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Blood Products Advisory Committee
102nd Meeting, May 15, 2012

The Hilton Washington DC North/Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland, 20877

Issue Summary

Topic: Safety and effectiveness of the proposed OraQuick® In-Home HIV Test

Issue: OraSure Technologies, Inc. submitted a premarket approval application for the OraQuick® In-Home HIV Test. If approved, this would be the first over-the-counter (OTC) home-use HIV test kit and the only OTC home-use test kit that would be available for any infectious agent. In previous discussions, the Blood Products Advisory Committee (BPAC) made recommendations on the performance expectations for OTC home-use HIV tests. FDA is now seeking input from BPAC on the safety and effectiveness of the OraQuick® In-Home HIV Test Kit based on its performance in Phase III clinical trials.

Background:

Knowledge of one's HIV status, linked to behavior change, is a major step that contributes both to personal health and to stemming the spread of HIV infection. However, knowledge of HIV status depends on access to and utilization of accurate HIV testing. Approaches to HIV testing have evolved with changing needs and advancing technology. Beginning in 1985 clinical laboratory-based testing for HIV came with rigorous oversight, namely pre-test counseling, quality controlled laboratory testing, confirmation prior to notification, post-test counseling and medical referral. However, this type of testing also came with potential hurdles to testing based on costs, logistics, the need to interface with the medical system and fears of stigma. In response to these concerns, FDA was approached in 1989 and 1990 by sponsors seeking over-the-counter (OTC) claims[1] for their test systems, but the state of technology and public health thinking at that time was not conducive to such a claim. Later, in 1996, FDA approved two OTC home-use blood specimen collection kits for HIV testing; with a specimen collection kit, the lay user collects his/her own sample, mails it to a laboratory, and receives a result over the phone or in the mail. For these collection kits, printed materials (instead of live pre-test counseling) contained important information for the lay user about the testing; test results and post-test counseling and referral were available by phone.

[1] An over-the-counter test is one that is available for purchase by a consumer for the purposes of self-testing. This is in contrast to a point-of-care test, which is typically designed for use by trained professionals outside of a clinical laboratory setting.

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Since 2001, FDA has approved a number of rapid (*e.g.*, 20 minute) HIV tests, (including some that were granted CLIA waiver[2]) for use by trained operators in outreach settings. In outreach settings, individuals are promptly given the results of a screening test by a health care practitioner, prior to confirmation. These tests are highly sensitive and specific, exceeding the Blood Products Advisory Committee (BPAC)-recommended, and FDA-accepted, criteria for sensitivity and specificity of 98%, expressed as the lower bound of the 95% confidence interval. Of the seven currently FDA-approved rapid tests, five make use of a fingerstick blood specimen and one test is also approved for use with an oral fluid specimen. These test characteristics have facilitated testing in outreach settings by providing an unconfirmed screening test result in a single visit (a reactive or "preliminary positive" result should be confirmed by additional testing), and four of the tests qualified for CLIA waiver, expanding test accessibility.

In 2005 OraSure Technologies approached FDA to discuss marketing its approved OraQuick ADVANCE HIV-1/2 rapid antibody test as a self-administered OTC test kit for home-use with oral fluid specimens, to further expand public access to testing. At this time there are no FDA-approved OTC home-use test kits for HIV or any other infectious agent. Since 2005, there have been several discussions at public meetings of BPAC of issues related to OTC home-use test kits for HIV. In November 2005 the committee discussed and provided recommendations for the validation of OTC home-use HIV test kits and asked FDA to outline a pre-clinical and clinical trial proposal and criteria for an OTC claim.(2) A study plan consisting of observed self-testing and interpretation (Phase II), followed by unobserved self-testing in an intended use setting (Phase III) was discussed at BPAC in March 2006.(3) BPAC recommended acceptable minimal performance for sensitivity and specificity each as 95%, expressed as the lower bound of the 95% confidence interval. This reduction of the performance that was expected in comparison to professional use tests was considered to represent a reasonable balance between risk and benefit. At the November 2009 BPAC meeting FDA presented a formal risk analysis of the performance characteristics for OTC home-use HIV test kits at various levels of sensitivity and specificity. (4) This model highlighted the benefit of HIV-infected individuals knowing their status versus the risks of false positive and false negative results both in terms of individual and public health.

The OraQuick® In-Home HIV Test System:

OraSure Technologies, Inc. has filed a premarket approval application for their OraQuick® In-Home HIV Test. This test is a modified version of their currently approved OraQuick® ADVANCE Rapid HIV-1/2 Antibody Test for use with oral fluid specimens (approved and then CLIA-waived in 2004). The OTC kit consists of the

[2] As defined by the Clinical Laboratory Improvement Amendments of 1988 (CLIA), CLIA waived tests are categorized as "simple laboratory examinations and procedures that have an insignificant risk of an erroneous result." FDA determines the criteria for tests being simple with a low risk of error and approves manufacturers' applications for test system waiver.

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testing device and reagents, step-by-step instructional material to assist an untrained user (the individual seeking to know his/her HIV status) in the testing process, information on interpreting the test results, and contact information for the OraQuick® Answer Center for support and local medical referral.

To perform the test, an oral fluid specimen is collected directly onto the test device pad by swabbing the upper and lower gums once each. The device is then inserted into a vial of developer solution. The developer solution flows through the device carrying with it a colored reagent that binds to antibodies in the specimen. If antibodies to HIV-1 or HIV-2 are present in the sample, they become immobilized by binding to a line on the membrane strip that contains HIV-1/2 antigens, generating a visible line. As the solution continues to flow along the strip, antibodies are captured nonspecifically by control material at a separate line on the membrane, also generating a visible line. The test result is read after 20 minutes but not longer than 40 minutes after inserting the device into the vial of developer solution. If antibodies to HIV-1 or HIV-2 are present in the oral fluid specimen, a line appears in the bottom (test) portion of the device window, along with a line in the upper (control) portion of the device window, thus generating two distinct lines. The result is interpreted as "you may have HIV." If no antibodies to HIV-1 or HIV-2 are present, then only the control line is present and indicates that an adequate specimen was collected with the device and that the test is functioning properly. The result is interpreted as "negative."

According to the clinical trials performed to support the original device approval, the sensitivity of the OraQuick® ADVANCE Rapid HIV-1/2 Antibody Test in the hands of trained users was 99.3% (95% confidence interval [CI]: 98.4% -99.7%) and the specificity was 99.8% (95% CI: 99.6% - 99.9%). The test device and developer solution in the OTC kit are identical to those in the OraSure rapid HIV test. The test kit for OTC use includes step-by-step instructional materials, a stand for the developer solution vial, and a drawer containing the test device (all integrated into the kit box), all device components, and two informational booklets (*HIV, Testing & **Me*** and *What your results mean to **You**!*). Also included in the instructional materials is contact information for the OraQuick® Answer Center, which is available 24 hours a day, seven days a week.

Summary of OraSure In-Home HIV Test Clinical Trial Study Results:

OraSure conducted its clinical trials for the OraQuick® In-Home HIV Test using the phased approach proposed by FDA and recommended by BPAC in 2006.[2]

- Phase I established performance of the test **in the hands of trained users**, characterizing the inherent sensitivity and specificity of the test. This was accomplished through studies conducted in support of the original approval in 2004 and was supplemented with additional studies to demonstrate that the test is robust under varying conditions that would potentially affect specimen and test integrity (*e.g.*, temperature and humidity extremes, exposure to food, drink, and chemicals, human factors, sampling variations).

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- Phase II established performance of the test system as a whole **in the hands of untrained intended and expected users under observation** (determined through qualitative research), prior to conducting studies of self-testing in an uncontrolled, intended use setting (Phase III), which presents a potentially higher risk to study participants due to lack of counseling when obtaining the test result. Phase II consisted of two parts:

    - Phase IIA: Test result interpretation of devices that were designed to indicate either high positive, low positive, negative, or invalid results. Acceptable agreement with the correct result was expected to be at least 98% for the positive, negative, and invalid devices and at least 95% for the weak positive devices.

      The initial results from the Phase IIA studies showed that performance expectations (lower bound of 95% confidence interval for agreement of interpretation) were not met (93.9% for the positive devices, 92.6% for the negative devices, 90.8% for the invalid devices, and 80.2% for the weak positive devices). To mitigate the risks of incorrectly interpreting the test result, OraSure modified the text of the labeling and improved the pictures to aid in interpretation.

      However, the results from the repeat of the Phase IIA studies showed that performance expectations (lower bound of 95% confidence interval for agreement of interpretation) were still not met (93.9% for the positive devices, 93.0% for the negative devices, 90.8% for the invalid devices, and 78.0% for the weak positive devices).

    - Phase IIB: Self-testing by individuals at high risk, unknown risk and low risk for HIV infection, and individuals known to be infected with HIV. Study participants conducted and interpreted the test on their own, but under observation. According to BPAC, the sensitivity and specificity in these studies should be at least 95%, expressed as the lower bound of the 95% confidence interval.

      The results from the Phase IIB studies showed that performance expectations were met for both specificity (lower 95% confidence bound of 98.8%) and sensitivity (lower 95% confidence bound of 95%).

- Phase III was designed to establish performance of the test system as a whole in the hands of untrained intended and expected users in the actual intended use (in-home) setting. In Phase III sensitivity was to be based only on prospectively identified HIV-infected individuals and not from those known to be infected with HIV, to better represent the sensitivity of the test in the hands of intended users.

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Phase III trial design

OraSure expects a broad range of users for the OraQuick® In-Home HIV Test, consisting of both the general population and individuals from higher prevalence populations, and conducted a study to determine the groups that would likely purchase the OTC test kit. The results of that study are shown in Table 1 below.

Table 1 Analysis of groups likely to purchase the OraQuick® In-Home HIV Test

Group	n	Definitely/Probably Would Buy
General population	305	20%
Age 18-35	134	27%
African American ages 18-35	77	49%
Homosexual men	93	47%
2 or more sexual partners/year	45	43%
Inconsistent condom users	68	32%

In addition, BPAC recommended in 2006 that clinical trials for OTC home-use HIV test kits also take into account gender, low income, and minorities.

In OraSure's clinical trial, study participants represented the breadth of intended and expected users of the test, taking into consideration age (14-86), gender, race, ethnicity, sexual orientation, socio-economic status, educational level, literacy, and language (English/Spanish). Approximately 81% of study participants came from higher risk populations in order to maximize the number of prospectively identified HIV infections in the clinical trial, and the clinical trial was conducted at 20 geographically distinct sites (3 low prevalence areas [average prevalence 0.1%] and 17 higher prevalence areas [average prevalence 2.6%]). *Appendix 1* contains additional details on the demographics of study participants.

OraSure conducted the Phase III clinical trial through a series of visits by study participants.

Visit 1 Subject undergoes screening and informed consent; blood sample is collected for testing with FDA approved EIA, and the sample is retained for further testing by Western blot, if required; subject is enrolled and Visit 2 is scheduled

Visit 2 Subject is presented with product and decides whether or not to take the test home for use (this mimics real world use in that subjects were allowed to opt out of the study similar to a consumer choosing not to purchase the product after reading the box); subject takes possession of the OraQuick®

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In-Home HIV Test; Visit 3 is scheduled at least 3 days (but not more than 5 days) from visit 2; subject is asked to self-test in a setting of his/her choice within 24 hours of Visit 2

Visit 3 Self-test result is compared with EIA serum testing results; either the subject returns to study site within 7 days after Visit 1 or the subject provides self-test result through Answer Center or follow-up with site by telephone; subject self-test is reviewed; serum EIA testing results, when available are reviewed; follow up visit is scheduled if necessary; site contacts subjects that fail to return for Visit 3

Visit 4 Follow-up visit for confirmatory testing results (if needed)

Number of Study Participants

6,001	Subjects who were screened for participation in Phase III
- 203	Subjects who were not enrolled
5,798	Subjects who enrolled in Visit 1 (gave initial blood sample)
-136	Subjects who did not complete Visit 2 (no investigational test dispensed)
5,662	**Subjects who completed Visit 2 (enrolled in the trial and were given the investigational device)**

Inclusion/exclusion criteria for the clinical trial are listed in *Appendix 2*.

Subjects were determined to be positive or negative for antibodies to HIV from the results of reference testing of the serum sample collected from each of the 5,662 subjects who were enrolled in the study and given an investigational device. Based on this reference testing, there were 120 individuals who were confirmed positive for HIV antibodies and 5,542 individuals who were negative for antibodies to HIV. Only those individuals who obtained a positive or a negative self-test result were included in the calculations of sensitivity and specificity, as follows:

- **120 Confirmed positive**
  -6 Subjects with no self-test result
  114 Confirmed positive subjects with self-test results

- **5,542 Negative**
  -157 Subjects with no self-test result
  5,385 Negative subjects with self-test results

The following table describes the reasons for “no self-test result.”

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Table 2 Categorization of individuals with "no self-test result"

Category	# of Subjects
Could not interpret test result	21
Could not run test (operational error)	14
Could not run test (no additional comments)	11
No lines developed	10
Self deselection from study (see *Appendix 1*)	13
Clinical trial protocol error	15
Lost test kit	19
Failed to return for Visit 3	60
TOTAL	**163***

*6 confirmed positive subjects and 157 subjects who reported no test result

Phase III Performance: Sensitivity, Specificity and Test System Failure Rate

From the clinical data submitted in the PMA, the estimated specificity of the OraQuick® In-Home HIV Test was 5384/5385 = 99.98% (95% CI: 99.90 – 100%). The lower bound of the 95% confidence interval of 99.90% is above the BPAC-recommended 95%. However, the estimated sensitivity was 106/114 = 92.98% (95% CI: 86.64 – 96.92%). The lower bound of the 95% confidence interval of 86.64% is below the BPAC-recommended threshold for test sensitivity. OraSure was unable to determine the root cause for the one false positive and eight false negative test results obtained in this trial. Those reporting false negative and false positive results were not associated with any specific demographic.

A "test system failure" may be defined as the inability of the test system as a whole (including instructional and informational material) to provide the user with an interpretable test result. Events contributing to test system failure (*i.e.*, could not interpret result, could not run test due to operational errors or other unspecified reasons, or no lines developed) are listed in Table 2 above. OraSure had observed a 5% test system failure rate in Phase IIB studies. BPAC suggested that a maximum test system failure rate of 2% be achieved in Phase III. The actual test system failure rate observed in Phase III was approximately 1%. This improvement in the test system failure rate may be attributed to most failures associated with Phase IIB subjects who knew they were infected with HIV. No known HIV-infected individuals participate in Phase III.

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Positive predictive and negative predictive values were 106/107 = 99.07% (95% CI: 94.90% - 99.98%) and 5384/5392 = 99.85% (95% CI: 99.71% - 99.94%), respectively.

Table 3 Summary of OraQuick® In-Home HIV Test Phase III Clinical Trial Performance

	Performance of the OraQuick® In-Home HIV Test Kit	**BPAC Minimum Recommended Performance**
Sensitivity (95% CI)	92.98% (**86.64** – 96.92%)	**95%** as the lower bound of the 95% CI
Specificity (95% CI)	99.98% (**99.90** – 100%)	**95%** as the lower bound of the 95% CI
Positive Predictive Value	99.07% (95% CI: 94.90 – 99.98%)	Not applicable
Negative Predictive Value	99.85% (95% CI: 99.71 – 99.94%)	Not applicable

Analysis of Public Health Impact:

To attempt to understand the public health impact of the OraQuick® In-Home HIV Test given the sensitivity and specificity observed in the Phase III clinical studies, FDA used the risk assessment model discussed at the November 2009 BPAC meeting.(4) This model is based on the projected number and sub-populations of individuals using the OraQuick® In-Home HIV Test who would not otherwise be tested, according to projected data from the Centers for Disease Control and Prevention and other published literature (a more detailed discussion of the risk assessment model is in *Appendix 3*). The risk assessment considered four potential sub-populations that might use the test: low-risk heterosexuals, high-risk heterosexuals, men who have had sex with other men, and injection drug users. All of the parameters in the risk assessment have some uncertainty associated with their estimates. We characterized this uncertainty by using probability distributions to represent the distribution of each parameter, and used a computer simulation with 10,000 iterations to estimate the distribution of possible public health outcomes given the uncertainty of the inputs. We then calculated the expected outcomes using three assumptions about sensitivity and specificity: (1) a probability distribution based on the Phase III clinical trial results, (2) the lower bound of the Phase III clinical

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trial results (this represents a worst case scenario given the results from the clinical trial), and (3) 95% sensitivity and specificity as the BPAC minimum recommended performance. The BPAC recommendation is that acceptable performance is 95% expressed as the lower bound of the 95% CI. FDA takes this recommendation to mean that a test that has an actual performance of 95% sensitivity and specificity should be found acceptable.

The results of this risk assessment modeling, which portray the average annual expected test results and consequent benefit to risk ratios, are shown in Table 4 below.

Table 4: Numbers and Ratio for Expected True Positive and False Negative Test Results
Numbers and Ratio for Expected True Negative and False Positive Test Results

Comparison	**OraQuick® In-Home HIV Test Performance**		**BPAC Minimum Recommended Performance**
	Distribution	**Lower Bound of the 95% CI**	
True Positive: False Negative	13 TP : 1 FN 45,000 TP : 3,800 FN per year	6 TP : 1 FN 42,000 TP : 7,000 FN per year	19 TP : 1FN 47,000 TP: 2,500 FN per year
True Negative: False Positive	3,750 TN : 1 FP 2,700,000 TN: 1,100 FP per year	770 TN : 1 FP 2,700,000 TN: 3,600 FP per year	19 TN : 1 FP 2,600,000 TN: 140,000 FP per year

This model predicts that, given the estimated sensitivity of the OraQuick® In-Home HIV Test in the Phase III clinical trials, we would expect one false negative test result for every 13 true positive test results, or approximately 3,800 false negative test results per year. If we assume that the true sensitivity of the OraQuick® In-Home HIV Test is equal to the lower bound of the 95% CI, then we would expect one false negative result for every six true positive test results, or approximately 7,000 false negative test results per year. Finally, we compare this projected false negative rate for the OraQuick® In-Home HIV Test to that which would be expected from a test with 95% sensitivity (corresponding to the BPAC-recommended minimum acceptable performance). We see from this analysis that we would expect one false negative result for every 19 true positive results, or approximately 2,500 false negative test results per year.

Given the estimated specificity of the OraQuick® In-Home HIV Test in the Phase III clinical trials, we would expect one false positive test for every 3,750 true negative test results, or approximately 1,100 false positive test results per year. If we assume that the true specificity of the OraQuick® In-Home HIV Test is equal to the lower bound of the 95% CI, then we would expect one false positive result for every 770 true negative test results, or approximately 3,600 false positive test results per year. Finally, we compare this projected false positive rate for the OraQuick® In-Home HIV Test to that which would be expected from a test with 95% specificity (corresponding to the BPAC-recommended minimum acceptable performance). We see from this analysis that we

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would expect one false positive result for every 19 true negative results, or approximately 140,000 false positive test results per year.

Understanding the public health implications of approving an over-the-counter test that performs at this level of sensitivity and specificity in the hands of lay users is challenging. There is considerable personal and public health value in informing infected, but otherwise untested, persons of their true positive HIV status. However, this benefit is offset in some measure by HIV-positive individuals who receive an incorrect message that they are not infected (false negatives).

In addition, we must consider that some individuals currently tested professionally may turn to the less sensitive, but more private, OTC testing alternative should this assay become available. However, at this time no studies have been conducted to assess this potential impact.

Questions for BPAC:

1. Do the projected benefits of the OraQuick® In-Home HIV Test outweigh the potential risks of false positive and false negative test results?

2. Do the available data provide reasonable assurance that the OraQuick® In-Home HIV Test is safe and effective for its intended use?

3. Please comment on any risk mitigation strategies that should be considered in addition to the current proposed labeling.

References:

1. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings, Morbidity and Mortality Weekly Report, September 22, 2006 / 55(RR14); 1-17.

2. Blood Products Advisory Committee 85th Meeting, session on Approach to Validation of Over-the-Counter (OTC) Home-Use HIV Tests, November 3, 2005 transcript. http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4190t1.htm

3. Blood Products Advisory Committee 86th Meeting, session on Proposed Studies to Support the Approval of Over-the-Counter (OTC) Home-Use HIV Tests, March 10, 2006 transcript. http://www.fda.gov/ohrms/dockets/ac/cber06.html#BloodProducts

4. Blood Products Advisory Committee 96th Meeting, session on Public Health Need and Performance Characteristics for Over-the-Counter Home-Use HIV Test Kits, November 17, 2009 transcript. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM193386.pdf

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Appendix 1: OraQuick® In-Home HIV Test Phase III Clinical Trial Demographic and Other Baseline Characteristics

Note: This information is taken from the PMA for the OraQuick® In-Home HIV Test.

Subjects enrolled in the study had a mean (SD) age of 39.9 (13.57) years, were equally distributed by gender (50.10% male, 49.53% female), were non-Hispanic (83.65%), and were primarily either White (43.05%) or Black / African American (46.98%). Subjects enrolled from investigational centers with high risk and unknown risk populations were similar in mean age. The populations differed, however, in regard to gender, race, and ethnicity. Specifically, subjects from the high risk population were more often male (53.51%), while subjects from the unknown risk population were more often female (64.29%). Subjects from the high risk population were also more often Black / African American (52.95%), while subjects from the unknown risk population were more often White (71.06%), with Black / African Americans representing 21.73% of that population.

The demographics of the subjects enrolled in the 2 analyses populations also differed in regard to gender and race. Specifically, while the mean age and ethnic composition of the populations were generally similar to one another, the subjects in the sensitivity analysis population were primarily male (67.83%) and Black / African American (77.39%), whereas the subjects in the specificity analysis population were equally distributed by gender (50.47% female, 49.19% male) and were primarily either Black / African American (45.69%) or White (44.15%).

A total of 89 (1.54%) subjects under the age of 18 were enrolled, with 60 subjects enrolled at investigational centers with high risk populations and 29 subjects enrolled at investigational centers with unknown risk populations. Of these 89 subjects, 53 were female and 36 were male, with race reported primarily as Black / African American (43.82%), Other (28.09%), and White (23.60%).

In all of the demographic comparisons, it is important to note that 80.87% of the subjects were enrolled at investigational centers with high risk populations. More importantly, the demographics within and across populations are representative of people in the general population who would be expected to use the OraQuick Test.

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Table 11-1: Summary of Subject Demographics (All Subjects)

	High Risk (n=4689)	Unknown Risk (n=1109)	All Subjects (n=5798)
Age (years)			
Mean (standard deviation)	39.8 (13.09)	40.2 (15.41)	39.9 (13.57)
Minimum to maximum	14 to 86	14 to 84	14 to 86
Gender			
Male	2509 (53.51%)	396 (35.71%)	2905 (50.10%)
Female	2159 (46.04%)	713 (64.29%)	2872 (49.53%)
Transgender	19 (0.41%)	0 (0.00%)	19 (0.33%)
Asked, but declined	2 (0.04%)	0 (0.00%)	2 (0.03%)
Ethnicity			
Hispanic	839 (17.89%)	95 (8.57%)	934 (16.11%)
Non-Hispanic	3840 (81.89%)	1010 (91.07%)	4850 (83.65%)
Asked, but declined	10 (0.21%)	4 (0.36%)	14 (0.24%)
Race			
White	1708 (36.43%)	788 (71.06%)	2496 (43.05%)
Black / African American	2483 (52.95%)	241 (21.73%)	2724 (46.98%)
Asian	24 (0.51%)	17 (1.53%)	41 (0.71%)
American Indian / Alaskan Native	55 (1.17%)	4 (0.36%)	59 (1.02%)
Native Hawaiian / Pacific Islander	18 (0.38%)	1 (0.09%)	19 (0.33%)
Other	388 (8.27%)	48 (4.33%)	436 (7.52%)
Asked, but declined	13 (0.28%)	10 (0.90%)	23 (0.40%)

Note: Risk is classified as high for subjects enrolled at investigational centers with established HIV prevalence rates averaging about 4% or greater, and is classified as unknown for subjects enrolled at investigational centers with established HIV prevalence rates below 1%.

The baseline characteristics were summarized for all subjects, for subjects enrolled at investigational centers with high risk and unknown risk populations, and for subjects included in the sensitivity and specificity analyses populations. In general, differences in baseline characteristics were often observed between subjects enrolled from high risk and unknown risk populations, as well as between subjects included in the 2 analyses populations; these differences were not considered clinically meaningful as they were often expected variations based on the population being considered and the relative differences in sample size. A summary of the overall baseline characteristics (i.e., characteristics for all enrolled subjects) follows.

Background characteristics at baseline (including education level, income level, REALM score, and English/Spanish competency): The largest percentage of subjects in the overall population reported their highest level of education as high school completion (32.11%), although more than 20% of the subjects reported either not having completed high school (21.58%) or having some college / technical school experience (28.60%). A majority of the subjects reported an income of less than $15,000 per year (54.07%). The subjects had a mean (SD) REALM score of 60.3 (9.24), which just exceeded the threshold corresponding to normal literacy (the threshold was a score >60). Despite this

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mean value, 70.78% of the subjects had REALM scores corresponding to normal literacy. Finally, nearly all of the subjects (98.98%) read, spoke, and understood English; 15.01% (n=870) of the subjects read, spoke, and understood Spanish. Of these 870 subjects, 59 reported that they did not read, speak, and understand English and spoke only Spanish.

Sexual activity and HIV risk factors: In the high risk population, the percentage of subjects reporting themselves as homosexual was 7.44% compared with 3.34% in the unknown risk population. The percentage of subjects in the high risk population who reported themselves as bisexual was 10.62% compared with 3.79% in the unknown risk population. In the high risk population, 18.47% reported they had ever injected nonprescription drugs, compared with 2.89% in the unknown risk population. A total of 20.26% of the subjects in the high risk population reported ever having traded sex for drugs or money, compared with 2.52% of the subjects in the unknown risk population. In the high risk population, 51.38% of the subjects reported having more than 1 sexual partner within the past year, compared with 20.76% of the subjects in the unknown risk population.

Baseline HIV status characteristics (including HIV status [never tested versus previously tested negative] and subject perception of the likelihood of being HIV positive at the time of enrollment): A total of 28.58% of the subjects in the high risk population reported never having been tested for HIV, compared with 48.60% of the subjects in the unknown risk population. The rating given by subjects in the high risk population for the likelihood that they would test positive for HIV was an average of 1.6 on a scale of 0 to 10, compared with an average of 0.3 for subjects in the unknown risk population. A total of 64.13% of the subjects in the high risk population answered 0 or 1 to this same question, compared with 92.16% of the subjects in the unknown risk population. These data suggest that most subjects from both populations regarded themselves at low risk for HIV. It should be noted that, of the 115 subjects in the sensitivity analysis population who were determined during the study to be HIV-infected (based on FDA-approved serum testing), a total of 85 subjects (73.9%) believed their likelihood to test positive was less than or equal to 5. These results suggest that subjects who are HIV-infected are generally not aware of their HIV risk prior to testing.

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Appendix 2: Phase III Clinical Trial Inclusion/Exclusion Criteria

Note: This information is taken from the PMA for the OraQuick® In-Home HIV Test.

Inclusion Criteria

To be included in the study, all of the following criteria must have been met:

1. Were male or female subjects of any race, not proportioned by gender or race
2. Were of unknown HIV status
3. Were at least 14 years of age
4. Read and understood English or Spanish
5. Were able to provide informed consent in English or Spanish, or assent for those under 18 years of age
6. Agreed to provide required medical history and specimens of oral fluid, and a maximum of 30 mL blood by venipuncture
7. Subject chose to complete the sexual preference questionnaire and agreed to do so accurately
8. Agreed to undergo testing with the OraQuick Test and serum testing for HIV antibodies with FDA-approved tests (EIA, Western blot, PCR).
9. Had adequate vision to read the packaging and instructions for use, with or without corrective lenses

For subjects evaluated at investigational centers with high HIV prevalence rates, the following additional inclusion criterion must have been met:

10. Had a self-reported history at visit 1 of any of the following:
    - Condom use reported as never, rarely, sometimes, or occasionally with multiple sex partners within the past year
    - Males who were homosexual/bisexual or men who have had sex with men
    - Had ever injected nonprescription drugs
    - Had ever traded sex for drugs or money
    - Had a current or prior history of sexually transmitted diseases
    - Had previously had sex with someone who was known to be HIV positive

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Exclusion Criteria

To be included in the study, none of the following criteria could have been met:

1. Were known to be HIV positive
2. Were sponsor or investigational center employees or immediate family members of sponsor or investigational center employees
3. Were trained users of the OraQuick ADVANCE® Rapid HIV-1/2 Test
4. Were personnel at an HIV outreach or counseling/testing center (or other facilities that perform HIV testing)
5. Did not meet the inclusion criteria
6. Had received any experimental HIV vaccine
7. Had participated in any prior or concurrent study of the potential OTC OraQuick® Test
8. Were, in the judgment of the investigator, unable to complete the study or were unlikely to comply with the study protocol

Removal of Subjects from the Study

Subjects could have discontinued from the study at any time by choice or by investigator option for any reason related to their health or their ability to comply with the study. The investigator attempted to acquire all study-related information prior to the subject exiting the study, including the reason for discontinuation (*e.g.*, consent withdrawal, adverse event). If a subject was lost to follow-up, the investigator made reasonable attempts to obtain the reason for discontinuation. The investigators also advised all subjects who discontinued the study because of an adverse event of any subsequent therapy and/or procedures required to treat relevant, ongoing medical conditions. Data collected up to the time of the subject's withdrawal may have been used without the inclusion of identifying personal information, consistent with the informed consent/assent document, unless the subject provided a written request to limit the use and sharing of their study data.

In the event that a subject received a defective OraQuick Test and contacted either the Answer Center or the investigational center, the subject was asked to return the test. The investigational center then discontinued the subject from the study and provided the subject with their laboratory-based test results.

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Appendix 3: Risk Analysis Model from the November 2009 BPAC Meeting

In November 2009 FDA presented the results of a risk analysis to examine the public health risks and benefits of an over-the-counter HIV test at varying levels of sensitivity and specificity. The model is designed to estimate the benefits (true positive and true negative test results) and risks (false negative and false positive test results and failed tests) of a hypothetical over-the-counter (OTC) HIV test across a range of sensitivity and specificity.

The following table describes benefits and risks associated with different types of test results.

Result	Benefit
True positive	Knowledge of individual HIV status allows for behavior modification to prevent HIV transmission, and allows for partner notification Allows earlier medical intervention and entry into care Knowledge of HIV prevalence can allow for better targeting of public health resources
True negative	Peace of mind Assistance in appropriate targeting of public health resources

Result	Risk
False negative	Unsuspected transmission of virus and continued high risk behavior Delayed medical intervention
False positive	Unnecessary personal anxiety Unnecessary exposure to antiretroviral treatment if confirmatory test not done Incorrect allocation of public health resources

Three global inputs apply to all the sub-populations. These are: 1) Percent of Failed Tests; 2) Sensitivity; and 3) Specificity. The benefits (true positive and true negative test results) and risks (false negative and false positive test results and failed tests) are estimated for 1) Low-risk individuals, 2) men who have had sex with men, 3) injectable drug users, and 4) high-risk heterosexuals (defined as having had two or more opposite sex partners in the past twelve months). Four inputs have values specific to each sub-population. These are: 1) Size of sub-population; 2) Percent of sub-population that is

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untested; 3) Percent of untested individuals who are HIV+; and 4) Percent of untested individuals who would use an OTC HIV test.

The results will show the number of each type of test result (true positive, false negative, true negative, false positive, failed for an HIV+ individual, and failed for an HIV- individual) for each of the four sub-populations.

The most important feature of the analysis is the impact of test sensitivity on the ratio of true positive test results (benefits) to false negative test results (risks) and of specificity on the ratio of true negative test results (benefits) to false positive test results (risks). The main public health tradeoff for an OTC HIV test is the benefit of newly identified HIV+ individuals through a true positive test result and the risk of a false negative result which may lead an individual to continue to engage in risky behaviors that may infect others and cause the individual to delay seeking treatment. A second public health tradeoff is the benefit of newly identified HIV negative individuals through a true negative test result and the risk of false positives that would potentially over-stress medical resources as individuals seek confirmatory testing or treatment.