Summary of 11/3/05 BPAC Session: Approaches to Validation of Over-the-Counter (OTC) Home-Use HIV Test Kits

CLIAC
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Purpose of Session

- FDA sought advice regarding the conditions necessary to support approval of a home-use HIV test kit.
- In particular, we asked the Committee to consider what studies are needed to validate

  test accuracy

  test interpretation and

  medical follow-up

  based on the provision of informational material in place of a trained test operator and counselor.

Prior FDA Considerations of Home-Use Tests

- 1986
  - Companies first expressed interest in developing and marketing home-use blood collection kits for HIV testing
- 1988
  - FDA notified, by letter, manufacturers and other interested parties of requirements for approval of such systems
- 1989
  - *Federal Register* notice on criteria for approval of home specimen collection systems for HIV testing: professional use only and test results not reported directly to person requesting test
  - Announced meeting to discuss home testing for HIV

Prior FDA Considerations of Home-Use Tests, cont.

- 1990
  - *Federal Register* notice
    - » HIV specimen collection kits should remain for professional use only
    - » FDA would work with manufacturers on requirements for a premarket approval application and to review data for home collection kits
  - BPAC meeting to discuss application for home specimen collection system
    - » Recommendation not to approve based on lack of sufficient data and questions remained regarding possible problems with such issues as confirmatory testing of positive samples, adequacy of telephone counseling, and compliance with state notification requirements while maintaining patient confidentiality

Prior FDA Considerations of Home-Use Tests, cont.

- 1990-1994
  - FDA discussed OTC home specimen collection kits extensively with other US public health agencies and with product sponsors
  - Changes in circumstances
    - » Advances in technology = potential for improved accuracy
    - » Change in treatment methods (availability of therapy for asymptomatic individuals)
    - » Public's increasing desire for greater involvement in personal health care decisions

Prior FDA Considerations of Home-Use Tests, cont.

- 1994
  - BPAC re-examination of home-use specimen collection systems
    - » Agreement that benefit of having alternative means of reaching previously unreachable populations for HIV testing outweighed potential risks
    - » Concerns expressed about accessibility of a home-use kit for target groups, adequacy of counseling while maintaining confidentiality and effectiveness of education and follow-up
    - » Recommendation for pilot studies to evaluate these issues

Prior FDA Considerations of Home-Use Tests, cont.

- 1995
  - *Federal Register* notice
    - » FDA revising guidance for specimen collection kits labeled for HIV antibody testing set forth in 2/17/89 FR notice
    - » OTC specimen collection kit systems may be approvable
    - » Listed specific kinds of data sponsors should submit for review of safety and effectiveness
    - » Did not address kits for home testing of specimens for evidence of HIV infection

What has changed since 1995?

- Early detection translates into better outcomes
- Changes in social awareness of HIV infection
- Tests that:
  - Have an extremely low risk of an incorrect result (unaffected by changes in operating conditions or conditions that could affect the integrity of the specimen)
  - Are simple to use
  - Do not require special storage conditions
  - Results within 20 minutes
  - Use of oral fluid eliminates concerns about biohazardous conditions (no blood and sharps)
- Experience with these tests in non-traditional testing settings

Rapid HIV Tests

- Results within 20 minutes
- Few steps to perform; visual readout
- No special storage conditions or instrumentation needed
- Detect antibodies to HIV
- Tests to be used as an aid in the diagnosis of HIV infection and not for blood donor screening
- 4 FDA-approved tests at this time

Rapid HIV Test Approval Requirements and Standards

- Performance standards and clinical trial/non-clinical requirements for rapid HIV tests: BPAC discussed/concurred on June 15, 2000
- Performance
  - Sensitivity: 98% (lower bound of the 95% confidence interval)
  - Specificity: 98% (lower bound of the 95% confidence interval)

Rapid HIV Tests are Restricted Devices

- Sale restricted to clinical laboratories
  - that have an adequate quality assurance program and
  - where there is assurance that operators will receive and use the instructional materials
- Approved for use only by an agent of a clinical laboratory
  - i.e., not for self-testing
- Test subjects must receive a “Subject Information” pamphlet and pre-test counseling prior to specimen collection, and appropriate counseling when test results are provided

Rapid HIV Test Restrictions, cont.

- Not approved for use to screen blood or tissue donors
- Customer letter included with all kits
  - "By purchasing this device, you are doing so as an agent of a clinical laboratory and agree that you or any of your consignees will abide by the…restrictions on the sale, distribution, and use of the device…"

Rapid HIV Tests Waived under CLIA

- Tests that are waived under CLIA
  - OraQuick® for use with whole blood (1/31/03)
  - OraQuick® for use with oral fluid (6/25/04)
  - Uni-Gold™ for use with venipuncture whole blood (6/23/04)
  - Uni-Gold™ for use with fingerstick whole blood (11/5/04)
- Sales and use restrictions apply to waived rapid HIV tests

Recurring Themes for Home-Use HIV Test Kits

- Benefits
  - Anonymous testing potentially leads to more people knowing their HIV status
  - Earlier diagnosis and therefore earlier intervention
  - Empowerment of consumers in healthcare decisions
  - Potential impact on behavior and public health

Recurring Themes for Home-Use HIV Test Kits, cont.

- Risks
  - Inappropriate use of test or test result
    - » Misinterpretation (relying on test to provide accurate result after a very recent exposure)
  - Potential adverse outcomes after obtaining a test result without live counseling
  - Inability to reach individuals for follow-up and to perform partner notification
  - Coercive testing
  - Testing by minors

Recurring Themes for Home-Use HIV Test Kits, cont.

- Additional issues
  - Obtaining a test result without a supplemental test
    - » False positive rate significant in low prevalence populations
  - Availability for those who need the test most
  - Potential conflict with state and/or federal health reporting requirements

BPAC Session Invited Speakers: OraSure

- Proposal by OraSure Technologies, Inc. for an OTC claim for the OraQuick ADVANCE Rapid HIV-1/2 Antibody Test for use with oral fluid specimens
  - Proposed studies to validate adequate performance in the hands of intended users
    - » Populations to be studied reflecting intended users
  - Ability of informational materials to provide counseling and other information in a comprehensible manner by intended users
    - » Accuracy of testing
    - » Correct test interpretation
    - » Management of psychological and social issues
    - » Medical referral

BPAC Session Invited Speakers: Bernard Branson, CDC

- Changes in HIV testing practices and counseling recommendations
  - Approximately one million HIV-infected individuals in the US, 25-30% of whom are not aware of their HIV infection. There continue to be an estimated 40,000 new infections annually.
  - Rapid HIV tests have been effective in identifying new HIV+ individuals in both clinical and non-clinical settings.
  - Post-marketing studies with OraQuick indicate that its performance is consistent with its package insert claims.
  - Individuals tested using rapid HIV tests received their test results more frequently than those receiving conventional testing

BPAC Session Invited Speakers: Branson, cont.

- Post-market surveillance for home specimen collection kits (1996-97) showed that approximately half of users who tested HIV positive had never been tested before
- Changes to testing and counseling recommendations
- Knowledge of HIV status is associated with substantial reduction in high-risk sexual behavior
- Availability of a home-use HIV test kit would allow testing of persons unwilling to be tested in other settings, would be well-suited to persons who retest frequently. Knowledge of a partner's HIV status is a key element in prevention.

BPAC Session Invited Speakers: Devery Howerton, CDC

- Role of quality systems for diagnostic tests
  - Testing is a process and running of the test is only a part
  - Person performing the test, testing environment, and test materials are all integral parts of the system
  - Described parts of quality system appropriate to consider for home-use HIV test kits
  - Described information from survey of CLIA-waived labs

BPAC Session Invited Speakers: Joseph Inungu, Central MI Univ.

- Psychological and social issues associated with HIV testing and OTC home-use tests
  - People seek HIV testing for various reasons. The fact that adolescents appear to seek HIV testing following a recent high risk exposure is a matter of concern. More HIV education is needed in this age group.
  - Majority of studies discussed were conducted in the 1980s and 1990s and their findings may not be applicable today. Studies on psychological symptoms among HIV+ people during the antiretroviral era are needed.

BPAC Session Invited Speakers: Inungu, cont.

- Majority of studies unanimous about relief of emotional distress following a negative test
- For people with positive results, effects not clear
  - » Some studies show increase in distress, some show insignificant increase, some show decrease
  - » Discrepancies suggest that factors other than notification of a positive test result play a more important role in evoking emotional distress
- Although death from suicide common among people with advanced HIV infection, notification of a positive HIV test does not appear to lead to sudden and substantial rise in suicide death
- Social adverse reactions occur following HIV diagnosis, associated with lack of knowledge, fear

BPAC Session Invited Speakers: Arleen Pinkos, CDRH/OIVD

- Overview of the OTC review process at FDA and human factors considerations
  - History of home-use test kits (none is approved or cleared for detection of infectious disease markers)
  - Information needed for the review of these products, to demonstrate that
    - » Device is accurate and reliable in the hands of lay users
    - » Device is adequately labeled to convey all information necessary to use the device safely and effectively
    - » Benefits outweigh the risks

Open Public Hearing Comments

- 18 speakers and 9 written comments for the record
- Opinions in 3 camps
  - Support of home-use HIV test kits (majority)
  - Against home-use HIV test kits
  - Unable to make recommendation (need more information)

Open Public Hearing Comments: Pro

- The benefits of having such a test available far outweigh the potential risks
- Likely that home-use HIV test kits will significantly increase the number of individuals who know their HIV status
- Home-use HIV test kits would destigmatize and routinize HIV testing
- Home-use HIV test kits particularly suited for young people who don't want to confront a live person with a test result - especially true in a small-town, where social stigma prevents people from getting tested
- People have a right to make choices about how to be tested, and how to understand their HIV status

Open Public Hearing Comments: Con

- Untrained individuals should not be performing tests for an agent that has significant implications for the individual and public health
- Incorrect test results due to improper performance of the test or incorrect test interpretation has the potential for significant risk of harm to patients and public health
- Accurate testing can only be performed in the context of a quality system
- No assurance that the person performing a self-test will take appropriate follow-up actions that would be taken if live counseling were involved
- Home-use HIV test kits could be used for inappropriate purposes, without legal limitations on the use of the results

Open Public Hearing Comments: Need more infomation

- Who will most likely use such a test?
- Measures in place to prevent bulk sales of a home-use HIV test kit to entities attempting to establish themselves as counseling and testing sites?
- Assessment of impact of such a test on public health reporting?
- Adequate performance of the test in its intended setting?
- Post-marketing studies are needed to assess safety, post-test behavior, effectiveness of the written materials to link to medical follow-up

Open Public Hearing Comments: Need more information, cont.

- Information provided in as many languages as possible
- Quality counseling 24/7 available by all means possible and appropriate referrals are essential
- Criteria for approval of a home-use HIV test kit must ensure correct test interpretation, that individuals who test positive have access to counseling, and that users have easy access to treatment and referral

Questions for the Committee

1. Are FDA's previously established criteria for sensitivity and specificity for rapid HIV tests also appropriate to support OTC use for home-use HIV test kits?

Committee Discussion

- A home-use HIV test kit should be no less accurate than tests approved for use under CLIA waiver
  - Home-use HIV test kits should have high analytical sensitivity and specificity
  - FDA could be flexible on performance levels in the intended use population
  - If requirements for performance are unattainable, then the availability of a home use test kit would be jeopardized
- Inclusion of Positive Predictive Value in package insert?
- Information should be provided on the reasons behind false positive and false negative results
- The gold standard for clinical studies should be true infectious state
- Package insert should contain extensive information about the window period considering that this test will detect antibodies to HIV

Questions for the Committee

2. Please comment on the design of clinical studies necessary to validate the safety and effectiveness of an OTC home-use HIV test kit.

Committee Discussion

- Clinical trials should be performed in collaboration with CBO's to assure that the intended use populations are adequately represented in the clinical trials
- The clinical trial should look not only at performance of test, but also at the effectiveness of the instructions for use
- Clinical trial could be performed in two phases
  - Phase II: Test subjects observed in the presence of others and second test performed by a technician
  - Phase III: Test kit in its intended use setting without monitoring
- Critical for users to understand limitations of test, especially concerning window period
- The proportion of invalid tests should be tracked during the clinical trial

Questions for the Committee

3. Please comment on the proposed content of the informational materials and the steps that should be taken to validate the adequacy of the 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. Availability of counseling
    f. Medical referral

Committee Discussion

- Linkage to counseling and medical follow-up is critical
- A clear way of discussing the performance of the test (sensitivity and specificity) should appear in the package insert.
- Literacy study should be performed and a pictorial package insert should be considered
- Validation of the informational materials could be done in a way similar to that for the blood donor questionnaire
- Phase IV studies should examine not only test performance, but also the effectiveness of integration of these tests into the community

Overall Message

- BPAC did not express opposition to the concept of a home-use HIV test kit
- Rather, discussion centered on what would be needed to validate a home-use HIV test kit as conditions for approval

Next Steps

- FDA is evaluating comments from BPAC meeting
- Set criteria for validation of home-use HIV test kits
  - Test performance
  - Ability of instructional materials to substitute for live counseling
  - Assure that benefits outweigh risks
- Discussion at March 10, 2006 BPAC

Status of Reports of Reduced Specificity with OraQuick Oral Fluid Testing

- December 2005
  - Press reports of higher than expected false positive results with OraQuick oral fluid tests in San Francisco, New York City, and Los Angeles
- Current status
  - Higher than expected false positives restricted to only a small number of sites in SF and NYC
  - Performance across US is well within package insert claims for specificity
  - OraSure, FDA, and CDC are actively investigating to determine a root cause for apparent reduced specificity in these few sites and are continuing to monitor test performance