

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

A. 510(k) Number:

k073487

B. Purpose for Submission:

Addition of plasma (Li heparin/EDTA) matrix claim to the predicate device

C. Measurand:

Immunoglobulin M (IgM)

D. Type of Test:

Quantitative immunoturbidimetric assay

E. Applicant:

Olympus America, Inc.

F. Proprietary and Established Names:

Olympus IgM reagent (OSR6X173)

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CFN Method, Nephelometric, Immunoglobulins (G, A, M)	Class II	21 CFR 866.5510 Immunoglobulins A, G, M, D, E Immunological Test System	Immunology (IM82)

H. Intended Use:

1. Intended use(s):

System reagent for the quantitative determination of IgM immunoglobulins in human serum and plasma on OLYMPUS analyzers

2. Indication(s) for use:

The spectrum of abnormalities in serum immunoglobulin concentration is broad. Abnormal concentrations range from a virtual absence of one or more of the three major classes of immunoglobulins (IgA, IgG and IgM) to polyclonal increases in one or more immunoglobulins. Measurement of these immunoglobulins aids in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infectious agents.

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

OLYMPUS analyzers: AU400/400^e, 600/640/640^e and 2700/5400

I. Device Description:

The device consists of two reagents: R1 buffer (Tris buffer pH 7.2, polyethylene glycol 6000) and R2 (goat anti-IgM antiserum). The reagents contain sodium azide as preservative.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Olympus IgM reagent (OSR6X46)

2. Predicate 510(k) number(s):
k950900
3. Comparison with predicate:

Similarities		
Item	Device	Predicate
	Olympus IgM reagent (OSR6X173)	Olympus IgM reagent (OSR6X46)
Intended Use	System reagent for the quantitative determination of IgM immunoglobulins in human serum <u>and plasma</u> on Olympus analyzers	Same but in serum only
Indications for Use	Aid in the diagnosis of abnormal protein metabolism and the body's lack of ability to resist infection	Same
Test principle	Immunoturbidimetric	Same
Antibody	Goat anti-IgM	Same
Reagent form and storage	Liquid, on-board storage	Same
On-board reagent stability	90 days	Same
Calibrator	Olympus Serum Protein Multi-calibrator	Same
Calibrator traceability	International Reference Preparation CRM 470	Same
Calibration frequency	90 days	Same
Expected values	45-281 mg/dL	Same

Differences		
Item	Device	Predicate
	Olympus IgM reagent (OSR6X173)	Olympus IgM reagent (OSR6X46)
Matrix	Serum, plasma (Li heparin or EDTA)	Serum only

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

EN14971 (2000) *ISO Medical Devices – Application of Risk Management to Medical Devices*; EP7-A2 (2005) *CLSI Interference Testing in Clinical Chemistry*; EP5-A2 (2004) *CLSI Evaluation of Precision Performance of Clinical Chemistry Devices*; EP9-A2 (2002) *CLSI Method Comparison and Bias Estimation Using Patient Samples*; CEN 13640 (2002) *Stability Testing of In Vitro Diagnostic Reagents*; C28-A2 (2000) *CLSI How to Define and Determine Reference Intervals in the Clinical Laboratory*; EP6-A (2003) *CLSI Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach*; FDA: *Draft Guidance document for 510(k) Submission of Immunoglobulins A, G, M, D and E Immunoglobulin Test System In Vitro Devices*

L. Test Principle:

When a sample is mixed with R1 buffer and R2 antiserum solution, human IgM reacts specifically with anti-human IgM antibodies to yield insoluble aggregates. Immune complexes formed in solution scatter light in proportion to their size, shape and concentration. The Olympus analyzer measures the decrease in intensity of light transmitted (increase in absorbance) through particles suspended in solution as a result of complexes formed during the antigen-antibody reaction.

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

Assays of 3 human serum pools (high, low and medium) were assayed in duplicate for 2 runs per day for 20 days (n=80) on the AU400/400^e, AU600/640/640^e, and AU2700/5400. The acceptance criteria for the within-run and total %CV were <4.2% and <10% respectively. The within-run precision covering the instrument platforms ranged from 1.12–2.19% and the total precision ranged from 2.60-4.08%.

AU400/400^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
48	1	1.95	2	4.03
117	2	1.40	3	2.95
234	3	1.19	6	2.60

AU600/640/640^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
48	1	1.69	2	3.44
114	2	1.36	4	3.29
217	5	2.19	8	4.08

AU2700/5400

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
48	1	1.52	2	3.79
114	1	1.12	4	3.31
218	3	1.30	8	3.52

Auto dilution:

To validate the accuracy and precision of automated sample dilution protocol, three auto-dilution samples were diluted manually and run on the instrument. The same samples were diluted automatically by the AU640. Accuracy (%difference) and precision (%CV) were determined.

Accuracy 1:5

Level	Automatic dilution (mg/dl)	Manual dilution (mg/dl)	% Difference
1	727	684	-6.3
2	592	588	-0.7
3	382	374	-2.1

Accuracy 1:10

Level	Automatic dilution (mg/dl)	Manual dilution (mg/dl)	% Difference
1	720	711	-1.3
2	566	583	2.9
3	446	450	0.9

Precision (within run) 1:5

Level	Mean (mg/dL)	SD (mg/dL)	CV (%)	Essential Specification	
1	64	1	1.36	≤4.2% CV	Pass
2	85	1	1.34		
3	107	1	1.24		

Precision (within run) 1:10

Level	Mean (mg/dL)	SD (mg/dL)	CV (%)	Essential Specification	
1	32	1	1.98	≤4.2% CV	Pass
2	41	1	1.75		
3	52	1	1.77		

b. Linearity/assay reportable range:

The measuring range for the assay is 20-500 mg/dL. The procedure used to determine linearity was based on CLSI EP6-A. A series of at least ten analyte concentrations, covering the linear dynamic range was prepared by dilution of a high pool sample. Each dilution was assayed in quadruplicate and the mean analytical results were plotted versus the relative analyte concentrations (% dilution). Studies were performed on the AU400, AU640 and AU2700 analyzers. The acceptance criteria for deviation from regression line for the 20-80 mg/dL and 80-500 mg/dL ranges were ± 8 mg/dL and $\pm 10\%$ respectively. The studies showed the assay was linear from 20-500 mg/dL. Hook effect may occur with highly elevated IgM samples >10,000 mg/dL, polyclonal.

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

The calibrator is traceable to the International Reference Preparation CRM470 (US designation RPPHS lot 91/0619).

Reagent on-board stability was demonstrated according to internal procedures where the linearity displayed at day 90 and the % drift from Day 0 from control recovery were calculated. A change of $\leq 10\%$ was demonstrated over the 90 days.

d. Detection limit:

The Limit of Quantitation (LoQ) for the new assay was determined by testing 3 patient pools, 40 fold at an analyte concentration below the lower end of the measuring range on the AU400, AU640 and AU2700. The analyte level with a CV of less than 20% was determined to be <10 mg/dL. This was determined using a method based on the CLSI protocol EP17-A.

	Mean Concentration (mg/dL)	SD	CV (%)
AU400	8.1	1.4	17.7
AU600	2.4	0.4	16.1
AU2700	2.4	0.4	17.0

The Limit of Detection (LoD) or the concentration of analyte which is significantly different from zero was determined by testing an analyte free sample twenty-fold on the AU400, AU640 and AU2700. LoD was calculated as the absolute mean + 3SD and the lowest detectable level was determined to be ≤ 2 mg/dL.

	Mean Concentration (mg/dL)	SD	LoD (mg/dL)
AU400	0.0	0.324	0.97
AU600	-0.29	0.293	1.17
AU2700	0.30	0.336	1.31

e. *Analytical specificity:*

The impact of bilirubin, lipids and hemoglobin were assessed in accordance with CLSI EP7-A2.

Substance	Levels up to	% Interference		
		AU400/400 ^c	AU600/640/640 ^c	AU2700/5400
Bilirubin	40 mg/dL	$\leq 4\%$	$\leq 3\%$	$\leq 8\%$
Lipids	300 mg/dL	$\leq 10\%$	$\leq 10\%$	
	200 mg/dL			$\leq 10\%$
Hemoglobin	500 mg/dL	$\leq 4\%$	$\leq 3\%$	$\leq 3\%$

f. *Assay cut-off:*

See reference range

2. Comparison studies:

a. *Method comparison with predicate device:*

Y method (new)	AU2700	AU2700/5400	AU2700/5400
X method (predicate)	AU2700	AU400	AU640/640 ^c
Slope	1.006	1.027	0.978
Intercept	2.8	-2.6	2.4
Correlation coefficient (r)	1.000	0.999	0.999
Number of samples	107	110	108
Range (mg/dL) Y method	22-468	20-468	21-468
Range (mg/dL) X method	22-467	21-443	21-469

b. *Matrix comparison:*

Studies were performed based on CLSI EP9-A2.

Y method	Li-heparin plasma	EDTA plasma
X method	Serum	Serum
Slope	0.96	0.942
Intercept	+0.892	+0.998
Correlation coefficient	1.000	1.000
Number of samples	45	45
Patient mean value – serum mg/dL	148.47	148.47
Patient mean value – plasma mg/dL	143.47	140.80
Reference range – serum mg/dL	27.46 – 450.23	27.46 – 450.23
Reference range - plasma mg/dL	26.26 – 436.86	25.96 – 429.84

3. Clinical studies:
 - a. *Clinical Sensitivity:*
Not determined
 - b. *Clinical specificity:*
Not determined
 - 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:
Expected values may vary with age, sex, diet and geographical location. The reference range of 45-281 mg/dL established for the predicate device was re-verified according to CLSI C28-A2 on the Olympus AU400, 600 and 5400.

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.