

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

A. 510(k) Number:

k060201

B. Purpose for Submission:

New Device

C. Measurand:

Rheumatoid Factor

D. Type of Test:

Quantitative and Semi-quantitative Immunoturbidimetric assay.

E. Applicant:

Olympus America, Inc.

F. Proprietary and Established Names:

Olympus RF Latex Reagent

Olympus RF Latex Calibrator

G. Regulatory Information:

1. Regulation section:

21 CFR 866.5775 - Rheumatoid Factor Immunological test system

21 CFR 862.1150 - Calibrator

Classification:

Class II

3. Product code:

DHR, System, Test, Rheumatoid factor

JIT, Calibrator, secondary

4. Panel:

Immunology 82

H. Intended Use:

1. Intended use(s):

RF Latex Reagent: System reagent for the quantitative determination of Rheumatoid Factor (RF) in human serum and plasma on OLYMPUS analyzers.

RF Calibrator: Intended for use with the Olympus RF Latex Reagent for the quantitative determination of Rheumatoid Factor (RF) on Olympus Analyzers.

2. Indication(s) for use:

Olympus RF Latex System Reagent for the quantitative determination of Rheumatoid Factor (RF) in human serum and plasma on OLYMPUS Analyzers. Measurement of rheumatoid factor may aid in the diagnosis of rheumatoid arthritis.

The Olympus RF Latex Calibrator is a liquid human serum based matrix calibrator intended to be used with the Olympus RF Latex reagent OSR61105 for the quantitative determination of Rheumatoid Factor (RF) on Olympus analyzers.

3. Special conditions for use statement(s):

Prescription device

4. Special instrument requirements:

Instruments required for testing are the Olympus Clinical Chemistry Analyzers. AU400[®]/AU400e[®] (k981743), AU600[®]/AU640[®]/AU640e[®] (k961274), AU2700[®] (k003721), AU5400[®] (k011720)

I. Device Description:

RF Latex Reagent consists of four 24 mL vials of R1 - RF Latex Buffer and four 8 mL vials of R2 - RF Latex reagent.

RF Latex Calibrator consists of five 1 mL tubes of human sera with RF values ranging from approximately 10 - 118 IU/mL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
Tina-Quant Rheumatoid Factor II test system
Preciset RF Calibrator
2. Predicate 510(k) number(s):
k000534
k002609
3. Comparison with predicate:

RF Latex Reagent

Similarities		
Item	Device	Predicate
Intended Use	System reagent for the quantitative determination of Rheumatoid Factor (RF) in human serum and plasma on OLYMPUS analyzers.	Immunoturbidimetric assay for the quantitative in vitro determination of rheumatoid factors in human serum and plasma on automated clinical chemistry analyzers. Measurements may be used as an aid in the diagnosis of rheumatoid arthritis.
Indications for Use	Measurement of rheumatoid factor may aid in the diagnosis of rheumatoid arthritis.	Rheumatoid factor measurements may be used as an aid in the diagnosis of rheumatoid arthritis.
Test principle	Particle enhanced immunoturbidimetric assay	Same
Expected Values	<14 IU/mL	Same
Specimen	Serum & Plasma	Same
Measurement type	Quantitative	Same
Stability (unopened) (opened)	Until expiration date on label (+2-8°C) 60-days in refrigerated compartment of analyzer (+2-8°C)	Until expiration date on label (+2-8°C) 8 weeks in refrigerated compartment of analyzer (+2-8°C)

RF Latex Reagent

Differences		
Item	Device	Predicate
Measuring range	5-120 IU/mL	7-130 IU/mL
Instrument	Olympus Analyzer systems: AU400/400 ^e , AU600/640/640 ^e , AU2700/5400	Hitachi Analyzer systems: 904/911/917/MOD P
Stability (unopened)	Until expiration date on label (+2-8°C)	Until expiration date on label (+2-8°C)
(opened)	60-days in refrigerated compartment of analyzer (+2- 8°C)	8 weeks in refrigerated compartment of analyzer (+2-8°C)

RF Latex calibrator

Similarities		
Item	Device	Predicate
Intended use	The OLYMPUS RF Latex Calibrator is a liquid human serum based matrix calibrator intended to be used with the Olympus RF Latex reagent OSR61105 for the quantitative determination of Rheumatoid Factor (RF) on OLYMPUS analyzers.	Preciset RF is for use in the calibration of quantitative Roche methods on Roche clinical analyzers as specified in the enclosed value sheet. (Calibration of quantitative RF methods.)
Preparation of Calibrator	Liquid stable ready to use Human Serum based.	Same
Contents	5 x 1 mL	Same
Traceability	WHO International reference material NIBSC 64/2	Same

RF Latex calibrator

Differences		
Item	Device	Predicate
Intended for use with	Olympus methods on Olympus clinical chemistry analyzers	Roche methods on Roche clinical chemistry analyzers
Stability (unopened)	13 mo. (+2-8°C)	Until expiration date on label (+2-8°C)
(opened)	60-days in refrigerated compartment of analyzer (+2-8°C)	24 hours at room temperature or 30 days at 2-8 °C (in refrigerated compartment of analyzer

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

- Review Criteria for Assessment of Rheumatoid Factor(RF) In Vitro Diagnostic Devices Using Enzyme-Linked Immunoassay (EIA), Enzyme Linked Immunosorbent Assay (ELISA), Particle Agglutination Tests, and Laser and Rate Nephelometry
- Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline (EP5-A)
- Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline (EP9-A 1995)
- Interference Testing in Clinical Chemistry; Approved Guideline (EP 7-A)
- How to Define and Determine Reference Intervals in the Clinical Laboratory; Approved Guideline (C28-A)
- Medical devices - Application of risk management to medical devices (14971:2000)
- Evaluation of the Linearity of Quantitative Measurement Procedures - A statistical approach (EP06-A)

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 Olympus procedure, the rate of decrease in light intensity transmitted (increase in absorbance) through particles suspended in solution is a result of complexes formed during the antibody-antigen reaction.

Reaction Principle: When a sample is mixed with R1 buffer and R2 IgG latex solution, RF reacts specifically with IgG coated on the latex particles to yield insoluble aggregates. The absorbance of these aggregates is proportional to the RF concentration in the sample.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. *Precision/Reproducibility:*

Four pooled samples, created from serum based control material were tested in duplicate, twice a day for 20 days on each instrument, yielding 80 observations for each sample. Acceptance criteria are as follows: Intra-assay Precision: $\leq 5\%$ or $SD \leq 1$ IU/mL, Total Precision (Inter-assay): $\leq 10\%$.

AU400:

Pooled serum values (IU/mL)		Intra-assay		Inter-assay	
Target	Mean	SD	CV%	SD	CV%
10	9.90	0.30	3.07	0.51	5.11
20	20.21	0.27	1.35	0.60	2.96
78	78.71	0.54	0.69	1.41	1.79
115	117.65	0.61	0.52	1.30	1.11

AU600/AU640E:

Pooled serum values (IU/mL)		Intra-assay		Inter-assay	
Target	Mean	SD	CV%	SD	CV%
10	10.26	0.38	3.72	0.77	7.51
20	20.06	0.45	2.24	0.79	3.96
78	76.87	0.75	0.97	2.04	2.66
115	114.81	0.93	0.81	2.97	2.59

AU2700/AU5400:

Pooled serum values (IU/mL)		Intra-assay		Inter-assay	
Target	Mean	SD	CV%	SD	CV%
10	9.99	0.46	4.63	0.79	7.89
20	19.74	0.47	2.39	0.64	3.25
78	75.37	0.47	0.62	0.88	1.16
115	112.93	0.98	0.87	1.24	1.10

b. *Linearity/assay reportable range:*

A high plasma pool sample (RF values were approximately 146.38-155.9 IU/mL) was diluted in 10% increments to a final value of 10%. The 10% sample was further diluted four times (5, 2, 1, and 0.5%). Each of the fifteen samples (14 dilutions ranging from 100-0.5% plus a buffer blank) was assayed in quadruplicate on all three instruments and the mean results were plotted relative to the analyte concentration. Acceptance criteria: $\pm 10\%$ or 1 IU/mL.

Instrument	Regression equation	R ²	% Recovery*
AU400	$y = 1.5554x + 0.3554$	0.9996	94.91-101.8
AU640E	$y = 1.4508x + 1.3028$	0.9962	86.2-104.6
AU2700	$y = 1.4575x + 1.0667$	0.9982	92.65-103.66

* within measuring range

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

Calibration materials have been evaluated against the WHO International Preparation of Rheumatoid Arthritis Serum NIBSC 64/2 as defined by the sponsor's value transfer protocol.

d. *Detection limit:*

Limit of Blank/Lowest Detectable Limit: An analyte free sample (0.9% saline) was measured 20 times. The lowest detectable level of RF was calculated as the mean recovery + 3SD for each instrument.

Instrument	Lowest Detectable Level (IU/mL)
AU400	2.22
AU640E	1.42
AU2700	1.38

Limit of Detection: A sample with an RF concentration below the measuring range (5 IU/mL) was tested forty times. Acceptance criterion: CV < 20%.

Instrument	Limit of Detection (IU/mL)	SD	%CV
AU400	2.745	0.468	17.1
AU640E	3.222	0.544	16.9
AU2700	3.093	0.531	17.2

e. *Analytical specificity:*

- i. Interference by endogenous substances: Aliquots of a sample containing 17.17-17.95 IU/mL RF were tested after the addition of up to 100 mg/L triglycerides/intralipids, 50 mg/L hemoglobin, or 4 mg/L bilirubin. Minimal interference was detected with these substances (< 3%, < 5% and < 5% from the assigned value, respectively). Interference due to common pharmaceuticals was also tested, over the reportable range of the assay. Minimal interference was observed (-5.35% to +3.67%)
- ii. Cross-reactivity with autoantigens common with other systemic autoimmune diseases was not assessed.
- iii. Antigen excess was analyzed by testing samples containing RF from zero to the highest level expected in a patient (2285 IU/mL) on all three instruments. A dose response curve was prepared, showing the measured RF value obtained versus the known actual concentration of RF in the sample. Samples demonstrating the effect of antigen excess (at > 500 IU/mL) were above the measuring range of the assay.

f. *Assay cut-off:*

The assay cut-off was determined to be the 95th percentile of 574 normal/healthy adult subjects from the Europe. Expected values may vary with age, sex, diet, and geographical location.

2. Comparison studies:

a. *Method comparison with predicate device:*

Samples submitted to two European hospitals for RF testing by clinicians were tested on the predicate device and the AU600/640E instrument. Samples were then used to compare the remaining Olympus analyzers by comparison to the AU600/640E instrument. Comparative results are summarized below.

		Roche		
		+	-	Total
Olympus AU640E	+	33	0	33
	-	6*	16	22
	Total	39	16	55

Positive percent agreement = 84.6% (33/39)

Negative percent agreement = 100% (16/16)

Overall percent agreement = 89.1% (49/55)

		AU640		
		+	-	Total
AU400	+	38	0	38
	-	0	72	72
	Total	38	72	110

Positive percent agreement = 100% (38/38)
 Negative percent agreement = 100% (72/72)
 Overall percent agreement = 100% (110/110)

		AU640		
		+	-	Total
AU2700	+	38	2*	40
	-	0	70	70
	Total	38	72	110

Positive percent agreement = 100% (38/38)
 Negative percent agreement = 97.2% (70/72)
 Overall percent agreement = 98.2% (108/110)

Results noted by an asterisk (*) were located near the 14 IU/ml cut-off.

The results were also analyzed by linear regression and yielded the following:

Study	Regression equation	R ²
Roche vs. Olympus AU640E	$y = 0.996x - 1.217$	0.996
Olympus AU640E vs. AU400	$y = 1.027x + 0.393$	1.000
Olympus AU640E vs. AU2700	$y = 1.003x + 0.484$	1.000

b. Matrix comparison:

Serum was compared to matched plasma samples (lithium heparin and K²⁺EDTA) covering the reportable range (5-120 IU/ml), were compared to determine if a bias existed between the two matrices. Results noted by an asterisk (*) were located near the 14 IU/ml cut-off.

Study	N	Regression equation	R ²
Serum vs. Li-heparin	88	$y = 1.001x - 0.402$	0.997
Serum vs. EDTA	31	$y = 0.988x + 0.219$	0.995

		Serum		
		+	-	Total
Li-Heparin	+	46	1*	47
	-	0	41	41
	Total	46	42	88

Positive percent agreement = 100% (46/46)
 Negative percent agreement = 97.6% (41/42)
 Overall percent agreement = 98.9% (87/88)

		Serum		
		+	-	Total
EDTA	+	26	0	26
	-	0	5	5
	Total	26	5	31

Positive percent agreement = 100% (26/26)
 Negative percent agreement = 100% (5/5)
 Overall percent agreement = 100% (31/31)

3. Clinical studies:
 - a. *Clinical sensitivity and specificity:*
Clinical samples submitted for RF testing by clinicians were assessed; however, information of the final diagnosis of the patients was not available to the sponsor.
 - b. *Other clinical supportive data (when a is not applicable):*
Not applicable.
4. Clinical cut-off:
See Analytical cut-off.
5. Expected values/Reference range:
The expected value of the normal, healthy adults is ≤ 14 IU/mL, but may vary with age, sex, diet, and geographical location.

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.