SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. General Information

Device Generic Name:	Rapid HIV-1/2 Antibody Test
Device Trade Name:	OraQuick® *ADVANCE*
Applicant's Name and Address:	OraSure Technologies, Inc. 220 East First Street Bethlehem, PA 18015 Phone: 610-882-1820 Fax: 610-882-1825 E-mail: www.orasure.com
PMA Number	BP010047/16
Date of Panel Recommendation*	
Date of Notice of Approval to the Applicant*	

(*to be completed by FDA unless known to the applicant)

II. Indications for Use

The OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test is a single-use, qualitative immunoassay to detect antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2) in oral fluid, fingerstick whole blood, venipuncture whole blood and plasma specimens. The OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test is intended for use as a point-of-care test to aid in the diagnosis of infection with HIV-1 and HIV-2. 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® *ADVANCE* Rapid HIV-1/2 Antibody Test is a manually performed, visually read, 20 minute immunoassay for the qualitative detection of antibodies to HIV-1 and HIV-2 in human oral fluid, whole blood obtained from a finger puncture or a venipuncture, and plasma. The OraQuick® *ADVANCE* rapid test is comprised of a single-use test device and a single-use vial containing a pre-measured amount of a buffered developer solution. Each component is sealed in separate compartments of a single pouch to form the test. The OraQuick® *ADVANCE* rapid test utilizes a proprietary lateral flow immunoassay procedure. The device plastic housing holds an assay test strip comprised of several materials that provide the matrix for the immunochromatography of the specimen and the platform for indication of the test results.

The assay test strip, which can be viewed through the test device result window, contains synthetic peptides representing the HIV envelope region and a goat anti-

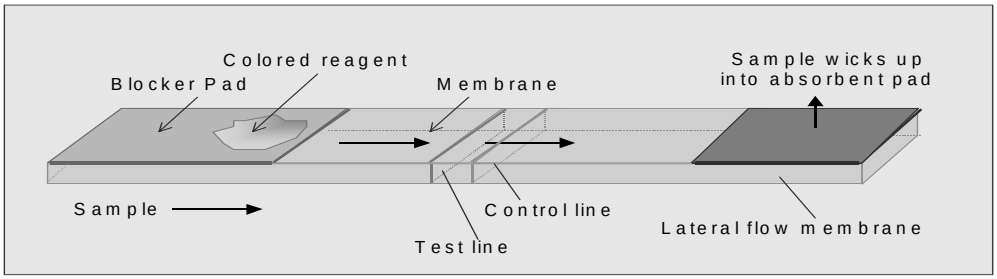
human IgG procedural control immobilized onto a nitrocellulose membrane in the Test (T) zone and the Control (C) zone, respectively.

An oral fluid specimen is collected using the flat pad on the test device, followed by the insertion of the test device into the vial of developer solution. A fingerstick whole blood, venipuncture whole blood or plasma specimen is collected and transferred into the vial of developer solution, 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 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 and/or HIV-2 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 C zone. This built-in procedural control serves to demonstrate that a specimen was added to the vial and that the fluid has migrated adequately through the test device. A reddish-purple line will appear in the C zone during the performance of all valid tests, whether or not the sample is positive or negative for antibodies to HIV-1 and/or HIV-2 (refer to the *Test Result and Interpretation of Test Result* section below).

The test results are interpreted after 20 minutes but not more than 40 minutes after the introduction of the test device into the developer solution containing the test specimen. No precision pipeting, predilutions, or specialized instrumentation are required to perform the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test.

OraQuick® Assay Design



IV. Contraindications, Warnings, and Precautions

WARNINGS

For *in vitro* Diagnostic Use

1. Read the package insert completely before using the product. Follow the instructions carefully. Not doing so may result in inaccurate test results.
2. Before performing testing, all operators MUST read and become familiar with Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and other Blood-borne Pathogens in Health-Care Settings.[1]
3. FDA has approved this kit for use with oral fluid, fingerstick whole blood, venipuncture whole blood, and plasma 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.
4. This test should be performed at ambient temperature (15^{o}-27^{o}C, 59^{o}-80^{o}F). If stored refrigerated, ensure that the Divided Pouch is brought to ambient temperature (15^{o}-27^{o}C, 59^{o}-80^{o}F) before performing testing.
5. If the test kit is stored or used at temperatures outside of ambient temperature (15^{o}-27^{o}C, 59^{o}-80^{o}F), use the Kit Controls to ensure performance of the test.
6. Individuals infected with HIV-1 and/or HIV-2 who are receiving highly active antiretroviral therapy (HAART) may produce false negative results.

PRECAUTIONS

Safety Precautions

1. Handle blood specimens and materials contacting blood specimens as if capable of transmitting infectious agents.

2. Do not drink, eat, or smoke in areas where specimens are being handled or testing is being performed.

3. Wear disposable gloves while handling blood specimens and performing testing of blood specimens. Change gloves and wash hands thoroughly after performing each test. Dispose of used gloves in a biohazard waste container.

4. Oral fluid is not considered potentially infectious unless it contains blood.[2] Use of gloves for oral fluid testing is optional. Test administrators with breaks in the skin (cuts, abrasions, or dermatitis) should wear gloves when performing oral fluid testing. Wash hands thoroughly after performing each oral fluid test and after contact with oral fluid.

5. Dispose of all test specimens and materials used in the test procedure in a biohazard waste container. Lancets and venipuncture materials should be placed in a puncture-resistant container prior to disposal. The recommended method of disposal of biohazard waste is autoclaving for a minimum of 1 hour at 121ºC. Disposable materials may be incinerated. Liquid wastes may be

mixed with appropriate chemical disinfectants. A freshly prepared solution of 10% bleach (0.5% solution of sodium hypochlorite) is recommended. Allow 60 minutes for effective decontamination. NOTE: Do not autoclave solutions that contain bleach.

6. Wipe all spills thoroughly with a solution of 10% bleach or other appropriate disinfectant.[3] Bleach solutions should be made fresh each day.

7. For additional information on biosafety, refer to "Universal Precautions for Prevention of Transmission of Human Immunodeficiency Virus, Hepatitis B Virus, and other Blood-borne Pathogens in Health-Care Settings"[1] and "Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis".[2]

Handling Precautions

1. Use all Specimen Collection Loops, Test Devices, and Developer Solution Vials only once and dispose of properly (see *Safety Precautions*). **Do not reuse any of these test components**.
2. Do not use the test beyond the expiration date printed on the Divided Pouch. Always check expiration date prior to testing.
3. Do not interchange Test Devices and Developer Solution Vials from kits with different lot numbers.
4. Avoid microbial contamination and exercise care in handling the kit components.
5. To ensure accurate results, the Test Device must be inserted into the Developer Solution Vial within 60 minutes after introducing the fingerstick whole blood, venipuncture whole blood or plasma sample.
6. After collecting oral fluid specimens the Test Device must be inserted into the Developer Solution Vial within 10 minutes of collection.
7. Adequate lighting is required to read a test result.

LIMITATIONS OF THE TEST

1. The OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test must be used in accordance with the instructions in this package insert to obtain an accurate result.
2. Reading test results earlier than 20 minutes or later than 40 minutes may yield erroneous results.
3. This test is approved by FDA for use with oral fluid, fingerstick whole blood, venipuncture whole blood, and plasma specimens only. Use of other types of specimens, testing of venipuncture whole blood specimens collected using a tube containing an anticoagulant other than EDTA, sodium heparin, sodium citrate, or ACD Solution A, or testing of plasma specimens collected using a tube containing an anticoagulant other than EDTA may not yield accurate results.

4. Individuals infected with HIV-1 or HIV-2 who are receiving highly active antiretroviral therapy (HAART) may produce false negative results.
5. Clinical data has not been collected to demonstrate the performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in persons under 12 years of age.
6. A reactive result using the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test suggests the presence of HIV-1 and/or HIV-2 antibodies in the specimen. The OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test is intended as an aid in the diagnosis of infection with HIV-1 and/or HIV-2. AIDS and AIDS-related conditions are clinical syndromes and their diagnosis can only be established clinically.
7. For a reactive result, the intensity of the test line does not necessarily correlate with the titer of antibody in the specimen.
8. 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.

V. Alternative Practices and Procedures

The detection of antibodies in human subjects against the HIV virus is primarily done using laboratory based assays with blood, serum, plasma and oral fluids. The majority of these tests use principles similar to the OraQuick® *ADVANCE* test device. Either peptides or isolated proteins are used to capture antibodies in a patient sample on a solid phase support. The detection of these captured antibodies is accomplished using any number of reporters including, enzymes, chemiluminescence or colloidal gold as with the OraQuick® *ADVANCE* test device. Once the test is complete the assays provide qualitative information that is usually reported as negative, equivocal, or positive. A secondary confirmation of the screening result is performed for all positive results. The OraQuick® *ADVANCE* device differs from laboratory operated tests in two ways; 1) the OraQuick® *ADVANCE* test is interpreted visually rather than with an instrument, 2) the OraQuick® *ADVANCE* test uses colloidal gold as the reporter which is typically not used in laboratory procedures.

VI. Marketing History

The OraQuick® *ADVANCE* test has been marketed in the United States since the approval of the original PMA in November 2002. Over 1 million tests have been distributed to-date.

VII. Potential Adverse Effects of the Device on Health

No known adverse effects have been found with the OraQuick® *ADVANCE* device in any study performed to date.

VIII. 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® *ADVANCE* device.

1. Assessment of OraQuick® *ADVANCE* Performance Using Seroconversion and Low Titer Panels for HIV-1.

Eleven HIV-1 seroconversion panels were tested in comparison with licensed anti-HIV EIA tests. Each panel consisted of sequential serum/plasma 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® *ADVANCE* Rapid HIV-1/2 Antibody Test was demonstrated to be capable of detecting seroconversion similar to currently available FDA licensed EIAs.

TABLE 1
Comparison of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test and Licensed Anti-HIV EIA Tests Using Seroconversion Panels

Specimen Information			Licensed Anti-HIV EIA Tests				
Panel	Relative Day of Bleed	**OraQuick® *ADVANCE* 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

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 serum/plasma specimens. The results of this study are shown in Table 2. In this study, the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test was demonstrated to be capable of detecting antibodies to HIV-1 similar to currently available FDA licensed EIAs.

TABLE 2
Comparison of the OraQuick® *ADVANCE* Rapid HIV-1/2 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® *ADVANCE* 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**

2. Evaluation of HIV Reference Panel and Worldwide Performance Panel

The HIV-1 Reference Panel 4 and HIV-2 Reference Panel 1 (FDA-CBER) are dilution series that are used for lot release of licensed kits. Performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody was within the acceptable range of results for these specimens.

To assess the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test for HIV-1 variants from various geographic regions, 215 confirmed HIV-1 antibody-positive serum/plasma specimens were obtained from various parts of the world. Of these 215 specimens, 214 were reactive using the OraQuick®

ADVANCE Rapid HIV-1/2 Antibody Test. One confirmed HIV-1 antibody-positive specimen from China was non-reactive using the OraQuick® *ADVANCE* test. An additional 13 specimens representing HIV-1 Subtypes A, B, C, D, F, and G, and Group O were tested and reactive on OraQuick® *ADVANCE*.

Samples (plasma) from a 45-member commercially available worldwide HIV-1 Performance Panel (BBI, WWRB301(M)), were tested with three lots of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test. Performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test was within the expected results for the reference panels. See Table 3 below.

Table 3
Worldwide Performance Panel WWRB301(M)

Expected Results	Total Samples	OraQuick® HIV-1Results	
		R	N
HIV-1 Positive	40	39	1*
HIV-1 Negative	5	0	5

R indicates a reactive result; N indicates a non-reactive result
*Western blot indeterminate, no p41 band present

3. Effect of Interfering Substances

Sensitivity

To assess the impact of unrelated medical conditions or interfering substances on the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test, 200 serum/plasma 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 4 below). All spiked specimens gave reactive results.

In addition, a study was performed to assess the potential effect of anticoagulants on assay sensitivity. Venipuncture whole blood collected from 20 subjects, in each of 4 tubes containing one of four anticoagulants (EDTA, sodium heparin, sodium citrate, and ACD Solution A) was spiked with an HIV-1 positive specimen to give a level of reactivity in the low positive range. The samples were then aliquoted and stored either refrigerated (2-8ºC) or at room temperature (18ºC) and tested over a 7-day period. There was no anticoagulant-specific effect observed on assay performance with samples held up to 30 hours at 2-18ºC.

As part of the oral fluid clinical studies, information was collected from the participants regarding concurrent diseases or medical conditions, oral pathologies, non-HIV viral infections, and other factors (e.g., use of tobacco products, mouthwash within 24 hours of testing, concomitant medications, dental fixtures, and food or drink immediately prior to testing). None of these

disease states, medical conditions or other factors interfered with test sensitivity. In a separate study of 40 individuals, consumption of alcohol, brushing of teeth, use of mouthwash or smoking tobacco 5 minutes prior to testing, were shown to have no effect on test sensitivity.

Specificity

To assess the impact of unrelated medical conditions or interfering substances on the specificity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test, 321 serum/plasma specimens from a variety of medical conditions unrelated to HIV infection and 119 specimens with interfering substances were analyzed. The results of this study are shown in Table 4. 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 false positive results.

In addition, a study was performed to assess the potential effect of anticoagulants on assay specificity. Venipuncture whole blood was collected from 20 HIV negative subjects, in each of 4 tubes containing one of the following anticoagulants: EDTA, sodium heparin, sodium citrate, and ACD Solution A. The samples were then aliquoted and stored either refrigerated (2-8ºC) or at room temperature (18ºC) and tested over a 7-day period. There was no anticoagulant-specific effect observed on assay performance with samples held up to 30 hours at 2-18ºC (refer to Table 4).

TABLE 4
OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test
Reactivity with Specimens from Individuals with Potentially Interfering Medical Conditions and Specimens with Interfering Substances

Medical Condition (n = 321)	OraQuick® *ADVANCE* 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 = 199)		
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
Sodium Heparin[3]	0	20
EDTA[3]	0	20
Sodium Citrate[3]	0	20
ACD Solution A[3]	0	20

[1] A total of 3 of the 20 HAV specimens were OraQuick® *ADVANCE* falsely reactive. Two of the 3 specimens were OraQuick® *ADVANCE* 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® *ADVANCE* non-reactive at the 20-25 minute read time and reactive at the 55-60 minute read time.

[3] The OraQuick® *ADVANCE* assay maximum read time for these specimens was 40 minutes.

As part of the oral fluid clinical studies, information was collected from the participants regarding concurrent diseases or medical conditions, oral pathologies, non-HIV viral infections, and other factors (e.g., use of tobacco products, mouthwash within 24 hours of testing, concomitant medications, dental fixtures, and food or drink immediately prior to testing). None of these disease states, medical conditions or other factors interfered with test specificity. In a separate study of 40 individuals, consumption of alcohol, brushing of teeth, use of mouthwash or smoking tobacco 5 minutes prior to testing, were shown to have no effect on test specificity.

4. Reproducibility

The reproducibility of the OraQuick® *ADVANCE* Rapid HIV-1/2 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® *ADVANCE* Rapid HIV-1/2 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.

5. Untrained User Study

An "Untrained User" study was conducted in which participants were given only the test instructions and asked to perform testing of a blinded panel comprised of 6 randomized specimens of three different levels (Negative, Low Positive and High Positive OraQuick® *ADVANCE* test reactivity) consisting of human plasma. The participants were not given any training on the use of the test or the interpretation of the test results, nor were they allowed to observe the performance of the Kit Controls by the Study Coordinator. The study protocol stipulated that professionally trained medical laboratory personnel or persons with prior experience using the OraQuick® *ADVANCE* device were excluded from participation. A total of 100 participants were enrolled from a total of four sites, representing a diverse demographic (educational, ethnic, age, gender, etc.) population.

The rate of correct results for the overall study was 98.6% (592/600). Refer to Table 5 below for a summary of the performance relative to the specimen type. The eight incorrect results were attributed to six participants. Of these six participants, four obtained 5 out of 6 correct results, and two participants obtained 4 out of 6 correct results.

Table 5

Untrained Users Rate of Correct Test Results

Negative	Low Positive	High Positive	Total
98.5% (197/200)	98.0% (196/200)	99.5% (199/200)	98.6% (592/600)
95% C.I. (95.7% - 99.7%)	95% C.I. (95.0% - 99.5%)	95% C.I. (97.3% - 99.9%)	95% C.I. (97.4% - 99.4%)

There were 1.7% (10/600) Invalid results reported, with 5 of the 10 Invalid results attributed to one participant. All tests were successfully repeated, with 8/10 of the repeat test results interpreted correctly. The 2 incorrect repeat results were attributed to one participant. As part of the Untrained User study, a Participant Feedback Questionnaire was completed. All participants rated the test as 'easy to use' and felt 'able to perform the test correctly'.

IX. Summary of Clinical Studies

Performance Characteristics

SENSITIVITY

DETECTION OF ANTIBODIES TO HIV-1 IN SPECIMENS FROM INDIVIDUALS INFECTED WITH HIV-1

ORAL FLUID

A sensitivity study was performed at eight clinical trial sites using freshly obtained oral fluid specimens collected from 767 individuals reported to be infected with HIV-1. Of the 767 specimens that were identified as seropositive using licensed confirmatory testing, 762 gave a reactive result on the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test. The results of this study are shown in Table 6.

A separate study was performed at four clinical trial sites using freshly obtained oral fluid specimens collected from 3150 previously unscreened individuals from populations at high risk for HIV-1 infection. The results of this study are also shown in Table 6. Of the 73 specimens that were identified as seropositive using licensed confirmatory testing, 72 were reactive using the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test.

TABLE 6
Detection of Antibody to HIV-1 in Oral Fluid Specimens from HIV-1 Seropositive Individuals

Test Group	Total Samples	OraQuick® *ADVANCE* Reactive	Licensed EIA Repeatedly Reactive	True Positive[1]
Known HIV-1 Positive	767	762	764	767
High-Risk	3150	72[2]	74[3]	73
TOTAL	3917	834	842	840

[1] Confirmation performed by licensed HIV-1 Western blot, with confirmation of indeterminate Western blot results by licensed immunofluorescence assay (IFA).
[2] Eight additional specimens were OraQuick® *ADVANCE* false positive (see Table 10).
[3] One specimen was EIA false positive, with a negative Western blot.

Combining the number of OraQuick® *ADVANCE* reactive results obtained from the study of confirmed positives with the number of OraQuick® *ADVANCE* reactive results obtained from the study of high-risk populations, the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 834/840 = 99.3% (95% C.I. = 98.4% - 99.7%).

PLASMA

A sensitivity study was performed at eleven clinical trial sites using EDTA-plasma specimens collected from 891 individuals reported to be infected with HIV-1. Of the 891 specimens that were identified as seropositive using licensed confirmatory testing, 887 gave a reactive result on the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test. The results of this study are shown in Table 7.

A separate study was performed at six clinical trial sites using EDTA-plasma specimens collected from 533 previously unscreened individuals from populations at high risk for HIV-1 infection. The results of this study are also shown in Table 7. All of the 14 specimens that were identified as seropositive using licensed confirmatory testing were reactive using the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test.

TABLE 7
Detection of Antibody to HIV-1 in Plasma Specimens from HIV-1 Seropositive Individuals

Test Group	Total Samples	OraQuick® *ADVANCE* Reactive	Licensed EIA Repeatedly Reactive	True Positive[1]
Known HIV-1 Positive	891	887	891	891
High-Risk	534	14	14	14
TOTAL	1424	901	905	905

[1] Confirmation performed by licensed HIV-1 Western blot, confirmation of indeterminate Western blot results by radioimmunoprecipitation assay (RIPA) or licensed IFA.

Combining the number of OraQuick® *ADVANCE* reactive results obtained from the study of confirmed positives with the number of OraQuick® *ADVANCE* reactive results obtained from the study of high-risk populations, the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 901/905 = 99.6% (95% C.I. = 98.9% - 99.8%).

FINGERSTICK WHOLE BLOOD

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® *ADVANCE* Rapid HIV-1/2 Antibody Test. The results of this study are shown in Table 8.

A separate study was performed at seven clinical trial sites using 625 freshly obtained fingerstick whole blood samples from previously unscreened individuals from populations at high risk for HIV-1 infection. The results of this study are also shown in Table 8. 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® *ADVANCE* Rapid HIV-1/2 Antibody Test.

TABLE 8
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® *ADVANCE* Reactive	Licensed EIA Repeatedly Reactive	True Positive[1]
AIDS	40	40	40	40
Known HIV-1 Positive	481	479	481	481
High-Risk	625	17	20 [2]	17
TOTAL	1146	536	541	538

[1] Confirmation performed by licensed HIV-1 Western blot, with confirmation of indeterminate Western blot results by RIPA.
[2] Two specimens were negative and one was indeterminate on Western blot with a negative RIPA.

Combining the number of OraQuick® *ADVANCE* reactive results obtained from the study of confirmed positives with the number of OraQuick® *ADVANCE* reactive results obtained from the study of high-risk populations, the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 536/538 = 99.6% (95% C.I. = 98.5% - 99.9%).

DETECTION OF ANTIBODIES TO HIV-2 IN SPECIMENS FROM INDIVIDUALS INFECTED WITH HIV-2

A total of 324 serum/plasma specimens reported to be HIV-2 antibody positive were obtained from various repository sources. Specimens were tested by licensed anti-HIV-1/2 EIA, licensed anti-HIV-2 EIA, licensed HIV-1 Western blot, an HIV-2 Western blot and HIV-2 specific PCR. A total of 6 specimens were found to be negative for antibodies to HIV-1 or HIV-2, all of which were OraQuick® *ADVANCE* non-reactive. Two of the 6 negative specimens were repeatedly reactive by licensed anti-HIV-1/2 EIA, negative by licensed anti-HIV-2 EIA, and indeterminate by licensed HIV-1 Western blot and by an HIV-2 Western blot.

Of the remaining 318 specimens, 151 were positive on an HIV-2 Western blot and 50 were positive using an HIV-2 specific PCR. One hundred and twenty-two specimens gave confirmatory results consistent with HIV-1 infection and were excluded from the analysis. One specimen was categorized as a dual infection based on additional testing by co-culture, and was not included in the sensitivity analysis. One specimen, while indeterminate on HIV-1 and HIV-2 Western blots, gave a positive result on an HIV-2 radioimmunoprecipitation assay (RIPA) and is also considered to be positive for antibodies to HIV-2. OraQuick® *ADVANCE* detected 201/201 (100%) of the specimens from individuals confirmed as positive for HIV-2 antibodies (see Table 9).

In a separate study, a total of 499 plasma specimens collected from an HIV-2 endemic area (Ivory Coast) were prepared as contrived whole blood and tested by OraQuick® *ADVANCE*, licensed anti-HIV-1/2 EIA, licensed anti-HIV-2 EIA, licensed HIV-1 Western blot, and an HIV-2 Western blot. Table 6 shows a summary of the results. OraQuick® *ADVANCE* was reactive with all of the 27 specimens that were repeatedly reactive by licensed anti-HIV-1/2 EIA, licensed anti-HIV-2 EIA and positive on licensed HIV-1 Western blot, and with all three specimens that were confirmed as positive for HIV-2 only by an HIV-2 Western blot. Two specimens were OraQuick® *ADVANCE* false positive.

TABLE 9
Detection of Antibody to HIV-2 in Samples from HIV-2 Seropositive Individuals and Individuals at High Risk of HIV-2 Infection

Test Group	Total Samples	OraQuick® *ADVANCE* Reactive	Licensed anti-HIV-2 EIA Repeatedly Reactive or HIV-2 PCR Positive	True HIV-2 Positive[1]
Known HIV-2 Positive	324[2]	201	201[3]	201[4]
High-Risk	499	32	33	3
TOTAL	823	233	234	204

[1] Confirmation performed by HIV-2 Western blot, with RIPA confirmation of Indeterminate Western blot results.
[2] One hundred and twenty-two specimens gave confirmatory results consistent with HIV-1 infection and were excluded from the analysis. In addition, one specimen was categorized as a dual infection based on additional testing by co-culture, and was not included in the sensitivity analysis.
[3] 151 specimens were tested with an anti-HIV-2 EIA alone. HIV-2 DNA or RNA PCR was performed on the remaining 50 specimens instead of EIA. All results were positive.
[4] One specimen was confirmed to be HIV-2 positive based on the positive results of an HIV-2 specific RIPA.

Combining the number of OraQuick® *ADVANCE* reactive results obtained from the study of confirmed positives with the number of OraQuick® *ADVANCE* reactive results obtained from the prospective study, the sensitivity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test for the detection of antibodies to HIV-2 in these studies was calculated to be 204/204 = 100% (95% C.I. = 98.2% - 100%).

In addition, 3 HIV-2 infected individuals located in the USA were tested by fingerstick whole blood and oral fluid OraQuick® *ADVANCE* tests. Fingerstick whole blood and oral fluid samples from all three subjects were reactive on the OraQuick® *ADVANCE* test.

SPECIFICITY

ORAL FLUID

A specificity study was performed at four clinical trial sites using freshly obtained oral fluid specimens collected from 605 previously unscreened individuals at low risk for HIV-1 infection. All of the 605 specimens were correctly non-reactive using the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test. Of the 3077 HIV antibody-negative specimens from the four study sites that examined populations at high risk for HIV-1 infection, the OraQuick® *ADVANCE* test was non-reactive for 3069. The results are summarized in Table 10.

TABLE 10
Performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test on Oral Fluid Specimens from Individuals Presumed to be Negative for HIV Infection

Test Group	Total Samples	OraQuick® *ADVANCE* Non-Reactive	Licensed EIA Non-Reactive	True Negative[1]
Low-Risk	605	605	599[2]	605
High-Risk	3150	3069	3076[3]	3077
TOTAL	3755	3674	3675	3682

[1] Confirmation performed by licensed HIV-1 Western blot, with confirmation of indeterminate Western blot results by RIPA or IFA.
[2] Six specimens were EIA false positive, five with a negative Western blot and one with an indeterminate blot which was confirmed negative by IFA.
[3]One additional specimen was OraQuick® *ADVANCE* false negative (see Table 6).
[4]One specimen was EIA false positive with a negative Western blot.

Combining the number of OraQuick® *ADVANCE* non-reactive results obtained from the study of the low-risk populations with the number of OraQuick® *ADVANCE* non-reactive results obtained from the study of the high-risk populations, the specificity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 3674/3682 = 99.8% (95% C.I. = 99.6% - 99.9%).

PLASMA

A specificity study was performed at seven clinical trial sites using EDTA-plasma specimens collected from 1102 previously unscreened individuals at low risk for HIV infection. All of the specimens, except for one, gave non-reactive results using the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test. In addition, 519 of the 520 HIV antibody-negative specimens from study sites that examined populations at high risk for HIV-1 infection also gave non-reactive results using the OraQuick® *ADVANCE* test. The results of this study are shown in Table 11.

TABLE 11
Performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test on Plasma Specimens from Individuals Presumed to be Negative for HIV Infection

Test Group	Total Samples	OraQuick® *ADVANCE* Non-Reactive	Licensed EIA Non-Reactive	True Negative[1]
Low-Risk	1102	1101	1096[2]	1102
High-Risk	534	519	516[3]	520
TOTAL	1636	1620	1612	1622

[1] Confirmation performed by licensed HIV-1 Western blot, with confirmation of indeterminate Western blot results by RIPA or IFA.
[2] Six specimens were EIA false positive, five with a negative Western blot and one with an indeterminate blot which was confirmed negative by IFA

[3] Four specimens were EIA false positive, with 1 negative and 3 indeterminate by Western blot, that confirmed negative by IFA.

Combining the number of OraQuick® *ADVANCE* non-reactive results obtained from the study of the low-risk populations with the number of OraQuick® *ADVANCE* non-reactive results obtained from the study of the high-risk populations, the specificity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 1620/1622 = 99.9% (95% C.I. = 99.6% - 99.9%).

FINGERSTICK WHOLE BLOOD

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® *ADVANCE* Rapid HIV-1/2 Antibody Test. In addition, all of the 608 HIV-1 antibody-negative specimens from the study sites that examined populations at high risk for HIV-1 infection also gave non-reactive results using the OraQuick® *ADVANCE* test. The results of this study are shown in Table 12.

TABLE 12
Performance of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test on Fingerstick Whole Blood Specimens from Individuals Presumed to be Negative for HIV Infection

Test Group	Total Samples	OraQuick® *ADVANCE* Non-Reactive	Licensed EIA Non-Reactive	True Negative [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® *ADVANCE* 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® *ADVANCE* non-reactive results obtained from the study of the low-risk populations with the number of OraQuick® *ADVANCE* non-reactive results obtained from the study of the high-risk populations, the specificity of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test in these studies was calculated to be 1856/1856 = 100% (95% C.I. = 99.7% - 100%).

X. Conclusions Drawn from the Studies

Risk/Benefit Analysis

The ability to conduct rapid tests for the identification of antibodies against HIV has significant benefits for the population at large. The small risk of a false positive or false negative result must be weighed against the significant benefit of being tested to public health. Pre- and post-test counseling, as well as patient lifestyle risk assessment are integral to the accurate diagnosis of HIV infection.

Safety

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

Effectiveness

The accuracy of the OraQuick® *ADVANCE* Rapid HIV-1/2 Antibody Test for all specimen types studied (fingerstick whole blood, venipuncture whole blood, plasma and oral fluid) is greater than 99% (with the lower boundary of the 95% CI greater than 98%) meeting the requirements established by FDA for approval of a rapid HIV test.

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