SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Trade Name: OraQuick® In-Home HIV Test

Applicant's Name and Address: OraSure Technologies, Inc.
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Premarket Approval Application (PMA) Number: BP120001

Date of Panel Recommendation: May 15, 2012

Office's Signatory Authority: Jay S. Epstein, M.D.
Director, OBRR/CBER

- □ **I concur with the summary review.**
- □ **I concur with the summary review and include a separate review to add further analysis.**
- □ **I do not concur with the summary review and include a separate review.**

Date of Notice of Approval to the Applicant: July 3, 2012

Material Reviewed/ Consulted: The PMA, amendments to the PMA, and other specific documentation used in developing the Summary of Safety and Effectiveness (SSE)

Review memos from the following reviewers were used in developing the SSE:

Discipline reviewed	Reviewer names
Clinical and Non-clinical/Analytical Review	Krishnakumar Devadas Xue Wang Hilary Hoffman Pradip Akolkar Pedro Piccardo German Anez-Gutierrez
Product Design	Hilary Hoffman Pradip Akolkar Uros Djekic
CMC Review	Krishnakumar Devadas Xue Wang Uros Djekic
Statistical Review	Paul Hshieh
Facility Review	Lori Peters
Risk Assessment	Richard Forshee
Bioresearch Monitoring	Janet White
Labeling and Promotional Advertizing	Hilary Hoffman Pradip Akolkar Dana Martin Lisa Stockbridge Laura Ulitzky Pedro Piccardo German Anez-Gutierrez
Policy	Elliot Cowan Indira Hewlett

II. Indications for Use

The OraQuick® In-Home HIV Test is a single-use, qualitative immunoassay to detect antibodies to Human Immunodeficiency Virus Type 1 (HIV-1) and Type 2 (HIV-2) in human oral fluid specimens. The OraQuick® In-Home HIV Test is intended as an over-the-counter (OTC) test for consumer use as an aid in the diagnosis of infection with HIV-1 and HIV-2. It is not intended to be used with specimens other than oral fluid.

III. Device Description

A. Overview

The OraQuick® In-Home HIV 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. The OraQuick® In-Home HIV Test is based on the current PMA-approved and CLIA-waived professional-use OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test for use with oral fluid specimens (PMA BP010047/16). No changes were made to either the design or manufacturing process of the test device (*i.e.*, the "Test Stick"). All design changes were made to the packaging and labeling of the product. The following table is a summary of the changes that were made to the OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test (professional-use product) to transition it to the OraQuick® In-Home HIV Test.

Table 1: Summary of changes made to the professional-use OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test for development of the OraQuick® In-Home HIV Test

Device Component	Change
Developer Solution Vial	The Developer Solution Vial cap in the professional-use test was modified to add thumb indentations to make it easier and more intuitive for the consumer to open the vial without spilling the Developer Solution. The cap is made of the same material as the cap of the approved professional product. The Developer Solution Vial label artwork has been revised to reflect consumer labeling. The Developer Solution Vial in the professional-use product is called the "Test Tube" in the OTC product. The solution contained in the Test Tube is the same Developer Solution as in the professional product.
Device Label	The artwork present on the Device Label was modified to reflect the branding for the OraQuick® In-Home HIV Test. Construct of the label is the same as the current Device Label.

Device Component	Change
Pouched Test Device and Developer Solution Vial	In the professional-use test, the Test Device and Developer Solution Vial are pouched in a divided pouch with separate compartments for the Test Device and Developer Solution Vial. The Test Device is called the "Test Stick" in the OTC product. The artwork was developed to show a pictorial of the Test Stick and Test Tube to allow the consumer to more easily follow the step-by-step instructions. The two sides of the divided pouch are separated into two pouches in the OTC product. The material used to make the two pouches is the same as that of the undivided foil laminate pouch of the professional product.
Test Stand	The Test Stand has been modified and is called the "Test Tube Holder" in the OTC product. The Test Tube Holder into which the Test Stick and Test Tube are placed to run the test was developed to physically incorporate it into the laptop box design. The angle at which the laptop opens to is consistent with the angle of the Test Stand used with the professional product.
Instructions for Use	The consumer instructions for use are provided in easy to follow step-by-step instructions. Graphics are used for emphasis and to assist with understanding. The consumer instructions for use make frequent reference to the toll free number of the Consumer Support Center.
Pre-Test Informational Booklet	The OraQuick® In-Home HIV Test provides a pre-test informational booklet called "HIV, Testing & **Me**." This booklet is found in the drawer containing all of the components needed for testing. The instructions for use reference the booklet in the introduction page and again at the point in the instructions where the user is waiting for their test results.
Post-Test Informational Booklet	The OraQuick® In-Home HIV Test provides a post-test informational booklet called "What your results mean to **You**!" This booklet is found in the drawer containing all of the components needed for testing. The instructions for use direct the user to read this booklet once they have interpreted their test results.
Packaging	The OraQuick® In-Home HIV Test contains components to perform a single HIV test. All of the contents are contained within the plastic laptop-like box that also serves as the test stand into which the Test Tube and Test Stick are placed in order for the test to run. The instructions for use are attached to the box and situated so that the pictures that help an individual conduct the test and interpret results are immediately adjacent to the consumer's Test Stick. The labeling references the toll free number to the Consumer Support Center throughout.

B. Test Kit Components

The OraQuick® In-Home HIV Test consists of the following items, illustrated in Figure 1:

- Outer carton containing plastic molded laptop box
- OraQuick® In-Home HIV Test Package Insert (not shown)
- Testing Directions (flipchart design) attached to the plastic molded laptop box
- 1 Test Stick, containing a nitrocellulose membrane with adsorbed HIV-1 and HIV-2 synthetic peptides and goat anti-human IgG, and a pad containing a blocking agent and protein-A colloidal gold
- 1 Test Tube, containing 1 mL of a phosphate buffered saline solution with polymers and an antimicrobial agent
- *HIV, Testing & **Me*** booklet (pre-test informational booklet)
- *What your results mean to **You!*** (post-test informational booklet)
- 1 Pencil for writing down the read times at which results are to be read (not shown)
- 1 Disposal Bag (not shown) (allows for discrete disposal)
- OraQuick® Consumer Support Center telephone number

Figure 1: OraQuick® In-Home HIV Test Components

C. *Principles of Operation*

The 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 antigens 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 directly onto the flat pad on the Test Stick by swabbing the upper and lower gums once each. This is followed by the insertion of the Test Stick into the Test Tube containing the developer solution. Both the Test Stick and the Test Tube are placed in the Test Tube Holder in the plastic box (Figure 2).

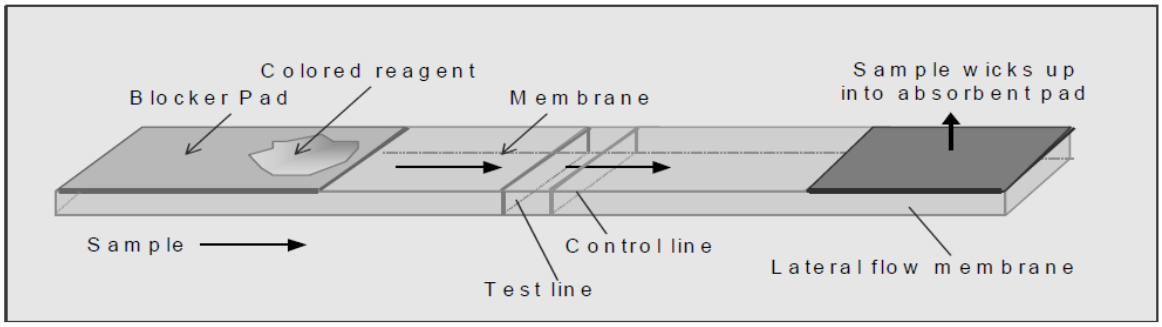
Figure 2: Running the OraQuick® In-Home HIV Test

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 (*i.e.*, "Test") zone. If the specimen contains antibodies that react with the HIV 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. The blocking agent in the Test Stick prevents non-specific binding of the reagents, improving the readability and interpretation of the test result.

Further up the assay strip, the sample will encounter the C (*i.e.*, "Control") zone. This built-in procedural control serves to demonstrate that a sufficient specimen was absorbed into the test device and that the developer solution 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. The T and C zones are clearly marked on the Test Stick for ease of interpretation. The test design is shown in Figure 3.

Figure 3: OraQuick Assay Design



Test results are read and interpreted after 20 minutes but not more than 40 minutes after the introduction of the Test Stick containing the test specimen into the Test Tube developer solution. Just as for the OraQuick *ADVANCE*® HIV-1/2 Antibody Test, no precision pipeting, predilutions, or specialized instrumentation are required to perform the OraQuick® In-Home HIV Test.

D. Test Results and Interpretation

If no antibodies to HIV-1 or HIV-2 are present, then only the control line (C) is visible and the result is interpreted as "negative" (Figure 4, left). If antibodies to HIV-1 or HIV-2 are present in the oral fluid specimen, two distinct lines appear in the test device window (T and C) (Figure 4, right). This is referred to as a "positive result" and labeling indicates to the user that, "you may have HIV," with further instructions that this test result should be confirmed by a healthcare professional. Any other pattern of lines in the test device (*e.g.*, no lines, a line at only the T position, lines that do not align with C or T, smeared background) is considered invalid and the user is instructed to contact the OraQuick® Consumer Support Center for additional information.

Figure 4: Examples of OraQuick Test Results

E. OraQuick® Consumer Support Center

If consumers encounter problems or have any questions regarding the testing process, they can call the OraQuick® Consumer Support Center.

The OraQuick® Consumer Support Center is a 24 hours a day/7 days a week/365 days a year Support Center with bilingual capability (English and Spanish). The Support Center was designed to provide consumers with basic HIV/AIDS information, assistance in how to correctly perform and interpret the test, and referrals for follow-up (confirmatory) testing and HIV care. The information conveyed to the caller by the agents is based on scripts that have been developed with information from the CDC website in addition to product specific information provided by OraSure. Additionally, the Support Center is designed with the capability to complete "warm" transfers if needed. This means that the Support Center personnel can transfer a user directly to a resource number.

Upon responding to calls, Support Center staff will ask the callers to specify a preferred language (English or Spanish). Callers will then be asked if they are calling about their test results, for help with performing the test, or for additional HIV/AIDS information. This allows calls to be prioritized and to provide immediate assistance to those who may have a positive result or are in the process of testing.

The following information can be collected from the Consumer Support Center once the system is operational.

- System generated:
  - Date of call
  - Agent
  - Language
  - Time call was answered
  - Resolution
  - Time call ended
  - Questions asked
  - Topic
  - Area Code
  - Action taken

- Other information requested from the caller:
  - ZIP Code
  - Gender
  - Repeating caller
  - Test results
  - Age group
  - Emotional status (inferred)

IV. Warnings, Precautions, and Limitations

1. The testing directions must be followed carefully. Not doing so may produce inaccurate test results.

2. Using this test earlier than 3 months since a risk event may not produce an accurate result.

3. This test should not be used by individuals who are anxious about using the test.

4. Reading test results earlier than 20 minutes or later than 40 minutes may yield erroneous results.

5. This test is approved by FDA for use with oral fluid specimens only. Use of other types of specimens may not yield accurate results.

6. Any positive result needs to be followed up with either a confirmatory test performed by a clinical laboratory or consultation with a medical professional to arrange a confirmatory test.

7. Individuals who test negative but engage in behavior that puts them at risk for HIV infection should test or be tested on a regular basis.

8. Persons with increased risk for HIV infection should not interpret a negative test to indicate that engaging in high-risk behavior is safe.

9. This test is not to be used by individuals under the age of 17.

10. Adequate lighting is required to read a test result.

11. This test is not for use by individuals who know they are HIV-positive or who are undergoing treatment for HIV infection.

12. This test should not be used after the expiration date.

13. If the tamper-evident seal has been broken or if any of the package contents are missing, broken, or have been opened, do not use this test.

14. The user should not open any of the packets until ready to begin the test.

15. Do not eat, drink or use oral care products (such as mouthwash, toothpaste or whitening strips) 30 minutes before starting the test.

16. Remove dental products such as dentures or clear braces that cover your gums prior to the oral collection.

17. Do not use the test if it has been exposed to household cleaning products.

18. A positive result may indicate the presence of antibodies to HIV-1 or HIV-2. A person who has antibodies to HIV-1 or HIV-2 is presumed to be infected with the virus, except that a person who has participated in an HIV vaccine study may develop antibodies to the vaccine and may or may not be infected with HIV.

V. Alternative Practices and Procedures

The diagnosis of HIV infection in the U.S. is primarily achieved using laboratory-based assays or rapid HIV tests performed in clinics or physicians' offices. These assays test samples of blood, serum, plasma, oral fluids, or urine. All initially positive results are confirmed using a second test. These tests are all performed by healthcare professionals. Individuals who wish to test anonymously may use an OTC home specimen collection system for HIV testing. In this case, the user purchases the system, collects a dried blood specimen and sends it to a laboratory for testing by trained personnel. Individuals who use a home specimen collection system receive results and post-test counseling by telephone.

The OraQuick® In-Home HIV Test differs from rapid HIV tests and laboratory tests in that the user is responsible for all aspects of the testing process from sample collection to test interpretation, and product labeling is used in lieu of live pre-test and post-test counseling. Live counseling is at the option of the user, through the Support Center.

VI. Marketing History

The OraQuick® In-Home HIV Test utilizes the same test device (Test Stick) and developer solution (Test Tube) as the approved OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test. The OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test was approved originally on November 2, 2002 as the OraQuick HIV-1 Rapid Antibody Test for use with fingerstick whole blood specimens. In 2003 OraSure submitted a supplement to allow for the additional use of venipuncture whole blood specimens. The supplement was approved on September 5, 2003. On June 24, 2004, OraSure obtained approval for the following additional claims: oral fluid, plasma, and detection of antibodies to HIV-2. At that time the name of the product was changed to OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test. CLIA Waiver was granted for the product on June 25, 2004. Since that time, over 20 million units have been used for HIV testing in the U.S.

VII. Potential Adverse Effects of the Device on Health

The OraQuick® In-Home HIV Test is an OTC home-use HIV test kit. This means that an untrained user is responsible for specimen collection, running the test and interpreting the test without the benefit of concurrent live counseling. Potential adverse effects of the device on health include:

- Emotional stress on the individual if a positive result is obtained without the benefit of counseling.
- Delayed entry into medical care if the individual obtains a false negative test result.
- False negative test results, *e.g.*, from testing during the window period or through procedural or interpretational errors, create risk of HIV transmission by the individual who is unaware of his/her true HIV status.

VIII. Non-clinical Studies

The following non-clinical laboratory-based studies that were conducted to assess the performance of the OraQuick HIV-1 Rapid Antibody Test (approved in 2002) and the OraQuick *ADVANCE*® HIV-1/2 Antibody Test for oral fluid (approved in 2004) were also used as a basis for approval of the OraQuick® In-Home HIV Test.

A. Justification of the OraQuick window period

Although there have been no direct studies on the duration of the window period prior to the appearance of detectable antibodies to HIV for the OraQuick® In-Home HIV Test, OraSure estimated this window period from recent publications [Owen SM, *et al*. J Clin Microbiol. (2008) 46: 1588-1595, Masciotra S, *et al*. J Clin Virol. (2011) 525: 517-522,

and Stekler JD, *et al*. Clin Infectious Dis. (2009) 49: 444-453]. These studies support a window period of approximately 55 days for the OraQuick® In-Home HIV Test, well-within the window period of 3 months (90 days) identified in the product labeling.

B. Studies using worldwide performance panels

To assess the ability of the OraQuick test to detect antibodies to 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 and one confirmed HIV-1 antibody-positive specimen from China was non-reactive. An additional 13 specimens representing HIV-1 Subtypes A, B, C, D, F, and G, and Group O were tested and found reactive on the OraQuick test.

Samples (plasma) from a 45-member commercially-available worldwide HIV-1 Performance Panel were tested with the OraQuick test. Performance of the OraQuick test agreed with the expected positive and negative results for the Reference Panel.

C. Effect of interfering substances

To assess the impact of unrelated medical conditions or interfering substances on the sensitivity of the OraQuick 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. All spiked specimens gave reactive results.

To assess the impact of unrelated medical conditions or interfering substances on the specificity of the OraQuick test, 321 serum/plasma specimens from a variety of medical conditions unrelated to HIV infection and 119 specimens with interfering substances were analyzed. 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.

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). Specimens from individuals with these disease states, medical conditions, or other factors were spiked with an HIV-positive specimen to give a level of reactivity in the low positive range. None of these disease states, medical conditions or other factors was seen to interfere with test sensitivity. In a separate study, 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 or specificity.

D. Flex studies

OraSure conducted additional studies ("flex" studies) to demonstrate suitable robustness of the product across a broad range of operational and environmental conditions consistent with OTC use (*e.g.*, temperature and humidity extremes, exposure of oral cavity to food, drink, and chemicals prior to sample collection, human factors, and variations in the sample collection process). OraSure revised labeling accordingly based on the results of these studies (see *Section IV, Warnings, Precautions, and Limitations*, above).

E. Stability studies

Expiration dating for this device was established by OraSure and approved by FDA at 30 months based on real-time stability studies for finished kits and kit components.

IX. Clinical Studies

OraSure conducted clinical studies for the OraQuick® In-Home HIV Test using a three-phased approach proposed by FDA and recommended by the Blood Products Advisory Committee (BPAC) in 2006 (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).

- Phase I established performance of the test in the hands of trained users, and characterized the inherent sensitivity and specificity of the test.
- Phase II established performance of the test system as a whole in the hands of untrained intended and expected users under observation. These studies were intended as a precursor to conducting studies of self-testing in an uncontrolled, intended use setting (Phase III), which presented a potentially higher risk to study participants due to lack of counseling when performing the test and obtaining the test result. Phase II consisted of two parts:
  - Phase IIA: Test result interpretation of contrived devices that were designed to indicate either positive, weak 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, according to BPAC recommendations at this meeting.
  - Phase IIB: Self-testing by individuals at high risk, unknown risk and low risk for HIV infection, and by individuals known to be infected with HIV. Study participants conducted and interpreted the test on their own, but under observation. The sensitivity and specificity in these studies was expected to be at

least 95%, expressed as the lower bound of the 95% confidence interval, according to BPAC recommendations.

- Phase III established 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 and expected users. The sensitivity and specificity in these studies were expected to be at least 95%, expressed as the lower bound of the 95% confidence interval, according to BPAC recommendations.

A. Phase I Studies

The sensitivity and specificity of the test in the hands of trained users was determined from studies using oral fluid specimens, conducted in support of the OraQuick *ADVANCE®* HIV-1/2 Antibody Test approval in 2004. The clinical study data are summarized in Table 2.

Table 2: Summary of Clinical Study Data for the OraQuick ADVANCE® HIV-1/2 Antibody Test Using Oral Fluid Specimens

Test Group	Total Samples	OraQuick Reactive	Licensed EIA RR[1]	True Positive
Known HIV +	767	762	764	767
High risk	3150	72	73	73
TOTAL	***3917***	***834***	***837***	***840***
Test Group	**Total Samples**	**OraQuick NR[2]**	**Licensed EIA NR**	**True Negative**
Low Risk	605	605	599	605
High risk	3150	3069	3076	3077
TOTAL	***3755***	***3674***	***3675***	***3682***

[1]RR = Repeatedly reactive
[2]NR = Non-reactive

These data show that the OraQuick *ADVANCE®* HIV-1/2 Antibody Test correctly detected 834/840 true HIV-positives in the clinical studies, giving a sensitivity of 99.3% (95% CI = 98.4-99.7%), and that the test correctly detected 3674/3682 true negatives, giving a specificity of 99.8% (95% CI = 99.6-99.9%).

B. Phase II Studies

1. Phase IIA

Phase IIA was divided into two sections: label comprehension and interpretation of contrived devices.

a. Quantitative Label Comprehension Study

The Quantitative Label Comprehension Study tested 427 individuals for their ability to correctly comprehend key messages from the packaging and labeling. These included proper self-selection, understanding of key warnings, proper test procedure and test result interpretation. The study included both English- and Spanish-speaking individuals and teenagers (ages 14-17 years). Demographics included subjects spanning both low and high incomes as well as different levels of education. Table 3 summarizes the results of the comprehension scores for key messages as assessed in the Quantitative Label Comprehension Study. The observed comprehension scores were all >80% with the majority being >90%, with the exception of key message "what to do next if you are negative" for which the comprehension score was lower (77.5%). Comprehension scores for correct actions following a negative result were generally lower throughout due to the open-ended nature of responses. OraSure presented these label comprehension results to FDA in January 2008 prior to the conduct of the Phase IIB observed use study.

Subsequently, label comprehension was tested as part of a Label Mitigation Study performed after the Phase IIB Observed Use Study, but prior to the Phase III Unobserved Use Study. OraSure conducted this additional study to evaluate labeling changes made to address errors observed in Phase IIB (see Section IX.B.2 below). These changes consisted of the following:

- Product
  - The Test Tube cap was redesigned to include a thumb indentation for ease of use by consumers. This targeted the operational error of spilling the Developer Solution contained in the Test Tube. Previously the cap design intuitively made the consumer twist the cap instead of popping it off, which causes the solution to spill. The motion of popping off the cap is now more intuitive with the new design.
  - The Laptop box was converted from a cardboard stock to a molded plastic box. This allowed for the design to be more robust and stable during use by the consumer.

- Instructions for Use
  - The names of the booklets were revised to represent the names that will be used for commercialization. The Pre-Test Informational booklet (HIV/AIDS Information) will now be called "HIV, Testing & **Me**" and the Post Test-Informational Booklet will now be called "What your results mean to **You**!"
  - The step for removing the cap from the Test Tube was revised for clarification to target the operational error of spilling the Developer Solution contained in the Test Tube.
  - The step for collecting the Oral Fluid sample was revised to add emphasis that both the top gums and the bottom gums needs to be swabbed to target the operation error of not swabbing the gums.
  - A statement was added to the page that provides the consumer with the directions for interpreting their test results. The statement "If your Test DID NOT WORK or you are NOT SURE what your result is, call the toll free number, 1-866-436-6527." This revision targeted those subjects who did not obtain a test result because they reported "Test Not Working" or "Don't Know/Not Sure."
  - A detailed list of the types of questions the Consumer Support Center could answer was added so the consumer will understand that there will be someone who can be called to obtain clarification.
- Outer Box
  - The section explaining the "window period" was revised to include an explanation of a risk event to further help the consumer self-select.

A total of 501 subjects were enrolled in the study. The criteria set for study success was to increase comprehension of what to do if the consumer is not sure of the test result. Study success was also dependent on reducing the operational errors observed in Phase IIB.

These product and labeling changes resulted in improved comprehension in some areas and decreased comprehension in others (see Table 3). The finding of reduced comprehension of "Use if pregnant" from 91.8% in the initial study to 71.9% in the repeat study was not explained.

Table 3: Comparison of Original and Repeat Phase IIA Quantitative Label Comprehension Studies

Question	Comprehension (Original Study)	Comprehension (Repeat Study – Label Mitigation Study)
What to do if your test is negative	77.5%	82.2%
Window Period	85.0%	98.6%
What to do if not sure of result	86.4%	97.4%
Last step before timing test	88.3%	84.6%
Not ok to use under 14 years of age	89.0%	92.8%
30 minutes after eating/drinking	90.2%	96.2%
Use if pregnant	91.8%	71.9%
Minimum time to read test	92.0%	96.4%
Not to use if already confirmed HIV+	93.2%	88.4%
Anxious about taking the test	95.3%	97.2%
End reading time $\leq$40 minutes	97.2%	98.2%
Positive results-what to do	98.1%	97.0%
What to do if user has questions	99.1%	99.2%
What is product used to test	99.3%	98.8%

b. Device Interpretation Study

The Device Interpretation Study tested 2001 individuals on their ability to interpret pre-determined test results. Devices were fabricated to represent a negative, positive, weak positive and invalid test result. Individuals were given the laptop-designed box containing each device and testing directions, and were asked to interpret the results. The study included both English- and Spanish-speaking individuals and teenagers (ages 14-17 years). Demographics included subjects spanning both low and high incomes as well as different levels of education. The results of the device interpretation study are shown in Table 4.

Expected 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, expressed as the lower bound of the 95% confidence interval. The initial results from the Phase IIA studies showed that performance expectations (% agreement) 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. The results from the repeat of the Phase IIA Label Mitigation study involving 501 individuals showed that performance expectations (% agreement) 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). OraSure was advised that they could proceed to Phase III studies despite these results.

Table 4: Comparison of Original and Repeat Phase IIA Studies on Interpretation of Contrived Devices

Test Device Result	**Lower bound of the 95% Confidence Interval**		
	Minimum Expected Agreement	Original Study Correct Interpretation	Repeat Study (Label Mitigation Study) Correct Interpretation
Positive	≥98%	93.9%	93.9%
Weak Positive	≥95%	80.2%	78.0%
Negative	≥98%	92.6%	93.0%
Invalid	≥98%	90.8%	90.8%

2. Phase IIB: Observed self-testing

The Phase IIB (observed use) study was designed to have subjects self-test while under observation by and in the company of a trained technician at the clinical site. The subject self-tested and interpreted his/her own test results. The observing trained technician did not interact with the subject but documented any errors seen during the performance of the test. Once the subject completed interpreting the test device, the

trained technician also interpreted the device. The subject was then tested by another trained technician that was blinded to the results of the first test, utilizing the professional OraQuick *ADVANCE*® Rapid HIV-1/2 Antibody Test with oral fluid.

The study was designed to allow testing of up to 2000 subjects of unknown HIV status and 2000 subjects that were HIV-positive. The population of unknown status included the general population (adults and teenagers (ages 14-17 years) enriched for the demographics and risk factors of intended users. The study also included Spanish-speaking individuals. Interim analyses at 500 and 1,000 subjects were planned for each arm of the study (HIV-positives and HIV unknown status) against the acceptance criteria, to allow for enrollment to be stopped for futility or if the acceptance criteria were met.

Acceptance criteria for sensitivity and specificity for the oral fluid self-test versus trained user were:

- Sensitivity = [TP / (TP + FN)] x 100, where:
  - TP (true positive) is positive oral fluid self-test in agreement with blinded trained user positive oral fluid test, and
  - FN (false negative) is negative oral fluid self-test discordant with blinded trained user positive oral fluid test.

  Expected performance recommended by BPAC (March 10, 2006 Meeting) was 95% expressed as the lower bound of the two-sided 95% confidence interval.

- Specificity = [TN / (TN + FP)] x 100, where
  - TN (true negative) is negative oral fluid self-test in agreement with blinded trained user negative oral fluid test, and
  - FP (false positive) is positive oral fluid self-test discordant with blinded trained user negative oral fluid test

  Expected performance recommended by BPAC (March 10, 2006 Meeting) was 95% expressed as the lower bound of the two-sided 95% confidence interval.

In addition, there was a requirement for the identification of 10 HIV infections from subjects of unknown HIV status.

A total of 1031 subjects were enrolled into the trial. Of those, 1013 completed the study (514 known HIV-positives and 499 of unknown HIV status). Table 5 below summarizes the demographics from the Phase IIB study. HIV risk factors information was collected from the subjects with unknown HIV status to ensure that a population having risk factors of the intended use population was being studied. The HIV risk

factors were self-reported through a questionnaire that was completed by subjects during the study.

FDA asked for specific at-risk populations to be included within the populations tested. The intent was to represent the demographics of users who are expected to purchase an OTC home-use HIV test kit, or to whom the kit might be distributed through existing public health systems. FDA concurred that the demographics of the study populations for both the observed use (Phase IIB) and unobserved use (Phase III) studies were consistent with these expectations.

Table 5: Phase IIB Study Demographics

Demographic Characteristics	Demographics by Percent
Male	66.9% (690/1031)
Female	31.9% (329/1031)
Black or African American	46.4% (478/1031)
Hispanic	20.7% (213/1031)
Low Literate	19.1% (197/1031)
High School or Less (adults only)	45.6% (470/1031)
HIV Risk Factors of Study Subjects with Unknown HIV Status	**HIV Risk Factors by Percent**
Homosexual / Bisexual	13.0% (65/500)
Ever Injected Non-prescription Drugs	11.2% (56/500)
Ever Traded Sex for Drugs or Money	8.4% (42/500)
Ever had a Sexually Transmitted Disease	22.6% (113/500)

Subjects who completed the self-test study interpreted their results as one of the following:

- May Have HIV/Preliminary Positive
- Don't Have HIV/Negative
- Test Not Working/Invalid
- Not Sure/Don't Know

Focusing on the calculation of sensitivity, there were a total of 526 HIV-positive subjects in the Phase IIB study. These were predominantly known HIV-positive subjects (514) along with 12 prospectively identified positives from the population of unknown HIV status. Of those 526 subjects, 24 did not obtain a test result either because they committed an operational error which resulted in an interpretation of Test Not Working or they responded with a result of "Not Sure/Don't Know." In addition, 22 subjects did not have a recorded self-test result. Of the 480 subjects who obtained a test result, 470 were True Positive and 10 were False Negative. **Based on these results, the sensitivity for this population was calculated to be 97.9% (470/480), with a 95% confidence interval of 95.0% - 99.4%.** This met the expected minimum sensitivity of 95% expressed as the lower bound of the two-sided 95% confidence interval.

Of the 10 false negatives (2.08%) observed in this study, all were known HIV-positive individuals.

There were a total of 12 newly identified HIV-positive individuals among the population of unknown status who correctly identified themselves as HIV-positive by self-testing. All results were confirmed by Western blot. The observed prevalence rate during this trial was 2.4%. Table 6 summarizes the characteristics of the newly identified HIV-positive subjects.

Table 6: Characteristics of Newly Identified HIV-Positive Subjects

Characteristics (self- reported)	n=12
Black	67% (8/12)
Female	42% (5/12)
Reported never testing previously	33% (4/12)
Likelihood of testing positive (0 Not at all - 10 Very likely)	Mean 4.1 Range 0 to 9 50% ≤ 4

Focusing on the calculation of specificity, there were a total of 499 subjects of unknown HIV status in the Phase IIB study. Of those 499 subjects, 12 were prospectively identified HIV-positive individuals and 9 did not obtain a test result either because they performed an operational error which resulted in an interpretation of Test Not Working or they responded with a result of "Not Sure/Don't Know". In addition, 5 subjects did not have a recorded self-test result. Of the 473 subjects who obtained a test result, 472 were True Negative and 1 was a False Positive. **Based on these results, the specificity for this population was calculated to be 99.79% (472/473), with a 95% confidence interval of 98.1% - 100.0%.** This met the expected minimum sensitivity of 95% expressed as the lower bound of the two-sided 95% confidence interval.

The Phase IIB studies are summarized in Table 7 below which shows the number of concordant and discordant test results between the untrained and trained users.

Table 7: Summary of Phase IIB Study Results

		Trained User Result	
		Positive	**Negative**
Self-Test Result	Positive	470*	1
	Negative	10	472
	Not Sure/Don't Know	24	9
	No Recorded Self-Test Result**	22	5
	TOTAL	526	487

* Includes 458 known HIV-positives and 12 prospectively identified HIV-positives.

**Subjects who did not have a recorded self-test result.

The error rate observed in the HIV known positive population, in which individuals failed to obtain either a positive or a negative result, was 4.88% (24/492). The error rate observed in the population of unknown HIV status was 1.82% (9/494). Table 8 summarizes the types of operational errors observed during the Phase IIB study.

Table 8: Operational Errors Observed in Phase IIB

Self-Test Issue	HIV Known Positives (n=492)	Unknown HIV Status (n=494)
Device interpretation error	7	4
Dipping device in developer prior to swabbing gums	7	4
Spilling the developer	4	0
Not swabbing the gums	4	1
Could not find developer vial	2	0
Total	24 (4.88%)	9 (1.82%)

During the Phase IIB Study, it was noted that a much larger proportion of operational errors was committed by the known HIV-positive subjects compared to those who were unaware of their HIV status. An additional analysis of the observational data indicated HIV-positive subjects were much less likely to read the instructions for use (Table 9). These observations suggested that the HIV-positive subjects were less invested in the outcome of the test because they already knew their HIV status.

Table 9: Observation of Reading Test Kit Instructions in Phase IIB

Self-Test Steps	HIV Known Positives	Unknown HIV Status
Read instructions on outside of box	**76.1%**[1]	**90.6%**
Read booklets supplied with test	**67.5%**[2]	**85.4%**

[1] $p<0.001$
[2] $p<0.001$

To address the error rate, OraSure modified the product and labeling (see Section IX.B.1.a above). Once packaging and labeling enhancements were completed, OraSure conducted the Label Mitigation Study described above to verify the changes.

3. Summary of Phase II studies

The purpose of the Phase II studies was to establish performance of the test system as a whole in the hands of untrained intended and expected users under observation, prior to conducting studies of self-testing in an uncontrolled, intended use setting (Phase III). These Phase II studies provided preliminary information about the test system performance, prior to undertaking Phase III studies which presented a potentially higher risk to study participants due to lack of live counseling prior to performing the test and after obtaining the test result.

The results of the Phase IIB studies (observed self-testing) showed that performance expectations were met for both sensitivity and specificity. However, the results of Phase IIA studies (interpretation of contrived devices) showed that performance expectations were not met initially or following labeling modifications that were designed to improve the level of interpretation.

FDA discussed the Phase II study results with the Blood Products Advisory Committee on November 17, 2009. BPAC recommended that OraSure could proceed with the Phase III studies. In addition, BPAC agreed with FDA's proposal to base sensitivity of the test from Phase III studies only on prospectively identified HIV-infected individuals, given that individuals known to be infected with HIV do not represent intended users of the test. BPAC also stipulated that the occurrence of test system failures in Phase III should be less than 2%. Test system failures were defined for subjects who attempted to run the OraQuick® In-Home HIV Test, but could not interpret their test result, could not run the test, or had no lines develop.

OraSure also made additional modifications to the product packaging and labeling that were designed to reduce the occurrence of operational errors and test system failures from approximately 5% (as observed in Phase IIB) to less than 2%. Once packaging and labeling enhancements were completed, OraSure conducted a study, the Phase IIA Label Mitigation Study, to verify the changes. Upon review of this study of enhanced labeling, OraSure was permitted to begin the Phase III study.

C. Phase III Studies

1. Phase III study design

The Phase III study (Unobserved Use Study) was designed to have subjects self-test as if they purchased the product. The study was designed to allow enrollment of up to 5000 subjects of unknown HIV status at high prevalence sites and 1000 subjects from a low prevalence cohort representative of the general population. The demographic composition of the high prevalence population reflected the major risk categories for HIV infection as defined by CDC. There were 17 high prevalence sites and 3 low prevalence sites representing broad geographic distribution across the U.S. The study population included both English and Spanish speakers.

Each subject made multiple visits to the study site. At Visit 1, enrolled subjects had blood drawn for HIV laboratory testing. Subjects then returned for Visit 2, were asked to read the outer package, and were given the option to self-test for HIV with the OraQuick® In-Home HIV Test. Unobserved self-testing occurred in a setting of the subject's choosing following Visit 2. At Visit 3, subjects retuned to the site and provided their self-test result by responding to questions asked by site staff according to a standardized script. At this visit, subjects were provided their laboratory test results and received appropriate counseling. Additional information on the intended next actions of both HIV-positive and HIV-negative subjects was collected. In the rare event that additional laboratory testing was required in order to definitively determine a subject's HIV status, a Visit 4 was scheduled to communicate the results. As noted above, in addition to self-testing with the OraQuick® In-Home HIV Test, all subjects were tested for HIV antibodies by an FDA-licensed laboratory test, *i.e.*, serum EIA and Western blot (as needed). The sensitivity and specificity of the OraQuick® In-Home HIV Test were estimated in comparison to the subject's true HIV serostatus as determined by FDA-approved laboratory testing. The OraQuick® Consumer Support Center was available 24/7 for access, as needed, by study subjects during the conduct of the study.

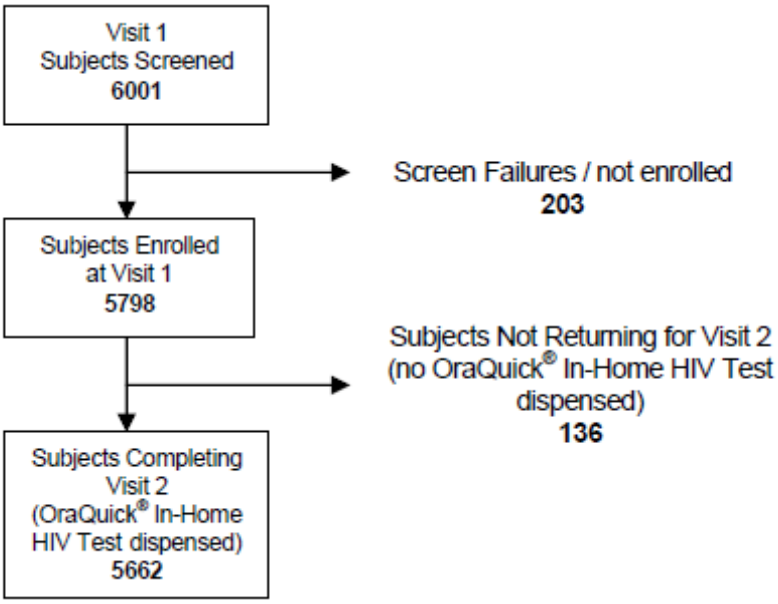
The Phase III study analysis planned to establish:

- Sensitivity – Calculated point estimate and the two-sided confidence interval in HIV-positive subjects newly identified from unknown risk and high risk populations.
- Specificity - Calculated point estimate and the two-sided confidence interval in HIV uninfected subjects identified from high risk populations and low prevalence (general) populations.
- Test Reliability – Percent of occasions when the user did not obtain positive or negative results; BPAC (November 17, 2009 Meeting) indicated that this should not exceed ~2%.
- Prospective identification of at least 100 previously undiagnosed HIV-positive subjects.

2. Phase III study participants

A total of 6001 subjects signed informed consent and were screened at Visit 1. Figure 5 provides a high level flow diagram of test subjects for Visits 1 and 2. A total of 203 subjects failed to meet the inclusion/exclusion criteria and were not enrolled. The remaining 5798 subjects were consented and enrolled. Of the 5798 subjects enrolled, 5662 subjects received the investigational OraQuick® In-Home HIV Test at Visit 2.

Figure 5: Numbers of Test Subjects for Visits 1 and 2



Subjects were enrolled across 20 clinical sites, with 17 sites enrolling subjects from a high prevalence population, and 3 sites enrolling subjects from a low prevalence (general) population. Table 10 summarizes the distribution of subjects by location and observed prevalence of the sites based on the subjects' true HIV status.

Table 10: Distribution of Subjects According to Geographical Location and Prevalence

	Subjects Enrolled	**Subjects Who Received Kit**	**HIV-positive (by FDA approved blood test)**	**Approximate Prevalence**
Higher Prevalence areas: EAST	1,417	1,381	43	3.1%
Higher Prevalence areas: SOUTH/CENTRAL	1,763	1,727	42	2.4%
Higher Prevalence areas: MT / WEST	1,509	1,454	34	2.3%
Higher Prevalence area sites: ALL	4,689	4,562	119	2.6%
Lower Prevalence area sites	1,109	1,100	1	0.1%
Total – ALL SITES	5,798	5,662	120	2.12%

3. Demographics

   Of the 5798 subjects enrolled, 1109 were from a low prevalence population and 4689 were from a high prevalence population. Table 11 below summarizes select demographics and HIV risk for subjects enrolled in the study. Information regarding HIV risk was self-reported by subjects through the use of a questionnaire completed at Visit 1.

Table 11: Selected Demographics of Enrolled Subjects

Demographic Characteristics	High Prevalence by Percent	Low Prevalence by Percent	Total by Percentage
Male	53.5% 2509/4689	35.7% 396/1109	50.1% 2905/5798
Female	46.0% 2159/4689	64.3% 713/1109	49.5% 2872/5798
Black	53.0% 2483/4689	21.7% 241/1109	47.0% 2724/5798
White	36.4% 1708/4689	71.1% 788/1109	43.0% 2496/5798
Hispanic	17.9% 839/4689	8.6% 95/1109	16.1% 934/5798
Low Literate	31.5% 1478/4689	13.2% 146/1109	28.0% 1624/5798
High School or Less	58.0% 2719/4689	35.5% 394/1109	53.7% 3113/5798

4. Most-affected subpopulations

   A total of 4689 subjects were enrolled from high prevalence populations. Table 12 below presents the HIV categories and seropositivity data among the 4562 subjects receiving an Investigational Kit. These categories align with select sub-populations identified by CDC.

Table 12: Summary of HIV Confirmed Positive Subjects in the High Prevalence Population by Select Sub-Population

Select Sub-Population	Received Investigational Kit (n)	Confirmed Positive by FDA-approved Serology	Positive Rate within Risk Category
White MSM	191	7	3.7%
Black MSM	189	29	15.3%
Hispanic MSM	71	6	8.5%
Black Heterosexual Male	1033	30	2.9%
Black Heterosexual Female	859	21	2.4%
Hispanic Heterosexual Female	370	2	0.5%
Hispanic Heterosexual Male	307	5	1.6%
White Heterosexual Female	414	2	0.5%
White Heterosexual Male	527	5	0.9%
All others	601	12	2.0%
Male IDU	201	4	2.0%
Female IDU	88	3	3.4%
Traded Sex* - All Races/Gender	913	33	3.6%
Prior STD - All Races/Gender	1624	52	3.2%

* Subjects may fall into multiple categories, therefore, the preceding numbers do not add up to the total number of subjects who received an Investigational Kit.

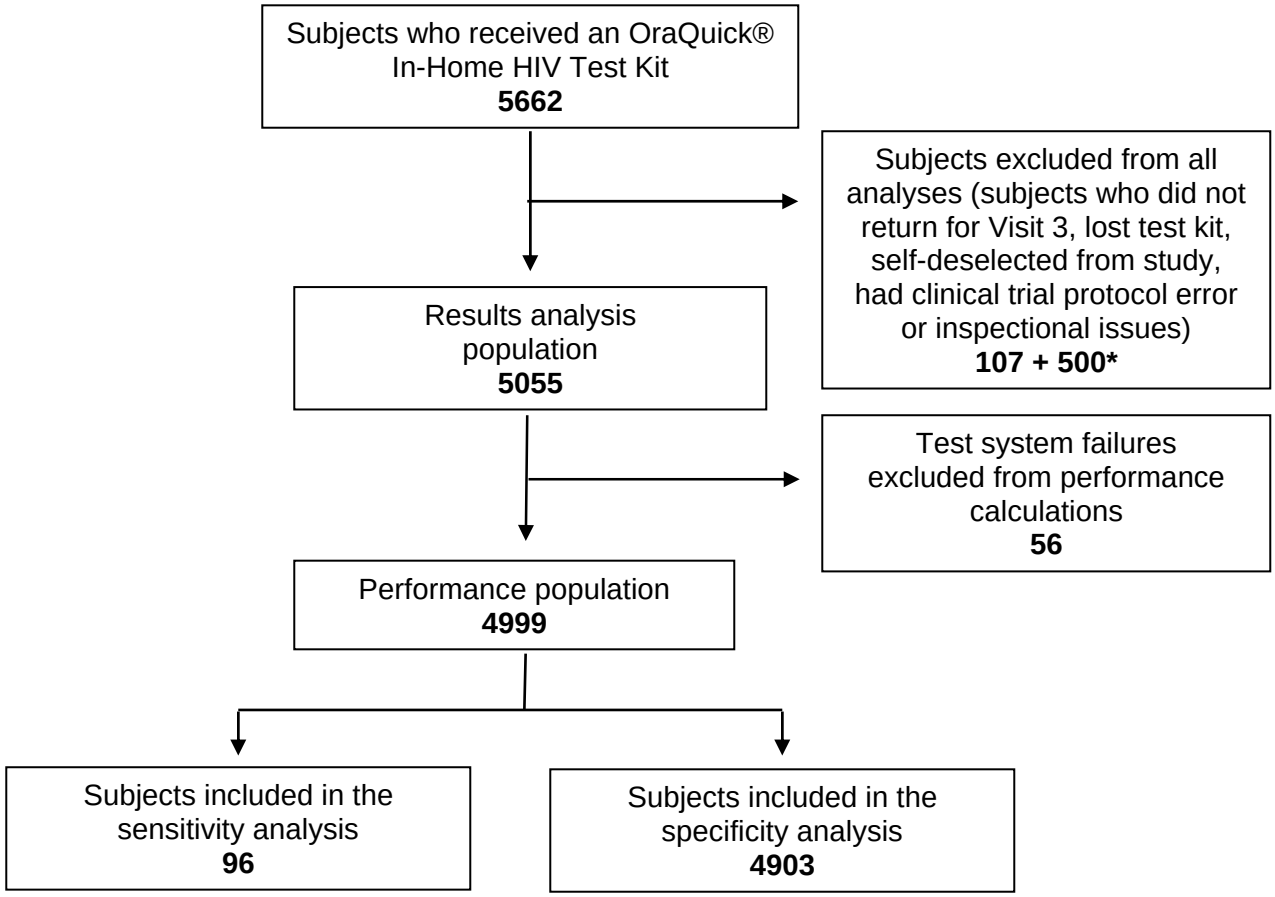
** Traded sex for drugs or money

5. Analysis populations

   a. Test Subjects

Of the 5662 subjects who received an OraQuick® In-Home HIV Test, 4999 were included in the analysis of sensitivity and specificity. Figure 6 provides this information in a flow diagram.

Figure 6: Numbers of Test Subjects in Analysis Populations



* Based on the results of a bioresearch monitoring inspection, FDA excluded the data (500 test subjects) from one of the clinical trial sites due to the need for further validation of the data from that site. See Section X.B.

b. Subjects excluded from performance analysis

Of the 5662 subjects who received an OraQuick® In-Home HIV Test, 663 subjects were not included in the sensitivity and specificity calculations. Information about these subjects is provided in Table 13. Twenty-four of these subjects were confirmed positive according to their laboratory test results. The 663 excluded subjects included all (500) subjects from one of the clinical study sites due to the need for further validation of the data from that site. Of the 500 subjects from that site, 482 were HIV-negative and 18 were HIV-positive. See Section X.B below.

Table 13: Summary of Subjects who were Excluded from the Sensitivity and Specificity Analyses

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	13
Clinical trial protocol error	15
Lost test kit	19
Failed to return for Visit 3	60
Site excluded (see Section X.B)	500
TOTAL	**663**

Among all test subjects in the OraQuick® In-Home HIV Test analysis population, there were 56 failed tests (56/5055 = 1.11%). These 56 subjects attempted to run the OraQuick® In-Home HIV Test, but either could not interpret their test result (21), could not run the test (25) or had no lines develop (10), as shown in Table 13 above. This rate of failed tests (1.11%) was below the 2% limit specified by FDA prior to the start of the Phase III clinical trial.

c. Reference testing/Testing algorithm

All subjects had their blood drawn at Visit 1 for HIV testing by a central clinical laboratory. The blood samples were processed to provide both serum and plasma specimens. Processing and shipping instructions were provided to the investigational centers by the central clinical laboratory. Testing was first done using an FDA-licensed laboratory-based enzyme immunoassay. Subsequent testing was done according to the algorithm shown in Table 14.

Table 14: Phase III Testing Algorithm

Self-Test Result	EIA Result[1]	HIV-1 Western Blot[2] Result	Additional Testing with HIV-2 Enzyme Immunoassay[3]	Additional Testing by PCR Nucleic Acid Test[4]	Final HIV Status for Analysis of Self-Test Performance
Negative	Negative	Not applicable	Not applicable	Not applicable	Not HIV-infected
Positive	Negative	Negative	Negative	Negative	Not HIV-infected
Negative or Positive	Repeatedly Reactive	Positive	Not applicable	Not applicable	Infected with HIV-1
	Repeatedly Reactive	Indeterminate	Positive	Not applicable	Infected with HIV-2
	Repeatedly Reactive	Indeterminate	Negative	Positive	Infected with HIV-1
	Repeatedly Reactive	Indeterminate	Negative	Negative	Not HIV-infected
	Repeatedly Reactive	Negative	Positive	Not applicable	Infected with HIV-2
	Repeatedly Reactive	Negative	Negative	Not applicable	Not HIV-infected

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d. Sensitivity analysis

A total of 96 subjects were included in the sensitivity analysis. Of these, 88 subjects were true positive, as their self-test results and lab result were both positive. Eight subjects were reported as false negative, with all eight reporting a negative self-test result and having a positive laboratory result.

Sensitivity in this study was calculated to be 91.67% (88/96) with a 95% confidence interval of 84.24%-96.33%.

The eight recorded false negative subjects provided a definitive answer of "negative" when asked to self-report their HIV status according to the OraQuick® In-Home HIV Test. Subjects with false negative results were not clustered in any

particular site and were not asymmetrically distributed according to race, gender, sexual orientation or measured literacy score. Select demographic and sexual orientation information is provided in Table 15.

Table 15: Summary Information for Subjects with False Negative Self-Test Results

Age	Gender	Race	Language	Sexual Orientation	REALM Score	WB Result
52	Female	Black	English	Heterosexual	65	Positive
53	Male	Black	English	Heterosexual	66	Positive
47	Male	Black	English	Heterosexual	62	Indeterminate
46	Female	Black	English	Heterosexual	49	Positive
23	Male	Other: Hispanic	English & Spanish	Homosexual	65	Positive
20	Male	Black	English	Homosexual	35	Positive
53	Male	Black	English	Heterosexual	64	Positive
26	Male	Black	English	Heterosexual	65	Positive

Abbreviations: REALM = Rapid Estimate of Adult Literacy in Medicine; WB = Western blot

One of the eight false negative subjects was indeterminate in initial confirmatory testing by HIV-1 Western blot, negative by HIV-2 EIA, and inconclusive by PCR. This subject was HIV-1 Western blot-positive in subsequent testing, indicating this subject was in the process of seroconverting at the time of testing, that is, during the antibody-negative window period. This lack of a fully developed antibody response could have resulted in this false negative result on the investigational test.

The remaining false negative subjects were all Western blot positive at the time of testing. The reasons for these false negative results based on self-reported outcomes of an individual's self-testing are unknown. Review of source documents did not lend any further information as to root cause.

e. Specificity analysis

A total of 4903 subjects were included in the specificity analysis. Of these, 4902 subjects were reported as true negative, as their self-test result and laboratory result were both negative. One subject reported a positive self-test result, but all laboratory testing (EIA, Western blot, PCR) gave negative results. Therefore, one subject was reported as false positive.

Specificity in this study was calculated to be 99.98% (4902/4903) with a 95% confidence interval of 99.89%-100%.

f. Summary of Phase III study results

The results of the Phase III studies are summarized in Tables 16 and 17.

Table 16: Summary of Phase III Study Results

	Test Algorithm Positive	**Test Algorithm Negative**
Self-Test Positive	106	1
Self-Test Negative	8	5384
No Self-Test Result	6	157
Total	120	5542
Total Used in Sensitivity and Specificity Calculations	96*	4903**

*120 total positives, minus 6 with a no self-test result, minus 18 positives from the clinical trial site excluded from the study (see Section X.B below).

**5384 negatives, minus 157 no self-test result, minus 482 negatives from the clinical trial site excluded from the study (see Section X.B below).

Table 17: Phase III Sensitivity and Specificity

	Minimum Recommended Value[1]	**Phase III Results[2]**
Sensitivity	≥95% at lower bound of 95% CI	91.67% (95% CI: 84.24 – 96.33%) (88/96)
Specificity	≥95% at lower bound of 95% CI	99.98% (95% CI: 99.89 – 100%) (4902/4903)

[1]BPAC minimum recommended value (March 10, 2006 Meeting)
[2]Excluding all participants with no self-test result

The sensitivity of the OraQuick® In-Home HIV Test in the Phase III study was below the minimum recommended performance of 95% expressed as the lower bound of the 95% confidence interval, at 84.24%. The specificity of the OraQuick® In-Home HIV Test in the Phase III study exceeded the minimum recommended performance of 95% expressed as the lower bound of the 95% confidence interval, at 99.89%.

g. Predictive values

The positive and negative predictive values are shown in Table 18, calculated using data from all subjects who were included in the sensitivity and specificity analyses.

Table 18: Positive and Negative Predictive Values

	Value	**95% Confidence Interval**
Positive Predictive Value	98.88% (88/89)	93.90-99.97%
Negative Predictive Value	99.84% (4902/4910)	99.68-99.93%

h. Studies in adolescent populations

Studies in adolescent populations included a lower age limit of 14 for users of the OraQuick® In-Home HIV Test. However, OraSure made the decision to use a minimum age limit of 17 to facilitate age verification at purchase. The data from the adolescent populations represented a small subset (89 subjects between ages 14 and 17 years) of the data in the study and were included in the calculations of sensitivity and specificity.

Of the 89, one male did not return for his Visit 2 and did not receive an investigational kit. Two other subjects did not return for their Visit 3. Among the 89 subjects in this category, 43.8% were Black, 23.6% were White, and 28% were unspecified. For ethnicity, 38.2% of the subjects described themselves as Hispanic. By gender, 60% of the subjects were female. Regarding sexual preference, 3.4% did not respond, 87.6% classified themselves as heterosexual and 9% as bisexual. A total of 29 adolescent subjects were enrolled from low prevalence sites with the remaining 60 subjects enrolled from the high prevalence sites.

All subjects who reported a self-test result at Visit 3 were concordant negative with their laboratory EIA (100%: 85/85). One additional subject self-reported an operational error by reason of not understanding where to place the Test Stick after sample collection.

i. Adverse events

There were two-device related adverse events reported during the clinical trial – gingival pain (described as "tingling to swab areas of mouth") and paresthesia oral (described as "stinging gums for 1 minute"). These two events were considered mild in severity and resolved without treatment.

Of the subjects who received post-test counseling during Visit 3 for their HIV-positive status, most (68.6%) were calm upon learning of their HIV status, with the remaining subjects (31.4%) verbally communicating some level of anxiety about their status. No intervention from investigational center staff was required for any of the subjects who were informed of their HIV-positive status, other than to provide counseling and recommendations for follow-up testing and medical care, and precautions to take to avoid infecting others.

No calls to the Consumer Support Center reported events or problems that qualified as a serious adverse event or required connection to the suicide prevention hotline.

j. Consumer Support Center usage

Of the subjects who returned to the site for Visit 3, at total of 151 documented they called the Consumer Support Center. The Consumer Support Center logged 217 calls during a span of 37 weeks (the duration from the time the first subject called the Center to the time the last subject called the Center). A reconciliation of the number of calls reported by subjects and the number of calls logged by the Consumer Support Center was not completed, as not all subjects who called the Consumer Support Center reported their complete study subject identification information. In addition, 9 calls were logged from non-study participants. The average call was 6.5 minutes in length. Most of the calls were conducted in English, rather than Spanish, and the most common questions were associated with the disposal of the OraQuick test or its components (n=120). The reason this question was asked most frequently was due to the fact that subjects were instructed to return the OraQuick Test kit to the investigational center, although the instructions within the OraQuick test recommended disposal of the kit under the assumption of use in a non-investigational setting. Other common questions were associated with the use/operation of the OraQuick Test and interpretation of test results (n=74).

X. Inspections

A. Manufacturing facilities

FDA conducted inspections at the following three facilities:

1. OraSure Technologies, Inc.
   Manufacturing Facility
   1745 Eaton Ave.
   Bethlehem, PA
   Establishment inspection dates: 4/26/12 – 5/9/12
   FEI #: 2528909
   Functions:
   - Manufacturing
   - Quality

   This inspection was classified as Voluntary Action Indicated (VAI) with the issuance of an FDA Form 483. One observation was identified, for inadequate validation of a pouching machine. OraSure committed to correct this deficiency.

2. OraSure Technologies, Inc.
   Manufacturing Facility
   220 East 1st St.
   Bethlehem, PA
   Establishment inspection dates: 5/14/12 – 5/30/12
   FEI #: 3004142665
   Functions:

- Corporate Headquarters
- Administrative
- Warehouse
- Manufacturing
- Engineering
- Quality

This inspection was classified as VAI with the issuance of an FDA Form 483. Two observations were identified, one for use of an unapproved industrial cleaner and the other for an inadequate root cause investigation for a failure in the manufacturing process. OraSure corrected the first observation deficiency and the material associated with the second observation was discarded.

3. OraSure Technologies, Inc.
   Design Facility/Specification Developer
   150 Webster St.
   Bethlehem, PA
   FEI #: 3003297763
   Establishment inspection dates: 5/14/12 – 5/23/12
   Functions:
   - Storage of complaints and design control documents (no manufacturing activity)

   This inspection was classified as No Action Indicated (NAI).

B. Bioresearch monitoring (BIMO)

Twenty clinical investigator sites participated in this study. Thirteen clinical investigator site inspections were performed in addition to inspections of the sponsor, the study monitor, and the Consumer Support Center. The factors used to select the sites for inspection included the following: prior inspection reports, the pivotal study protocol, study subject enrollment, enrollment of adolescents, clinical investigators not previously inspected, and serious adverse events. The inspections focused on specific questions concerning the study protocol and the comparison of information from the PMA to source documents.

The inspections at 12 of the 13 sites revealed no deviations from applicable regulations for clinical research involving investigational devices. Validation of data from one of the clinical study sites is pending. Therefore, FDA excluded the data from that site for the calculations of sensitivity and specificity. The clinical trial data from the remaining sites are sufficient to make a determination of safety and effectiveness.

XI. Benefits and Risks for the OraQuick® In-Home HIV Test

The OraQuick® In-Home HIV Test is a test that allows lay users to determine, anonymously and within the privacy of their own home, whether they are infected with HIV. Many individuals in the U.S. are unaware of their HIV status. The OraQuick® In-Home HIV Test offers an additional option for testing and therefore may increase access to testing for at-risk individuals. When using this test, some individuals will learn that they may be infected with HIV. This allows them to seek confirmatory testing and medical care, as appropriate. Also, individuals who become aware of their HIV status may take appropriate steps to prevent the transmission of HIV to others. Therefore, the OraQuick® In-Home HIV Test has benefits to the individual patient (access to diagnosis and medical follow-up) and public health benefits (prevention of HIV transmission).

The risks of the OraQuick® In-Home HIV Test arise primarily from false negative and false positive test results. The Phase III clinical study estimated that one false negative result would be expected to occur out of approximately every 12 test results in HIV infected individuals. False negative test results can delay an individual's access to medical treatment and may falsely reassure an individual about engaging in risky behavior. Lack of awareness of an HIV infection may put others at risk for disease transmission. The clinical study also estimated that one false positive test result would be expected out of every 5,000 test results in uninfected individuals. False positive test results can cause unnecessary emotional distress.

In an attempt to better understand the benefit-risk profile of the OraQuick® In-Home HIV Test, FDA developed a benefit-risk model. This model is based on the projected number and sub-populations of individuals that would use 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. It also considers that the availability of self-testing may cause some individuals to perform self-testing instead of using a professional-use test. The lesser sensitivity of the self-test as compared to professional-use tests could result in increased rates of HIV transmission given the increased number of false negative results expected. The risk model 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 benefit-risk model have some uncertainty associated with their estimates. FDA 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. FDA then calculated the expected outcomes.

FDA was able to estimate from this benefit-risk model the number of new HIV diagnoses and the number of HIV transmissions expected to be averted in the first year of OraQuick® In-Home HIV Test use. The model predicted that the use of the OTC test kit would lead to approximately 44,000 new true positive test results and avert approximately 4,000 HIV transmissions in the first year of use. These model outcomes indicate both an individual health benefit (new diagnosis) and a net public health benefit (HIV transmissions averted). The model also showed an individual health risk in the form of false negative test results among people who would not otherwise be tested (approximately 4,500 false negative results

in the first year of use). There will also be additional false negative results of a lesser or similar magnitude among people who switch from a professional-use test to a home-use test. These outcomes are estimates that are highly dependent on the number of individuals from at-risk populations who will choose to use the OraQuick® In-Home Test.

The sensitivity of the OraQuick® In-Home HIV Test observed in the Phase III clinical studies fell below the pre-specified minimum level of 95%, contributing to a high false negative rate. However, at the observed sensitivity of 91.7% a public health benefit was still projected based on the number of test subjects who might learn their positive HIV status and the potential to prevent transmission of new HIV infections. Taken together, these findings indicate a favorable benefit/risk profile. Test kit labeling is an important factor in addressing the risks associated with use of the test.

XII. Device Panel Recommendations

On May 15, 2012, the Blood Products Advisory Committee (BPAC) met as a device panel to assess the safety and effectiveness of the OraQuick® In-Home HIV Test. BPAC heard presentations by OraSure Technologies on the design and performance of the OraQuick® In-Home HIV Test, by FDA on its benefit-risk model, by CDC on public health implications of a home-use HIV test kit, and by FDA on currently-marketed home-use test kits and on its evaluation of the OraQuick® In-Home HIV Test PMA. BPAC also heard opinions from numerous members of the public.

FDA posed two questions to BPAC and asked for comments on one issue.

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

   On this question, BPAC voted 17 in favor, 0 against, with no abstentions.

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

   On this question, BPAC voted 17 in favor, 0 against, with no abstentions.

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

   On this issue, BPAC recognized the importance of OraQuick® In-Home HIV Test labeling in communicating the limitations of the test. They emphasized the importance of stressing three messages:

   - a positive result with this test does not mean that you are definitely infected with HIV, but rather that additional testing should be done in a medical setting:

- a negative result with this test does not mean that you are definitely not infected with HIV, particularly when exposure may have been within the previous three months; and

- retesting is recommended if you test negative and continue to engage in behavior that puts you at risk for HIV infection.

Following the BPAC meeting, FDA worked with the manufacturer to enhance the product labeling in accordance with BPAC recommendations and to add a message that a negative result does not imply it is safe to engage in risk behavior for HIV infection.

XIII. CBER Decision

The information provided in the PMA and the benefit-risk model developed by FDA indicate that the projected benefits of the OraQuick® In-Home HIV Test outweigh the risks of false positive and false negative test results. The available data provide reasonable assurance that the OraQuick® In-Home HIV Test is safe and effective for its intended use and support approval of the OraQuick® In Home HIV Test.

XIV. Post-approval Requirements

1. In order to validate changes made to the OraQuick® In-Home HIV Test labeling after completion of the clinical trials, OraSure must conduct a study to assess comprehension of the labeling in both English and Spanish. These studies will follow the same label comprehension study design as in the clinical trials and include intended use populations that speak only English, only Spanish, and are bilingual (English and Spanish). OraSure must submit the results of these studies within six months of the approval of the PMA.

2. OraSure will conduct surveillance of the Consumer Support Center usage to collect information on the number of individuals reporting positive results, negative results and unknown results, as well as demographic information that does not breach caller confidentiality. Within two months OraSure must submit a protocol for this surveillance, and provide this surveillance information annually in PMA Post-Approval Study Reports.

3. OraSure will provide a certificate of translation for all final labeling printed in Spanish.