510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k041863

B. Purpose for Submission:
New device

C. Analyte:
Rheumatoid Factor

D. Type of Test:
Quantitative, Immunoradiometric

E. Applicant:
Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:
VITROS Chemistry Products Rheumatoid Factor Reagent
VITROS Chemistry Products Calibrator Kit 16
VITROS Chemistry Products FS Calibrator 1
VITROS Chemistry Products RF Performance Verifiers I and II

G. Regulatory Information:

1. Regulation section:
   21 CFR §866.5775, Rheumatoid Factor Immunological Test System
   21 CFR §862.1550, Calibrator
   21 CFR §862.1660, Quality control material (assayed and unassayed)

2. Classification:
   RF and calibrator-Class II
   Quality control material –class I

3. Product Code:
   DHR, Rheumatoid Factor
   JIT, Calibrator, secondary
   JJX, Single (specified) analyte controls (assayed and unassayed)

4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended use

VITROS RF Reagent is used to quantitatively measure rheumatoid factor concentration in human serum and plasma. Measurement of rheumatoid factor may aid in the diagnosis of rheumatoid arthritis.
Calibrator kit 16 is used in conjunction with VITROS FS calibrator I to calibrate VITROS 5,1 FS Chemistry System.
Performance Verifiers I and II are assayed controls used to monitor the performance of RF reagent on the FS 5,1 Chemistry System.

2. Indication(s) for use:
   As an aid in the diagnosis of Rheumatoid Arthritis.

3. Special condition for use statement(s):
   The devices are for prescription use only.

4. Special instrument Requirements:
   VITROS 5,1 FS Chemistry system (k031924).

I. Device Description:

The VITROS Chemistry Products RF Reagent consists of two reagents –R1(Buffers, inorganic salt, Protein and preservative and R2 (Latex particles coated with human IgG).

The VITROS Chemistry Products Calibrator kit 16 contains rheumatoid factor, bovine serum albumin, sodium chloride, and sodium azide and available in vials of 2, 3, 4, 5 and 6 mL/vial.

The VITROS Chemistry Products FS Calibrator I is a lyophilized control which contains rheumatoid factor, C-reactive protein, Hemoglobin, Hemoglobin A1c, HDL cholesterol and LDL cholesterol. Immunoglobulin G, A and M, C3, C4, and sodium azide.

The VITROS Chemistry Products RF Performance Verifiers I and II Performance verifiers are lyophilized reagents which contain rheumatoid factor processed from human serum, bovine serum albumin and preservatives.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   COBAS Integra Rheumatoid Factor II

2. Predicate K number(s):
   k000534

3. Comparison with predicate:

DEVICE	PREDICATE
A. Similarities	
Intended Use. Quantitatively measure RF factor in serum and plasma	Same
Assay type – Immunoturbidimetric	Same
Antigen capture - Latex particles coated with human IgG	Same
Assay Format – Quantitative	Same
Verifiers I and II – Low and high levels	Same
B. Differences	
Instrument - VITROS 5,1 FS system	COBAS Integra System
Wavelength – 575 nm	583 nm
Matrix - freeze dried human serum to which human proteins, bovine serum albumin and preservatives	freeze dried human serum to which enzymes, electrolytes, and organic analytes are added
Anticoagulant - Heparin and EDTA	Heparin, EDTA and Citrate

K. Standard/Guidance Document Referenced (if applicable):
NCCLS Guide line EP9-A, EP5-A and EP-6A, EP-7A

L. Test Principle:
VITROS RF device is a dual chambered package containing ready to use liquid reagents that are used in a two step reaction to quantitatively measure rheumatoid factor. In the first step the sample is diluted with buffer (reagent 1). In the second step an antigen antibody reaction occurs between rheumatoid factor in the sample and denatured human IgG adsorbed to latex particles in reagent 2 results in agglutination. The agglutination is detected as an absorbance change at 575 nm which is proportional to the quantity of RF in the sample. RF concentration is determined using a calibration curve.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. Precision/Reproducibility:
   Two runs were performed on each of 26 days using the VITROS 5,1FS system. Each run included 3 evaluation samples (two control sera and one calibrator) were assayed in duplicate. In addition, 6 calibrator samples were run on alternate days with first run of each day. Runs within the day were at 2 hour intervals. Three reagent lots were evaluated with each lot assayed on a separate analyzer. The calibrator samples tested at the beginning of each week were used to generate a calibration curve. The results of the test samples for each matrix were analyzed using NCCLS EP 5A Guideline.

RF Reagent (Serum) IU/mL	%CV	#observed	#Days

Mean Conc	Within Day (SD)	Within Lab (SD)			
15.34	0.72	1.22	7.97	100	26
28.14	0.48	1.03	3.66	100	26
81.0	1.50	2.13	2.62	100	26

b. Linearity/assay reportable range:

Linearity of RF reagent was evaluated and compared with calculated analyte concentration of serum pools, prepared at concentrations covering the range of the assay (according to NCCLS EP 6A). A high level pool was created using a high level calibrator having a concentration of 120 IU/mL. The low level pool was saline. A mid level pool was created by mixing the high and low level pools in a 1:1 ratio. Five determinations of each of 13 pools were made together with six determinations of the RF verifiers. This experiment was performed three times with each of the three lots using the VITROS 5,1 FS system. RF linearity for one lot was shown as y=1.2173x - 0.379, R2=0.9995. The data supports a reportable range of 6-120 IU/mL RF.

Dilution and recovery studies were performed using serum and 5 plasma samples were evaluated using various dilution ratios. Results are shown below.

Matrix	Undiluted	Diluted	Dilution Factor	%Recovery	Dil Limit%
Serum	76.05	81.54	2	107.2	84.9-115.1
Serum	351.02	386.48	6	110.0	82.7-117.3
Plasma	349.9	400.83	6	114.6	82.8-117.0
Plasma	286.8	307.7	6	107.1	83.0-117.0

c. Traceability (controls, calibrators, or method):

Values assigned to the Calibrator kit 16 and FS Calibrator 1 for RF are traceable to the International Reference Preparation of Rheumatoid Arthritis serum –WHO standard, NIBSC 64/2.

d. Detection limit (functional sensitivity):

Three determinations of lower limit of detection (LLD) were made using 3 reagent lots on 3 VITROS 5,1 FS systems. Each assay consisted of 6 determinations of the calibrators and controls together with consecutive replicates of a low RF concentration fluid. A normal patient sample diluted with saline (1:2) was used as the low concentration sample. The first 20 replicates were used for analysis. The data were analyzed for each of the three determinations to calculate the LLD defined as 3.3 times the square root of the sum of squares of the calibration error standard deviation (SD) plus the pooled replicate SD. Calibration error at the mean response level of

the low analyte fluid was estimated by Monte Carlo simulation using 6 replicates per calibrator level. The LLDs calculated ranged from 4.8 to 6.3 IU/mL.

e. Analytical specificity:
Serum sample was spiked with high RF fluid to yield a target RF of approximately 25 IU/mL. Seven serum samples were tested for bilirubin, hemoglobin, intralipid and ascorbic acid for interference according to NCCLS EP-7A for paired difference method. In addition, a number of drugs and chemicals such as Ibuprofen, lidocaine, theophylline, salicylic acid etc. were also tested for interference with the assay. Results showed that patient samples containing high levels of IgG can result in a bias greater than predetermined acceptance limit (due to competitive inhibition of the assay). For the other substances, minimal interference was observed at the concentrations tested.

f. Assay cut-off:
Not provided. See expected value section.

2. Comparison studies:

a. Method comparison with predicate device:
One hundred and eleven serum samples were assayed using the VITROS RF assay and the COBAS Integra RF assay (RFII). All samples were run in triplicate on VITROS SF 5,1 system and in singleton on COBAS analyzer on the same day. The results showed that 14 samples were below the VITROS RF reportable range (6-120 IU/mL) and 3 were above the range. Analysis of the results showed a relationship between the two methods and 3 lots of reagents tested. For Lot 97-5563 – VITROS RF assay = 0.925 (RFII) - 3.596 (IU/mL) with a correlation coefficient of 0.990. For Lot 83-5688, the result was VITROS RF assay = 0.904 (RFII) - 4.0445 (IU/mL) with a correlation coefficient of 0.986. For the third lot –VITROS RF assay = 0.895 (RF II) - 3.1324 with a correlation coefficient of 0.990.

b. Matrix comparison:
Whole blood samples were spiked with various amounts of high RF samples. In addition, 25 whole blood samples were collected into serum separator tubes (with heparin or EDTA) or plasma separator tubes. Individual results were reviewed for outliers per NCCLS EP5-A. No outliers were identified. Serum is used as control sample because it is the specimen matrix used to establish overall accuracy of the method. Bias values were calculated using the equation: Bias or difference = Test condition prediction –serum sample prediction. Anticoagulants were deemed acceptable if the bias between the test

condition and serum sample was within predetermined acceptance criteria i.e. within predefined target and essential limits. Twenty-four patient samples were tested and results for serum vs heparin plasma met the target and essential limits (target limit was +/-3.369 and essential limit as +/-11.495). The results showed the maximum difference between serum plasma as -4.42 IU/mL and the least as -0.17 (these results are for one lot tested).

3. Clinical studies:
   a. *Clinical sensitivity:*
   Not provided.

   b. *Clinical specificity:*
   Not provided.

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

4. Clinical cut-off:
   Not provided.

5. Expected values/Reference range:
   Reference interval for RF = <12 IU/mL. The reference interval is defined as the 97.5th percentile value of results from a study of 507 apparently healthy adults.

N. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.