

**510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION  
DECISION SUMMARY  
DEVICE ONLY TEMPLATE**

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

k061542

**B. Purpose for Submission:**

De Novo clearance

**C. Measurand:**

*Plasmodium* antigens

**D. Type of Test:**

Qualitative, *in vitro* immunochromatographic assay

**E. Applicant:**

Binax, Inc., d/b/a Inverness Medical Professional Diagnostics

**F. Proprietary and Established Names:**

Binax NOW<sup>®</sup> Malaria

**G. Regulatory Information:**

**a) Regulation section:**

*Plasmodium* species antigen detection assay 21 CFR 866.3402.

**b) Classification:**

Class II

**Product Code:**

OAX

**c) Panel:**

83 Microbiology

**H. Intended Use:**

**a) Intended use(s):**

The Binax NOW<sup>®</sup> Malaria Test is an *in vitro* immunochromatographic assay for the qualitative detection of *Plasmodium* antigens circulating in human venous and capillary EDTA whole blood of individuals with signs and symptoms of malarial infection. The test targets the histidine-rich protein II (HRPII) antigen specific to *Plasmodium falciparum* (P.f.) and a pan-malarial antigen, common to all four malaria species capable of infecting humans - *P. falciparum*, *P. vivax* (P.v.), *P. ovale* (P.o.), and *P. malariae* (P.m.). It is intended to aid in the rapid diagnosis of human malaria infections and to aid in the differential diagnosis of *Plasmodium falciparum* (P.f.) infections from other less virulent malarial infections. Negative results must be confirmed by thin / thick smear microscopy.

**b) Indication(s) for use:**

The Binax NOW<sup>®</sup> Malaria Test is for the laboratory diagnosis of malaria in individuals with signs and symptoms consistent with malaria infection.

**c) Special condition for use statement(s):**

The device is for prescription use only

**d) Special instrument Requirements:**

NA

**I. Device Description:***In vitro* immunochromatographic immunoassay**J. Substantial Equivalence Information:**

N/A De Novo

**K. Standard/Guidance Document Referenced (if applicable):****L. Test Principle:**

The Binax NOW® Malaria Test is an immunochromatographic membrane assay that uses monoclonal antibodies to detect *Plasmodium falciparum* antigen and pan-malarial antigen (an antigen shared by all *Plasmodium* species causing human malaria) in venous and capillary whole blood specimens. These antibodies, and a control antibody, are immobilized on a membrane support as three distinct lines and are combined with a sample pad, which is impregnated with visualizing particles conjugated to control and anti-malaria antibodies, to create a test strip. This test strip is mounted in a book-shaped, hinged test device, along with wash and absorbent pads, intended to aid in the clearing of the membrane when the device is closed.

To perform the test, whole blood is applied to the sample pad. Malarial antigen present in the sample reacts to bind the anti-malaria conjugated antibody. Reagent A is added to the bottom of the test strip and allows the antigen-conjugate complexes to migrate along the test strip, where they are captured by the immobilized antibodies, forming the Test Line(s). Immobilized control antibody captures control conjugate, forming the Control Line. Once the blood sample has migrated the length of the test strip, the device is closed, allowing Reagent A that has been added to the wash pad to clear the test strip of excess blood.

Test results are interpreted by the presence or absence of visually detectable pink-to-purple colored lines. A positive test result, read in 15 minutes, will include the detection of both a Test Line (or Test Lines) and a Control Line. A negative test result, read in 15 minutes, will produce only a Control Line, indicating that malarial antigens were not detected in the sample. Failure of the Control Line to appear, whether the Test Line(s) is present or not, indicates an invalid result.

**M. Performance Characteristics (if/when applicable):**Analytical performance:**a) *Precision/Reproducibility:***

A blind study of the Binax NOW® Malaria Test was conducted at 3 separate sites using panels of blind coded specimens containing negative, limit of detection, and low positive P.f. and P.v. samples. Participants tested each sample multiple times on 3 different days. There was 97% (140/144) agreement with expected test results, with no significant differences within run (replicates tested by one operator), between run (3 different days), between sites (3 sites), or between

operators (6 operators). The overall percent detection of each sample type is summarized below.

**Overall Percent Detection of P.f. and P.v. Samples**

Sample Type	% Detection
P.f. Low Positive	94% (17/18)
P.f. LOD	97% (35/36)
P.v. Low Positive	94% (17/18)
P.v. LOD	100% (36/36)
Negative	3% (1/36)*

\* One operator called a negative sample a P.f. positive.

a. **Linearity/assay reportable range:**

NA

b. **Traceability, Stability, Expected values (controls, calibrators, or method):**

NA

c. **Detection limit:**

**P.f. and P.v. Limits of Detection:**

In the study described above, Binax NOW® test clinical limit of detection (LOD) for P.f., defined as the parasitemia level in infected blood that produces positive Binax NOW® test results approximately 95% of the time, was determined to be 1001-1500 parasites per  $\mu\text{l}$  and the clinical LOD for P.v. was determined to be 5001-5500 parasites per  $\mu\text{l}$ .

d. **Analytical specificity:**

To determine the analytical specificity of the Binax NOW® Malaria Test, 28 pathogenic microorganisms (7 bacteria, 5 protists and 16 viruses) that may be present in whole blood were tested. All were negative when tested at the concentrations listed below.

TYPE	PATHOGEN TESTED	CONCENTRATION TESTED
Bacteria	<i>Borrelia burgdorferi</i> (N40 strain)	$2.3 \times 10^6$ organisms/ml
	<i>Leptospira interrogans</i> (icterohaemorrhagiae)	$1.0 \times 10^7$ organisms/ml
	<i>Leptospira biflexa</i> (andamana)	$1.0 \times 10^7$ organisms/ml
	<i>Treponema pallidum</i>	$1.0 \times 10^5$ organisms/ml
	<i>Rickettsia conorii</i> (Malish 7)	$1.0 \times 10^7$ organisms/ml
	<i>Rickettsia typhi</i> (Wilmington)	$1.0 \times 10^7$ organisms/ml
	<i>Orientia tsutsugamushi</i> - <i>Rickettsia</i> (Karp)	$1.0 \times 10^7$ organisms/ml
Protists	<i>Babesia microti</i> (RMNS strain)	$4.4 \times 10^7$ parasites/ml
	<i>Trypanosoma cruzi</i> (Y strain)	$1.3 \times 10^6$ parasites/ml
	<i>Leishmania donovani</i>	$1.0 \times 10^6$ parasites/ml
	<i>Leishmania infantum</i>	$1.0 \times 10^6$ parasites/ml
	<i>Leishmania chagasi</i>	$1.0 \times 10^6$ parasites/ml
Viruses	Cytomegalovirus (CMV) (AD169)	$1.2 \times 10^5$ PFU/ml
	Epstein-Barr virus (EBV)	$1.1 \times 10^4$ copies/ml
	Dengue virus - West Pac 74	$1.2 \times 10^5$ PFU/ml
	Dengue virus – S16803	$3.9 \times 10^4$ PFU/ml
	Dengue virus – CH53489	$1.3 \times 10^4$ PFU/ml
	Dengue virus – TVP360	$1.4 \times 10^5$ PFU/ml
	Yellow Fever virus	$7.9 \times 10^6$ PFU/ml
	West Nile virus	$1.6 \times 10^5$ PFU/ml
	Chikungunya virus	$4.0 \times 10^5$ PFU/ml
	Ross-River virus	$1.0 \times 10^6$ PFU/ml
	Influenza A – Bayern/7/95	$2.5 \times 10^7$ TCID <sub>50</sub> /ml
	Influenza B – Victoria/2/87	$1.0 \times 10^7$ TCID <sub>50</sub> /ml
	HIV-1 (Subtype B)	$1.4 \times 10^5$ copies/ml
	Hepatitis B	$2.0 \times 10^5$ IU/ml
	Hepatitis C	$1.9 \times 10^5$ IU/ml
	Rubella virus	$\geq 2.0 \times 10^2$ TCID <sub>50</sub> /ml

**Interference from Exogenous Blood Components:**

The following substances that may be artificially introduced into whole blood were evaluated in the Binax NOW® Malaria Test at the concentrations listed and were found not to affect test performance. Note: The analytical effects of these drugs on the Binax NOW® test were studied by taking whole blood and spiking it with quantities at high therapeutic concentrations and then testing these samples.

Substance Type	Substance	Concentration
Anti-malarial drugs (prevention)	Mefloquine (Lariam®)	1 mg/ml
	Doxycycline* (Vibramycin®)	1 mg/ml
	Chloroquine	1 mg/ml
	Hydroxychloroquine sulfate	1 mg/ml
	Paludrine (Proguanil®)	1 mg/ml
	Primaquine	1 mg/ml
	Quinine	1 mg/ml
	Sulfadoxine and Pyrimethamine (Fansidar®)	1 mg/ml
Antibiotic (treatment)	Amoxicillin (Trimox®)	0.1 mg/ml
	Cephalexin	0.1 mg/ml
	Ciprofloxacin	0.1 mg/ml
	Erythromycin	0.1 mg/ml
Anti-Inflammatory Drugs (treatment)	Aspirin	1 mg/ml
	Acetaminophen	1 mg/ml
	Ibuprofen (NSAID)	1 mg/ml

\* Doxycycline is also used as an antibiotic, typically at a lower dose than that tested in this study.

**Interference from Endogenous Blood Components:**

The Binax NOW® Malaria test was evaluated for possible interference from high levels of endogenous blood components, based on guidelines described in CLSI EP7. EDTA whole blood samples were tested that contained hemoglobin, protein, bilirubin (conjugated and unconjugated) or triglycerides at concentrations above physiological levels. None of the endogenous blood components affected test performance.

**Interference from Unrelated Medical Conditions:**

To assess the impact of unrelated medical conditions on the specificity of the Binax NOW® Malaria Test, 116 specimens from subjects with a variety of medical conditions unrelated to malaria were tested. Only five (5) of the 116 specimens tested produced a false positive result on the Binax NOW® Test, four (4) from subjects known to be positive for rheumatoid factor and one (1) from a subject with a positive human anti-mouse antibody (HAMA) titer.

Comparison studies:***a. Method comparison with predicate device:***

N/A

***b. Matrix comparison:***

N/A

Clinical studies:*a. Clinical sensitivity:***Clinical Sample Performance – Binax NOW® Malaria Test Sensitivity & Specificity – Endemic Population:**

The performance of the Binax NOW® test was compared to Giemsa malaria microscopy in a multi-center prospective study conducted in 2001 outside the U.S., in regions considered endemic for malaria. A total of 4,122 whole blood specimens collected from patients presenting with malaria-like symptoms were evaluated on the Binax NOW® test. Microscopy was considered positive only when asexual malaria forms were detected, since asexual forms (not gametocytes) are indicative of active infection.

Forty-four percent (1,796/4,122) of the tested population was microscopy positive for malaria, including 557 patients with P.f., 1,187 with P.v., 16 with P.m., 2 with P.o., and 34 with mixed P.f./P.v. infections. Fifty-nine percent of patients were male, 41% female, 19% pediatric (<18 years) and 81% adult (≥18 years). Binax NOW® test performance for detection of the individual malaria species and for mixed P.f./P.v. infections is summarized below.

No differences in Binax NOW® Malaria Test performance were observed based on patient age or gender. Binax NOW® test specificity for P.f. trends slightly lower (89.4%) in the 5% of patients who were on anti-malarial drug therapy, than in patients not receiving therapy (94.4%), but does not achieve statistical significance.

*Detection of P.f. Infection*

Binax NOW® test sensitivity and specificity for detection of P.f. vs. microscopy is presented below. Sensitivity was evaluated based on the levels of parasitemia (parasites per µl) observed in microscopy.

**Binax NOW® Malaria Test Sensitivity and Specificity for P.f. vs. Microscopy**

<b>SENSITIVITY FOR P.f.</b>		
<b>Parasitemia Level</b>	<b>% Sensitivity</b>	<b>95%CI</b>
> 5000	99.7% (326 / 327)	98 - 100%
1000 – 5000	99.2% (126 / 127)	96 - 100%
500 – 1000	92.6% (25 / 27)	76 - 99%
100 – 500	89.2% (33 / 37)	75 - 97%
0 – 100	53.9% (21 / 39)	37 - 70%
Overall	95.3% (531 / 557)	93 - 97%

<b>SPECIFICITY FOR P.f.</b>	
% Specificity	95% CI
94.2% (3297 / 3500)	93-95%

#### *Detection of P.v. Infection*

Binax NOW® test sensitivity and specificity for detection of P.v. vs. microscopy is presented below. Sensitivity was evaluated based on the levels of parasitemia (parasites per  $\mu$ l) observed in microscopy. There were 68 samples generating two Binax NOW® test lines that were microscopy positive for P.v. only. When these samples are included in the true positive calculation, Binax NOW® test sensitivity for overall detection of P.v. increases from 68.9% to 74.6% (886/1,187).

#### **Binax NOW® Malaria Test Sensitivity and Specificity for P.v. vs. Microscopy**

<b>SENSITIVITY FOR P.v.</b>		
Parasitemia Level	% Sensitivity	95%CI
> 5000	93.5% (462 / 494)	91 - 96%
1000 – 5000	81.0% (277 / 342)	76 - 85%
500 – 1000	47.4% (37 / 78)	36 - 59%
100 – 500	23.6% (34 / 144)	17 – 31%
0 – 100	6.2% (8 / 129)	3 – 12%
Overall	68.9% (818 / 1187)	66 - 72%

<b>SPECIFICITY FOR P.v.</b>	
% Specificity	95% CI
99.8% (2863 / 2870)	99– 100%

#### *Detection of P.m. and P.o. Infection*

Binax NOW® test sensitivity was 43.8% (7/16) for detection of P.m. and 50% (1/2) for detection of P.o. When five P.m. microscopy positive samples that generated two test

lines in the Binax NOW® test are included in the true positive calculation, Binax NOW® test sensitivity for P.m. increases from 43.8% to 75.0% (12/16).

*Detection of Mixed P.f./P.v. Infection*

Thirty four samples were both P.f. and P.v. positive by microscopy, based on the detection of asexual forms of both species. The Binax NOW® test detected 32 of these samples by generating both test lines, for a sensitivity of 94.1% (95% CI of 81-98%).

**b. Clinical specificity:**

The performance of the Binax NOW® test was compared to Giemsa malaria microscopy in a prospective study conducted in the eastern US in 2006-2007. One hundred (100) whole blood specimens collected from febrile patients were evaluated on the Binax NOW® test and on microscopy. All 100 samples were negative for malaria on microscopy, and 99 of these samples generated negative Binax NOW® test results, yielding a specificity of 99% (99/100) in this low incidence population. Binax NOW® test specificity versus microscopy is presented below.

**Binax NOW® Malaria Test Specificity vs. Microscopy**

	- / -	+ / -	% Spec	95% CI
<b>P.f.</b>	100	0	100%	96-100%
<b>P.v., P.o., P.m.</b>	99	1	99%	95-100%

**N. Proposed labeling:**

The labeling is sufficient and it satisfies the requirement of 21 CFR Part 809.10.

**WARNING**

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

Clinical performance has not been adequately established for *P. ovale* (P.o.) and *P. malariae* (P.m.). The user must establish performance characteristics of this test with these *Plasmodium* species.

The test is not intended for use in screening asymptomatic populations.

**O. Conclusion:**

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