510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
   k073490
B. Purpose for Submission:
   Addition of plasma (Li-heparin and EDTA) and cerebrospinal fluid (CSF) matrix
   claim to the predicate device
C. Measurand:
   Immunoglobulin G (IgG)
D. Type of Test:
   Quantitative immunoturbidimetric assay
E. Applicant:
   Olympus America, Inc.
F. Proprietary and Established Names:
   Olympus IgG reagent (OSR6X172)
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. <u>Intended use(s):</u>
      System reagent for the quantitative determination of IgG immunoglobulins in
      human serum and plasma on OLYMPUS analyzers
   2. <u>Indication(s) for use:</u>
      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. <u>Special conditions for use statement(s):</u>
      For prescription use only
   4. <u>Special instrument requirements:</u>
      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 IgG reagent (OSR6X45)
   Roche Tina QUANT IgG Gen. 2
2. Predicate 510(k) number(s):
   k951013
   k050113
3. Comparison with predicate:

Similarities: SERUM/PLASMA		
Item	Device	Predicate
	Olympus IgG reagent (OSR6X172)	**Olympus IgG reagent (OSR6X45)**
Intended Use	System reagent for the quantitative determination of IgG immunoglobulins in human serum, <u>plasma and CSF</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-IgG	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	635-1741 mg/dL	Same

Differences: SERUM/PLASMA		
Item	Device	Predicate
	Olympus IgG reagent (OSR6X172)	**Olympus IgG reagent (OSR6X46)**
Matrix	Serum, plasma (Li heparin or EDTA)	Serum only

Similarities: CSF		
Item	Device	Predicate
	Olympus IgG reagent (OSR6X172)	**Roche Tina Quant IgG**
Intended Use	System reagent for the quantitative determination of IgG immunoglobulins in human serum, <u>plasma and CSF</u> on Olympus analyzers	In Vitro test for the quantitative determination of IgG in human serum, plasma and cerebrospinal fluid on Roche/Hitachi Cobas c systems
Matrix	Serum, plasma (Li-heparin or EDTA), CSF	Same
Test principle	Immunoturbidimetric	Same
Antibody	Goat anti-IgG	Same
Reagent form and storage	Liquid, on-board storage	Same
Calibrator traceability	International Reference Preparation CRM 470	Same
Calibration	Multipoint	Same

Differences: CSF		
Item	Device	Predicate
	Olympus IgG reagent (OSR6X172)	**Roche Tina Quant IgG**
Expected values	15-20y, 3.5 mg/dL ± 2.0mg/dL 21-40y, 4.2 mg/dL ± 1.4mg/dL 41-60y, 4.7 mg/dL ± 1.0mg/dL	1-3 mg/dL
Instrument required	Olympus AU400/400^e, 600/640/640^e and 2700/5400	Roche/Hitachi Cobas c systems
Reagent on-board stability	Open reagents stable 90 days stored in refrigerated compartment	Open reagents stable 84 days stored in refrigerated compartment
Calibration frequency	2 days	As required

K. Standard/Guidance Document Referenced (if applicable):
<u>EN14971</u> (2000) ISO *Medical Devices – Application of Risk Management to Medical Devices;* <u>EP7-A2</u> (2005) CLSI *Interference Testing in Clinical Chemistry;* <u>EP5-A2</u> (2004) CLSI *Evaluation of Precision Performance of Clinical Chemistry Devices;* <u>EP9-A2</u> (2002) CLSI *Method Comparison and Bias Estimation Using Patient Samples;* <u>CEN 13640</u> (2002) *Stability Testing of In Vitro Diagnostic Reagents;* <u>C28-A2</u> (2000) CLSI *How to Define and Determine Reference Intervals in the Clinical Laboratory;* <u>EP6-A</u> (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 IgG reacts specifically with anti-human IgG 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:*

    Serum/Plasma

    Precision is checked, based on CLSI EP5-A2, by testing low, medium and high analyte human serum pools; 2 runs in duplicate for 20 days (n=80) on the AU400/400^e, AU600/640/640^e, and AU2700/5400. The within run precision covering the platforms ranged from 0.88–3.41% and the total precision ranged from 1.51-4.66%.

AU400/400^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
432	4	0.88	9	2.18
1098	14	1.27	25	2.29
2237	76	3.41	77	3.43

AU600/640/640^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
431	5	1.14	14	3.29
1088	16	1.45	38	3.49
2173	49	2.24	101	4.66

AU2700/5400

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
444	4	0.95	7	1.51
1060	17	1.87	20	1.87
2191	26	2.03	44	2.03

    CSF

    Precision is checked, based on CLSI EP5-A2, by testing low, medium and high analyte human serum pools (set to cover the reportable range for CSF); 2 runs in duplicate for 20 days (n=80) on the AU400/400^e, AU600/640/640^e, and AU2700/5400. The within run precision ranged from 0.89-7.93% and the

total precision ranged from 2.81-10.24%.

AU400/400^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
3.5	0.1	2.88	0.3	9.82
10.2	0.1	1.44	0.4	4.08
35.8	0.6	1.65	1.3	3.61

AU600/640/640^e

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
3.5	0.1	2.68	0.3	9.53
10.1	0.1	0.89	0.4	3.67
35.6	0.3	0.93	1.0	2.81

AU2700/5400

N=80	Within-run		Total	
Mean (mg/dL)	SD	%CV	SD	%CV
3.6	0.1	7.93	0.4	10.24
10.1	0.1	2.91	0.6	6.29
35.4	0.6	1.31	1.3	3.83

Auto dilution:
Accuracy: Three auto-dilution samples were diluted manually and run on the instrument. The same samples were diluted automatically by the AU640 and %difference was calculated

Accuracy 1:5

Level	Automatic dilution (mg/dl)	Manual dilution (mg/dl)	% Difference
1	3911	3680	-6.3
2	3123	3051	-2.4
3	1986	1906	-4.2

Accuracy 1:10

Level	Automatic dilution (mg/dl)	Manual dilution (mg/dl)	% Difference
1	3767	3613	-4.3
2	2997	2923	2.5
3	2263	2176	4.0

Precision: Three auto-dilution samples were run with the automated dilution protocol on the AU640 to generate 20 replicates per sample. %CVs were calculated.

Precision (within run) 1:5

Level	Mean (mg/dL)	SD (mg/dL)	CV (%)	Essential Specification	
1	392	4	1.01	≤4.2% CV	Pass
2	521	6	1.11		
3	653	7	1.08		

Precision (within run) 1:10

Level	Mean (mg/dL)	SD (mg/dL)	CV (%)	Essential Specification	
1	197	3	1.60	≤4.2% CV	Pass
2	256	3	1.16		
3	322	5	1.65		

b. *Linearity/assay reportable range:*
    Serum/Plasma
    The measuring range for the assay is 75-3000 mg/dL. The procedure used to demonstrate 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 the regression line for 75-375 mg/dL and 375-3000 mg/dL ranges were ± 30 mg/dL and ± 8%. The studies showed the assay was linear from 75-3000 mg/dL. There was no high dose hook effect up to 30,000 mg/dL.

    CSF
    The measuring range for the assay is 2-50 mg/dL. The procedure used to demonstrate 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 the deviation from the regression line for 2-5 mg/dL and 5-50 mg/dL ranges were ± 0.5 mg/dL and ± 10% respectively. The studies showed the assay was linear from 2-50 mg/dL. There was no high dose hook effect up to 6,000 mg/dL.

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).
    Serum/Plasma
    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 ≤ 8% was demonstrated over the 90 days. Data confirm the calibration stability of 90 days.

CSF

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 ≤ 10% was demonstrated over the 90 days. Data confirm the calibration stability of 2 days for CSF.

d. *Detection limit:*

Serum/Plasma

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 <74 mg/dL. This was determined using a method based on the CLSI protocol EP17-A.

	Mean Concentration (mg/dL)	CV (%)
AU400	33	16.8
AU640	35	6.6
AU2700	21	12.4

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. The lowest detectable level was determined to be ≤7 mg/dL.

CSF

The Limit of Quantitation (LoQ) for the new assay (CSF) was determined by testing 3 patient pools, 40 fold at an analyte concentration below the lower end of the measuring range. The analyte level with a CV of less than 20% was determined to be 2 mg/dL. This was determined using a method based on the CLSI protocol EP17-A.

The Limit of Detection (LoD) or the concentration of analyte which is significantly different from zero was determined by testing an analyte free sample (water) twenty-fold on the AU400, AU640 and AU2700. The lowest detectable level was determined to be ≤1 mg/dL.

e. *Analytical specificity:*

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

Serum/Plasma

Substance	Levels up to	Interference		
		AU400/400[e]	AU600/640/640[e]	AU2700/5400
Bilirubin	40 mg/dL	≤ 2%	≤ 3%	≤ 1%
Lipids	1000 mg/dL	≤ 3%	≤ 5%	≤ 2%
Hemoglobin	500 mg/dL	≤ 3%	≤ 3%	≤ 3%
RF	1200 IU/mL	≤ 7%	≤ 7%	≤ 7%

CSF

Substance	Levels up to	% Interference		
		AU400/400[e]	AU600/640/640[e]	AU2700/5400
Bilirubin	36 mg/dL	≤ 10%	≤ 10%	≤ 10%
Hemoglobin	500 mg/dL	≤ 10%	≤ 10%	≤ 10%

 f. *Assay cut-off:*
    See reference range
2. Comparison studies:
   a. *Method comparison with predicate device:*
      Serum/Plasma

Y method (new)	AU2700	AU2700/5400	AU2700/5400
X method (predicate)	AU2700	AU400	AU640/640[e]
Slope	0.945	1.026	0.990
Intercept	37.2	-23.4	5.8
Correlation coefficient (r)	0.998	0.996	0.998
Number of samples	120	120	120
Range (mg/dL) Y method	195-2986	195-2986	195-2986
Range (mg/dL) X method	118-2973	177-2906	190-2963

      CSF

Y method (new)	AU2700	AU2700/5400	AU2700/5400
X method (predicate)	Tina Quant	AU400	AU640/640[e]
Slope	1.067	0.996	0.969
Intercept	-0.069	-0.127	0.14
Correlation coefficient (r)	0.998	0.998	0.998
Number of samples	55	85	86
Range (mg/dL) Y method	2.0-42.9	2.1-47.2	2.1-47.2
Range (mg/dL) X method	1.98-40.0	2.2-47.8	2.1-48.6

   b. *Matrix comparison:*
      Studies were performed based on CLSI EP9-A2.

Y method	Li-heparin plasma	EDTA plasma
X method	Serum	Serum
Slope	0.940	0.910
Intercept	24.1	35.9
Correlation coefficient	0.999	0.998
Number of samples	45	45
Patient mean value – serum mg/dL	1111.4	1111.4
Patient mean value – plasma mg/dL	1068.2	1047.2
Reference range – serum mg/dL	214.6-2904.7	214.6-2904.7
Reference range - plasma mg/dL	201.2-2581.4	202.2-2512.6

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. <u>Clinical cut-off</u>**:**
   Not applicable

5. <u>Expected values/Reference range:</u>
   Expected values may vary with age, sex, diet and geographical location.
   <u>Serum/Plasma</u>
   The reference range of 635-1741 mg/dL established for the predicate device was re-verified according to CLSI C28-A2 on the Olympus AU400/AU600 and AU5400.
   <u>CSF</u>
   Reference ranges for CSF are 15-20 years: 3.5 mg/dL ± 2.0 mg/dL; 21-40 years: 4.2 mg/dL ± 1.4 mg/dL; and 41-60 years: 4.7 mg/dL ± 1.0 mg/dL. These ranges are based on <u>Tietz Textbook of Clinical Chemistry</u>, 1999.

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.