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.

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REVIEW CRITERIA FOR PREMARKET APPROVAL OF IN VITRO DIAGNOSTIC DEVICES FOR DETECTION OF ANTIBODIES TO PARVOVIRUS B19

This is a flexible document representing the current major concerns and suggestions regarding in vitro diagnostic devices employing immunochemical or other methodologies for detection of antibodies to Parvovirus B19 (B19) in human serum or plasma specimens. It is based on 1) current basic science, 2) clinical experience, and 3) the Safe Medical Devices Act of 1990 (SMDA) and 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 to accommodate new knowledge.

PURPOSE: The purpose of this document is to provide guidance on information to present to the Food and Drug Administration (FDA) before a device to detect antibodies to B19 in serum or plasma specimens may be approved for marketing. This document is an adjunct to the CFR and the FDA 87-4214 Premarket Approval (PMA) Manual.

DEFINITION: This generic type device is intended for use in clinical laboratories as an in vitro diagnostic test for qualitative or semi-quantitative measurement of antibodies to B19 in human serum or plasma by immunochemical and other methodologies. A PMA submission must show the device has clinical utility and that there is reasonable assurance of its safety and efficacy.

In addition to this guidance, refer to the National Committee for Clinical Laboratory Standards (NCCLS), "Specifications for Immunological Testing for Infectious Diseases"[1]. The NCCLS document may be used for definitions of terms used in this guidance document.

PRODUCT CODE(S): To be assigned

CLASSIFICATION: III

PANEL: MICROBIOLOGY (83)

REVIEW REQUIRED: Premarket Approval (PMA)

I. CLINICAL INDICATION/SIGNIFICANCE/INTENDED USE

Provide a concise discussion to include the following as appropriate. Support the discussion with key literature citations.

A. Background description of the virus and infectious process(es).

B. Description of etiology for the disease syndromes for which this device was developed.

C. Salient concerns of the medical community including relevant

medical/societal issues that may impact the review process or possibly the development of public policy.

D. Significance of false positive and false negative results.

E. Historical summary of all test methodologies used to detect antibodies to B19.

II. DEVICE DESCRIPTION

Key issues in the PMA review of a new device are the specific intended use (the analyte detected, the clinical utility, and the indications for use), the type of specimen tested, and the technology utilized. The following descriptive information must be included to adequately characterize the new in vitro device. Appropriate literature references that have been subjected to peer review should be attached.

A. Intended Use.

Describe the intended use based on the technology/methodology employed in the device. The following questions should be addressed:

1. What patient populations should be tested?

2. What are the conditions and limitations for use of the device when used to diagnose or manage a specific syndrome?

3. What is the clinical utility of the device in specific patient populations?

B. Detailed Principle of the Test Methodology.

Discuss the principle of the test methodology(ies). For new types of technologies, provide information to substantiate application of the methodology to the detection of specific antibodies. Cite literature references where appropriate. If available, furnish copies of appropriate scientific references for any recombinant or synthetic protein utilized. If scientific references are not available, discuss how the antigen was determined to be representative of the native antigen. Include a complete description of the following components if appropriate:

1. Any pretreatment procedure.

2. Antigen utilized in the assay.

   a. If a native antigen, from what source was the antigen obtained.

   b. If a recombinant antigen or synthetic peptide (oligonucleotide), from what source was the native

antigen derived and what nucleic acid or protein sequence was used to prepare the recombinant.

3. Define antisera used in the assay.

   a. Specify the species in which antisera was produced.

   b. If a native antigen was used as the immunogen, identify the source from which the antigen was obtained.

   c. If a recombinant antigen was used as the immunogen, furnish the source of the native nucleic acid and provide the sequence for the derived recombinant.

   d. Explain how the specificity of the antisera was determined.

4. Enzymatic, fluorescent, or other substrate used to detect the antigen-antibody complexes.

5. Determination of the cut-off value(s) or endpoint(s) for the assay. Provide validation data as described in III.A.1.

6. Controls/calibrators included in the assay kit and what aspects of the procedure are verified.

   Quality control material should be representative of and correlate with the intended use and clinical utility of the device. In addition to the specific requirements listed below, the manufacturer should refer to the current FDA CLIA '88 Quality Control Guidance.

   Qualitative assay:

   a. At a minimum, include in the device or make available two controls (positive and negative) in the same matrix as test specimens indicated for use with the assay. Controls should be within a statistically significant range of the cut-off. This range should be appropriate for the statistical method used to determine the cut-off. Provide documentation and justification for the value selected for the control.

   b. Make recommendations and justify the frequency of testing control material.

   Semi-quantitative assay:

   In addition to the controls and recommendations listed for a qualitative assay, include a control at the upper end of the linear range with a known expected value.

7. Any additional reagents or methods which contribute to

the effectiveness of the device.

8. Collection and transport materials provided in the kit or recommended for use.

9. Software elements and dedicated instrumentation that are responsible for specimen handling and/or that are used to calculate assay results. See requirements for Minor Level of concern in Reviewer Guidance for Computer Controlled Medical Devices Undergoing 510(k) Review (available from the Division of Small Manufacturers Assistance). Furnish the following for dedicated instrumentation and software elements:

   a. Reference premarket notification [510(k)] submission for any dedicated instrument.

   b. Algorithms used to calculate results in either dedicated or non-dedicated instruments.

   c. Mathematical curve-fitting method(s) used when results are calculated non-manually.

C. Merits and Limitations of the Methodology(s).

Discuss the merits and limitations/advantages/disadvantages of the test methodology(ies) of the new device.

D. Specimen Type(s).

List all specimen types (matrices) indicated for use with the device.

III. SPECIFIC PERFORMANCE CHARACTERISTICS

The FDA requests different types and amounts of data and statistical analyses to market in-vitro diagnostic devices. The amount and types of data requested depend on the intended use and the technological characteristics of the new device. The data and statistical evaluation should be sufficient to determine if the device is safe and effective for all claimed specimen type(s). Additional data may be necessary to substantiate certain claims of intended use or clinical significance, and to validate use of a new technology.

Clearly document all protocols for in vitro testing. Present test data with analyses and conclusions. Summarize results and include explanations for unexpected results and any additional testing performed. When appropriate, charts (scattergrams, histograms, ROC curves, etc.) may be used as part of analyses and conclusions. Furnish all raw laboratory data.

Submission of the following data is required to determine the device's ability to detect B19-specific antibodies:

A. Analytical Laboratory Studies.

1. Validation of Cut-off and/or Calibration Curve.

   Describe the rationale for determination of the assay cut-off(s). Furnish descriptive information and laboratory data to show how the cut-off (CO) (distinction between positivity and negativity) was determined for the assay.

   a. Define the population used, including the following information:

      (1). geographical area(s) from which the population was derived;

      (2). number of samples comprising the population, with samples summarized according to sex and age groups in decades.

      (3) the month of the year during which sample was collected.

      (4). graphical (e.g., histogram, scattergram, etc.) representation of population characteristics.

   b. Define the statistical method used to determine the cut-off.

   c. Present ROC analysis of cut-off selection and other graphical representations as appropriate.

   d. Define the basis for the equivocal zone.

   e. If semi-quantitative, perform appropriate clinical studies to show the relationship of results to the diagnostic stage (e.g., early, acute, waning infection) for which value ranges have been established. For each diagnostic stage, present results from a minimum of 10 patients.

   f. For devices which determine interpolated values (e.g., ELISAs), verify the accuracy and working range of the calibration curve used by serially diluting patient samples.

2. Establish the prevalence of the analyte in two diverse asymptomatic populations using the specified CO.

   a. Assay a statistically significant number of specimens which are representative of the intended use, clinical utility, and matrix of the specimens.

   b. Summarize the distribution of males and females according to age groups in decades, geographical area, month of year specimens were collected, and the number of positive, negative, and equivocal results.

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3. Assay Specificity

   a. Perform cross-reactivity studies with sera containing relatively high titers against rubella, rubeola (measles), mumps, influenza A, influenza B, parainfluenza, HSV1, HSV2, CMV, EBV, VZV, and Mycoplasma pneumoniae. Test sera from five (5) patients with each disease; the predominate antibody class should be the class measured in the device. Furnish the antibody "titer" of the potential cross-reactant samples and the method used to determine the "titer".

   b. If the antigen utilized in the device is a recombinant, test sera containing antibodies against the organism in which the vectors were induced for cross-reactivity with the organism.

   c. If the antisera utilized in the device were produced by using a recombinant as the immunogen, test sera containing antibodies against the organism in which the vectors were induced for cross-reactivity with the antisera.

   d. For immunoglobulin class-specific devices, test ten sera positive in moderate to high levels for specific antibody class other than what is detected in the device for type specificity (i.e., if the assay is for IgG antibody then test ten sera which are positive for IgM antibody to show the device will not detect specific IgM antibody). Retest following removal of IgM or IgG.

      NOTE: Serum samples may be artificially produced; describe method of preparation.

   e. If an absorbent is used to remove interference of RF, ANA, and specific IgG, document the amount of IgG removed in mg/dL or mg/sample volume. State this value in the LIMITATIONS section of the package insert.

   f. If device is for the detection of IgM antibodies the following studies are required:

      (1). Test five sera containing high levels of RF and ANA with virus-specific IgG. Provide levels of RF and ANA tested.

      (2). Describe the methods used to determine the amounts of virus-specific IgG, RF, and ANA present. Devices used should be legally marketed devices.

4. Interference Studies.

Any potentially cross-reacting or interfering substances potentially encountered in specific specimen types or conditions should be tested using the assay system, e.g., storage conditions, hemolysis, lipemia, freeze-thawing, etc.

a. Verify that recommended storage conditions are compatible with the assay. State the optimal conditions based on specimen storage stability studies. Both false positivity and false negativity should be evaluated.

b. If the use of plasma is claimed, a study with each anticoagulant must be performed to show the anticoagulant does not interfere with the assay.

(1). For each anticoagulant, test 10 concurrent serum and plasma specimens which have reactivity near the CO. These specimens may be artificially produced as long as the matrix is maintained and it is noted in the submission that the samples were artificially created.

(2). For each anticoagulant, test 10 concurrent non-reactive serum and plasma specimens.

c. If heating of the specimen is claimed not to interfere with the assay:

(1). Test 10 specimens with reactivity near the CO, for each matrix type claimed, heated and not heated. These specimens may be artificially produced as long as the matrix is maintained and it is noted in the submission that the samples were artificially created.

(2). Test 10 specimens which are non-reactive for each matrix claimed, heated and not heated.

5. Reproducibility

The National Committee for Clinical Laboratory Standards (NCCLS) recommends an analysis of variance experiment that permits estimation of within-run and total standard deviations (SD).[2] See the NCCLS Guideline for recommended data collection formats and calculations. Perform separate calculations for each specimen tested for within-run and total precision.

Test six to ten patient blinded sera with varying degrees of reactivity plus controls supplied with device in triplicate on three different days at three laboratory sites (6-10 sera tested X 3 X 3 days X 3 sites). One testing site may be in-house.

For calculated endpoint tests (e.g., ELISAs), present coefficients of variation for each set of values for with-in run and total precision, using absorbance values and reporting units defined in the test procedure.

For single endpoint assays, provide percentage of results that are negative, borderline/equivocal, or positive for each set of tests.

If dedicated instrumentation is used in specimen handling, or reading and interpreting results, use a different instrument at each site. If non-dedicated instruments are used, state specifications of instrument(s) used at each site.

6. Stability

Document stability from three different manufactured lots that represent real time studies. Accelerated stability studies are acceptable as interim data only. Include testing to show that the reagents are stable under variable shipping temperatures.

B. Clinical Studies.

Clinical studies provide data on the ability of the system to accurately detect antibodies to B19. It should be demonstrated that the performance of the device is safe and effective when used as an aid in the diagnosis of specific B19 infections.

Provide the names and telephone numbers of principal investigators and sites at which testing was performed. Clinical testing should be performed by at least three independent investigators at separate independent locations not affiliated with the manufacturer. Identify the clinical laboratory sites by institutional name and address; include the name, title, and phone number of the responsible investigators at each site.

The tests should be performed on an adequate number of positive and negative clinical specimens (following collection, storage, and testing instructions recommended in the package insert) from a population consistent with the intended use of the device. The sensitivity and specificity calculated from this population should be stated in the PERFORMANCE CHARACTERISTICS section of the package insert.

1. Test samples submitted to the clinical laboratory for the rule out of illness associated with rash or other symptoms of B19 infection.

2. Clinical confirmation of infection may be done by clinical diagnosis, immune electron microscopy, or other standard methods.

a. Clinical diagnosis may be based on the following criteria:

(1). documented contact with infected individuals during a community outbreak (usually April through May).

(2). typical "slapped-cheek" rash which during clearing may take on a lacelike appearance on the trunk of the body.

(3). symmetric polyarthropathy.

(4). absence of increased markers to other illnesses associated with rash (measles, rubella, etc.).

(5). reticulocytopenia and a fall in hemoglobin concentration

(6). bone marrow cytology.

For pediatric patients (1) and/or (2) is considered diagnostic. For immunocompetent adults, (1), (2) (with or without trunk rash), and (3) is diagnostic. When the symptomatology is not diagnostic, at least two of the criteria (1-6) must be documented for establishing the diagnosis.

b. If other standard testing methods are used, the antigen should be different than the antigen present in the device. This additional testing may be performed at the manufacturer's or other site(s). Note in the submission where this testing was performed. Provide a description of the antigen used, criteria for positivity and negativity, and quality control performed. Furnish copies of any pertinent scientific references for the testing method with the submission.

3. As an option, results obtained from a well-documented panel of sera such as the CDC panel or a panel established by the manufacturer may be included with the submission. If a manufacturer's sera panel is used, furnish the criteria for defining the diagnosis and/or disease stage of the patients from whom samples were obtained. This study may be conducted at the manufacturer's facility or at a clinical laboratory site.

4. Test sera from documented illnesses which produce symptoms similar to B19 illness. Provide the assay results, final diagnosis, and how the diagnosis was determined with the data. Examples of diseases to include are:

a. Kawasaki disease

b. Aplastic anemia caused by other than B19 infection

c. Thyroiditis

d. Hemolytic uremic syndrome

e. Rheumatoid arthritis

f. Lupus erythematosus

g. Contact dermatitis and other diseases which may include a rash (e.g., Lyme disease, Rocky Mountain spotted fever, syphilis, meningococcal disease, streptococcal infections, toxoplasmosis, etc.)

5. Additional testing of sera from a small group of chronically B-19-infected patients may be appropriate depending on the intended use.

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)].

A. The Intended Use Statement

The intended use statement should be a concise description of the essential information about the product. It should communicate the following information:

1. Test methodology.

2. Whether the assay detects a specific antibody class.

3. Indications for use.

   These conditions for use may be addressed further in either the Summary and Explanation, Limitations, or Performance Characteristics section of the package insert.

4. What specimen source(s) may be tested.

5. If the assay is to be used only with special instrumentation.

C. Specimen Collection and Handling

1. State the type of specimen to be collected, and the types of collection devices which may be used.

2. State the conditions for patient preparation, e.g.,

timing of collection, order of collection, etc.

3. Provide adequate directions for sample collection and/or references for appropriate collection procedures, e.g., textbooks, journals, etc.

4. Identify interfering substances or conditions.

5. State the specimen storage conditions and stability periods.

D. Quality Control

Information provided in a Quality Control section should include the following information:

1. Provide recommendations for frequency of quality control.

2. Provide directions for interpretation of the results of quality control samples.

3. The Quality Control section should conclude with a statement similar to the following: "If controls do not behave as expected, results are invalid and patient results should not be reported".

4. Refer to the current CLIA '88 FDA Quality Control Guidance for additional information.

E. Expected Results

1. Reference expected prevalence of antibodies to B19 in different populations.

2. Indicate that prevalence may vary depending on geographical location, age, sex of population studied, type of test employed, specimen collection and handling procedures, clinical and epidemiological history of individual patients, etc.

F. Limitations of the Test.

List important test limitations and all known contraindications, with references when appropriate. The following are examples of statements which may apply:

1. Anti target-specific viral IgG antibodies may compete with the less avid target specific viral IgM antibodies, which would decrease the sensitivity of the assay.[3] Test only indicated specimen types. Testing of other specimen types may result in false negative or positive results.

2. The predictive value of a positive test decreases when prevalence decreases. Interpretation of positive

results in a low risk patient population should be made with caution. Usefulness of this test has only been established in testing sera from a specific population (e.g., adult patients with arthropathies).

G. Performance Characteristics:

Summarize the data upon which the performance characteristics are based, e.g., clinical sensitivity and specificity compared to clinical diagnosis; also include summary of reproducibility studies. Positive and negative predictive values should be based on specific populations sampled for each disease syndrome. State the prevalence at each testing site. Also show the effect of prevalence on positive and negative predictive values in different test populations.

1. Present cross-reactivity studies in a tabular form, indicating negative, positive, and borderline/equivocal/indeterminate results for each condition/disease.

2. Summarize within-run and total reproducibility.

3. Present data from clinical studies, using separate categories for different patient categories. All borderline/equivocal/indeterminate results should be clearly displayed. Discrepancies between test and clinical diagnosis may be discussed and presented as footnotes.

V. BIBLIOGRAPHY

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