

Blood Products Advisory Committee
82nd Meeting, March 9-10, 2005
Gaithersburg, Maryland

Issue Summary

Topic III: Proposed Studies to Support the Approval of Over-the-Counter (OTC) Home-Use HIV Test Kits

Issue

FDA seeks the advice of the Committee on proposed studies that would be needed to validate a home-use HIV test kit with regard to test accuracy, test interpretation, and medical follow-up based on the provision of informational material in place of a trained test operator and counselor.

Background

Rapid HIV Tests:

- Over the past four years, FDA has approved a number of rapid HIV tests of low complexity, which are simple to use, require no special storage conditions and provide a highly accurate test result within 20 minutes for the detection of antibodies to HIV. Two of these tests were found to be simple enough to perform that they received a CLIA waiver, expanding the availability of testing. FDA has required, as a condition of approval, that the lower 95% confidence bound for estimated test sensitivity and specificity should be 98% or greater.
- Whereas most HIV tests require the use of a blood specimen, FDA also approved the OraQuick ADVANCE Rapid HIV-1/2 Antibody Test in March 2004 to detect antibodies to HIV-1 and HIV-2 in oral fluid specimens. The labeled sensitivity of the test is 99.3% (95% CI = 98.4%-99.7%) and the specificity is 99.8% (95% CI= 99.6%-99.9%), which is within the acceptance performance set by FDA (1). A CLIA waiver for this indication was granted in June 2004. [Note that reports of reduced specificity of the test (to a level as low as 99.1%) in some locations are under investigation at this time.]
- Testing using oral fluid involves swabbing the device against the upper and lower gums once, inserting the device into a buffer vial, and reading the test result after 20 minutes. The test result is read visually. A single control line (controls for adequate specimen collection and proper functioning of the device) is a non-reactive result that is interpreted as negative for antibodies to HIV-1 or HIV-2. The presence of both a control line and a test line (consisting of HIV-1 and HIV-2 peptides) is a reactive test result that is interpreted as “preliminary positive” for HIV-1 and/or HIV-2 antibodies and reported to the test subject. Reactive test results should be confirmed using an additional, more specific test. However, this

requires an independent action that may not always occur. Those with confirmed positive test results should be counseled appropriately and be referred for medical follow-up.

- Since 2002, all rapid HIV tests were approved as restricted devices, with sales and use restrictions in place:
 1. Sale is restricted to clinical laboratories
 - that have an adequate quality assurance program, including planned systematic activities to provide adequate confidence that requirements for quality will be met, and
 - where there is assurance that operators will receive and use the instructional materials.
 2. The test is approved for use only by an agent of a clinical laboratory.
 3. Test subjects must receive a “Subject Information” pamphlet and pre-test counseling prior to specimen collection and appropriate counseling when test results are provided.
 4. The test is not approved for use to screen blood, cell, plasma, or tissue donors.

Purchasers of the test receive a customer letter stating that by purchasing the test they agree to abide by these restrictions.

Home use tests:

- Home-use tests are used at home by untrained persons without the help of a healthcare professional. Most home-use tests, such as tests for blood glucose, cholesterol, and pregnancy, are available OTC without a prescription. There are two types of home-use tests: test kits and collection kits. With a test kit, you take your own sample, test the sample, and read your own result. There are currently no home-use test kits approved for the detection of any infectious agent. With a collection kit, you take your own sample, mail it to a laboratory, and get your result over the phone or in the mail. There is currently one FDA approved home-use collection kit on the market for HIV testing.

Key Issues

- There are a number of potential benefits to home-use HIV test kits:
 - Of the approximately one million HIV-infected individuals in the US, approximately 25% are not aware of their HIV status. Anonymous testing could potentially lead to more of these people knowing their HIV status.
 - Home-use test kits empower consumers in their healthcare decisions.
 - Home-use HIV test kits may lead to earlier diagnosis of HIV infection and therefore earlier intervention, translating into better clinical outcomes with currently available therapies.
- There are a number of potential risks associated with home-use HIV test kits:

- Inappropriate use of the test or test result, including misinterpretation (*e.g.*, relying on the test to provide an accurate result after a very recent exposure), may lead to a false sense of security. Continued high risk behavior may result in additional HIV infections.
- Home-use tests kits rely on informational material for pre-test and post-test counseling. Without live counseling there is a potential for adverse outcomes following obtaining a positive test result.
- Individuals may not be able to be reached for follow-up and for partner notification (though partners may be informed by the self-tested individual).
- Home-use HIV test kits may lead to coercive testing for HIV.
- OTC tests would be available for use by minors. Providing an HIV test result to minors in the absence of live support raises ethical concerns.
- Additional issues include:
 - Obtaining a test result without a supplemental test
 - The cost and availability of an home-use HIV test kit for those who need the test the most
 - Potential conflict with state and/or federal public health reporting requirements
- Consideration of a home-use test kit by FDA will require the test kit manufacturer to demonstrate that the test is both safe and effective and that the benefits of such a test clearly outweigh the risks.

History of FDA consideration of OTC for HIV tests:

- FDA has discussed HIV home-use test kits and home-use collection kits over the past 10 years in various forums. This included communications with manufacturers of home collection systems in 1988-89, the BPAC in June 1994, and in Federal Register notices in 1989, 1990, 1995, and, most recently, in 2005 (Ref. 2-5).

In the course of discussions held prior to 2005, appropriate regulatory criteria were identified for home-use specimen collection kits for HIV testing, but not for home-use HIV test kits. With improved test kit technology (ease of use, freedom from biohazards, and excellent performance characteristics), we believe it may be feasible to identify regulatory criteria for home-use HIV test kit.

- On November 3, 2005, FDA brought the issue of approaches to the validation of over-the-counter (OTC) home-use HIV test kits to BPAC for discussion in response to renewed interest in home-use HIV test kits.

At that meeting, the Committee heard presentations from OraSure Technologies for a home-use test kit based on its currently approved OraQuick ADVANCE Rapid HIV-1/2 Antibody Test when used with oral fluid specimens; from CDC on changes in HIV testing practices and counseling recommendations, including the role of rapid HIV tests in the HHS *Advancing HIV Prevention* initiative and the results of post-

marketing surveillance for rapid HIV tests and home sample collection HIV tests; from CDC on quality system considerations for home-use HIV test kits; from an expert on psychological and social issues associated with HIV testing, including the finding that, although death from suicide is common among people with advanced HIV infection, notification of a positive HIV test does not appear to lead to a sudden and substantial rise in suicide death; and from CDRH on its review practice for OTC IVDs.

Eighteen individuals spoke at the Open Public Hearing, including those who spoke in favor of home-use HIV test kits, those against home-use HIV test kits, and those who recommended a cautious approach.

Committee discussions addressed acceptable levels of test performance, approaches to clinical trials to evaluate test performance in the hands of potential users, and the content of test kit informational materials that would be needed to allow the test to be performed in the absence of live counseling. By virtue of this discussion, the Committee acknowledged that criteria could be established to permit FDA approval of a home-use HIV test kit.

Discussion

What test characteristics favor possible approval of an OTC home-use HIV test?

- The risk of an incorrect test result is extremely low in the hands of trained operators. This would be supported by a demonstration of analytical and clinical sensitivity and specificity, as well as demonstration that the test is not affected by conditions of operational stress.
- The test is simple to use compared to other types of HIV tests and earlier versions of rapid HIV tests, suggesting that untrained persons will be able to perform the test properly.
- The test does not require special storage conditions.
- The test provides highly accurate results for the detection of antibody to HIV within 20 minutes.
- The use of a non-infectious oral fluid specimen eliminates concerns about biohazardous conditions (no blood and no sharps).
- Informational materials supplied with the test are sufficient to provide adequate information to potential users on performing the test and to substitute for live counseling.

What information will be discussed at the BPAC meeting?

- After considering comments from the BPAC at the November 3, 2005 meeting, FDA has drafted a set of proposed studies that would be needed to support the approval of home-use HIV test kits, addressing the following:

- Identification of potential users of home-use HIV test kits through qualitative research
- Acceptable minimal levels of test performance (analytical and clinical sensitivity and specificity)
- Determination of analytical sensitivity and specificity
- Validation of test performance under conditions of operational stress, including collection of an adequate specimen
- Validation of test performance in the hands of potential users who are monitored and tested in parallel by a professional healthcare worker
- Validation of test performance in the hands of potential users, unmonitored in sites of intended use
- Validation of comprehensibility of informational materials in the hands of potential users
- Validation of informational materials to provide adequate pre-test and post-test counseling, including:
 - Information on the accuracy of testing
 - Correct test interpretation
 - Limitations of the test kit
 - Prevention of adverse psychological effects
 - Medical referral for follow-up testing and treatment
- At this meeting, FDA will be presenting to the BPAC, for concurrence, details of the proposed studies above that could support approval of home-use HIV test kits. The proposed studies appear in an Appendix to this Issue Summary.

Questions for the Committee

1. Does the Committee concur with FDA's proposed criteria for test performance (analytical and clinical sensitivity and specificity) for home-use HIV test kits?
2. Does the Committee concur with FDA's proposal for the Phase II study?
3. For Phase III studies, which of the options presented does the committee recommend?
4. Does the Committee concur with FDA's proposed content for informational materials provided with home-use HIV test kits and the steps that should be taken to validate the adequacy of those informational materials to communicate or provide pathways to adequately address issues including:
 - a. Accuracy of testing
 - b. Correct test interpretation

- c. The importance of supplemental testing for confirmation of positive results
 - d. Management of psychological and social issues
 - e. Medical referral
5. If the Committee does not concur with any of the proposals in Questions 1-4, what additional information/modification would be needed to support approval of a home-use HIV test kit?

References

1. Blood Products Advisory Committee Sixty-Sixth Meeting, session on Development of Rapid HIV tests, June 15, 2000.
<http://www.fda.gov/ohrms/dockets/ac/00/transcripts/3620t1.pdf>
2. Federal Register, 2/17/89 (54 FR 7279), Blood Collection Kits Labeled for Human Immunodeficiency Virus Type 1 (HIV-1) Antibody Testing; Home Test Kits Designed to Detect HIV-1 Antibody; Open Meeting
3. Federal Register, 7/30/90 (55 FR 30982), Blood Collection Kits Labeled for Human Immunodeficiency Virus (HIV-1) Antibody Testing; Availability of a Letter for Interested Persons
4. Federal Register, 2/23/95 (60 FR 10087), Home Specimen Collection Kit Systems Intended for Human Immunodeficiency Virus (HIV-1 and/or HIV-2) Antibody Testing; Revisions to Previous Guidance
5. Blood Products Advisory Committee Sixty-Sixth Meeting, session on Approach to Validation of Over-the-Counter (OTC) Home-Use HIV Tests, November 3, 2005.
<http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4190t1.htm>

APPENDIX

PROPOSED STUDIES TO SUPPORT THE APPROVAL OF OVER-THE-COUNTER (OTC) HOME-USE HIV TEST KITS

1. STUDIES TO IDENTIFY POTENTIAL USERS OF THE TEST

Potential users of the test should be identified by means of qualitative research. Clinical trial study populations should reflect the demographics of those users identified in these studies.

2. PHASE I STUDIES:

NOTE: If the proposed home-use HIV test kit has been approved by FDA for professional use, these studies will have already been performed to support the initial test kit approval. Thus, Phase I studies would not be necessary in such cases.

Objective: To establish the inherent sensitivity and specificity of the test and to demonstrate that the test is capable of withstanding operational stress. These studies should be performed by trained personnel.

a. *Determination of analytical sensitivity and specificity*

The analytical sensitivity and specificity of the test kit should be evaluated in the hands of trained personnel. These studies will be similar to those required for HIV diagnostic test kits approved for professional use, including the evaluation of test kit performance on seroconversion panels, dilutional panels, the effect of potentially interfering substances, the effect of unrelated medical conditions, etc., in a head-to-head comparison with an FDA approved or licensed test kit.

Expected results: Analytical sensitivity and specificity is expected to be comparable to approved professional use tests.

b. *Evaluation of test performance under conditions of operational stress (“flex studies”)*

We expect that a home-use HIV test kit will be more robust than HIV test kits for professional use. Therefore, a thorough hazard analysis should be performed to identify potential sources of error, including test system failures and operator errors. The ability of the test to withstand these errors should then be evaluated in flex studies. The application should include a report describing the hazard analysis for the test kit, a summary of the design and results of the flex studies,

and conclusions drawn from the flex studies. Errors to be addressed in these flex studies include, but are not limited to:

- Operator error/Human factors
 - Use of incorrect specimen type
 - Incorrect application of the specimen to the device.
 - Incorrect placement of the device (e.g., non-level surface).
 - Incorrect placement of reagents
 - Use of incorrect reagents (e.g., reagents that are not specific for the particular device or lot, or generic reagents)
 - Incorrect order of reagent application
 - Use of incorrect amount of reagent
 - Incorrect timing of analysis (e.g., specimen application, running the test, or reading results)

- Specimen integrity and handling
 - Inadequate specimen collection (the test kit should give no result or an invalid result if an inadequate specimen is collected)
 - Excessive specimen application
 - Error in specimen processing and handling
 - Presence of interfering substances

- Reagent integrity
 - Use of improperly stored reagents
 - Use of outdated reagents
 - Use of contaminated reagents

- Environmental factors
 - Impact of key environmental factors (heat, humidity, sunlight, surface angle, device movement, lighting, displacement of the device while the test is running, etc.) on reagents, specimens, and test results.

The device should be designed with a procedural control that is adequately sensitive to all applicable system errors.

3. PHASE II STUDIES:

Objective: To evaluate, in a controlled setting, (a) the effectiveness and safety of sample collection by untrained potential users; (b) the ability of untrained potential users to perform the test properly; (c) the ability of untrained potential users to read and interpret test results; (d) the performance of the test (sensitivity and specificity) in the hands of untrained potential users; and (e) reactions to test results by untrained potential users.

Phase II studies are observational studies in which untrained users perform the test by themselves while being observed by individuals trained in the use of the test. Untrained users will be provided a test kit and instructed to perform the test using only the informational materials supplied with the test kit and without any intervention by the trained tester. An actual testing setting should be simulated as closely as possible, physically separating the trained tester from the test subject. The informed consent for these studies should indicate that the study participant may or may not be observed during and after the testing process.

a. Evaluation of effectiveness and safety of sample collection by untrained potential users

Monitor the ability of study participants to properly collect a test specimen. Note any deviations from the procedure described in the test kit, along with impact on the test result (no impact, invalid test result, incorrect test result) (see *c.* below).

b. Evaluation of the ability of untrained potential users to perform the test properly

Monitor study participants for their ability to follow the instructional materials on the running of the test after the specimen is collected, including application of the specimen to the device, the addition of reagents, and proper timing of the test. Note any deviation from the instructional materials.

c. Evaluation of the ability of untrained potential users to read and interpret test results

This aspect of the studies consists of three parts.

- Interpretation of self-testing

Monitor study participants for their ability to correctly interpret their own test results (negative, preliminary positive, invalid) and identify any follow-up actions that should be taken consistent with the informational materials provided with the test kit (e.g., additional counseling, follow-up testing). Compare the results of testing by untrained potential users to the results of testing by trained personnel using appropriate statistical methods, including percent positive agreement and percent negative agreement, each with 95% two-sided confidence interval lower bounds of at least 95%.

- Interpretation of testing of weak reactive and negative specimens

Evaluate study participants for their ability to correctly run and interpret tests using weak positive and negative specimens. A spiked sample should be prepared to give a result that is correctly interpreted as reactive by trained users 98% of the time. Prepare 120 aliquots of this weak reactive specimen and 120 aliquots of a negative specimen and have testing performed by randomly selected study participants (one aliquot per subject, 240 study participants). Calculate the percent reactive results for the weak reactive

sample and percent non-reactive results for the negative specimen, each with two-sided 95% confidence intervals. Expected performance is a point estimate of at least 95% for the weak positive specimen and 99% for the negative specimen.

- Interpretation of examples of test results

Study participants whose HIV status was not known prior to testing will be evaluated for their ability to correctly interpret a set of test results obtained with the investigational test (i.e., a random mix of devices with non-reactive, weakly reactive, strongly reactive, and invalid test results). Each study participant will be asked to interpret approximately 10 test results of each type. Results will be evaluated using appropriate statistical methods, including calculations of percent agreement for each type of result, each with 95% two-sided confidence interval lower bounds of at least 98% for non-reactive, strong reactive, and invalid results and at least 95% for weak reactive results.

d. Evaluation of the performance of the test in the hands of untrained potential users

The number of untrained users participating in these studies should be sufficient to demonstrate that the lower bound of the two-sided 95% confidence interval is at least 95% for both sensitivity and specificity. At least three geographically diverse clinical trial sites with a high prevalence of HIV infection should be used.

We recognize that large numbers of untrained users would be required to demonstrate this level of sensitivity considering the prevalence of HIV infection in the US. Therefore, known HIV-positive individuals may be included in this part of the clinical trial, but we propose that at least 10 HIV-positive individuals will be identified from testing by/of the study participants who are unaware of their HIV status.

e. Evaluation of reactions by untrained potential users to test results

Monitor study participants for their actions following interpretation of the test result. This may take place through interviews following completion of the testing process or by questionnaire, for example. This evaluation will be a validation of the adequacy of the informational materials to:

- Inform the test subject about the limitations of the test (window period testing, etc.)
- Inform the test subject about the need to confirm a reactive test result
- Inform the test subject about the availability of resources for counseling and medical follow-up
- Have the test subject properly dispose of test-related waste

The likelihood of appropriate follow-up given the test result should be assessed. In addition, we recommend that cognitive evaluation be used to assess the ability of users to understand their test results and take appropriate actions. Adverse reactions should be noted and appropriate actions taken.

Phase II will include reference testing by trained users. Following testing by the untrained user, the trained tester will perform a test on an independent specimen properly collected from the test subject using the investigational test and an additional specimen using an FDA licensed/approved test, taking into account any required minimum waiting period between specimen collections according to the package insert. A follow-up specimen will be collected from individuals with reactive rapid test results for confirmatory testing.

4. PHASE III STUDIES

The objective of Phase III studies is to evaluate the home-use HIV test kit in an unobserved and uncontrolled (intended use) setting. There are multiple options for Phase III studies, with varying scope.

Option 1

In Option 1, Phase III studies will evaluate the performance of the test (sensitivity and specificity) in the hands of study participants and evaluate post-test reactions of study participants. In addition, Phase III studies will validate the ability of the informational materials to communicate the proper use of the test, to communicate test limitations, have the test subject seek follow-up testing and referral to care, effectively provide a route to counseling, and validate the counseling system.

Central to this study is the need for the test to be performed in a potential use setting by study participants, reflecting as closely as possible real-world use of the test kit. This will be done to demonstrate that the test kit is safe and effective in the hands of the potential untrained users. This includes:

- Providing a test kit to study participants to perform unsupervised testing at a time and in a place of their choosing
- Having a mechanism to communicate the test result to the study monitor
- Having a mechanism to collect a specimen from study participants for reference testing
- Validation, through cognitive evaluation, of the ability of the informational materials to:
 - Be understood by potential untrained users
 - Communicate limitations of the test kit (window period testing, etc.)
 - Communicate the need to confirm a reactive test result

- Communicate and achieve follow-up to counseling, testing, and referral resources
- Evaluation of post-test reactions and monitoring for adverse events
- Validation of the adequacy of counseling to provide the desired response and to reduce or eliminate any adverse potential consequences

The number of untrained potential users participating in these studies should be sufficient to demonstrate that the lower bound of the two-sided 95% confidence interval is at least 95% for both sensitivity and specificity. At least three geographically diverse clinical trial sites should be used, enrolling both known positive individuals and individuals who are unaware of their HIV status.

We recognize that large numbers of untrained potential users would be required to demonstrate this level of sensitivity considering the prevalence of HIV infection in the US. Therefore, known HIV-positive individuals may be included in this part of the clinical trial, but we propose that at least 10 HIV-positive individuals will be identified from testing by/of the untrained potential users who are unaware of their HIV status.

Option 2

In Option 2, Phase III studies would be limited to evaluating the ability of the informational materials to communicate the proper use of the test, to communicate test limitations, have the test subject seek follow-up testing and referral to care, effectively provide a route to counseling, and validate the counseling system. Sensitivity and specificity would be determined from the Phase II studies. This option is based on the premise that test performance derived from the Phase II studies is expected to reflect test performance in potential use settings.

Option 2 Phase III studies would involve:

- Providing a test kit to study participants to perform unsupervised testing at a time and in a place of their choosing
- Validation, through cognitive evaluation, of the ability of the informational materials to:
 - Be understood by potential untrained users
 - Communicate limitations of the test kit (window period testing, etc.)
 - Communicate the need to confirm a reactive test result
 - Communicate and achieve follow-up to counseling, testing, and referral resources
- Evaluation of post-test reactions and monitoring for adverse events
- Validation of the adequacy of counseling to provide the desired response and to reduce or eliminate any adverse potential consequences

Option 3

In Option 3, Phase III studies would not be necessary. This option is based on the premise that the Phase II studies will be sufficient to establish test performance in potential use settings and validate the effectiveness of the informational materials.

5. ADDITIONAL RECOMMENDATIONS ON INFORMATIONAL MATERIALS, AND COUNSELING, TESTING, AND REFERRAL

- Labeling must clearly communicate the need to read the informational materials prior to conducting the test.
- The reading level of the informational materials should be easy to comprehend by potential users of the test.
- The informational materials must clearly communicate the expected performance of the test kit based on the clinical studies, including the number of false positive and false negative results observed.
- The informational materials must clearly communicate the limitations of window period testing.
- The test manufacturer should be prepared to offer users advice and referral mechanisms to obtain proper medical follow-up of test results.
- The informational materials must clearly communicate the actions to be taken in the event of a reactive test result.
- Clear and convenient methods for follow-up testing and referral must be established and communicated in the informational materials.
- Counseling must be accessible by means appropriate to potential desired users and be available at any time. This information must be clearly communicated in the informational materials.