the quantitative determination of C-Reactive Protein on OLYMPUS Analyzers. Measurements of CRP is useful for the detection and evaluation of infection, tissue injury, inflammatory disorders and associated diseases. Measurements may also be used as an aid in the identification of individuals at risk of future cardiovascular disease. High sensitivity CRP (hsCRP) measurements, when used in conjunction with traditional clinical laboratory evaluation of acute coronary syndromes, maybe useful as an independent marker of prognosis for recurrent events, in patients with stable coronary disease or acute coronary

Similarities		
Item	Device	Predicate
		syndromes.
Calibrator Preparation	Liquid stable ready to use Human serum based calibrators	Liquid stable ready to use Human serum based calibrators.

Differences		
Item	Device	Predicate
Application	2 Applications- Normal (NA) and Highly Sensitive (HS) (Cardiac/Neonatal)	3 Applications- Normal (NA), Sensitive (Cardiac), Highly Sensitive (HS)
Range	Normal- 1.0-480 mg/L and Highly Sensitive- 0.2-160 mg/L	Normal- 5-170 mg/L, Sensitive- 0.5-20.0 mg/L and Highly Sensitive- 0.05-2.00 mg/L.
Matrix	Serum and Plasma	Serum
Calibrator Application	2 Application- Normal and Highly Sensitive	1 Application- CRP normal
Calibrator Manufacture	OEM Supplied	In house
Zero Calibrator	0.9% Saline	None

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

NCCLS Evaluation Protocols:

EP6-P Evaluation of the linearity of quantitative analytical methods.

EP5-A Evaluation of precision performance of clinical chemistry devices.

EP7-P Interference testing in clinical chemistry.

EP9-A Method comparison and bias estimation using patient samples

L. Test Principle:

Immune complexes formed in solution scatter light in proportion to their size, shape, and concentration. Turbidimeters measure the reduction of incidence light due to reflection, absorption, or scatter. In this procedure, the measurement of the rate of decrease in light intensity transmitted (increase in absorbency) through particles suspended in solution is the result of complexes formed during the immunological reaction between the CRP of the patient serum and rabbit antibodies coated on latex particles.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Precision was conducted and within run and total CV was calculated according to NCCLS EP5-A. Three sample pools were tested twice daily for twenty days (the highly sensitive application measured medically relevant points for 10 days) with serum based controls. Both applications were tested on all 6 OLYMPUS analyzers and are summarized in the charts below.

OLYMPUS AU400/400*

N=80	Within Run		Total	
Mean, mg/L	SD	CV%	SD	CV%
Normal Application				
6.44	0.05	0.80	0.20	3.12
64.02	0.56	0.87	1.83	2.86
137.70	1.02	0.74	3.63	2.63
Highly Sensitive (Cardiac/ Neonatal) Application				
1.01	0.02	1.53	0.02	2.32
3.01	0.02	0.76	0.0	1.22
9.80	0.08	0.86	0.15	1.50

OLYMPUS AU600/640/640*

N=80	Within Run		Total	
Mean, mg/L	SD	CV%	SD	CV%
Normal Application				
6.56	0.07	1.009	0.12	1.85
64.79	0.78	1.20	2.16	3.34
137.71	0.96	0.70	2.26	1.64
Highly Sensitive (Cardiac/ Neonatal) Application				
1.05	0.03	2.96	0.03	2.50
2.99	0.02	0.62	0.03	0.92
10.00	0.09	0.95	0.15	1.53

OLYMPUS AU2700/5400

N=80	Within Run		Total	
Mean, mg/L	SD	CV%	SD	CV%
Normal Application				
6.59	0.21	3.22	0.25	3.79
62.84	0.64	1.02	1.21	1.92
137.52	1.28	0.93	2.27	1.65
Highly Sensitive (Cardiac/ Neonatal) Application				
1.03	0.03	3.22	0.03	2.78
3.05	0.04	1.21	0.04	1.33
9.70	0.09	0.92	0.19	1.94

b. Linearity/assay reportable range:

Linearity was conducted and checked according to NCCLS EP6-A. A series of 10 dilutions of a high pool sample are run in quadruplicate on each of the 6 instruments and the mean results were plotted versus the relative analyte concentrations. Linearity was also conducted with the reagent after being onboard the analyzer for 30 days. The best fit line was determined by linear regression and the sponsor's acceptance criteria are as follows:

Normal Application- 1.0- 480 mg/L [less than 10% or 2.0 mg/L SD]

Highly Sensitive Application- 0.2-160 mg/L [less than 12% or 0.15 mg/L SD]

The following results are for the instruments, applications and ranges indicated.

AU400

Application	Range	N	Slope	Intercept
Normal	0.090 – 52.393	7	0.949	-0.118
Normal	0.090 – 471.730	11	1.044	1.012
Normal	0.013- 539.333	11	1.014	-0.641
Normal (30 day onboard)	0.035- 491.750	11	1.023	-0.795
Highly Sensitive (low)	0.0- 21.683	7	1.022	-0.018
Highly Sensitive	0.017 – 175.420	11	1.037	-0.053
Highly Sensitive (30 day onboard)	0.010 – 171.910	11	1.025	-0.045

AU640

Application	Range	N	Slope	Intercept
Normal	0.008 – 53.847	7	0.951	-0.040
Normal	0.008 – 481.678	11	1.016	1.339
Normal	0.055 – 483.043	11	1.032	0.728
Normal (30 day onboard)	0.040 – 489.560	11	1.031	0.372
Highly Sensitive (low)	-0.035 - 171.738	7	1.098	0.088
Highly Sensitive	0.015 – 174.058	11	1.043	-0.063
Highly Sensitive (30 day onboard)	0.005 – 170.170	11	1.045	-0.070

AU 2700

Application	Range	N	Slope	Intercept
Normal	-0.010 – 52.113	7	0.966	0.293
Normal	-0.010 – 488.428	11	1.028	0.565
Normal	0.018 – 498.578	11	1.003	0.359
Normal (30 day onboard)	-0.13 – 481.714	11	1.029	-0.9126
Highly Sensitive (low)	-0.050 – 176.315	11	1.003	0.359
Highly Sensitive	0.000 – 169.178	11	1.032	-0.101
Highly Sensitive (30 day onboard)	-0.008 – 170.373	11	1.038	0.047

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

The CRP Latex calibrators (normal and highly sensitive) are liquid human serum matrix containing a predetermined level of human CRP that is traceable to an external standard.

The unopened product is stable for 24 months at 2-8° C. Open product is stable for 30 days when stored in the analyzers' refrigerated compartments- (see linearity data for 30 day onboard stability). Recovery studies were conducted for 3 lots of calibrators and the results are summarized in the chart below. The sponsor recommends using 0.9% saline as a zero calibrator.

Calibrator CRP concentration	Mean Recovery Range (%)	Application
2.5 mg/L	92-100	Highly Sensitive
10	98-100	Normal and Highly Sensitive
20	98-99	Highly Sensitive
40	95-100	Normal
80	98-100	Highly Sensitive
160	97-101	Normal and Highly Sensitive
320	98-100	Normal
480	98-100	Normal

d. *Detection limit:*

The lower limit of detection was determined by testing an analyte-free sample twenty –fold on each of the 6 instruments. The lower limit of detection was calculated as the mean plus three times the standard deviation. The results met the sponsor's criteria of less than 0.15 mg/L for the normal application and less than 0.07 mg/L for the highly sensitive application and are listed in the table below.

Instrument	Application	Mean	SD	LLD
AU400	Normal	0.02	0.027	0.10 mg/L
AU640	Normal	0.02	0.024	0.09 mg/L
AU2700	Normal	0.03	0.036	0.135 mg/L
AU400	Highly Sensitive	0.00	0.006	0.02 mg/L
AU640	Highly Sensitive	0.00	0.007	0.02 mg/L
AU2700	Highly Sensitive	0.22	0.14	0.065 mg/L

e. *Analytical specificity:*

Interference evaluations were conducted and performed based on the NCCLS EP7-P. A pooled sample with analyte level corresponding to a medical

decision point for the assay was used. The sample was spiked with different levels of the potential interferent up to the maximum level which could be present in samples and tested four-fold at each level. The mean analytical result at each level is compared with that for the non-spiked sample. Interference from Bilirubin, hemolysis and lipemia results are shown below and are reported in the package insert.

Inaccuracies due to bilirubin (40 mg/dL) are less than 5% at CRP concentrations of 1.0 mg/L.

Inaccuracies due to hemolysate (500 mg/dL) are less than 5% at CRP concentrations of 1.0 mg/L.

Inaccuracies due to intralipid* (1000 mg/dL) are less than 10% at CRP concentrations of 1.0 mg/L.

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

Method comparison was performed based on NCCLS EP9-A. The current Olympus C-reactive Protein Reagent was compared to the predicate Olympus C-reactive Protein Reagent using the AU600 as the reference analyzer.

Normal Application			
Y Method	AU640	AU2700	AU400
X Method	Predicate	AU640	AU640
Slope	1.024	0.998	1.023
Intercept	0.594	-0.390	-.393
Correlation Coeff.	0.998	0.999	1.000
# of Samples	113	114	68
Range (mg/L)	0.78 to 167.38	0.96 to 477.89	1.04 to 456.01
Highly Sensitive Application			
Y Method	AU640	AU2700	AU400
X Method	Method 2	AU640	AU640
Slope	0.993	1.039	1.025
Intercept	-0.825	-0.569	-0.022
Correlation Coeff.	0.997	0.999	0.999
# of Samples	118	105	109
Range (mg/L)	0.20 to 155.86	0.40 to 143.52	0.28 to 147.21

A separate method comparison study was also conducted for 60 samples that ranged between 0.59 and 8.87 mg/L using the highly sensitive application. The linear regression statistics were as follows: Slope = 1.018, intercept = 0.177, $r = 0.999$.

All samples were tested in duplicate for 5 days.

b. Matrix comparison:

A matrix comparison study was performed between serum and plasma (EDTA and Lithium Heparin treated) using the proposed new Olympus C-reactive protein reagent for the both applications on a maximum of 30 patient samples.

EDTA plasma versus serum (normal application) revealed a linear regression equation of $Y = 0.984X - 0.001$ with a correlation coefficient of 0.999 on 19 samples ranging from 1.01 to 7.22 mg/L.

EDTA plasma versus serum (highly sensitive) gave a linear regression equation of $Y = 0.973X + 0.015$ with a correlation coefficient of 1.000 on 28 samples ranging from 0.41 to 6.13 mg/L.

Lithium Heparin plasma versus serum (normal application) revealed a linear regression equation of $Y = 0.979X - 0.013$ with a correlation coefficient of 1.000 on 2 samples ranging from 1.01 to 7.22 mg/L.

Lithium Heparin plasma versus serum (highly sensitive) revealed a linear regression equation of $Y = 0.976X + 0.018$ with a correlation coefficient of 0.999 on 28 samples ranging from 0.41 to 6.13 mg/L.

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):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The expected values of CRP concentrations <1mg/L was established through literature, and the cardiac risk assessment categories are recommended by the American Heart Association (AHA) are as follows:

Low <1 mg/L, Average 1.0 to 3.0 mg/L and High > 3.0 mg/L

Newborns with no evidence of infection have CRP concentrations of <1 mg/L (established through literature).

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.