

Guidance for Industry and FDA Staff

Class II Special Controls Guidance Document: *Plasmodium* Species Antigen Detection Assays

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For questions regarding this document contact Freddie M. Poole at 240-276-0712 or by email at freddie.poole@fda.hhs.gov.



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety
Division of Microbiology Devices**

Preface

Public Comment

Written comments and suggestions may be submitted at any time for Agency consideration to Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD, 20852. Alternatively, electronic comments may be submitted to <http://www.regulations.gov>. Please identify all comments with the docket number FDA-2008-D-0230. Comments may not be acted upon by the Agency until the document is next revised or updated.

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. Introduction

This special controls guidance document was developed to support the classification of *Plasmodium* species antigen detection assays into class II (special controls). A *Plasmodium* species antigen detection assay is a device that employs antibodies for the detection of specific malaria parasite antigens, including histidine-rich protein-2 (HRP2) specific antigens, and pan malarial antigens in human whole blood. These devices are used for testing specimens from individuals who have signs and symptoms consistent with malaria infection. The detection of these antigens aids in the clinical laboratory diagnosis of malaria caused by the four malaria species capable of infecting humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, and aids in the differential diagnosis of *P. falciparum* infections from other less virulent *Plasmodium* species. The device is intended for use in conjunction with other clinical laboratory findings.

This guidance provides recommendations to manufacturers regarding preparation of premarket notifications and labeling for a *Plasmodium* species antigen detection assay. It is issued in conjunction with a *Federal Register* notice announcing the classification of *Plasmodium* species antigen detection assays¹. Any firm submitting a 510(k) premarket notification for a *Plasmodium* species antigen detection assay will need to address the issues covered in the special controls guidance document. However, the firm need only

¹ Unlike some of the other classification regulations in 21 CFR part 866, subpart D which use the term “reagents” in their titles, FDA is using “assays” to refer to this device type because this term more accurately reflects the devices within this type.

show that its device meets the recommendations of the guidance or in some other way provides equivalent assurances of safety and effectiveness.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

The Least Burdensome Approach

The issues identified in this guidance document represent those that we believe should be addressed before your device can be marketed. In developing the guidance, we carefully considered the relevant statutory criteria for Agency decision-making. We also considered the burden that may be incurred in your attempt to follow the statutory and regulatory criteria in the manner suggested by the guidance and in your attempt to address the issues we have identified. We believe that we have considered the least burdensome approach to resolving the issues presented in the guidance document. If, however, you believe that there is a less burdensome way to address the issues, you should follow the procedures outlined in the document, “**A Suggested Approach to Resolving Least Burdensome Issues.**” It is available on our Center web page at: <http://www.fda.gov/cdrh/modact/leastburdensome.html>.

2. Background

FDA believes that special controls, when combined with the general controls, will be sufficient to provide reasonable assurance of the safety and effectiveness of *Plasmodium* species antigen detection assays. A manufacturer who intends to market a device of this generic type should (1) conform to the general controls of the Federal Food, Drug & Cosmetic Act (the Act), including the premarket notification requirements described in 21 CFR 807 Subpart E, (2) address the specific risks to health associated with *Plasmodium* species antigen detection assays identified in this guidance document and, (3) obtain a substantial equivalence determination from FDA prior to marketing the device.

This guidance document identifies the classification regulation and product code for *Plasmodium* species antigen detection assays (Refer to Section 3 – [Scope](#)). In addition, other sections of this guidance document identify the risks to health and describe measures that, if followed by manufacturers and combined with the general controls, will generally address the risks associated with these assays and lead to a timely premarket notification [510(k)] review and clearance. This document supplements other FDA documents regarding the specific content of a 510(k) submission. You should also refer to 21 CFR 807.87 and other FDA documents on this topic, such as **Premarket Notification: 510(k)**, available on the web at: <http://www.fda.gov/cdrh/devadvice/314.html>.

As explained in “The New 510(k) Paradigm - Alternate Approaches to Demonstrating Substantial Equivalence in Premarket Notifications; Final Guidance,” a manufacturer may submit a Traditional 510(k) or an Abbreviated 510(k). FDA believes an Abbreviated 510(k) provides the least burdensome means of demonstrating substantial equivalence for a new device, particularly once FDA has issued a guidance document that provides recommendations on what should be addressed in a submission for the device. Guidance on the content and format for abbreviated and traditional 510(k)s is available at <http://www.fda.gov/cdrh/ode/guidance/1567.html>. Also, see Section 514(c)(1)(B) of the Act and the FDA guidance, “Use of Standards in Substantial Equivalence Determinations” at <http://www.fda.gov/cdrh/ode/guidance/1131.pdf>, for additional information. The Special 510(k) is available for manufacturers considering modifications to their own cleared devices. Information on how to prepare a Special 510(k) is available at <http://www.fda.gov/cdrh/devadvice/3144.html>.

3. Scope

The scope of this document is limited to the following devices as described in 21 CFR 866.3402 (product code: OAX):

Identification: A *Plasmodium* species antigen detection assay is a device that employs antibodies for the detection of specific malaria parasite antigens, including histidine-rich protein-2 (HRP2) specific antigens, and pan malarial antigens in human whole blood. These devices are used for testing specimens from individuals who have signs and symptoms consistent with malaria infection. The detection of these antigens aids in the clinical laboratory diagnosis of malaria caused by the four malaria species capable of infecting humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, and aids in the differential diagnosis of *P. falciparum* infections from other less virulent *Plasmodium* species. The device is intended for use in conjunction with other clinical laboratory findings.

Classification. Class II (special controls). The special control is FDA's guidance document entitled "Class II Special Controls Guidance Document: *Plasmodium* species Antigen Detection Assays." See § 866.1(e) for the availability of this guidance document.

This guidance document does *not* address devices intended for testing asymptomatic individuals (i.e. screening). Different types of study designs would be appropriate for an intended use that includes screening.

4. Risks to Health

Clinical Background

Malaria, especially that caused by the species *Plasmodium falciparum*, is an acute infection with high morbidity and mortality, particularly in the very young, the elderly, pregnant women and the non-immune. *P. falciparum* infection is often fatal if untreated

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in non-immune patients; therefore, patients with fever occurring during or after time spent in a malaria-endemic region are tested to rule out this diagnosis.

Risks of improper test performance

Failure of the test to perform as indicated may lead to improper patient management and/or inappropriate public health responses. For example, false negative results may lead to delays in providing, or even failure to provide, definitive diagnosis and appropriate treatment. This would place individuals, especially those infected with *P. falciparum*, at risk by not receiving appropriate therapy. In addition, there are no clinical features that distinguish *P. falciparum* infection from infection by the other less virulent *Plasmodium* species (*P. vivax*, *P. ovale*, and *P. malariae*); the test is used to aid in the differentiation of *P. falciparum* from the other species. Therefore, a false test result could result in mistreatment for these other endemic parasitic diseases. False results in pregnant women and newborns, or other unique populations, may entail additional risk due to limited treatment opportunities (e.g., for preventing consequences of congenital infection).

False positive test results may subject individuals to unnecessary and/or inappropriate treatment for malaria, and failure to appropriately diagnose and treat the actual disease condition. The unnecessary use of alternative drugs, such as quinine, mefloquine and artemisinin, typically used in high resistant areas outside the US, is problematic because these drugs are less safe than the first and second line treatments.

Malaria is a significant public health issue and local and state health departments conduct case investigations upon receiving a report of a malaria infection. A false positive test result could place an undue burden on local and state health department resources and could also lead to unnecessary public health actions (e.g., unnecessary or inappropriate treatment and management of others in the community). On the other hand, a false negative result could lead to a delay in recognition of increased transmission of the parasitic infection.

Risks of improper interpretation of results

An error in interpretation of results, especially those leading to treatment decisions without confirmation of negative results by microscopy (which is more sensitive than antigen detection assays for detecting malaria parasites in blood), could pose a risk.

In the table below, FDA has identified the risks to health generally associated with the use of this device. Measures recommended to mitigate the identified risks are described in this guidance document, as shown in the table below. You should conduct a risk analysis, prior to submitting your premarket notification, to identify any other risks specific to your device. The premarket notification should describe the risk analysis method including any additional risks you identify and the approach you use to address the risk. If you elect to use an alternative approach to address the risks identified in this

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document, or have identified risks additional to those in this document, you should provide sufficient detail to support the approach you have used to address that risk.

Identified Risks	Mitigation measures
Failure of the assay to perform properly, i.e., false negative or false positive results which can lead to improper patient management and/or inappropriate public health responses	Section 6. Performance Characteristics Section 7. Labeling
Failure to properly interpret test results	Section 6. Performance Characteristics Section 7. Labeling

5. Device Description

In your 510(k) submission, you should identify the regulation and product code of the legally marketed predicate device for which you claim substantial equivalency. In order to help FDA efficiently review all the aspects of your device, as compared with the predicate, you should include a table that outlines the similarities and differences between the predicate and your device.

Key issues in the review of a device are the specific intended use, and the technology utilized.

Technology utilized

Your 510(k) should include the following assay technology information:

- A description of the method to detect *Plasmodium* specific antigens and/or pan malarial antigens used in your device (e.g., immunochromatographic assay).
- A description of the reagent components included with the kit, including antibody sources.
- Information on the antigens detected.
- Internal controls and a description of their specific function in the assay.
- External controls that you provide to users, or recommend for use.
- Related peer-reviewed literature references describing the test methodology if applicable.
- Illustrations or photographs of any non-standard equipment or methods, if applicable.

In addition to the descriptive information you may submit appropriate peer-reviewed literature references relevant to the technology of the device.

Intended use

Your 510(k) should specify what the assay measures, the clinical indications for which the test is to be used, and the specific population for which the test is intended. You should include clinical and demographic description of patients (e.g., gender, age, symptoms) for whom clinical performance has been demonstrated. The intended use should specify whether the test is qualitative or quantitative. It should also specify the type of site for which the test is intended (e.g., clinical laboratory, POL (physician office lab), POC (point of care) site).

6. Performance Characteristics

General Study Recommendations

In your 510(k) you should detail the study design you used to evaluate each of the performance characteristics outlined below. In general, for the clinical and precision studies we recommend you conduct testing at 3 sites, representative of where you intend to market the device e.g., clinical laboratory or point-of-care sites.

You should evaluate performance of your assay, for all the specimen types that you recommend for your assay (e.g., venous blood, finger stick samples).

To facilitate an accurate interpretation of acceptance criteria and data summaries during review, we recommend that you provide appropriate specific information concerning protocols in your 510(k). This information is also important to aid users in interpreting information in your labeling. For example, when referring to CLSI (Clinical and Laboratory Standards Institute) protocols or guidelines, we recommend that you indicate which specific aspects of the protocols or guidelines you followed. This type of information is also important to aid users in interpreting results, and should be provided in the labeling as well.

We recommend that you contact the Division of Microbiology Devices in the Office of In Vitro Diagnostic Device Evaluation and Safety to obtain feedback regarding your planned study and the clinical claims you intend to support. FDA offers an opportunity to obtain this type of input by a process referred to as a pre-IDE review.

We recommend that you address the following performance characteristics in your 510(k):

A. Specimen collection and handling conditions

You should evaluate all recommendations in your labeling concerning specimen collection, transport, and storage options. You should ensure that the test is evaluated using specimens that are handled in the same manner as recommended in the device package insert. You should determine whether the device can maintain acceptable performance (e.g., accuracy, reproducibility) over the storage times and temperatures recommended to users. For example, an appropriate study may include an analysis of aliquots stored under the conditions of time, humidity, and temperature that you recommend to users of the device.

B. Precision Testing (Repeatability/Reproducibility)

You should provide data demonstrating the precision (i.e., repeatability and reproducibility) of your device. The CLSI documents, "User Verification of Performance for Precision and Trueness" (CLSI Guideline EP15-A2) and "User Protocol for Evaluation of Qualitative Test Performance" (CLSI Guideline EP12-A), include guidelines for developing experimental design, computations, and a format for establishing performance claims. We recommend you follow these guidelines. Ideally, you should design your evaluation to identify all sources of assay variability.

We recommend that you evaluate precision across various *Plasmodium* levels that a laboratory might encounter, and that you include levels near (above and below) the limit of detection. For the precision evaluation, you should use patient samples as well as the quality control materials that you supply or recommend for use with your device.

We recommend that you include the following in your 510(k).

- Estimates of the concentrations of levels used.
- Sites at which the precision protocol was run.
- Number of days, runs, and observations.
- Number of sites and/or operators.
- Description of those factors held constant and those varied during the evaluation (e.g., reagent lots and operators).
- Percent agreement within and among sites.

You should describe your computational methods, if they are different from those described in CLSI EP15-A2 and CLSI EP12-A.

C. Interference

You should characterize the effects of potential interferents on assay performance. Guidelines for developing experimental designs and selecting interferents for testing are described in detail in the CLSI document, "Interference Testing in Clinical Chemistry", EP7-A2. Potential sources of interference that you should test include over-the-counter or prescription medications that may be introduced into whole blood of individuals within the intended population (i.e. anti-malarial drug therapy, antibiotics and anti-inflammatory drugs). Other potential sources of interference to test include compounds normally found in clinical samples, such as triolein (triglycerides), hemoglobin, bilirubin, and serum protein. Typically, these types of interference studies involve adding the potential interferent to the whole blood sample and determining any bias in the test result relative to a control sample (to which no interferent has been added).

You should also test whole blood samples containing the following:

- Abnormally high levels of leukocytes (potentially present in patients with fever).
- Abnormally high levels of gametocytes.

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- High hematocrit levels.
- Positive titers of rheumatoid factor (known to cause false positives in these types of assays).
- Positive titers for other autoimmune antibodies, such as systemic lupus erythematosus, antinuclear antibodies, and human anti-mouse antibodies.

You should describe the following in your 510(k):

- The types and levels of interferents tested.
- The levels of malaria antigen in the sample, including a description of how the levels were determined.
- Numbers of replicates tested.
- Definition or methods for evaluating interference.
- Results, including any observed bias (negative or positive) due to interference, as well as your criteria for determining non-interference.

D. Analytical Specificity (Cross reactivity)

You should provide data demonstrating assay specificity by measuring the cross-reactivity of your device with other relevant microorganisms, including bacteria, viruses and parasites. In particular, you should characterize performance of the test in the presence of microorganisms that may present similar clinical symptoms that may be confused with malaria infection, e.g., *Borrelia burgdorferi*, *Babesia microti*, *Trypanosoma cruzi*, *Trypanosoma rangeli*, leptosporosis, Cytomegalovirus (CMV), Dengue, and Epstein-Barr virus (EBV). If your antigen and/or antisera are recombinant, we recommend that you provide cross-reactivity studies against the recombinant vector.

E. Limit of Detection (Analytical Sensitivity)

You should determine the limit of detection of your assay for each of the four species of *Plasmodium* known to infect humans. We define this as the lowest level of *Plasmodium* species, parasites or antigen that can be reliably detected with stated probability by the test. We recommend that you describe the sample type and define your measures of sensitivity in terms of parasites/uL as measured by microscopy. We recommend that you refer to the CLSI document “Protocols for Determination of Limits of Detection and Limits of Quantitation”, EP17-A for guidelines for determining the limits of detection of your assay.

F. Analytical Reactivity

You should provide data to support the ability of your assay to detect variations within-species, and specifically to recognize diversity of the target antigen. The reactivity of the assay can vary depending on the stage of parasites circulating in peripheral blood. If relevant for your device you should provide the stages of development of the parasite noted in your microscopic evaluations as supporting data for reactivity.

G. Prevalence (Expected Values)

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You should establish the prevalence of malaria in an endemic population with symptoms consistent with malaria infections, or in individuals who would be tested for malaria using the new device. You should assay a statistically significant number of specimens that are representative of the intended use including the specified matrix. You should provide these results based on your new device performance when compared to the reference method (thick and thin film microscopy). We recommend that you summarize the distribution of the population according to age groups (children < 18, and adults \geq 18 years), gender, and geographical area, and indicate the number of positive and negative results. Because this device is not intended for use in screening blood or tissue donors, blood donors should not be used for this study.

H. Method Comparison

You should describe the method comparison of your device to thick and thin film microscopy, the “gold standard” for laboratory diagnosis of malaria. This evaluation should include all the specimen types (i.e. venous blood, fingerstick, different anticoagulants etc.) indicated in your labeling.

You should evaluate your assay at three different geographical sites representing the testing environment where the device will ultimately be used (e.g., clinical laboratory, point-of-care sites), by individuals who will use the test in clinical practice

We recommend prospective collection of specimens from individuals representing the intended use population, i.e., those with signs and symptoms consistent with malaria infections. Since malaria prevalence is relatively low in the U.S., prospective testing can be done in non-U.S. sites. You may supplement these studies with well-characterized specimens obtained from repository banks. Specimen characterization should include information supporting sample integrity, appropriate selection supporting the intended use, and clinical laboratory testing results (thick and thin film microscopy). Samples should be masked to avoid testing bias. The information you provide concerning sample characterization of non-U.S. specimens should be the same as that for specimens from the U.S.

We recommend that you include samples from individuals from both an endemic normal population and a non-endemic population in order to evaluate the clinical specificity of your device. You should include individuals with febrile disease to ensure that test performance is properly challenged.

Appropriate sample size of the indicated population depends on factors such as estimated incidence of each *Plasmodium* species in the study locations, precision of the test, interference, and other performance characteristics of the test. In your 510(k) you should provide a statistical justification and the statistical model used to determine the sample size.

We suggest you contact the Division of Microbiology Devices for feedback on your study design before you initiate your study.

I. Presentation of Results

In your 510(k) you should describe how the samples were selected, and any reasons that samples were excluded.

We recommend that you initially analyze and present data from each study site separately to evaluate any inter-site variation and include results of the analysis in the 510(k). It may be possible to pool clinical study results from the individual sites in the package insert if you can demonstrate that there are no significant statistical or clinical differences in the results or populations among sites. We also recommend that you analyze performance separately for various parasitemia levels and other demographic variables (e.g., age, gender, presence or absence of anti-malarial therapy), as well as hematocrit values.

We recommend that you provide line data for all studies. You may supply this information electronically using Microsoft EXCEL, delimited text files, or SAS files.

7. Labeling

The premarket notification must include labeling in sufficient detail to satisfy the requirements of 21 CFR 807.87(e). Labeling for the marketed device must comply with the requirements of 21 CFR part 801 and 21 CFR 809.10 before a medical device is introduced into interstate commerce.

The following suggestions are aimed at assisting you in submitting labeling that satisfies these requirements, and in preparing final labeling.

A. Intended use

The intended use should specify what the test measures, the clinical indications for which the test is to be used and the specific population for which the test is intended. It should include a description of patients, e.g., gender, age, symptoms, countries visited or resided in, for whom clinical performance has been demonstrated. The intended use should specify whether the test is qualitative or quantitative. The intended use should also specify the testing environment (e.g., clinical laboratory, point of care).

B. Device Description

You should describe the test methodology used in your device.

C. Directions for Use

You should provide clear instructions that delineate the technological features of the specific device and how the device is to be used on patients. You should include a general description of the analysis procedure, from sample collection up to, and including, result reporting. Instructions should encourage users to familiarize themselves with the features of the device and how to use it safely and effectively.

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You should include handling and storage instructions. You should describe stability (i.e., expiration dating) under the opened and closed storage conditions that you recommend to users.

D. Quality Control

You should provide quality control recommendations in the labeling. This should include a clear explanation of which control materials are to be used in the assay and the expected results for the control materials. You should also specify what function of the procedure your quality control material will assess.

The analyte level of your positive control should challenge your assay cutoff.

If quality control material is not provided with the kit for the end-user, you should place a bolded warning under the Intended Use and on the kit outer box label. This warning should convey the following:

Warning: This test should only be used by laboratories that have or can acquire blood containing *Plasmodium falciparum* for use as a positive control material. It is recommended that the level of the positive control used challenge the assay cutoff.

E. Precautions, Warnings and Limitations

You should clearly describe any assay limitations, warnings, and precautions relevant to your assay, including those that a health care provider needs to know prior to ordering the test.

We recommend that you address issues concerning safe use of your assay with statements in the labeling, such as the following:

Human samples and blood-derived products may be routinely processed with minimum risk using the procedures described. Because no test method can offer complete assurance that laboratory specimens do not contain HIV, hepatitis B virus, or other infectious agents, specimens should be handled at the Biosafety Level 2 (BL2) as recommended for any potentially infectious human serum or blood specimen in the CDC NIH manual, Biosafety in Microbiological and Biomedical Laboratories, 3rd Edition, 1993 and CLSI Approved Guideline M29-A, Protection of Laboratory Workers from Instrument Biohazards and Infectious Disease Transmitted by Blood, Body Fluids, and Tissue.

The following limitations should be included when appropriate:

- The test detects antigen from both viable and non-viable *Plasmodium* species organisms, including gametocytes and sequestered *P. falciparum* parasites. Test performance depends on antigen load in the specimen and may not directly correlate with microscopy performed on the same specimen.

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- Performance of the test has not been established for monitoring treatment of malaria. Residual *Plasmodium* antigen may be detected for several days following elimination of the parasite by anti-malarial treatment.
- Samples with positive rheumatoid factor (RF) titers may produce false positive results in the test.
- Testing should only be performed on patients with clinical symptoms of malaria.
- This test is not intended for screening asymptomatic individuals

F. Interpretation of Results

You should address issues concerning patient safety and significance of test results with statements in the labeling, such as the following:

- In cases of presumptive negative results for *Plasmodium* species antigens, infection due to *Plasmodium* species cannot be ruled out. *Plasmodium* antigen in the sample may be below the detection limit of the test. Negative results must be confirmed by thick and thin film microscopy.
- A negative test result does not exclude a malarial infection, particularly if *Plasmodium* species were present, but at low parasitemia counts. Therefore, the results obtained with the test should be used in conjunction with other laboratory and clinical findings to make an accurate diagnosis. As is often done in serial microscopy testing, another sample can be collected and retested.
- The test detects antigen from both viable and non-viable *Plasmodium* species organisms, including gametocytes and sequestered *P. falciparum* parasites. Test performance depends on antigen load in the specimen and may not directly correlate with microscopy performed on the same specimen.

G. Prevalence

You should include the prevalence of the test with an explanation of the result. You should also summarize the study used to determine the prevalence, including the number of samples, age, gender, and demographics of the population.

H. Performance Characteristics

You should include in the package insert a summary of the study designs and the results of the studies described in Sections 6 that would aid users in interpreting test results. This includes clinical and analytical performance characteristics.