Issue Summary

BLOOD PRODUCTS ADVISORY COMMITTEE

111th Meeting, December 2, 2014

1. Issue

FDA will provide the Blood Products Advisory Committee (BPAC) with a detailed update on recent discussions and recommendations from the November 13, 2014, meeting of the HHS Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) regarding reconsideration of the current policy for blood donation by men who have had sex with another man, even one time, since 1977. In addition, the FDA seeks recommendations from the BPAC regarding the value of HIV incidence measures in blood donors that may be suitable for inclusion in a planned general blood safety monitoring effort based upon laboratory markers detected at the time of blood donation.

2. Background

Since the earliest recognition that Acquired Immunodeficiency Syndrome (AIDS) was transmitted by blood transfusion, the identification and self- or interviewer directed deferral of individuals recognized to have a history of behaviors that placed them at risk of acquiring HIV infection has provided an important safeguard for the blood supply. Donor screening remains an important safeguard in blood manufacturing even in the face of highly sensitive laboratory testing of all donated blood. Since 1983, FDA has provided a series of recommendations for donor screening to decrease collection from individuals at increased risk of acquiring and transmitting HIV/AIDS. Currently, FDA recommends deferral as blood donors of men who have had sex with another man (MSM), even one time, since 1977 (1). In June 2010, the HHS Advisory Committee on Blood Safety and Availability (ACBSA) discussed the current MSM blood donor deferral policy and concluded:

"the current donor deferral policies are suboptimal in permitting some potentially high risk donations while preventing some potentially low risk donations, we find that currently available scientific data are inadequate to support change to a specific alternative policy; therefore, until further evaluation, the committee recommends that the current indefinite deferral for men who have had sex with another man even one time since 1977 not be changed at the present time". (2)

Based on the recommendations of the ACBTSA, an HHS Blood, Organ, and Tissue Safety (BOTS) MSM Working Group was formed to coordinate research studies that would generate information needed to consider a policy change. Working through PHS Agencies, studies were designed, funded and completed in three specific areas. An operational assessment and root cause assessment of blood component quarantine

release errors (QRE) was also conducted through an FDA-sponsored workshop and a Working Group sponsored by the AABB.

3. The REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study (3)

It was reported at the June, 2010 ACBSA meeting that nationally representative data reflecting the epidemiology of transmissible infection markers and associated behavioral risk factors had not been collected in the US in the past fifteen years. The availability of current data was considered to be necessary in order to gauge the extent to which prevalence, incidence, and associated risk factors had changed over the ensuing time period. Marker rates in blood donors, particularly estimates of incidence among donors, can be used to estimate the overall level of blood safety. In response to the ACBSA June, 2010 recommendations , the existing NHLBI-sponsored REDS-II program was leveraged to collect and standardize confirmed positive marker rates for HIV, HCV, HBV, and HTLV-I/II and NAT-yield rates for HIV, HCV, and HBV across the five large REDS-II blood collection sites. These sites represented greater than 50% of the US blood supply. For each infection type, incidence and prevalence data were determined and donors with positive markers were interviewed to determine their deferrable risk factors. Donors with false positive markers served as controls. The primary behavioral risk factors identified were found to be consistent with the known epidemiology of the viruses studied. The study also identified donors who did not disclose a range of deferrable risk behaviors. For HIV seropositive donors, sex with an HIV-positive partner and a history of MSM remain the two leading independent risk factors for HIV (as originally observed in the early 1990's). Because of the extensive work that was done to harmonize test results across the different sites, the REDS II program serves as both an excellent model, and a source of baseline data for a future ongoing US blood donor monitoring effort for donor transfusion-transmissible infections and associated risk factors.

4. Evaluation of the Current Blood Donation History Questionnaire (4)

Using new methods of questionnaire evaluation, investigators from the National Center for Health Statistics (NCHS) assessed the current 48 question standardized blood donor history questionnaire (DHQ) using respondent variables based on a conceptual framework of comprehension, retrieval, judgment, and response. These data were then used to identify potential response errors and differing patterns of question interpretation across respondent groups, including those with different demographic, geographic, and behavioral characteristics. The study group was deliberately enriched for representation of MSM.

The NCHS study was conducted with 166 respondents from five geographic areas. The non-random sample was 63% male, 37% female, and 36% MSM. After reading the

donor educational materials and completing the DHQ as if donating blood, subjects were asked a series of probing questions by trained interviewers about their responses to the questionnaire. Subjects were also asked supplemental questions to help assess their understanding. Conclusions were consistent across all respondent subgroups. Participants uniformly understood that the purpose of the questionnaire was to assure blood safety. Participant responses reflected the fact that questions were often not taken at face value, but rather were answered based on an overall self-perception of the safety of their individual blood donation, i.e. the whole questionnaire was interpreted and answered as "is my blood safe?" Future possible steps in DHQ improvement suggested by the authors included: shortening the educational materials, including local terms for some elements of the questionnaire, using specific language to de-emphasize the dominant "is my blood safe?" interpretation , clarifying what is meant by "sex," and including a "don't know" response option.

5. NHLBI REDS-III BloodDROPS Study (5)

Worldwide, most blood donation deferral criteria for MSM include a time-based deferral that exceeds the duration of known window periods associated with current testing regimens for donated blood. For this reason, complete accuracy of donor responses to the behavioral screening questions (if attainable) would provide protection from transmission of HIV infection from individuals with risks that are specifically addressed by the screening process (e.g., MSM risk). There have now been numerous observations both within and outside of the US that have documented measurable levels of non-compliance with current deferral criteria among MSM whose behavioral risks should have precluded them from blood donation. The NHLBI REDS-III BLoodDROPS study was designed to provide further information about this observation. BloodDROPS included focus group studies, survey research, and telephone interviews with blood donors and community members who reported recent blood donation despite MSM deferrable risk. Rates of MSM deferrable risk within this study averaged 2.6% of active male donors. Other key observations included:

- *Non-compliance with the current MSM donation policy was evident and may be increasing compared to earlier time periods.*
- *MSM opinions about changing the deferral policy are mixed with non-compliant donors much more likely than compliant donors to support policy change.*
- *Roughly half of the interviewed non-compliant MSM donors indicated that they would adhere to a 1-year deferral policy.*
- *Current HIV transfusion-transmission risk (1 in 1.5 million donations) and observed MSM non-compliance (0.7 - 2.6%), taken together, indicate that HIV prevalence in donating MSM is lower than has been previously modeled.*

- *MSM who do not comply with the current MSM donation policy have a much higher risk of being HIV-positive than non-MSM donors, but have a lower risk than the overall MSM population.*
- *A significant proportion of non-compliant MSM are likely to remain so if policy is changed for various reasons, including:*
    - *Self-determination of HIV risk*
    - *Value of donation to help others outweighs risk concerns*
    - *Belief that HIV testing will identify all infected blood*
    - *Current MSM deferral policy is not scientifically based*
    - *Donation is done in protest for various reasons*
    - *Disclosure of MSM is linked to "coming out" – fear of stigma or discrimination may prevent disclosure*
- *In contrast, the other 50% of MSM who currently donate say that they would not do so if the current policy is changed.*

Based on the focus group survey, the investigators concluded that future MSM donation policy would likely benefit from communication of a clear rationale as well as outreach in the form of donor and public education and assertive stakeholder engagement. Also, based on the results of the BloodDROPS study, additional measures that may be useful to help improve the donor screening process may include, donor and public education, outreach, questionnaire improvement, and resource placement that may help to educate potential donors regarding accurate self-evaluation of their risks and appropriate self-deferral.

6. Quarantine Release Errors and Transfusion Safety

A separate effort to investigate and reduce quarantine release errors (QRE) in blood collection facilities has been conducted over the past several years by a joint effort of the FDA and the blood community, including an FDA-sponsored Workshop in September, 2011 (6), and a comprehensive white paper published by the AABB Working group in August, 2013 (7). QREs result from the inadvertent release of blood or blood components before testing is completed, before other criteria affecting the safety, purity or potency of the manufactured product have been met, or when information is obtained after donation that would have caused the donor to have been deferred. The previous importance of QREs to the safety of transfused blood was emphasized through its prominent role as a factor in the FDA risk prediction model developed and published by the FDA in 2009. (8) In recent years, the comprehensive introduction of computerization into blood collection operations and blood inventory control have led to the general conclusion that overall QREs have now been greatly

reduced in blood collection facilities. Those that persist appear to have their root cause in the human factors that necessarily remain a part of the manufacturing process.

In addition to presentation of the above studies, two additional presentations in support of the anticipated MSM policy discussions were made at the November 13th ACBTSA meeting:

7. Current Epidemiology of HIV Infection in the United States (9)

The Centers for Disease Control and Prevention (CDC) conducts HIV/AIDS epidemiologic surveillance in the US through many different approaches. CDC epidemiologists presented highlights of recent HIV studies in the US including observations regarding prevalent and new HIV infections in the US population that were relevant to the US blood supply. Overall, as of 2010, there are > 1 million individuals in the US currently living with HIV in the United States, Among newly diagnosed males and females in 2012, 64% were males who reported MSM sexual contact and an additional 4% overall were males who reported MSM plus infecting drug use (IDU) exposure. There is a large disparity in HIV burden vs population size for MSM in that 64% of newly diagnosed HIV cases in 2012 were in MSM compared with an estimated background prevalence of 2-3.5% for MSM in the general population.

Lack of awareness of HIV infection status is important in the blood donation setting, because individuals who are unaware of their infection may donate. While testing for prevalent HIV infection is very sensitive and reliable, the presence of HIV positive units in quarantine within the blood center creates an unnecessary risk of inadvertent quarantine release error and increased risk of staff exposure. In 2010, an estimated 19% of MSM were undiagnosed as having HIV infection. This was similar to the proportion of undiagnosed heterosexual individuals (18%). The percent of undiagnosed prevalent infections measured in 2010 was markedly higher in younger age males (58.3% among males 13-24, and 25.9% among males 25-34).

The HIV Incidence report recently published by CDC shows that, while the incidence of new HIV infection in most US general population subsets (such as females) is stable or falling each year, the incidence of new HIV infection among MSM has been rising. Comparing 2008 to 2010, the number of new HIV infections among MSM increased 12%, with a 22% increase among MSM aged 13–24. Although MSM represent about 7% of the male population in the United States, in 2010 MSM accounted for 78% of the new HIV infections among males. (10)

8. Data Driven policy change for the Australian MSM Blood Donor Deferral Experience (11)

Two recent reports from Seed, et al at the Australian Red Cross were summarized at the ACBTSA meeting. The first report found no evidence that the implementation of a 12 month deferral for male-male sex in 2000 resulted in any increased risk for HIV transmission by transfusion in Australia. This finding was based on comparison of numbers of HIV+ donors identified five years prior and five years after implementation of the changed policy. The authors also concluded that noncompliance with the deferral policy was the factor most likely to influence overall risk, rather than the duration of the deferral period itself. (12)

Subsequently in May 2012, an Independent review commissioned by the Australian Red Cross found sufficient evidence to support reduction of the deferral period for all sexual activity-based deferrals from 12 months to six months (twice the maximum observed window period for HCV testing) without reducing safety. This recommendation was conditional, however, on an assessment and confirmation of a low "non-compliance rate" to the 12 month deferral. A study to measure compliance was conducted among 100,000 recent successful male donors and assessed male-male sexual contact in the past year. The study demonstrated a non-compliance rate of 0.23% (95% ci 0.16 - 0.33 %) with no difference between first time and repeat donors (13). Most non-compliance was associated with younger, less-educated donors with multiple partners, discomfort with the sensitive nature of the question, or a history of IDU. The Australian estimate of non-compliance is lower than estimates from other countries, even when corrected for differences in deferral policy.

In contrast, based on the recent US estimate of non-compliance (2.6% for indefinite deferral) and data from the BloodDROPS study indicating that 60% of currently non-compliant MSM were abstinent from male-male sex for one year or more, we estimate that 1% of male donors gave blood in the US within one year of having had male-male sex. (14, 15)

Despite the reported data regarding non-compliance, the six month deferral period has not been approved to date by the Therapeutic Goods Administration (TGA) regulatory authority for Australia, citing concern that the risk of HIV transmission could increase with a six month deferral with no significant boost to donor numbers or to the blood supply. The TGA also noted that national data have shown a 10% increase in newly-diagnosed cases of HIV in Australia in 2012 - the largest increase in 20 years and predominantly occurring among MSM.

It was noted that since 1984, the Australian Red Cross has maintained a policy of requiring donors to sign a statement in the presence of a witness, verifying that their answers to the medical history interview are accurate under the threat of fines and penalties. While the signed donor statement has persisted since that time, there have not been reports to date about the impact of this statement, or the extent to which penalties for untruthfulness have been imposed.

9. HHS Advisory Committee on Blood and Tissue Safety and Availability – Recommendations (16)

At the November 13, 2014 meeting, following considerable discussion, the Committee voted favorably on three questions related to reconsideration of the current MSM blood donation deferral, as well as providing additional recommendations for future HHS action.

1. Do the completed HHS MSM Blood Donor Deferral Studies, along with other additional studies and data, provide the ACBTSA with sufficient information to support a change from the current MSM deferral policy (deferral for MSM, even once, since 1977) to an alternative policy that would permit blood donations by some MSM? ***Y = 16; N = 2***

2. After hearing the MSM study results, if the committee determines that a policy change is supported by the evidence, what deferral time frame does the committee recommend for a change to the MSM Blood Donor Deferral Policy recommendations? Voted for one-year ***Y = 16; N = 2***

3. Based on the Donor History Questionnaire (DHQ) study performed by CDC's NCHS, and the data from the REDS Blood DROPS study, what approaches does the ACBTSA recommend for exploration of potential enhancements to the ***DHQ*** *format and associated public health education and outreach to blood donors and public stakeholders?*

The ACBTSA recommends to the Secretary the following in regards to the recommended change in MSM policy:

- *Implementation of the recommendations made during the December 2013 ACBTSA meeting, especially those regarding surveillance of transmissible diseases*
- *Develop and implement a coordinated communication plan regarding a change in MSM deferral policy focused on all relevant stakeholders*

In addition, the ACBTSA recommends for all donations that the Secretary:

- *Undertake studies to evaluate the effectiveness of the administration of the DHQ*
- *Take steps to improve transparent communication to recipients of the relative risks and benefits of blood, organs, cells and tissues*
- *Evaluate and revise the donor education material in order to improve its uptake, comprehension, and utility to promote accurate disclosures of risk*
- *Improve the sensitivity and specificity of the donor selection criteria to identify donors at increased risk of transmissible diseases*

Vote: Y = 18; N = 0

10. Donor Marker and Risk Factor Monitoring Program - Purpose and General Design

Robust and ongoing biovigilance programs have been recommended for implementation in the US a number of times over the past two decades. There have been several formal recommendations specific to the monitoring of US blood donors for markers of transfusion transmissible infections and use of the data for continuous process improvement.

While not specific to development of a monitoring system for transfusion transmissible infections, the Institute of Medicine recommended in its 1995 report HIV and the Blood Supply: An Analysis of Crisis Decisionmaking: Recommendation #11:

- *The FDA should develop reliable sources of the information that it needs to make decisions about the blood supply. The FDA should have its own capacity to analyze this information and to predict the effects of regulatory decisions. (19)*

Other recommendations have included the following:

- *ACBSA 2006: "federal actions and programs to support and facilitate biovigilance in partnership with private sector initiatives" (17)*

- *2009 HHS Gap Analysis White Paper - Defined the "need for accurate tracking of all donor infectious disease test data…"(18)*

- *ACBSA, June 2010 - Establish ongoing national hemovigilance program for TTID markers in blood donors linked to analysis of demographic, behavioral, and other risk factors:*
    a. *Obtain a baseline on prevalence and incidence of TTIDs,*
    b. *Characterize risk in different donor subgroups (e.g., younger age), and*
    c. *Use above characteristics for continuous quality improvement of the donor deferral process; (17)*

- *December, 2013 ACBTSA: recommended that the Secretary establish and fund an ongoing, integrated, coordinated, and nationally representative US transfusion transmissible infections monitoring system.(17)*

- *November, 2014 ACBTSA recommended implementation of the recommendations made during the December 2013 ACBTSA meeting, especially those regarding surveillance of transmissible diseases (17)*.

There is currently an opportunity to leverage the progress made by the NHLBI REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study to design and implement a long-term blood safety monitoring effort that will be representative of blood collections in the US. As part of its mission to assure the safety of blood and blood products, FDA has committed to collect and analyze infectious disease marker rates in a majority of US blood donations, as well as establish a capability to assess newly emergent or re-emergent infectious diseases of concern.

This is being done as a precautionary measure to help confirm the expectation that blood safety will be maintained at its current high level following any future change in donor deferral or other manufacturing or operational policies. FDA intends to work cooperatively with other PHS Agencies and US blood organizations to collect and analyze these data. Key elements of blood safety monitoring that are needed include: statistical tracking of data to identify meaningful changes over time in donor incidence, prevalence, or risk factors that may suggest a need for intervention, and ongoing data availability to objectively assess the value of new blood safety initiatives. Incident infection in donors is the most important measure to obtain, because it relates directly to potential recipient risk. It is also the most difficult parameter to measure, due to its very low frequency.

11. Defining HIV Incidence in a Blood Donation Environment

The high level of current blood safety in the US creates an inherent difficulty in conducting effective monitoring for transfusion-transmitted infections due to the infrequency of transfusion-transmitted infection outcomes. While the blood donor screening environment readily provides local measures of transmissible infection marker prevalence in first time and repeat blood donors, prevalent seropositive donations are quarantined and destroyed and do not directly impact blood safety. Incident infection (new infection that may create recipient risk related to the seronegative window period) occurs infrequently. However when incident infection is identified (through a combination of laboratory and statistical measures), it provides the best direct estimate of potential risk to blood recipients. Using HIV infection as an example, transfusion safety risk related to HIV incidence in the US blood supply can be estimated mathematically by considering the rate of observed seroconversion among repeat blood donors and the calculated interdonation interval for overall repeat donors (20). While accurate and effective, this incidence calculation is limited by the degree of blood establishment database sophistication that is necessary to calculate interdonation intervals, and by the fact that seroconversion events can only be observed in repeat blood donors.

A second observation that can be used to estimate incident HIV infection in donated blood is the detection of HIV infection by Nucleic Acid Testing (NAT) in the absence of HIV antibodies (NAT yield). (20) When a NAT yield pattern is observed (and confirmed) it reflects the presence of early HIV infection that must have occurred within the past 22 days (i.e., the window period for detection of antibodies). Because of the possibility of false positive NAT results, a confirmatory step (accomplished by re-sampling the donor after full seroconversion or sequencing the HIV from an alternate sample collected at the time of donation) may be needed to verify that the NAT-only reaction is valid.

Major international interest has been focused on serological tests that can directly reflect “recent” HIV infection as a measure of incidence. Because of the long duration of overall HIV antibodies in prevalent infection, accurate estimates of HIV incidence can

provide a much more focused assessment of infection dynamics in populations over time, and in response to prevention initiatives.

Several IgG-based recency tests are available, including those based on an original less-sensitive “de-tuned” assay design (21). Considerable work is ongoing internationally to characterize the performance of these and additionally modified incidence assays, as well as multi-analyte assay combinations. One parameter for assessing assay performance is the Mean Duration of Recency (MDR) which is the time after seroconversion that a selected biomarker cut-off is reached. A second parameter is the False Recency Rate (FRR), the probability that a person has actually been infected for a longer period than the targeted recency period. Experiences with each of these assay types and algorithms have varied in different laboratories, and factors such as the nature of the population tested, the infecting virus strain, and the baseline level of HIV prevalence in the population tested have all proven to be important.(22-26)

The BPAC discussion will include an overview of the various methods to determine HIV incidence in a blood donor population, as well as considerations regarding the potential performance of currently available assays to identify recent infections from among a limited size sample of HIV antibody seropositive blood donors that might be obtained in conjunction with a monitoring effort.

Committee Question: Please comment whether serological tests for recency of HIV infection in HIV antibody positive donors are sufficiently accurate to be useful for blood safety monitoring.

12. References

1. Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products FDA Memo April 23, 1992.

2. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resolutions.html

3. All content for this section was presented by Simone Glynn, MD : 11/13/2014 ACBTSA Meeting

4. All content for this section was presented by Kristen Miller, Ph.D. and Stephanie Willson Ph.D.: 11/13/2014 ACBTSA Meeting

5. All content for this section was presented by Brian Custer, MD: 11/13/2014 ACBTSA Meeting

6. http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm277952.htm

7. http://www.aabb.org/research/whitepapers/Pages/default.aspx

8. Anderson SA, et al Quantitative estimate of the risks and benefits of possible alternative blood donor deferral strategies for men who have had sex with men. Transfusion 2009; 49:1102-14

9. All content for this section (except as otherwise referenced) was presented by Amy Lansky, PhD, MPH at the 11/13/2014 ACBTSA Meeting

10. http://www.cdc.gov/hiv/statistics/surveillance/incidence/

11. All content for this section (except as otherwise referenced) was presented by Richard Benjamin, MD, Ph.D. : 11/13/2014 ACBTSA Meeting)

12. Seed, CR et al. No evidence of a significantly increased risk of transfusion-transmitted HIV infection in Australia subsequent to implementing a twelve month deferral for men who have had sex with men. Transfusion 2010; 50:2722-2730.

13. Seed, CR, et al. Compliance with the 12-month deferral for male-to-male sex in Australia. Vox Sanguinis (2014) 106, 14-22

14. Custer, B Noncompliance with the MSM deferral among US male blood donors. Presented at the AABB Annual Meeting, Philadelphia, PA. October, 2014

15. Alan Williams, Ph.D.: 11/13/2014 ACBTSA meeting

16. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/

17. http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/resolutions.html

18. http://www.hhs.gov/ash/bloodsafety/biovigilance/

19. Leveton, LB, Sox, Jr, HC, and Stoto, MA eds. HIV and the Blood Supply: An Analysis of Crisis Decisionmaking Chapter 8. Conclusions and Recommendations. Recommendation 11, page 231. National Academy press Washington, D.C. 1995

20. Busch MP, Glynn SA, Stramer SL, et al. A new strategy for estimating risks on transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion 2005; 45:254-264.

21. Robert S. Janssen, MD; Glen A. Satten, PhD; Susan L. Stramer, PhD, et al. New Testing Strategy to Detect Early HIV-1 Infection for Use in Incidence Estimates and for Clinical and Prevention Purposes. J*AMA.* 1998;280(1):42-48. doi:10.1001/jama.280.1.42.

22. Curtis, KA, Hanson, DL, Kennedy, MS, Owen SM. Evaluation of Multiplex Assays for Estimation of HIV-1 Incidence . PLOS ONE May 2013 (Vol 8) Issue 5 e64201

23. Laeyendecker, O, Latimore A, Eshleman SH, et al. The effect of sample handling on cross sectional HIV incidence testing results. PLoS One 2011, 6: e25899 PMCID: 3203521

24. Kassanjee, R, Pilcher CD, Keating, et al. Independent assessment of candidate HIV Incidence Assays on Specimens in the CEPHIA repository. AIDS Oct 23, 2014; 28(16) 2439-2449.
25. Meeting Report: Annual Meeting of the WHO Technical Working Group on HIV Incidence Assays – 26=27 September, 2012 Geneva Switzerland. WHO Document Production Services http://apps.who.int/iris/bitstream/10665/86397/1/9789241506069_eng.pdf
26. Busch, MP, Pilcher, CD, Mastro, TD, et al. Beyond Detuning: 10 years of progress and new challenges in the development and application of assays for HIV incidence estimation. AIDS 2010, 24:2763-2771.