**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**

This guidance was written prior to the February 27, 1997 implementation of FDA’s Good Guidance Practices, GGP’s. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP’s.

**This document is intended to provide guidance in the preparation of a regulatory submission. It does not bind the FDA or the regulated industry in any manner.**

Immunology Branch

Division of Clinical Laboratory Devices

Office of Device Evaluation

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While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to: Peter Maxim, Ph.D., Branch Chief, Immunology (HFZ-440). For questions regarding the use or interpretation of this guidance, contact: Peter Maxim, Ph.D., Branch Chief, Immunology at (301) 594-1293.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Devices and Radiological Health

**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.**

This is a flexible document representing the current concerns and suggestions regarding Rheumatoid Factor (RF) in vitro diagnostic devices employing EIA, ELISA, agglutination, and laser or rate nephelometry. It is based on (1) current basic science, (2) clinical experience, (3) the Safe Medical Devices Act of 1990 (SMDA) and (4) FDA regulations in the Code of Federal Regulations (CFR). As advances are made in science and medicine, these review criteria will be re-evaluated and revised as necessary.

**PURPOSE**

The purpose of this document is to provide guidance and clarification on information to present to the Food and Drug Administration (FDA) before a device to detect and/or quantitate RF in clinical specimens can be cleared for marketing. Devices to detect or quantitate RF isotypes other than IgM may require additional data.

**DEFINITION**

This generic type of device is intended for use in clinical laboratories or physician's office laboratories\* as an in vitro diagnostic test for the qualitative, semi-quantitative, and/or quantitative measurement of RF by EIA, ELISA, particle agglutination tests, and laser and rate nephelometry.

\* Devices may be cleared for use in alternative testing sites when additional data are submitted to demonstrate equivalent performance in these settings.

**PRODUCT CODE:** DHR

**REGULATION NUMBERS:** 21 CFR 866.5775 Rheumatoid Factor immunological test system.

Identification. "A Rheumatoid Factor immunological test system is a device that consists of the reagents used to measure by immunochemical techniques Rheumatoid Factor (antibodies to immunoglobulins) in serum, other body fluids, and tissues. Measurement of Rheumatoid Factor may aid in the diagnosis of rheumatoid arthritis."

**CLASSIFICATION:** Class II (Performance Standards)

**PANEL:** Immunology (82)

**REVIEW REQUIRED:** Premarket notification (510(k))

**I. CLINICAL INDICATIONS/SIGNIFICANCE/INTENDED USE**

**A. INTRODUCTION**

Rheumatoid Factors are immunoglobulins of any isotype with antibody activity directed against antigenic sites on the Fc region of human or animal immunoglobulin G (IgG). After the discovery by Waaler 1 and the independent rediscovery by Rose and co-workers 2 that the sera from patients with rheumatoid arthritis agglutinated sheep erythrocytes coated with rabbit anti-sheep erythrocyte antibody, it was determined that the serum factor responsible for the agglutination was a high-molecular immunoglobulin of the IgM class. IgM-RF is the main isotype identified by clinically available diagnostic assays for RF detection. Assays for RF are the most widely used serological tests as an aid for the diagnosis of rheumatoid arthritis (RA).1,2

As rheumatoid arthritis develops in an individual, the most consistent serological finding is an increase in the concentration of RF in blood and synovial fluid. 1,2 RF has been reported to occur in approximately 70-80% of patients with confirmed RA. 3,4,5 The concentration of RF tends to be highest when the disease peaks and tends to decrease during prolonged remission. This high RF frequency in RA cases makes their detection useful as a diagnostic tool, however these factors are not unique to Rheumatoid Arthritis. RF is found in 1 to 4% of the general population. RF is present in 75% of adult patients with the highest incidence of RF occurring in persons over 65 years of age and nearly all patients with Felty and Sjogren's Syndrome. Increased titers may accompany a variety of acute immune responses, particularly viral infections and a number of other diseases (infectious mononucleosis, tuberculosis, leprosy, various parasitic diseases, liver disease, sarcoidosis, and systemic lupus erythematosus). 6

Raised levels of IgM, IgG, and IgA RF have been reported in patients with Rheumatoid Arthritis. Several groups have reported that a high level of IgA RF is prognostic for a more severe disease outcome. 7,8,9 When RF Isotype levels are compared with radiological abnormalities of the joints, the strongest correlation is with raised levels of IgA RF. High levels of IgA RF withing three years of the onset of symptoms have been associated with a more severe disease after six years of onset. 9 Literature from as early as 1984 suggests that the detection of IgA RF in early disease indicates poor prognosis and justifies a more aggressive course of treatment. 10

Some studies have indicated that IgG RF correlates with disease status more closely than IgM RF. Two different groups demonstrated that raised levels of IgG antiglobulins are virtually confined to the sera of patients with rheumatoid arthritis and not other arthritides. 12,13 The most striking clinical association with IgG RF appears to be RA vasculitis. 11,12

Conventional methods for the measurement of RF-IgM have depended upon the agglutination of particles (e.g. latex, charcoal, bentonite, or erythrocytes) coated with human or animal IgG. The latex agglutination test is sensitive, but it can result in a fairly high number of false positives. 21 Nonspecific agglutination of latex particles by sera from normal individuals is not uncommon. 22 Quantitative serological tests such as EIA, RIA, and nephelometry utilize the advantage of objective instrument measurement on a single sample dilution.

**B. INSTRUCTIONS:**

A concise discussion may be provided which included the following as appropriate. The discussion can be supported with key literature citations.

1. Clinical indication, significance, and intended use.
2. Background description of the rheumatic disease involved, including the type of population affected (sex, age, etc.).
3. Significance of a positive result (disease indication and follow up testing).
4. Significance of false positive and false negative results.
5. A brief historical summary of all test methodologies used to detect the antibody(ies).
6. Merits/advantages and limitations/disadvantages of the device methodology(ies) compared to other available methodologies.
7. Matrices.

**II. DEVICE DESCRIPTION:**

The determination of substantial equivalence is based on the specific intended use (what analyte is detected and the indications for use) and the technology/methodology utilized in the device. Discuss the principles of the device methodology and whether it is well-established or new and unproven.

**A. ENZYME-LINKED IMMUNOASSAY (EIA) OR ENZYME-LINKED IMMUNOSORBENT ASSAY (ELISA)**

EIA or ELISA are used for the qualitative, quantitative or semi-quantitative determination of IgM RF in human serum. Purified RF antigen (human IgG) is attached to the wells of a polystyrene micro-titer plate. Diluted patient specimens, controls and calibrators are incubated at room temperature in the microwells. Any RF-IgM antibody present binds to the immobilized human IgG to form antigen-antibody complexes. Unbound antibody is washed from the wells, and enzyme-conjugated anti-human IgM is added. The enzyme conjugate binds to the antigen-antibody complex. Excess conjugate is washed away and a specific substrate added. Bound enzyme conjugate begins a hydrolytic reaction causing color development. After a specific time, the reaction is stopped.

The intensity of the generated color is proportional to the amount of RF specific IgM antibody bound to the wells. The results are read on a spectrophotometer (ELISA reader). The net absorbance is calculated by subtracting the absorbance value for the specimen blank from the value for the antigen coated microwell. A calibration standard that is assayed with each plate is then used to calculate the RF-IgM activity in I.U./mL. from the net absorbance value.

**B. PARTICLE AGGLUTINATION TESTS**

The earliest tests, and those still most widely used clinically rely on the agglutinating properties of the IgM class of RF. IgG, usually human or rabbit, is bound to a particulate carrier, and the presence of RF is then detected by agglutination or flocculation of the respective indicator system. Carrier particles frequently used include latex, charcoal, bentonite, and erythrocytes.

Semi-quantitative analysis to determine the antibody content of a serum involves doubling dilutions of the serum and determination of an end point (the last doubling dilution at which agglutination can be visualized). The reciprocal of this dilution is known as "antibody titer".

**C. LASER AND RATE NEPHELOMETRY**

Mixing antigen and antibody under antibody excess conditions results in the formation of antigen-antibody complexes whose concentration can be determined by light dispersion. When a beam of light is passed through tubes containing a fixed amount of antibody and variable concentrations of antigen, the concentration of immune complexes formed in the tube will determine the extent of light scattering. The amount of light scattered will be measured at angles varying from 0 ° to 90 °. Since antibody concentration remains constant, the light scattered is proportional to the concentration of antigen in the mixture.

**III. CLINICAL AND NONCLINICAL LABORATORY STUDIES: SPECIFIC PERFORMANCE CHARACTERISTICS:**

FDA requests different types and amounts of data and statistical analyses in pre-market notification applications to market **in vitro** diagnostic devices. The amount and type of data requested depends on the intended use, technological characteristics of the new device, whether the test is qualitative or semi-quantitative and on certain claims made by the manufacturer.

All claims for substantial equivalence and specific performance characteristics for using the device should be supported with data. It is recommended that all protocols for **in vitro** testing are included. Present test data results with analyses and conclusions. Summaries of results and explanations for unexpected results and any additional testing performed are helpful. Charts (scattergrams, histograms, etc.) may be used as part of the analyses and conclusions when appropriate.

**A. ANALYTICAL/LABORATORY/IN VITRO STUDIES**

1. **Validation of the Cut-off**

Descriptive information and laboratory data to show how the cut-off point (distinction between positivity and negativity or medical decision limit) was determined by the assay is important.

a. The population(s) used should be defined using the following parameters:

i. Number of samples in the normal population (used to determine initial screening dilution) with samples summarized according to gender and age groups. 16

ii. Number of specimens included in each disease group summarized according to gender and age groups.

iii. Geographical area(s) from which the population was derived.

iv. Graphical (e.g., scattergrams, histograms) representation of population characteristics.

b. It is recommended that the statistical method used to determine the cut-off point(s) be described.

c. If an equivocal zone is used, a definition of the basis for the equivocal zone should be included.

1. **Reagent characterization**

a. A brief description of the antigen(s) and antibody(ies) used in the assay is appropriate. Purification and characterization descriptions are needed.

b. If any recombinant technology was used in the preparation of the antigen(s), a description of the method used is needed.

1. **Assay Specificity/Interfering Substances**

Potentially cross reacting or interfering substances encountered in specific specimen types or conditions, e.g., hemolysis, lipemia, microbial contamination, additional analytes or other autoantibodies present, and storage or freeze-thawing should be evaluated. When interfering substances are shown to affect results, instruct the user that samples containing those substances should not be tested.

a. The optimal conditions based on specimen storage stability studies should be presented. Evaluate false positivity and negativity (if applicable).

b. If the use of plasma is claimed, present data to show that each anticoagulant recommended for use does not interfere with the assay.

i. For each anticoagulant, 10 matched serum and plasma specimens which are positive at the cut-off point should be tested.

ii. Similarly, it is suggested that 10 matched negative serum and plasma specimens be tested. These studies may not be indicated if the assay has a high dilution factor (i.e. 1:100).

c. Indicate if interference from other autoimmune antibodies could occur.

d. If the assay kit employs mouse monoclonal antibodies, include a warning that specimens from patients who have received preparations of mouse monoclonal antibodies for diagnosis or therapy may contain human anti-mouse antibodies (HAMA) and may show either falsely elevated or depressed values when tested.

e. A discussion of the possible interference from high levels of IgM RF and/or IgA RF (prozone or hook effect) when trying to measure IgG-RF is suggested.

1. **Performance Characteristics**

Include the following performance characteristics:

**a. Analytical Sensitivity** (if applicable)

The analytical sensitivity or detection limit is defined as the lowest quantity differentiated from zero (95% confidence intervals or 2 standard deviations (SD) above the mean of the Zero control are commonly used). 16,17 The Zero standard (Zero diluent) may be run at least 20-25 times in the same run and the mean of the Zero standard and 2 SD of the mean (counts, OD's, etc.) calculated. If low levels of the analyte are not clinically significant, determination of the detection limit may be irrelevant.

**b. Relative Sensitivity and Specificity**

The relative sensitivity and specificity as determined by comparison to a legally marketed RF device or to a reference method should be determined and reported in the Performance Characteristics section of the package insert.

**c. Linear Range**

The linear range of the assay with normal and abnormal specimens covering the entire reportable range of the assay should be validated. 18

**d. Reproducibility and Repeatability Studies** 16,17,18,19,20  
Controls simulating patient samples or actual patient runs representing at least two clinically significant levels near medical decision limits (normal or elevated) each day for 20 days to permit separate estimation of between-day, between-run and within-day standard deviations (SDs), as well as within-run and total SDs. 20

**i. Qualitative/Semi-quantitative Tests:**

In devices with a titration format, e.g., latex agglutination assays, it is suggested that intra-run reproducibility be within the commonly accepted limits of plus or minus one two-fold dilution.

**ii. Quantitative Tests:**

Total, between- and within-day and between- and within-run means and coefficients of variation of imprecision for each set of values are helpful.

**iii. Means, SDs, and Coefficients of Variation:**

It is recommended that the appropriate means, SDs, and/or coefficients of variation with confidence levels according to number of times the sample is repeated and are included in the Performance Characteristics Section of the Package Insert. The number of runs per day are also helpful.

**e. Prozone or High-Dose Hook Effect Studies**

Test a sample with the highest titer available, serially diluted and undiluted. If prozone problems are encountered, the Performance Characteristics section of the package insert should indicate the titer at which prozone problems were detected and a procedure for the user to follow to correct the problem. Where appropriate, describe the appearance of a prozone reaction for subjective tests.

**f. Alternative Testing Sites**

Include reproducibility studies performed in these settings. It is recommended that in-site testing for new technologies include at least three independent alternative testing sites. At each of the three sites, the precision and accuracy of the device could be evaluated. A statistically valid number of split samples should be tested by the site personnel and by professional laboratory personnel, and the results compared, to determine how the device performs in the hands of the intended user.

1. **Comparison Studies**

Compare the new device to a legally marketed device. Include the package insert for the legally marketed device.

A recognized reference method (if available) is to be employed for comparison to enable a fair evaluation of the proposed device's performance characteristics, particularly if there are broad differences in methodology/technology between the new device and the legally marketed device.

**a. Qualitative/Semi-quantitative Tests:**

It is recommended that the studies be performed on an adequate number of positive and negative specimens to support statistical significance. (An appropriate number may be suggested by a statistician.) The data comparing the device to a legally marketed predicate may be presented in a 2 X 2 table.

**b. Quantitative Tests:**

An assay is considered quantitative only if a recognized reference material of known concentration is available for standardization of a calibrator or standard used in the assay to calculate results.

If the same reference material is used in the new device as in the predicate device to substantiate the quantitative claim, comparison data may be presented to show correlation between the two assays when running the reference material as samples. Serially diluted reference material assayed by the new device and the predicate device should show equivalent results.

Compare results obtained using positive RF samples free from interfering substances from a minimum of 40 persons covering the whole assay range (from low to high levels of antibodies). 19,21 A linear regression comparing the device to the predicate device if the assays are quantitative is helpful.

**c. Comparison Discrepancies:**

Equivocal results or discrepancies between the new device and the comparison method could be resolved using clinical diagnosis or other legally marketed devices.

1. **Specimen Collection and Handling Conditions**

State specimen collection, storage and handling conditions in the package insert and provide data or appropriate literature references in the submission to substantiate claims.

1. **Computer Controlled Medical Devices**

For information regarding computer assisted clinical laboratory devices, refer to "Review Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review" available from the Division of Small Manufacturers Assistance (DSMA), 1-800-638-2041.

**B. CLINICAL INVESTIGATIONS**

In certain instances it may be necessary to require clinical data to establish safety and effectiveness. When a new or unfamiliar methodology, technological feature, or modification of the analyte, such as isotypes of RF other than IgM RF, are introduced in a device category, clinical performance will be necessary to support a claim of substantial equivalence.

For 510(k) submissions, perform a clinical study done at three independent clinical sites. One of these sites may be the manufacturer. The investigators should be identified by institutional name and address.

1. **Adequate Clinical Investigations**

a. Experimental design should be adequate to prove all claims for the intended use and specific performance parameters for using the device.

If RF isotypes other than IgM are measured, provide literature references explaining the clinical significance. It is recommended that clinical data be presented to support these claims. Indicate correlations between isotype levels and clinical disease activity.

b. Describe all protocols for clinical studies and establish monitoring to assure that all sites consistently adhere to the protocols.

c. Determine the sample size, prior to beginning the study, that will be statistically sufficient to support the testing hypothesis.

d. Sampling Method:  
Describe sampling method used in the selection and exclusion of patients.

i. Patient selection:

Include samples from individuals with diseases or conditions that may cause false positive or false negative results with the device. Ideally, a prospective study is preferred. However, if a retrospective study is used, include all eligible patients who meet the patient selection criteria as specified in the protocol.

ii. Account for all patients and samples. Insure that data points are included for every sample for every patient.

1. **Establishing Reference Ranges**

**a. Normal individuals:**

Establish a normal reference range with a statistically sufficient number of samples from normal persons characterized by age, sex, geographical location and any other factors that would influence the values obtained. 22,23

**b. Patient groups:**

i. Confirm that the new device detects the percentage of positives generally expected for each disease for which the device is intended. Use a statistically sufficient number of patients characterized by age, sex, geographical location, any symptoms of disease, clinical presentation, and any other factors that would influence the values obtained. 22,23

ii. False results:

Provide reports, if any, of false positive and false negative results for each disease as appropriate.

**c. Sample Types Claimed:**

Investigate all sample type(s) claimed in the intended use statement unless other data proves that there is no difference between them.

**IV. LABELING CONSIDERATIONS**

The following are additional details for some of the points in the statute [502(f)(1)] and regulations [21 CFR 809.10(b)].

**Package Insert**

Include the draft package insert for the new RF device in the 510 (k) submission. Support the statements throughout the document with key literature citations.

**A. INTENDED USE**

Briefly describe the intended use based on the technology/methodology used in the device. Include the following information:

1. Whether the assay is qualitative, quantitative, or semi-quantitative. Please remember that in order to claim to provide a quantitative result, the calibrators or standards must be calibrated to a reference material of known, established value.
2. Specimen type(s).
3. Indicate if the device is for use in clinical laboratories and/or alternative care sites. The Limitations section should include any specific training required for test performance.

A typical Intended Use statement would be:

"ABC's \*\*\* test system is an **in vitro** diagnostic device for the quantitation of RF in human serum by nephelometry and is intended as an aid in the diagnosis of Rheumatoid Arthritis."

**B. QUALITY CONTROL (QC)**

The package insert should recommend levels of quality control samples and their number, matrix type, placement, and interpretation to ensure that the system meets its performance claims. Include a statement that if controls do not behave as expected, assay results are considered invalid and should be repeated.

Controls should be handled in the same manner as patient samples. For example, if the patient sample is diluted or titered the control material should also be diluted or titered using the same diluent.

**C. RESULTS**

Give an adequate description of expected results and interpretation.

1. **EIA OR ELISA**

a. Explain the procedure for calculating the value of the unknown including a sample calculation.

b. Explain the procedure for determining the cutoff values and indicate what action should be taken when an equivocal value is obtained (e.g. the sample should be retested or analyzed in a different assay system).

c. Explain the procedure for repeating samples which are above the linearity of the assay. Give instructions for dilution of samples including the dilution factor and type of diluent to be used.

1. **PARTICLE AGGLUTINATION TESTS**

a. If the test is semi-quantitative, explain the procedure for determining titer on samples that are positive.

b. Indicate the minimum level of RF the qualitative screening method will detect.

c. Give a clear description of the appearance of a positive result.

1. **LASER AND RATE NEPHELOMETRY**

a. Indicate the measuring range of the nephelometer and include instructions for diluting samples which exceed this range.

b. If results are not calculated by the instrument, include any calculations that may need to be performed to derive the results.

c. State which isotypes of RF are being measured.

**D. LIMITATIONS OF THE PROCEDURE**

It is suggested that a statement of limitations of the procedure is incorporated including the following:

1. A negative result does not exclude rheumatoid arthritis. Approximately 25% of patients with a diagnosed case of rheumatoid arthritis may present with a negative result for RF. 24
2. Certain non-rheumatoid conditions, connective tissue disorders and a variety of other disease states such as hepatitis may elicit a positive RF test.
3. RF exists in three major immunoglobulin classes: IgA, IgG, and IgM. Most test systems for RF are designed to detect IgM RF because the molecules are large and react more readily with human IgG coated on the solid phase of the test system. Consequently, these tests will only detect RF of the IgM class.
4. Reproducible results with an EIA or ELISA system require careful pipetting, strict adherence to incubation periods and temperature requirements, as well as thorough washing of the test wells and thorough mixing of all solutions.
5. Hemolytic, icteric, or lipemic samples may interfere with nephelometry, turbidimetry, EIA, or ELISA. Indicate what the user should do with samples that exhibit these characteristics.

**E. EXPECTED VALUES**

1. The expected value in the normal population is negative. However, apparently healthy, asymptomatic individuals may have RF. These individuals usually have low titers. The incidence of false positives increases with age and is similar in females and males.
2. The frequency (percent) of rheumatoid arthritis patients in which RF is detected by the assay should be indicated.
3. The clinical significance of a positive test must be determined by evaluation of the patient's total clinical picture.

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