

**QUICK MINUTES**  
**for the**  
**BLOOD PRODUCTS ADVISORY COMMITTEE**  
**85th Meeting –Nov 3-4, 2005**

On **November 3, 2005**, the Committee listened to the following briefings and updates: An update on the West Nile Virus was given by Dr. Hira Nakhasi and Dr. Theresa Smith from CDC. Dr. Paul Mied presented draft guidance on NAT for HIV-1 and HCV: Testing, Product Disposition and Donor Deferral and Re-entry. Dr. David Asher summarized the TSEAC meeting from Oct 31, 2005 and Dr. Jerry Holmberg summarized the DHHS Advisory Committee meeting on Blood Safety and Availability from Sept 19-20 meeting. Re-entry of Donors Deferred based on anti-HBc Test Results was presented by Dr. Gerardo Kaplan, followed by a briefing by Dr. Susan Stramer of the American Red Cross data on this topic.

**TOPIC 1**

**Approaches to Over-the-Counter (OTC) Home-Use HIV Test Kits**

The purpose of this session was to seek advice from the BPAC on validation criteria necessary to support approval of a home-use HIV test kit. In particular, the Committee was asked to consider what studies would be needed to validate test accuracy, test interpretation, and medical follow-up based on the provision of informational material in place of a trained operator and counselor.

*Invited Speakers*

The session was opened by Dr. Elliot Cowan (FDA/CBER/OBRR), who oriented the BPAC on FDA's prior consideration of home-use tests, recurring issues from those prior discussions, background on rapid HIV tests, and the questions that BPAC would consider. Invited speakers provided additional background information:

- Ms. Sue Sutton-Jones from OraSure Technologies presented a proposal 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, including proposals for untrained user studies to validate:
  - Device safety and effectiveness
  - Effectiveness of sample collection by untrained users
  - Accuracy of test interpretation
  - Ability of labeling and printed materials to ensure counseling and linkage to care (24/7 access to counseling by phone, internet, mail; referral to local healthcare options; continued evaluation in post-market studies)
  - Ability of package design to assure that informational material is read prior to testing

- Dr. Bernard Branson (CDC/NCHSTP) discussed 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. Key points raised were:
  - There are 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 tested using conventional testing.
  - 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 include:
    - Routine HIV screening in healthcare settings in areas of high prevalence
    - Opt-out consent for pregnant women with written or verbal notification that testing will be done
    - Provide written or verbal information about HIV to all tested
    - Prevention counseling in conjunction with HIV testing is not required in healthcare settings (but should occur in some setting for HIV risk individuals)
    - Those at high risk should be retested at least annually
    - Persons who test positive should have linkage to care
  - 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 and would be well-suited to persons who retest frequently. Knowledge of a partner's HIV status is a key element in prevention.
  
- Dr. Devery Howerton (CDC/CCHIS) discussed quality system considerations for home-use HIV test kits, emphasizing that testing is a process and that the running of the test is only a part. The person performing the test, the testing environment, and the test materials are all integral parts of the system.
  
- Dr. Joseph Inungu (Central Michigan University) discussed psychological and social issues associated with HIV testing. Key points raised were:
  - 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.

- The majority of studies discussed in this presentation were conducted in the 1980s and 1990s. Their findings may not be applicable today. Studies on psychological symptoms among HIV+ people during the antiretroviral era are needed.
  - The majority of these studies were unanimous about the relief of emotional distress following a negative test.
  - For people with positive results, effects are not clear - some studies show increase in distress, some show insignificant increase, some show decrease. Differences in subjects and site selection, as well as the scales and/or instruments used may account for the differences observed among these studies. However, the discrepancies may suggest that factors other than notification of a positive test result play a more important role in evoking emotional distress.
  - 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.
  - Social adverse reactions do occur following HIV diagnosis. They are often associated with fear and lack of knowledge.
- Arleen Pinkos (FDA/CDRH/OIVD) discussed CDRH's review practice for OTC IVDs, providing a history of home-use test kits (of which none is approved or cleared for detection of infectious disease markers) and information needed for the review of these products to demonstrate that the device is accurate and reliable in the hands of lay users, that the device is adequately labeled to convey all information necessary to use the device safely and effectively, and that the benefits outweigh the risks.

### *Open Public Hearing*

Eighteen individuals spoke at the Open Public Hearing and nine written statements were submitted for the record. Opinions fell into three categories:

1. In favor of home-use HIV test kits (community-based organizations, the AIDS Healthcare Foundation, an epidemiologist, the National Association of People with AIDS, the American Social Health Association, and individuals). Reasons cited were:
  - It is likely that home-use HIV test kits will significantly increase the number of individuals who know their HIV status. The benefits of having such a test available far outweigh the potential risks.
  - Home-use HIV test kits would lessen the stigma of HIV testing and allow it to be more routine.
  - Home-use HIV test kits are particularly suited for young people who don't want to confront a live person with a test result. This is 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.

- FDA should encourage manufacturers to submit applications for home-use HIV test kits.
  - Lower sensitivity may be tolerated for a home-use HIV test kit compared to professional-use tests, given the benefit of more people knowing their HIV status.
2. Against HIV home-use test kits (professional organizations such as American Medical Technologists and the American Society for Microbiology). Reasons cited were:
- 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.
  - There is 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.
3. Unable to make a recommendation at this time; proceed cautiously and consider resolution of issues (State Departments of Health, American Association of Clinical Chemistry, National Association of State and Territorial AIDS Directors, AIDS Institute, San Francisco AIDS Foundation). Issues cited were:
- The utility of such a test - who will most likely use it?
  - Will there be 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? Some states carefully regulate those who are permitted to perform counseling.
  - 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, and longitudinal follow-up.
  - Information should be provided in as many languages as possible to reflect the users of the test, and referrals should be appropriate considering the primary language of the user.
  - Information in should be written at an appropriate educational level considering those who will use the test.
  - Quality counseling available 24/7 by all means possible is essential, as well as appropriate referrals.

- The package insert of the test should recommend follow-up testing for reactive test results.
- Criteria for approval of a home-use HIV test kit must ensure correct test interpretation, access to counseling for individuals who test positive, and easy access to treatment and referral.
- Price will be a factor in the use of the test. A survey by Spielberg showed that a cost of  $\geq$ \$20 would be a significant deterrent to acquiring the test.

Most of the Open Public Hearing speakers spoke in favor of home-use HIV test kits, though it should be noted that transportation costs for a number of those speakers were paid by OraSure.

Committee comments on the questions posed were as follows:

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?*

- Concern was expressed about the number of false positive results in a low prevalence population. There was, therefore, a recommendation to include positive predictive values in the package insert. However, others felt that positive predictive values would be of little value, considering the wide range of individuals who would use a home-use HIV test kit.
- Information should be provided on the reasons behind false positive and false negative results. Since positive predictive values are dependent upon the population, it would be more important to explain what the likelihood would be for a positive result.
- The gold standard for clinical studies should be true infectious state.
- The package insert should contain extensive information about the window period. Considering that this test will detect antibodies to HIV, there should be a statement in the package insert mentioning that nucleic acid testing could be used to detect infection earlier after an exposure.
- There was discussion about lowering the bar on performance of the test relative to a lab based test, especially for specificity. In addition, concern was expressed over requiring too high a level of clinical sensitivity for the test. If the requirements for performance are unattainable, then the availability of a home use test kit would be jeopardized. The general sentiment of the committee, however, was that 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, but FDA could be flexible on performance levels in the intended use population.

2. *Please comment on the design of clinical studies necessary to validate the safety and effectiveness of an OTC home-use HIV test kit.*
  - Clinical trials should be performed in collaboration with community-based organizations to assure that the intended use populations are involved in the clinical trials. This would include Latinos, women and adolescents. Every phase of the clinical study needs to undergo rigorous evaluation.
  - The clinical trial should look not only at the performance of the test, but also at the effectiveness of the instructions for use.
  - The false negative rate of the test when used with patients on HAART should be examined in the clinical trial.
  - The frequency of confirmatory testing for reactive results should be examined during the clinical trial.
  - It was suggested that the clinical trial be performed in two phases. In Phase II, the test kit would be given to test subjects who would be observed in the presence of others. A second test would then be performed by a trained tester and the results compared. In Phase III, the test kit would be used in its intended use setting without being monitored. The user would mail the test result anonymously to the company, along with a completed questionnaire on the test system. It was also suggested that an incentive may be included in the test kit package to encourage test subjects to respond.
  - Understanding the limitations of the test, specifically concerning the window period, is critical. This is not a “morning after” device.
  - The proportion of invalid tests should be tracked during the clinical trial.
  - Concern was expressed over the performance of a home-use HIV test kit with specimens other than oral fluid. No data was available to examine this, although one committee member cited anecdotal studies which indicated that other fluids such as vaginal fluids could be used successfully (recognizing that this constitutes off-label use).
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*

- The window period should be clearly discussed the package insert.
- A clear way of discussing the performance of the test (sensitivity and specificity) should appear in the package insert.
- The package insert should clearly indicate what the user is to do if the result is reactive or if the result is nonreactive and the likelihood of a correct result. However, it was recommended not to include issues related to positive predictive value in the package insert, but rather to indicate that if the result is reactive, that result needs follow-up.
- The package insert should contain a statement to the effect that if the user may have been exposed to HIV within a certain period of time, the user should wait and be retested after an appropriate time. Clear language should also be included on the outer packaging to state that this test will not be effective for determining HIV status after a recent exposure.
- A literacy study should be performed and a pictorial package insert should be developed, since it is likely that some users would not be able to, or would not want to, read the informational materials. For this reason, it is also critical to display contact information clearly on the outer packaging.
- Validation of the informational materials could be done in a way similar to that used for the blood donor questionnaire. Study participants could be asked if they understood the informational material, and this could be transmitted back to the company by telephone with auto entry so that a live individual would not be in contact with the participant. In addition, individuals completing this validation study could be rewarded with, for example, a coupon for free tests, in an effort to increase participation in the validation studies.
- Phase IV studies should examine the effectiveness of integration of these tests into the community.
- Standardized instructional materials should be established for home-use HIV test kits.
- Issues question 3d through 3f could be addressed in the same study.
- A card could be included in the test kit to take to a physician for follow-up, with information appropriate to the test result.
- Information on insurance and job resources should be included in the instructional materials to assist people in the event of a reactive result.
- CDC requested that its hotline not be used as the major point of contact for counseling.

- What is the basis to assess the effectiveness of the informational materials to substitute for live counseling? While this could be done comparing to conventional testing and counseling, the effectiveness of counseling associated with conventional testing has not been studied (there is no baseline).
- A variety of other hotlines should be considered for inclusion in the package insert. Public testing sites could assist in determining whether individuals undergoing home-use HIV testing will follow up their test results by seeking medical assistance.
- Concern was expressed over the inclusion of too many informational items in the test kit, which may drive up the kit cost and increase the complexity of the system. Informational materials can serve as a start that should lead to follow-up by the person being tested.

### ***NEXT STEPS***

- Working group (FDA/CDC) to establish criteria for approval of home-use HIV test kits
- Present criteria to BPAC for concurrence

On **November 4, 2005** the BPAC Committee re-assembled to hear an informational brief on a Serious Adverse Event following falsely elevated glucose measurements resulting from administration of an IGIV product containing maltose. Drs. Gaines and Pierce and Ms. Bernhardt discussed this event, the Medline warning system and how this occurred. It was noted that certain glucometers using GDH-PQQ or glucose-dye-oxidoreductase methods could be misinterpreted if certain sugars other than glucose were given to the individual through infusion of various products. The Committee noted that the tracking systems of such incidents were lacking in this country and the rest of the world. Octapharma was allowed to make a statement regarding the situation and what plans it has implemented to prevent such an event in the future.

## **TOPIC II**

### **Heterogeneity of Commercial Alpha-1-Proteinase Inhibitor (Human) Products – Implications for Longer-Term Safety and Efficacy**

#### *Invited Speakers*

Dr. Andrew Shrake presented the background for bringing this issue to the Committee for discussion. Dr. Ewa Marszal provided FDA observations on marketed alpha-1-proteinase inhibitor products. Dr. Mark Brantly of the University of Florida presented a talk on the identification and possible implications of a human plasma purified anodal variant of

Alpha-1-Antitrypsin. Dr. Hans Peter Schwartz of Baxter Healthcare responded to the finding of this variant in a presentation of Aralast compared to other A<sub>1</sub>PI preparations. He described the biochemical characterization methods applied to these protein preparations in describing the molecular alterations responsible for the observed differences in isoelectric focusing patterns. This talk was followed with a briefing by Dr. Tina Khoie regarding the post-marketing safety reporting for Alpha-1-PI products. Post-marketing study commitments for licensed Alpha-1 PI products and their rationale was then discussed by Dr. L. Ross Pierce. Finally, Drs. Andrew Chang and Kurt Brorson presented data for licensed therapeutic protein products with known structural modifications. It was noted that several licensed biological products have many modifications and/or variants, including a monoclonal antibody.

During the Open Public Hearings, representatives from the Alpha-1 Association and the Alpha-1 Foundation spoke. Additionally, the two other manufacturers (Talecris Biotherapeutics and ZLB Behring) of Alpha-1 PI gave brief talks on their products and what clinical efficacy trials they were starting or had already initiated.

The Committee was presented with the following questions for discussion:

1. Based on the difference in primary structure of alpha-1 PI and the concentrations of polymers in A1PI products, does the Committee have any comments and/or recommendations regarding:
  - a. The adequacy of the requested/planned post-marketing commitment studies to evaluate the longer-term safety and efficacy of A1PI products, as measured by specified clinically meaningful endpoints?
  - b. The adequacy of the proposed safety monitoring programs?
  - c. Any other suggested actions (e.g., additional communications through labeling or other venues)

No committee member expressed overt concern regarding the described heterogeneity of the 3 US-licensed A1-PI products and their differences from A1-PI as it exists in normal MM or pooled plasma, however, all committee members who spoke on the topic expressed the opinion that passive postmarketing surveillance was inadequate to assure the [longer-term] safety of the products. One committee member expressed the opinion that the postmarketing clinical efficacy and safety studies requested by FDA were a good start. At least 2 committee members recommended that postmarketing safety studies be open-ended in terms of duration, i.e., “continuous follow-up.”

There was a strong consensus among committee members that it was very important to determine whether these products are clinically efficacious in terms of A1-PI lung disease. Placebo controlled studies are preferred, but need to be carried out [primarily] in countries where the products are not commercially available for ease of enrollment. Several committee members recommended that the various sponsors conduct similarly designed postmarketing studies to facilitate cross-study comparisons and combined

analyses. The clinical endpoint postmarketing study design that ZLB Behring presented got favorable comments. The committee encouraged NHLBI lung disease branch to become involved in helping to determine the clinical efficacy of these products, possibly including contributing funding. Several committee members stressed the potential importance of early intervention in the course of the disease when planning studies. One member recommended the NHLBI registry study be reactivated to help collect long-term safety data. FDA was encouraged to send a transcript of the meeting to NHLBI. One committee member stated that the sponsor of the innovator product, Prolastin, should not be “let off the hook” and should be asked to conduct a randomized controlled clinical efficacy study, just like the sponsors of the newer products (notwithstanding the fact that the sponsor of the innovator product had submitted an NHLBI-sponsored epidemiology study to fulfill its postmarketing commitment). Talecris revealed that they have an ongoing voluntary [European] placebo controlled [randomized] clinical endpoint trial ongoing with Prolastin that will enroll approximately 70 additional subjects.

There seemed to be a general consensus that a single postmarketing registry for all A1-PI products was highly desirable and far preferable to passive postmarketing surveillance.

In response to one of the FDA questions, a majority of committee members who spoke on the issue favored a suggestion by Miriam O’Day, Consultant to the Alpha One Foundation, to issue a Dear Dr. letter that would describe briefly describe the heterogeneity of the products and stress the importance of reporting adverse reactions to FDA (with sufficient clinical detail to make them more useful). The Dear Dr. Letter would not be alarmist in nature, but would help make clinicians more aware that these products are not so simple and uniform and are not necessarily completely the same as the native protein.

*This quick summary is provided as an unofficial overview of the committee discussions. Please refer to the meeting transcripts for a detailed account of the meeting*