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

**A. 510(k) Number:**
k100499

**B. Purpose for Submission:**
New Device

**C. Measurand:**
Rheumatoid Factors IgG, IgM and IgA and Rheumatoid Factor Total

**D. Type of Test:**
Quantitative, Immunometric Enzyme Immunoassay

**E. Applicant:**
ORGENTEC Diagnostika GmbH

**F. Proprietary and Established Names:**
Orgentec Rheumatoid Factor IgG, IgM, IgA, and RF Total EIAs

**G. Regulatory Information:**

1. Regulation section:
   21 CFR §866.5775, Rheumatoid Factor Immunological Test System
2. Classification:
   RF and Calibrator – Class II
3. Product code:
   DHR, System, Test, Rheumatoid Factor
4. Panel:
   Immunology (82)

**H. Intended Use:**

1. Intended use(s):
   Rheumatoid Factor IgA is an indirect solid phase enzyme immunoassay (ELISA) for the quantitative measurement of IgA class rheumatoid factor antibodies in human serum or plasma (Citrate plasma, Na-heparin Plasma, EDTA plasma).

   Rheumatoid Factor IgG is an indirect solid phase enzyme immunoassay (ELISA) for the quantitative measurement of IgG class rheumatoid factor antibodies in human serum or plasma (Citrate plasma, Na-heparin Plasma, EDTA plasma).

   Rheumatoid Factor IgM is an indirect solid phase enzyme immunoassay (ELISA) for the quantitative measurement of IgM class rheumatoid factor antibodies in human serum or plasma (Citrate plasma, Na-heparin Plasma, EDTA plasma).

   The assays are intended for in vitro diagnostic use only as an aid in the diagnosis of Rheumatoid Arthritis (RA), in conjunction with other laboratory and clinical findings.

   Rheumatoid Factor Total is an indirect solid phase enzyme immunoassay (ELISA) for the qualitative measurement of IgG, IgM and IgA class rheumatoid

factor antibodies in human serum or plasma (Citrate plasma, Na-heparin plasma, EDTA plasma).
The assay is intended for in vitro diagnostic use only as an aid in the diagnosis of rheumatoid arthritis (RA) in conjunction with other laboratory and clinical findings.

2. Indication(s) for use:
   Same as above.
3. Special conditions for use statement(s):
   For prescription use only.
4. Special instrument requirements:
   Single or dual wave length microplate reader with 450 nm filter. If dual wave length is used, set the reference filter to 620 nm.

**I. Device Description:**

The kit contains

- a divisible microplate consisting of 12 modules of 8 wells each, with coated Fc fragments of highly purified human Immunoglobulin G.
- 5 vials, (1.5 mL each) of calibrators (with human IgG for RF IgG, or IgM for RF IgM, or IgA for RF IgA, or combined calibrator with IgG, IgM and IgA for the RF Total) class rheumatoid factor antibodies (AE) in a serum/buffer matrix containing: 0; 15; 50; 150; 500 U/mL.
- 2 vials, (1.5 mL each) Rheumatoid factor positive and negative controls in a serum/buffer matrix.
- 1 vial, (20 mL, 5x concentration) of Sample buffer.
- Antibody is provided as 1 vial, (15 mL) Enzyme conjugate solution (PBS, Proclin 300 <0.5% (v/v)), (light red) containing polyclonal rabbit anti-human antibody; labelled with horseradish peroxidase.
- TMB substrate solution, 1 vial, (15 mL)
- Stop solution (contains hydrochloric acid), 1 vial, (15 mL)
- Wash solution (1 vial, 20 mL)

Components containing human serum were tested and found negative for HBsAg, HCV, HIV1 and HIV2 by FDA approved methods. No test can guarantee the absence of HBsAg, HCV, HIV1 or HIV2, and so all human serum based reagents in this kit must be handled as though capable of transmitting infection.
Some kit components (i.e. Controls, Sample buffer and Buffered Wash Solution) contain Sodium Azide as preservative. Sodium Azide (NaN3) is highly toxic and reactive in pure form. Despite the classification as non-hazardous, at the provided concentration of 0.9%, it is strongly recommended prudent laboratory practices be used.

**J. Substantial Equivalence Information:**

1. Predicate device name(s):
   Autostat II RF IgG, Autostat II RF IgM, Autostat II RF IgA
2. Predicate K number(s):
   k993304, k994338, k993557
3. Comparison with predicate:

| Similarities | | |
|---|---|---|
| Item | Device – ORGENTEC RF Antibody EIAs | Predicate - Autostat II RF Antibody test kits |
| Intended Use | Rheumatoid Factor EIAs are indirect solid phase enzyme immunoassay (ELISA) for the quantitative measurement of IgG, IgM and IgA class rheumatoid factor antibodies in human serum or plasma. For use as an aid in the diagnosis of rheumatoid arthritis (RA). | Enzyme-linked immunosorbent assay method for the quantitative determination of specific IgG, IgA, and IgM Rheumatoid Factor in human serum. The results of the RF assays can be used as an aid in the diagnosis of Rheumatoid Arthritis |
| Controls | Negative control<br>Positive control | Negative control<br>Positive control |
| Test results | Same | Quantitative |
| Storage | Same | 2-8 °C (35 - 46 °F) |
| Type of substrate | Same | TMB (3,3´,5,5´-Tetramethyl-benzidine) |
| Test kit composition | Same | Microplate |
| Controls | Same | Positive and Negative controls |

| Differences | | |
|---|---|---|
| Item | Device – ORGENTEC RF Antibody EIAs | Predicate - Autostat II RF Antibody test kits |
| Sample material | Serum or Plasma | Serum |
| Required sample size | 10 µL of sample to be diluted 1:100 with Diluent; 100 µL prediluted sample per single determination | 5 µL of sample to be diluted 1:100 with Diluent; 100 µL prediluted sample per single determination |
| Total incubation time | 60 minutes at room temperature (18-28°C) | 75 minutes at room temperature (18-25°C ( 64 - 77 °F) |
| Matrix | Human Rheumatoid Factor antibodies with sodium azide as preservative | Human Serum with sodium azide as preservative |
| Calibrators | 5 calibrators | 4 calibrators |
| Open Vial claim | 30 days | 90 days |
| Measuring range | 3.4 – 500 U/mL for IgG<br>2.5 – 500 U/mL for IgA<br>2.0 – 500 U/mL for IgM<br>3.0 – 500 U/mL for Total | 5.7 - 1265 IU/mL for IgG,<br>10 - 8590 IU/mL for IgM<br>10 – 1152 IU/mL for IgA |
| Assay cut-off | 20 U/mL for IgG, IgA, IgM and 25 U/mL for RF Total | 30 IU/mL for IgG,<br>16 IU/mL for IgM<br>20 IU/mL for IgA |

**K. Standard/Guidance Document Referenced:**

None referenced.

**L. Test Principle:**

Rheumatoid Factor IgA/IgG/IgM/RF Total is an indirect solid phase enzyme immunoassay (ELISA). Fc fragments of highly purified human Immunoglobulin G are bound to microwells. Antibodies against this antigen, if present in diluted serum or plasma, bind to the respective antigen. Washing of the microwells removes unspecific serum and plasma components. Horseradish peroxidase (HRP) conjugated anti-human IgG (for RF IgG), or anti-human IgA (for RF IgA), or anti-human IgM (for RF IgM), or containing all 3 anti-human IgG, anti-human IgA, anti-human IgM (for RF Total) immunologically detects the bound patient antibodies forming a conjugate/antibody/antigen complex. Washing of the microwells removes unbound conjugate. An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue colour. The addition of an acid stops the reaction forming a yellow end-product.

The intensity of this yellow colour is measured photometrically at 450 nm. The amount of colour is directly proportional to the concentration of antibodies present in the original sample.

**M. Performance Characteristics):**

1. Analytical performance:

*a. Precision/Reproducibility:*

Inter-Assay, Inter-Lot and Intra-Assay reproducibility studies were performed for ORGENTEC RF IgG, IgA, IgM and RF Total assays. Coefficients of variation (CV) were calculated for each of ten samples from the results of 20 determinations in a single run for Intra-Assay precision. Run-to-run precision was calculated from the results of 20 different runs with double determinations of each sample. Inter-Lot precision was calculated from the results of three different kit lots with double determinations using seven samples. Results are shown in the below tables.

**Reproducibility of Orgentec RF IgG Assay**

| **Intra-Assay – RF IgG** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 12.6 | 6.1 |
| 2 | 15.6 | 7.4 |
| 3 | 10.9 | 6.2 |
| 4 | 17.5 | 7.2 |
| 5 | 22.8 | 5.5 |
| 6 | 31.1 | 5.6 |
| 7 | 37.2 | 5.5 |
| 8 | 65.3 | 7.4 |
| 9 | 160.7 | 6.9 |
| 10 | 502.7 | 7.0 |

| **Inter-Lot – RF IgG** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 4.2 | 7.3 |
| 2 | 15.9 | 9.5 |
| 3 | 57.6 | 8.2 |
| 4 | 120.0 | 2.8 |
| 5 | 205.7 | 7.3 |
| 6 | 470.5 | 10.3 |
| WHO | 72.1 | 14.4 |

| **Inter-Assay – RF IgG** | | |
|---|---|---|
| Sample No. | Mean | CV |

| | [U/mL] | [%] |
|---|---|---|
| 1 | 27.1 | 6.5 |
| 2 | 54.0 | 7.2 |
| 3 | 136.8 | 7.8 |

**Reproducibility of Orgentec RF IgA Assay**

| **Intra-Assay – RF IgA** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 12.9 | 7.4 |
| 2 | 10.3 | 6.8 |
| 3 | 16.8 | 4.8 |
| 4 | 21.1 | 6.4 |
| 5 | 24.0 | 7.2 |
| 6 | 27.0 | 3.4 |
| 7 | 78.3 | 5.6 |
| 8 | 109.9 | 6.3 |
| 9 | 116.6 | 5.3 |
| 10 | 238.9 | 7.2 |

| **Inter-Lot – RF IgA** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 10.5 | 10.8 |
| 2 | 16.0 | 9.5 |
| 3 | 47.4 | 8.0 |
| 4 | 89.2 | 10.0 |
| 5 | 136.8 | 9.4 |
| 6 | 314.9 | 12.8 |
| WHO | 82.8 | 4.4 |

| **Inter-Assay – RF IgA** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 25.6 | 6.1 |
| 2 | 90.7 | 5.8 |
| 3 | 114.7 | 7.8 |

**Reproducibility of Orgentec RF IgM Assay**

| **Intra-Assay – RF IgM** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 8.5 | 4.7 |
| 2 | 9.4 | 7.1 |
| 3 | 13.2 | 4.2 |
| 4 | 17.1 | 4.3 |
| 5 | 24.8 | 3.4 |
| 6 | 33.9 | 4.5 |
| 7 | 59.7 | 4.6 |
| 8 | 147.7 | 4.3 |
| 9 | 495.7 | 6.9 |

| **Inter-Lot – RF IgM** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 9.5 | 11.8 |
| 2 | 23.2 | 7.9 |
| 3 | 34.5 | 3.6 |
| 4 | 35.4 | 4.8 |
| 5 | 87.6 | 8.7 |
| 6 | 180.6 | 9.1 |
| 7 | 330.1 | 11.0 |
| 8 | 104.0 | 8.5 |
| WHO | 21.5 | 10.7 |

| **Inter-Assay – RF IgM** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 24.5 | 8.2 |

| | | |
|---|---|---|
| 2 | 59.4 | 5.9 |
| 3 | 122.8 | 8.1 |

**Reproducibility of Orgentec RF Total Assay**

| **Intra-Assay – RF Total** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 5.2 | 6.7 |
| 2 | 10.5 | 7.6 |
| 3 | 23.8 | 3.4 |
| 4 | 29.0 | 5.5 |
| 5 | 32.0 | 6.4 |
| 6 | 34.0 | 4.8 |
| 7 | 89.5 | 5.5 |
| 8 | 317.0 | 7.2 |
| | | |

| **Inter-Lot – RF Total** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 8.2 | 8.9 |
| 2 | 21.1 | 4.0 |
| 3 | 38.5 | 12.0 |
| 4 | 95.7 | 12.4 |
| 5 | 143.4 | 11.3 |
| 6 | 312.9 | 8.5 |
| WHO | 311.6 | 10.9 |

| **Inter-Assay – RF Total** | | |
|---|---|---|
| Sample No. | Mean [U/mL] | CV [%] |
| 1 | 26.1 | 5.9 |
| 2 | 92.2 | 5.5 |
| 3 | 320.5 | 8.0 |

*b. Linearity/assay reportable range:*

For each of the assays, namely, ORGENTEC RF IgG, IgA, IgM and RF Total assays, a series of three patient samples containing high levels of antibody were serially diluted in buffer from 1:1.2 up to 1:128 to demonstrate the upper end of linearity and throughout the dynamic range of the assay.

From these dilutions, the concentration of the samples was calculated from Calibrator curves. Claimed range for RF IgG is 3.4 U/mL to 500 U/m; for RF IgA is 2.5 U/mL to 500 U/mL; for RF IgM is .2.0 U/mL to 500 U/mL and for RF Total is 3.0 to 500 U/mL.

**Linearity for ORGENTEC RF IgG Assay:**

| **ORGENTEC RF IgG** | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|
| Concentration U/mL | 652.3 | 490.2 | 610.3 |
| Regression $R^2$ | 0.9955 | 0.9962 | 0.9956 |
| % Recovery | 86-116 | 83-112 | 84-117 |

**Linearity for ORGENTEC RF IgA Assay:**

| **ORGENTEC RF IgA** | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|
| Concentration U/mL | 550 | 424.2 | 512.7 |

| | | | |
|---|---|---|---|
| Regression $R^2$ | 0.9917 | 0.9972 | 0.9974 |
| % Recovery | 83-119 | 84-112 | 88-114 |

**Linearity for ORGENTEC RF IgM Assay:**

| **ORGENTEC RF IgM** | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|
| Concentration U/mL | 482.7 | 549.3 | 496.2 |
| Regression $R^2$ | 0.9954 | 0.9976 | 0.9951 |
| % Recovery | 87-112 | 91-109 | 87-112 |

**Linearity for ORGENTEC RF Total Assay:**

| **ORGENTEC RF Total** | Sample 1 | Sample 2 | Sample 3 |
|---|---|---|---|
| Concentration U/mL | 629.7 | 691.2 | 497.6 |
| Regression $R^2$ | 0.9972 | 0.9981 | 0.9951 |
| % Recovery | 91-116 | 84-105 | 88-113 |

c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*
Calibrators: The external calibrators (standards) are a series of four patient samples that were diluted in buffer from 1:2 to 1:32. Kit Calibrators are calibrated against WHO International Reference Preparation Rheumatoid Arthritis Serum 64/2, 1st Brit. Std., established 1965 for IgM, IgA and IgG. Stability of open kit calibrators and controls is at least 30 days when stored at 2-8 °C.

d. *Detection limit:*
Limit of Blank:
IgG:
**Limit of Blank - LoB**
Sample Buffer was diluted and measured 40 times on one plate.
Calibrators and Controls were analyzed in duplicate. The detection limit was calculated as the (mean + 3 SD) was 0.025 OD for the Sample Buffer, which corresponded to an analytical sensitivity of 0.6 U/mL.
**Limit of Quantitation - LoQ**
Functional sensitivity was determined from the coefficient of variation of four very low serum samples run in replicates of 16 in three assay runs. The lowest concentration which could be measured with a coefficient of variation below 20% is 5.9 U/mL
IgA:
**Limit of Blank - LoB**
Sample Buffer was diluted according to instructions for use and measured 40 times on one plate. Calibrators and Controls were analyzed in duplicate. The detection limit was calculated as the mean + 3 SD was 0.026 OD for the Sample Buffer, which corresponded to an analytical sensitivity of 0.1 U/mL.
**Limit of Quantitation - LoQ**
Functional sensitivity was determined from the coefficient of variation of four very low serum samples run in replicates of 16 in three assay runs. The lowest concentration which could be measured with a coefficient of variation

below 20% is 5.3 U/mL

IgM:

**Limit of Blank - LoB**

Sample Buffer was diluted according to instructions for use and measured 40 times on one plate. Calibrators and Controls were analyzed in duplicate. The detection limit was calculated as the mean + 3 SD was 0.021 OD for the Sample Buffer, which corresponded to an analytical sensitivity of 0.1 U/mL.

**Limit of Quantitation - LoQ**

Functional sensitivity was determined from the coefficient of variation of four very low serum samples run in replicates of 16 in three assay runs. The lowest concentration which could be measured with a coefficient of variation below 20% is 3.2 U/mL

RF Total:

**Limit of Blank - LOB**

Sample Buffer was diluted according to instructions for use and measured 20 times on one plate. Calibrators and Controls were analyzed in duplicate. The detection limit was calculated as the mean + 3 SD was 0.024 OD for the Sample Buffer, which corresponded to an analytical sensitivity of 0.4 U/mL.

**Limit of Quantitation - LOQ**

Functional sensitivity was determined from the coefficient of variation of four very low serum samples run in replicates of 16 in three assay runs. The lowest concentration which could be measured with a coefficient of variation below 20% is 8.4 U/mL

e. *Analytical specificity:*

Interferences studies for IgG, IgA and IgM:

Interference due to unconjugated bilirubin, hemolysis and lipemia (Glycerl Trioleate) was evaluated using a negative serum, a low positive serum and a high positive serum spiked with the respective interfering substance in increasing concentrations. Hemolysis up to 1000 mg/dL, bilirubin up to 40 mg/dL, and lipemia (i.e. triglyceride concentration) up to 3000 mg/dL in human serum do not interfere with RF IgG or IgA or IgM or the combined RF Total ELISA results.

Potentially cross-reacting diseases: A series of 68 samples obtained from adult and juvenile patients diagnosed with various other arthritic and autoimmune disease conditions were collected from hospitals sent for routine testing. These 68 samples were tested in the Orgentec Rheumatoid Factor IgG or IgA or IgM or RF Total assay to identify RF positivity in these populations.

| Patient Group | # of samples | Percent positive for RF IgG | Percent Positive for RF IgA | **Percent Positive for RF Total** | Percent Positive for RF IgM |
|---|---|---|---|---|---|
| Juvenile Arthritis | 14 | 7% | 0% | 0% | 0% |
| Other autoimmune | 10 | 10% | 0% | 0% | 0% |
| Borreliose | 2 | 0% | 0% | 0% | 0% |
| Rheumatologic samples | 11 | 18% | 27% | 27% | 18% |

| | | | | | |
|---|---|---|---|---|---|
| Psoriasis Arthritis | 10 | 0% | 0% | 10% | 10% |
| Sjögren Syndrome | 4 | 0% | 0% | 0% | 0% |
| SLE | 17 | 47% | 41% | 47% | 29% |

*f. Assay cut-off:*
≥20 U/mL for RF IgG, RF IgA and RF IgM; for RF Total ≥25 U/mL

2. Comparison studies:

*a. Method comparison with predicate device:*
233 patient samples were analyzed on an Orgentec RF ELISA and compared to a corresponding commercially available RF IgG or IgA or IgM ELISA. The quantitative results were calculated from a calibration curve on the basis of tested calibrators. Following are the tabulated results of percent positive and negative agreement between Orgentec RF assay and the predicate Hycor RF assay for each of the Immunoglobulins – IgG, IgA and IgM.
For the Orgentec RF Total assay, 233 samples were compared to commercially available (Hycor) RF IgG, IgA and IgM ELISA assays. The results are tabulated below.

| | | **Hycor RF IgG** | | **SUMMARY** | |
|---|---|---|---|---|---|
| | | **POS** | **NEG** | **%Agreement and (CI)** | |
| **Orgentec RF IgG** | **POS** | 140 | 4 | Positive | 99.3% (96.1-100%) |
| | **NEG** | 1 | 88 | Negative | 95.7% (89.2-98.8%) |
| | **Totals** | 141 | 92 | Overall | 97.9% (95.1-99.3%) |

| | | **Hycor RF IgA** | | **SUMMARY** | |
|---|---|---|---|---|---|
| | | **POS** | **NEG** | **%Agreement and (CI)** | |
| **Orgentec RF IgA** | **POS** | 139 | 7 | Positive | 96.5% 92.1 - 98.9%) |
| | **NEG** | 5 | 82 | Negative | 92.1% (84.5 - 96.8%) |
| | **Totals** | 144 | 89 | Overall | 94.8% (81.2 – 97.3%) |

| | | **Hycor RF IgM** | | **SUMMARY** | |
|---|---|---|---|---|---|
| | | **POS** | **NEG** | **%Agreement and (CI)** | |
| **Orgentec RF IgM** | **POS** | 162 | 0 | Positive | 98.8% (95.7 – 99.8%) |
| | **NEG** | 2 | 69 | Negative | 100.0 % (94.8-100%) |
| | **Totals** | 164 | 69 | Overall | 99.1% (96.9 - 99.9%) |

| | | **Hycor RF IgG, IgA, IgM** | | **SUMMARY** | |
|---|---|---|---|---|---|
| | | **POS** | **NEG** | **%Agreement and (CI)** | |
| **Orgentec RF Total** | **POS** | 170 | 1 | Positive | 98.3% (95.0 – 99.6%) |
| | **NEG** | 3 | 59 | Negative | 98.3% (91.1 - 100%) |
| | **Totals** | 173 | 60 | Overall | 98.3% (95.7 - 99.5%) |

*b. Matrix comparison:*

In order to demonstrate that the test system gives the same results for serum, separate tubes of Na-heparin plasma, citrate plasma and EDTA plasma were drawn from the same patient and tested in the various RF Ig assays (G/A/M) and RF Total antibody test. Thirteen samples ranging from serum concentrations 12. 5 U/mL to 350 U/mL were tested. Acceptance criteria for this study were that the percent deviation between serum and plasma results should not be greater than ±25 %. The slopes and $R^2$ values obtained are tabulated below.

| **Matrix Comparison** | **RF IgG** | **RF IgA** | **RF IgM** | **RF Total** |
|---|---|---|---|---|
| EDTA Plasma v/s Serum | y=1.0376x - 3.9231 | y=1.0708x - 3.8338 | y=1.0332x - 3.1197 | y=0.9406x + 2.2874 |
| | 0.9981 | 0.9931 | 0.9976 | 0.9949 |
| Citrate Plasma v/s Serum | 1.0406x - 4.3266 | y=0.9546x - 0.9377 | y= 1.0302x - 3.175 | y= 0.9957x - 0.6148 |
| | 0.9959 | 0.996 | 0.9937 | 0.9991 |
| Na-Heparin Plasma v/s Serum | y=0.932x + 1.2659 | y=0.8556x + 3.7448 | y=1.0859x - 3.4606 | y=0.9976x - 0.4368 |
| | 0.9994 | 0.9969 | 0.999 | 0.9979 |

3. Clinical studies:

Studies were performed to establish the clinical sensitivity and specificity of the Orgentec RF Assays, which detect RF IgG, RF IgA, and RF IgM in serum and plasma samples. The clinical sensitivity and specificity were calculated by comparing the Orgentec RF Ig Assay result interpretations to the clinical diagnosis of RA patients, presumptive normal samples and patients with other diseases both autoimmune and non-autoimmune. The available clinical diagnosis for the RA patients was defined by ACR criteria.

Four hundred and seventy-one (471) sera were tested by the ORGENTEC RF IgG or IgA or IgM or 469 samples by the ORGENTEC RF Total ELISA to determine clinical diagnostic agreement. Based on clinical diagnosis, the following tables list the results of patients seropositive or negative for IgG, or IgA or IgM or RF Total with the calculated clinical diagnostic sensitivity and specificity values respectively.

| | | **Clinical Diagnosis** | | |
|---|---|---|---|---|
| | | **Pos** | **Neg** | |
| **ORGENTEC RF IgG Assay** | **Pos** | **252** | **16** | **268** |
| | **Neg** | **50** | **153** | **203** |
| | | **302** | **169** | **471** |
| **Clinical Sensitivity:** | **83.4%** | (95% C.I. =79.3 - 87.6%) | | |
| **Clinical Specificity:** | **90.5%** | (95% C.I. = 85.1 - 94.5%) | | |
| **Clinical Agreement:** | **86.0%** | (95% C.I. = 82.9 – 89.1%) | | |

| | | Clinical Diagnosis | | |
|---|---|---|---|---|
| | | **Pos** | **Neg** | |
| | **Pos** | **235** | **12** | **247** |
| **ORGENTEC** | **Neg** | **67** | **157** | **224** |
| **RF IgA Assay** | | **302** | **169** | **471** |
| **Clinical Sensitivity:** | **77.8%** | (95% C.I. =73.1 - 82.5%) | | |
| **Clinical Specificity:** | **92.9%** | (95% C.I. = 87.9 - 96.3%) | | |
| **Clinical Agreement:** | **83.2%** | (95% C.I. = 79.9 - 86.6%) | | |

| | | Clinical Diagnosis | | |
|---|---|---|---|---|
| | | **Pos** | **Neg** | |
| | **Pos** | **276** | **11** | **287** |
| **ORGENTEC** | **Neg** | **26** | **158** | **184** |
| **RF IgM Assay** | | **302** | **169** | **471** |
| **Clinical Sensitivity:** | **91.4%** | (95% C.I. =87.6 – 94.3%) | | |
| **Clinical Specificity:** | **93.5%** | (95% C.I. = 88.7 - 96.7%) | | |
| **Clinical Agreement:** | **92.1%** | (95% C.I. = 89.3 - 94.4%) | | |

| | | Clinical Diagnosis | | |
|---|---|---|---|---|
| | | **Pos** | **Neg** | |
| | **Pos** | **288** | **19** | **307** |
| **ORGENTEC** | **Neg** | **12** | **150** | **162** |
| **RF Total Assay** | | **300** | **169** | **469** |
| **Clinical Sensitivity:** | **96.0%** | (95% C.I. =91.2 – 98.2%) | | |
| **Clinical Specificity:** | **88.8%** | (95% C.I. = 84.0 – 93.5%) | | |
| **Clinical Agreement:** | **93.4%** | (95% C.I. = 88.6 - 94.8%) | | |

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

4. Clinical cut-off**:**
Rheumatoid Factor IgG, IgA and IgM ≥ 20 U/mL
Rheumatoid Factor Total ≥ 25 U/mL
5. Expected values/Reference range:
The cut-off was determined by measuring a total of 200 samples, for each of the IgG, IgM, IgA and RF Total assays, from apparently healthy blood donors equally distributed by sex and age from blood banks and hospital labs.
The mean concentration plus 3 S.D. of RF IgG antibodies was 7.7 U/mL, and a 3 S.D. and 98 percentile values of 17.2 U/mL. Three patients were positive yielding

a 1% positive rate. This is consistent with published rates for a normal population.

The mean concentration of RF IgM antibodies plus 3 S.D. and 98 percentile values of 15.9 U/mL. One patient was positive yielding a 0.5% positive rate.

The mean concentration plus 3 S.D and 98 percentile values of RF IgA were 13.9 U/mL and 15.4 U/mL respectively.

Based on these results the cut-off for IgG, IgM and IgA was determined to be ≥20 U/mL.

The mean concentration of RF Total antibodies was 11.3 U/mL and mean plus 3 S.D. and 98 percentile values were 23.0 U/mL and 21.0 U/mL respectively. Two patients were positive yielding a 1% positive rate. Based on these results the cut-off for RF Total was determined to be ≥ 25 U/mL

**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.