SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name: Rapid HIV-1 Antibody Test

Device Trade Name: OraQuick® Rapid HIV-1 Antibody Test

Applicant's Name and Address: OraSure Technologies, Inc.
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Premarket Approval Application (PMA) Number: BP010047

Date of Notice of Approval to the Applicant: November 7, 2002

II. Indications for Use

The OraQuick® Rapid HIV-1 Antibody Test is a single-use, qualitative immunoassay to detect antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) in fingerstick whole blood specimens. The OraQuick® Rapid HIV-1 Antibody Test is intended for use as a point-of-care test to aid in the diagnosis of infection with HIV-1. This test is suitable for use in multi-test algorithms designed for statistical validation of rapid HIV test results. When multiple rapid HIV tests are available, this test should be used in appropriate multi-test algorithms.

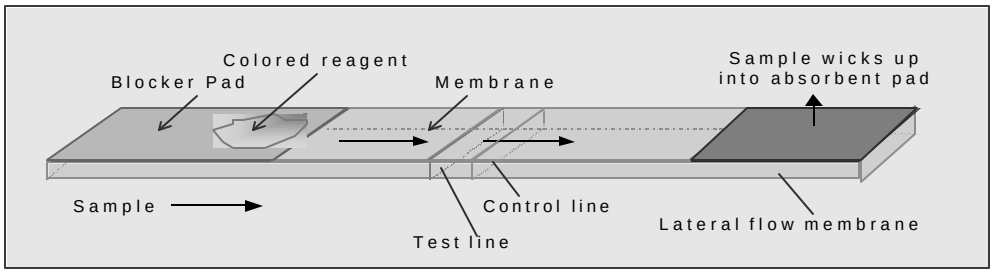
III. Device Description

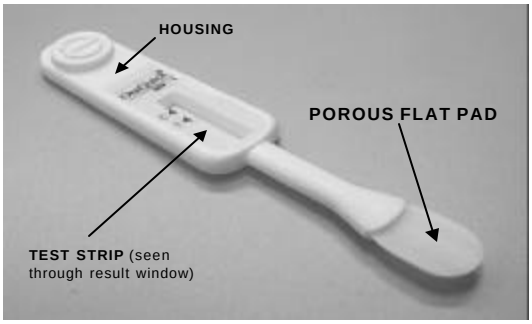
The OraQuick® Rapid HIV-1 Antibody Test consists of four components: (1) a Specimen Collection Loop, (2) a Reusable Test Stand, (3) the Test Device, and (4) a Developer Solution Vial containing 1 mL of developer solution. The latter two components are sealed in a split Mylar pouch. Kit Controls are sold separately as a necessary accessory to perform routine quality control procedures as stipulated in the Product Insert.

The single-use Specimen Collection Loop is designed to collect a 5 µL specimen. The Reusable Test Stand is designed to hold the Developer Solution Vial and Test Device in the proper position to run the test. The Developer Solution Vial contains 1 mL of a phosphate buffered saline solution containing polymers and an anti-microbial agent. The developer solution serves as a specimen diluent and a solution to carry the specimen through the Test Device. The plastic-enclosed Test Device consists of a porous flat pad that serves as a wick for absorption of diluted specimen into the

device, a pad impregnated with material to minimize non-specific interactions, a pad impregnated with a red-colored indicator reagent, a nitrocellulose strip containing HIV peptide antigens and a biochemical that recognizes human antibodies, and an absorbent material to facilitate flow through the device.

OraQuick® Assay Design





To perform a test, a fingerstick whole blood specimen is collected with a Specimen Collection Loop and transferred into the Developer Solution Vial, followed by the insertion of the Test Device. The developer solution facilitates the flow of the specimen into the device and onto the test strip. As the diluted specimen flows through the device, it rehydrates the protein-A gold colorimetric reagent contained in the device. As the specimen continues to migrate up the strip, it encounters the Test (T) zone. If the specimen contains antibodies that react with the antigens immobilized on the nitrocellulose membrane, a reddish-purple line will appear, qualitatively indicating the presence of antibodies to HIV-1 in the specimen. The intensity of the line color is not directly proportional to the amount of antibody present in the specimen.

Further up the assay strip, the sample will encounter the Control (C) zone. This built-in procedural control serves to demonstrate that a specimen was added to the vial and that the specimen has migrated adequately through the device. A reddish-purple line will appear during the performance of all valid tests, whether or not the sample is positive or negative for antibodies to HIV-1.

The test results are interpreted after 20 minutes but not more than 60 minutes after the introduction of the Test Device into the Developer Solution Vial containing the test

specimen. No precision pipeting, predilutions or specialized instrumentation are required to perform the OraQuick® Rapid HIV-1 Antibody Test.

IV. Restrictions

1. Sale of the OraQuick® Rapid HIV-1 Antibody Test is restricted to clinical laboratories
    - that have an adequate quality assurance program, including planned systematic activities to provide adequate confidence that requirements for quality will be met; and
    - where there is assurance that operators will receive and use the instructional materials.
2. The OraQuick® Rapid HIV-1 Antibody Test is approved for use only by an agent of a clinical laboratory.
3. Test subjects must receive the "Subject Information" pamphlet prior to specimen collection and appropriate information when test results are provided.
4. The OraQuick® Rapid HIV-1 Antibody Test is not approved for use to screen blood or tissue donors.

V. Warnings

For *in vitro* Diagnostic Use

1. The product insert must be read completely before using the product. The instructions must be followed carefully. Not doing so may result in inaccurate test results.
2. FDA has approved this kit for use with fingerstick whole blood specimens only. Use of this test kit with specimen types other than those specifically approved for use with this device may result in inaccurate test results.
3. This test should be performed at ambient temperature (15^{o}-27^{o}C).
4. The two small holes on the back of the test device must not be covered. Doing so may impair the flow of fluid through the device.
5. Reading test results earlier than 20 minutes or later than 60 minutes may yield erroneous results.
6. Adequate lighting is required to read a test result.

VI. Limitations of the Test

1. A Reactive result using the OraQuick® Rapid HIV-1 Antibody Test suggests the presence of anti-HIV-1 antibodies in the specimen. The OraQuick® Rapid HIV-1 Antibody Test is intended as an aid in the diagnosis of infection with HIV-1. AIDS and AIDS-related conditions are clinical syndromes and their diagnosis can only be established clinically.

2. For a Reactive result, the intensity of the test line does not necessarily correlate with the titer of antibody in the specimen.

3. A Non-Reactive result does not preclude the possibility of exposure to HIV or infection with HIV. An antibody response to recent exposure may take several months to reach detectable levels.

VII. Alternative Practices and Procedures

The detection of antibodies in human subjects against the HIV-1 virus is primarily done using laboratory based assays with blood, serum, plasma, oral fluids, or urine. The majority of these tests use principles similar to the OraQuick® HIV-1 Rapid HIV-1 Antibody Test. Peptides, recombinant antigens, isolated proteins, or whole viral lysate are used to capture antibodies in a patient sample on a solid phase support. The detection of these captured antibodies is accomplished with an instrument using a variety of reporters such as colored or chemiluminescent products from enzymatic reactions. A secondary confirmation of the screening result is performed for all Reactive results. Once the testing is complete the assays provide qualitative information that is usually reported as negative or positive. The OraQuick® test differs from laboratory tests in two ways: 1) the OraQuick® test is interpreted visually rather than with an instrument and 2) the OraQuick® test uses colloidal gold as the reporter.

VIII. Potential Adverse Effects of the Device on Health

No known adverse effects have been found with the OraQuick® Rapid HIV-1 Antibody Test in any study performed to date.

IX. Summary of Preclinical Studies

Following are brief summaries of the non-clinical laboratory based studies that have been conducted to assess the performance of the OraQuick® Rapid HIV-1 Antibody Test.

1. Evaluation of Worldwide Performance Panel

To assess the sensitivity of the OraQuick® Rapid HIV-1 Antibody Test for HIV-1 variants from various geographic regions, 215 confirmed HIV-1 antibody-positive specimens were obtained from various parts of the world. Of these 215 specimens, 214 were Reactive using the OraQuick® Rapid HIV-1 Antibody Test. One confirmed HIV-1 antibody-positive specimen from China was Non-Reactive using the OraQuick® test.

2. Evaluation of HIV-1 Seroconversion Panels

Eleven HIV-1 seroconversion panels were tested in comparison with licensed anti-HIV EIA tests. Each panel consisted of sequential specimens obtained from a single individual during seroconversion. The eleven seroconversion panels consisted of 69 specimens. The results of this study are shown in Table 1. In this study, the OraQuick® Rapid HIV-1 Antibody Test was demonstrated to be capable of detecting seroconversion at time points similar to currently available FDA licensed EIAs.

TABLE 1
Comparison of the OraQuick® Rapid HIV-1 Antibody Test and Licensed Anti-HIV EIA Tests Using Seroconversion Panels

Specimen Information			Licensed Anti-HIV EIA Tests				
Panel	Relative Day of Bleed	**OraQuick Test**	EIA #1	EIA #2	EIA #3	EIA #4	EIA #5
K	1	NR	NR	NR	NR	NR	NR
	7	NR	NR	NR	NR	NR	NR
	9	NR	NR	NR	NR	NR	NR
	14	**R**	NR	**RR**	NR	NR	NR
	16	**R**	NR	**RR**	NR	NR	NR
	21	**R**	NR	**RR**	NR	**RR**	**RR**
	23	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	30	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	34	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	37	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
N	1	**R**	**RR**	**RR**	NR	NR	NR
	5	**R**	**RR**	**RR**	NR	**RR**	NR
	8	**R**	**RR**	**RR**	NR	**RR**	NR
	26	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	32	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
Q	1	NR	NR	NR	NR	NR	NR
	54	NR	NR	NR	NR	NR	NR
	58	NR	NR	NR	NR	NR	NR
	61	NR	NR	**RR**	NR	NR	NR
	66	**R**	NR	**RR**	NR	NR	NR
	68	**R**	**RR**	**RR**	NR	NR	NR
	73	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
R (M)	3	NR	NR	**RR**	NR	NR	NR
	8	NR	NR	**RR**	NR	NR	NR
	14	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	16	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	22	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
S	1	NR	NR	NR	NR	NR	NR
	10	**R**	**RR**	**RR**	NR	NR	NR
	12	**R**	**RR**	**RR**	NR	**RR**	NR
W	1	NR	NR	NR	NR	NR	NR
	8	NR	NR	NR	NR	NR	NR
	13	NR	NR	NR	NR	NR	NR
	15	NR	NR	NR	NR	NR	NR
	29	NR	NR	NR	NR	NR	NR
	31	NR	NR	NR	NR	NR	NR
	36	NR	NR	NR	NR	NR	NR
	38	NR	NR	NR	NR	NR	NR
	48	NR	NR	**RR**	NR	NR	NR
	85	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	87	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	146	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	162	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
AB	1	NR	NR	NR	NR	NR	NR
	29	NR	NR	**RR**	NR	NR	NR

	34	**R**	**RR**	**RR**	NR	NR	NR
	36	**R**	**RR**	**RR**	NR	NR	**RR**
	41	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
AC	1	NR	NR	NR	NR	NR	NR
	112	NR	NR	**RR**	NR	NR	NR
	121	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	126	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	131	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
AE	1	NR	NR	NR	NR	NR	NR
	4	NR	NR	NR	NR	NR	NR
	8	NR	NR	**RR**	NR	NR	NR
	11	NR	**RR**	**RR**	NR	**RR**	NR
AF	1	NR	NR	NR	NR	NR	NR
	3	NR	NR	NR	NR	NR	NR
	8	NR	NR	NR	NR	NR	NR
	10	NR	NR	NR	NR	NR	NR
	16	NR	NR	NR	NR	NR	NR
	29	**R**	NR	**RR**	NR	NR	NR
	34	**R**	**RR**	**RR**	NR	**RR**	**RR**
	36	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	43	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
AI	1	NR	NR	NR	NR	NR	NR
	8	**R**	**RR**	**RR**	NR	NR	**RR**
	12	**R**	**RR**	**RR**	NR	**RR**	**RR**

NR = Non-Reactive; R = Reactive; RR = repeatedly reactive

3. Evaluation of Low-Titer HIV-1 Antibody Panels

Two low titer HIV-1 antibody panels were tested in comparison with licensed anti-HIV EIA tests. The low titer antibody panels consisted of 30 specimens. The results of this study are shown in Table 2. In this study, the OraQuick® Rapid HIV-1 Antibody Test was demonstrated to be capable of detecting antibodies to HIV-1 at levels similar to currently available FDA licensed EIAs.

TABLE 2
Comparison of the OraQuick® Rapid HIV-1 Antibody Test and Licensed Anti-HIV EIA Tests Using Low Titer HIV-1 Antibody Panels

Specimen Information			Licensed Anti-HIV EIA Tests				
Panel	Member	**OraQuick® Test**	EIA #1	EIA #2	EIA #3	EIA #4	EIA #5
LT106	1	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	2	NR	NR	**RR**	NR	NR	NR
	3	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	4	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	5	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	6	NR	NR	NR	NR	NR	NR
	7	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	8	NR	**RR**	**RR**	NR	NR	NR
	9	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	10	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	11	**R**	**RR**	**RR**	NR	NR	**RR**
	12	**R**	**RR**	**RR**	NR	NR	**RR**
	13	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	14	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	15	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
LT107	1	NR	NR	**RR**	**RR**	NR	NR
	2	**R**	NR	**RR**	**RR**	**RR**	NR
	3	**R**	NR	**RR**	NR	NR	NR
	4	**R**	**RR**	**RR**	**RR**	**RR**	NR
	5	NR	NR	NR	NR	NR	NR
	6	**R**	**RR**	**RR**	**RR**	**RR**	NR
	7	NR	NR	**RR**	**RR**	NR	NR
	8	NR	NR	**RR**	NR	**RR**	NR
	9	NR	NR	**RR**	NR	NR	NR
	10	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	11	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	12	NR	NR	**RR**	NR	NR	NR
	13	NR	NR	**RR**	**RR**	NR	NR
	14	**R**	**RR**	**RR**	**RR**	**RR**	**RR**
	15	**R**	**RR**	**RR**	**RR**	**RR**	**RR**

NR = Non-Reactive; R = Reactive; RR = repeatedly reactive

4. Effect of Unrelated Medical Conditions and Interfering Substances

To assess the impact of unrelated medical conditions or interfering substances on the sensitivity of the OraQuick® Rapid HIV-1 Antibody Test, 200 specimens from a variety of medical conditions unrelated to HIV-1 infection and 125 specimens with interfering substances were spiked with an HIV-1 positive specimen to give a level of reactivity in the low positive range (see list of medical conditions and interfering substances in Table 3 below). All spiked specimens gave Reactive results.

To assess the impact of unrelated medical conditions or interfering substances on the specificity of the OraQuick® Rapid HIV-1 Antibody Test, 321 specimens from a variety of medical conditions unrelated to HIV-1 infection and 119 specimens with interfering substances were analyzed. The results of this study are shown in Table 3. One specimen from subjects known to be positive for EBV, for HBV, or for rheumatoid factor, one from a multiparous woman, and three specimens from known HAV infected subjects gave falsely Reactive results.

TABLE 3
OraQuick® Rapid HIV-1 Antibody Test Reactivity with Specimens from Individuals with Potentially Interfering Medical Conditions and Specimens with Interfering Substances

Medical Condition (n = 321)	OraQuick® Results	
	Reactive	Non-Reactive
Multiparous women	1 [2]	14
Anti-nuclear antibody (ANA)	0	17
Lupus	0	15
Rheumatoid factor	1 [2]	17
Cytomegalovirus (CMV)	0	15
Epstein Barr virus (EBV)	1 [2]	14
Hepatitis A virus (HAV)	3 [1]	17
Hepatitis B virus (HBV)	1 [2]	16
Hepatitis C virus (HCV)	0	15
Human T-cell Lymphotropic virus Type I (HTLV-I)	0	15
Human T-cell Lymphotropic virus Type II (HTLV-II)	0	15
Rubella	0	15
IgG gammopathies	0	13
IgM gammopathies	0	12
Syphilis	0	15
Toxoplasmosis	0	15
Tuberculosis	0	15
Influenza	0	10
Multiple transfusions	0	10
Hemophiliacs	0	10
Herpes Simplex virus	0	5
Cirrhosis	0	5
Dialysis patient	0	4
Colon cancer	0	4
HTLV I/II	0	2
Chlamydia	0	3
Anti-scl or anti-rnp antibody	0	3
Breast cancer	0	1
Anti-DNA antibody	0	1

Gonorrhea	0	1
Interfering Substances (n = 119)		
Elevated Bilirubin	0	20
Elevated Hemoglobin	0	20
Elevated Triglycerides	0	20
Elevated Protein	0	20
Bacterially Contaminated	0	25
Visual Hemolysis (hemolytic)	0	5
Icteric	0	5
Lipemic	0	4

[1] A total of 3 of the 20 HAV specimens were OraQuick® false positive. Two of the 3 specimens were OraQuick® Non-Reactive at the 20-25 minute read time and Reactive at the 55-60 minute read time. The remaining specimen was Reactive at both read times.
[2] One of the specimens was OraQuick® Non-Reactive at the 20-25 minute read time and Reactive at the 55-60 minute read time.

5. Reproducibility

The reproducibility of the OraQuick® Rapid HIV-1 Antibody Test was tested at 3 sites using 3 lots of the device on 3 different days with 9 operators (3 per site). A blind-coded panel was tested that consisted of 5 contrived blood specimens (4 antibody-positive and 1 antibody-negative). Test results were recorded at 20-25 minutes and at 55-60 minutes. A total of 405 tests were performed (135/site), with a total of 81 tests per panel member. The overall reproducibility of the OraQuick® Rapid HIV-1 Antibody Test was 405/405 = 100%. Concordance between the specified assay read time limits was 99.8% (404/405); a single HIV-1 low positive panel member that was Non-Reactive at the 20-25 minute read time was Reactive at the 55-60 minute read time.

6. Animal Studies

No animal studies were performed using the OraQuick® Rapid HIV-1 Antibody Test.

X. Summary of Clinical Studies

SENSITIVITY

A sensitivity study was performed at eight clinical trial sites using freshly obtained fingerstick whole blood samples from 481individuals known to be infected with HIV-1 and 40 AIDS patients. Of the 521 specimens that were repeatedly reactive using a licensed EIA and positive by Western blot, 519 gave a Reactive result on the

OraQuick® Rapid HIV-1 Antibody Test. The results of this study are shown in Table 4.

A separate study was performed at seven clinical trial sites using 625 freshly obtained fingerstick whole blood samples from previously unscreened individuals from high-risk populations at six sites of intended use. The results of this study are also shown in Table 4. Of the 625 specimens tested, 20 were repeatedly reactive using a licensed EIA, of which 17 were positive by Western blot. These same 17 specimens gave a Reactive result using the OraQuick® Rapid HIV-1 Antibody Test.

TABLE 4
Detection of Antibody to HIV-1 in Fingerstick Whole Blood Samples from Patients with AIDS and from HIV-1 Seropositive Individuals

Test Group	Total Samples	OraQuick® Reactive	Licensed EIA Repeatedly Reactive	Western Blot Positive
AIDS	40	40	40	40
Known HIV-1 Positive	481	479	481	481
High-Risk	625	17	20 [1]	17
TOTAL	1146	536	541	538

[1] Two specimens were negative and one was indeterminate on Western blot.

Combining the number of OraQuick® Reactive results obtained from the study of confirmed positives with the number of OraQuick® Reactive results obtained from the study of high-risk populations, the sensitivity of the OraQuick® Rapid HIV-1 Antibody Test in these studies was calculated to be 536/538 = 99.6% (95% C.I. = 98.5% - 99.9%).

SPECIFICITY

A specificity study was performed at eight clinical trial sites using freshly obtained fingerstick whole blood samples from 1250 previously unscreened individuals at low risk for HIV-1 infection. In the course of this study, two specimens were confirmed to have antibodies to HIV-1 and were removed from the specificity calculation. All of the remaining specimens gave Non-Reactive results using the OraQuick® Rapid HIV-1 Antibody Test. In addition, all of the 608 HIV-1 antibody-negative specimens from the high-risk study also gave Non-Reactive results using the OraQuick® test. The results of this study are shown in Table 5.

TABLE 5
Performance of the OraQuick® Rapid HIV-1 Antibody Test on Specimens from Individuals Presumed to be Negative for HIV Infection

Test Group	Total Samples	OraQuick® Non-Reactive	Licensed EIA Non-reactive	True Non-reactive [3]
Low-Risk	1250 [1]	1248	1247 [2]	1248
High-Risk	625	608	605	608
TOTAL	1875	1856	1853	1856

[1] Two specimens in the low-risk study that gave Reactive results using the OraQuick® test, repeatedly reactive results using a licensed EIA, and positive results using a licensed Western blot were removed from the calculation of specificity.
[2] One specimen was EIA repeatedly reactive, Western blot negative.
[3] True negative status based on negative or indeterminate test results using a licensed Western blot.

Combining the number of OraQuick® Non-Reactive results obtained from the study of the low-risk populations with the number of OraQuick® Non-Reactive results obtained from the study of the high-risk populations, the specificity of the OraQuick® Rapid HIV-1 Antibody Test in these studies was calculated to be 1856/1856 = 100% (95% C.I. = 99.7% - 100%).

XI. Conclusions Drawn from the Studies

Risk/Benefit Analysis

The ability to conduct rapid tests for the identification of antibodies against the HIV-1 virus has significant benefits for the population at large. Using a rapid HIV test increases the number of HIV-infected persons who may be diagnosed. The Centers for Disease Control and Prevention (CDC) estimates that nearly one third of the estimated one million HIV-infected persons in the United States have not been tested for HIV or if tested, do not return for their test results. As a result, they cannot benefit from early intervention with effective antiviral therapy. Rapid HIV testing addresses this issue by providing results during the initial visit and enabling immediate counseling. Additionally, CDC estimates that 20% of pregnant women do not know their HIV status at the time of delivery. Rapid HIV testing permits therapy to be initiated for these mothers during labor, and to their infants post partum, substantially reducing the chance that the infants will become infected with HIV. Likewise, rapid HIV testing is instrumental in the decision to initiate treatment for health care workers after accidental exposures to body fluids from infected

individuals. In the U.S., a reported one million "needlestick injuries" occur each year. Critical decisions about treatment depend on the availability of accurate, rapid HIV test results.

Safety

No adverse reactions were observed in any of the studies conducted. All operators conducted testing in accordance with the training provided.