Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products

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Guidance for Industry

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Contains Nonbinding Recommendations

Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products

Guidance for Industry

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I. INTRODUCTION

This guidance document provides you, blood establishments that collect blood or blood components, including Source Plasma, with FDA's revised donor deferral recommendations for individuals with increased risk for transmitting human immunodeficiency virus (HIV) infection. We (FDA) are also recommending that you make corresponding revisions to your donor educational materials, donor history questionnaires and accompanying materials, along with revisions to your donor requalification and product management procedures. This guidance also incorporates certain other recommendations related to donor educational materials and testing contained in the memorandum to blood establishments entitled, "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," dated April 23, 1992 (1992 blood memo) (Ref. 1). This guidance finalizes the draft guidance of the same title dated May 2015 (80 FR 27973, May 15, 2015) and supersedes the 1992 blood memo. The recommendations contained in this guidance apply to the collection of blood and blood components, including Source Plasma.

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II. BACKGROUND

The emergence of Acquired Immune Deficiency Syndrome (AIDS) in the early 1980s and the recognition that it could be transmitted by blood and blood products had profound effects on the United States (U.S.) blood system (Refs. 2, 3, 4). Although initially identified in men who have sex with men (MSM) and associated with male-to-male sexual contact, AIDS was soon noted to

be transmitted by transfusion of blood products, and by infusion of clotting factor concentrates in individuals with hemophilia (Refs. 5, 6). Subsequently, AIDS was also found to be associated with heterosexual transmission through commercial sex work and with intravenous drug use (Refs. 7, 8). The understanding of risk factors for AIDS in 1983 informed the first blood donor deferral policy, which at that time was the only way to reduce the chance of transmission of AIDS through blood product transfusion. In 1984, AIDS was reported to be associated with the virus now known as HIV, opening the door to development of donor screening tests.

A. History of Efforts to Reduce HIV Transmission by Blood Products

Beginning in 1983, the FDA issued recommendations for providing donors with educational material on risk factors for AIDS and for deferring donors with such risk factors in an effort to prevent transmission of the agent responsible for AIDS (later understood to be caused by HIV) by blood and blood products (Refs. 2, 9, 10, 11). Providing donor educational material and asking at-risk donors not to donate was demonstrated to have a significant impact on preventing HIV transmission prior to the availability of testing (Ref. 12). However, thousands of recipients of blood and blood components for transfusion and recipients of plasma-derived clotting factors became infected with HIV before the causative virus was identified and the first screening tests for HIV were approved in 1985 (Refs. 2, 4, 10).

Since September 1985, FDA has recommended that blood establishments indefinitely defer male donors who have had sex with another male, even one time, since 1977, due to the strong clustering of AIDS illness and the subsequent discovery of high rates of HIV infection in that population (Ref. 13). On April 23, 1992, FDA issued the 1992 blood memo, which contains recommendations regarding the deferral for MSM as well as for other persons with behaviors associated with high rates of HIV exposure, namely commercial sex workers, those who inject illicit drugs, and certain individuals with other risk factors.

The use of donor educational material, specific deferral questions, and advances in HIV donor testing (e.g., HIV antibody assays, p24 antigen assays, and nucleic acid tests (NAT)) have reduced the risk of HIV transmission from blood transfusion from about 1 in 2500 units prior to HIV testing to a current estimated residual risk of about 1 in 1.47 million transfusions (Refs. 14, 15). The development of pathogen inactivation procedures for products manufactured from pooled plasma in the 1980s improved the safety of these products by inactivating lipid-enveloped viruses. No transmissions of HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) have been documented through U.S.-licensed plasma-derived products in the past two decades (Ref. 16).

Relating in large part to the development of more sensitive HIV testing methodologies, there have been calls in the social and scientific literature to revisit the blood donor deferral policies that were established about three decades ago, in particular, with regard to the deferral of MSM. During the period from 1997 to 2010, FDA held a number of public meetings, including workshops and Blood Product Advisory Committee (BPAC) meetings to further review evidence and to discuss its blood donor deferral policies to

help prevent the transmission of HIV (Refs. 17, 18, 19, 20). In June 2010, the Department of Health and Human Services (HHS) brought the issue of deferral of men who have had sex with another man, even one time, since 1977, for public discussion at a meeting of the Advisory Committee on Blood Safety and Availability (the Committee). The Committee heard presentations of currently available scientific data as well as comments from the public. The Committee recommended to the HHS Secretary "that the current MSM deferral policy, while suboptimal, should be retained pending the completion of targeted research studies that might support a safe alternative policy" (Ref. 21).

Based on these recommendations, in September 2010, an Interagency Blood, Organ & Tissue Safety Working Group on MSM (BOTS Working Group), consisting of representatives from the Centers for Disease Control and Prevention (CDC), Health Resources and Services Administration (HRSA), National Institutes of Health (NIH), HHS Office of Civil Rights, Office of the Assistant Secretary for Health (OASH), and FDA, was charged by the Assistant Secretary for Health with exploring the feasibility of a data and science-driven policy change. Subsequently, the BOTS Working Group designed and implemented one operational assessment and three research studies to gain more information to help inform a potential policy change. In addition, it considered the possibility of conducting a pilot study to assess the effect of a policy change. However, following review of comments received in response to a *Federal Register* notice titled, "Request for Information (RFI) on Design of a Pilot Operational Study To Assess Alternative Blood Donor Deferral Criteria for Men Who Have Had Sex With Other Men (MSM)" (77 FR 14801, March 13, 2012) (Ref. 22), requesting comment on potential pilot study designs, as well as further considerations regarding the significant statistical, financial and logistical challenges in implementing such a study, the BOTS Working Group decided that such a pilot study examining the potential effects of a policy change would not be feasible. Instead, the BOTS Working Group determined that resources at HHS could be used in more efficient ways to carefully review the studies that had been initiated (results of which are summarized in section II.C. of this document), to complete its review of the blood donation deferral criteria, and to establish a national blood safety monitoring system.

B. Current Risk of HIV Infection Associated with Specific Behaviors

Recent data indicate that commercial sex work (CSW) and injection drug use (IDU) are behaviors that continue to place individuals both at a relatively high risk of HIV infection and at a relatively high risk of window period transmission of HIV (Ref. 23) and few data are available on the HIV risk in individuals who have discontinued CSW and IDU (Ref. 24). Deferral policies for CSW and IDU are also based on risks for transfusion transmitted infectious diseases, in addition to HIV, that are associated with these behaviors (Ref. 25).

Together, these findings continue to support an indefinite deferral of individuals currently or previously involved in CSW and IDU behaviors pending the availability of additional

scientific evidence regarding the safety of alternative strategies for evaluating the risk of these individuals. Therefore, we have not revised the deferral policies for CSW or IDU.

Although MSM represent a small percentage of the U.S. male population (approximately 7% of men report that they have ever participated in MSM activity and approximately 4% of men report that they engaged in MSM activity in the last 5 years[1]) (Ref. 26), they comprise a large proportion of adults in the United States with existing and newly diagnosed HIV infections. Among persons living with HIV in 2012, CDC estimates that 56% were MSM (including MSM who were also IDU) (Ref. 27). MSM remain at increased risk of HIV infection. In 2010, the majority of new HIV infections were attributed to male-to-male sexual contact: 63% among all adults and 78% among men, indicating that male-to-male sexual contact remains associated with high risk of HIV exposure (Ref. 28).

C. Recent Data Relevant to the Deferral for MSM

The following results became available by mid-2014, from the operational assessment and all three of the research studies recommended by the BOTS Working Group.

1. Operational Assessment

   The operational assessment examined quarantine release errors. Such errors occur when a blood establishment accidentally releases a unit of blood that should not have been released due to issues with donor qualification or testing. It became clear at an FDA workshop held in September 2011 that HIV risk from quarantine release errors has been minimized effectively by increased use of computerized inventory management, with a remaining small risk of human errors. Following the workshop, a White Paper was produced by AABB on this topic which describes a number of measures that could be taken to characterize and prevent such errors (Ref. 29). Quarantine release errors currently appear to contribute minimally to the risk of HIV transmission through the blood supply (Ref. 30).

2. Donor History Questionnaire Study

   The Donor History Questionnaire (DHQ) Study involved cognitive interviews with potential donors. After receiving donor educational materials, the potential donors completed the donor history questionnaire, and were then interviewed regarding their responses (Ref. 31). The key result of this study, which was highly consistent for both individuals who only have sex with partners of the opposite sex and MSM, was that individuals respond to questions posed by the questionnaire as if they were

[1] Purcell et al., have reported that the estimation of the MSM population as a percent of all males over 13 years differ by recall period: Past 1 year = 2.9%; past 5 years = 3.9%; and ever = 6.9%.

answering the more general and subjective question in the self-assessed context of "is my blood safe," rather than providing an answer to the literal questions as asked. In addition, the study found that potential donors might have benefited from shorter donor educational materials and the ability to answer "I don't know" to questions that currently accept only "yes" or "no" responses.

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

The REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study 2011-2013 was a pilot blood donor surveillance study that evaluated four viral markers (HBV, HCV, human T cell lymphotrophic virus (HTLV), and HIV) in just over 50% of the nation's blood supply (Ref. 32). It also determined behavioral risk factors that were associated with donations of blood that tested positive for one of these viruses compared with control donations. In addition to demonstrating the feasibility of conducting such a surveillance program, there were several key findings. These included the finding that for each of these viral infections, the primary behavioral risk factors were consistent with the known epidemiology for each infection in the United States and validated the current blood donor deferral criteria. Sex with an HIV-positive partner and a history of male-to-male sexual contact remained the two leading independent risk factors for HIV infection in blood donors as originally observed in CDC-funded studies from the early 1990's. Sex with an HIV-positive partner was associated with a 132-fold increase in risk (multivariable adjusted odds ratio) for being HIV-positive, and a history of male-to-male sexual contact was associated with a 62-fold increase in risk. By comparison, the increase in risk for a history of multiple sexual partners of the opposite sex in the last year was 2.3-fold.

4. Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) Blood Donation Rules Opinion Study (BloodDROPS)

BloodDROPS examined the opinions of MSM regarding the blood donor deferral policy through web-based surveys of the MSM community and non-compliant MSM who donated blood (Ref. 33). A key finding of particular note was that MSM, who comprise approximately 7% (Ref. 26) of the U.S. male population, represented an estimated 2.6% of male blood donors. Although the data were determined by different methodologies, they suggest an increase in the proportion of blood donors reporting MSM behavior from 0.6% in 1993 and 1.2% in 1998. The qualitative responses by both donating and non-donating groups of MSM revealed that these individuals view the current policy as discriminatory and stigmatizing, and that some individuals knowingly donate despite the deferral. When asked about shortening the deferral period, since last male-to-male sexual

contact, the most common response was that one year was "acceptable as a compromise," especially if shorter periods might be considered after confirming the safety of the new policy. The web-based community survey revealed that approximately 90% of MSM think the MSM blood donation deferral should change, and 59% of MSM reported they would comply with a change to a one-year deferral. In the male blood donor survey, 83 of 3183 respondents reported donating after male-to-male sexual contact; 50.6% reported that they would adhere to a one-year deferral and 18.1% reported "don't know" (Ref. 33).

The prevalence of HIV infection in male blood donors who reported that they were MSM was determined to be 0.25%, which is much lower than the estimated 11-12% HIV prevalence in the population of individuals reporting regular MSM behavior (Ref. 33). This indicates that considerable self-selection likely took place in individuals who presented to donate.

5. Supportive Data on Australian MSM Policy Change

Some epidemiologic data are available from countries that have changed their deferral policy for MSM (Refs. 34, 35). The most robust data measuring the impact of these policy changes are available from Australia (Ref. 36). Australia also has a voluntary blood donor system and has a similar percentage of men reporting male-to-male sexual contact at some time during their lives (5% compared with 7% in the United States (Ref. 26). During the five years before and five years after a change from a lifetime deferral to a one-year deferral in Australia, there was no change in risk to the blood supply, defined by the number of HIV positive donations per year and the proportion of HIV-positive donors with male-to-male sex as a risk factor. In addition, the compliance rate with the one-year MSM deferral among male donors in Australia following the policy change was >99.7% (Ref. 37). Of note, donors in Australia must sign a declaration in the presence of blood center staff that they understand that there are penalties, including fines and imprisonment, for providing false or misleading information. No such declaration is required in the United States, nor are donors advised of penalties for providing false or misleading information.

While a number of countries in addition to Australia have adopted a 12 month deferral policy for MSM, at this time, a number of other countries in Western Europe and the Middle East continue to maintain an indefinite or permanent deferral policy for MSM. To comply with global regulatory requirements on deferral policies, manufacturers of blood and blood components, including Source Plasma, collected in the U.S. and intended for further manufacturing use in other countries, may not be able to

implement FDA's recommended 12 month donor deferral policy for MSM and instead may maintain longer deferral policies.

D. Considerations of the BOTS Working Group

Over the course of its deliberations, the BOTS Working Group reviewed and discussed several different options for the MSM policy:

- no change,
- change to a five-year deferral,
- change to a one-year deferral,
- change to a deferral less than one year,
- pre-testing of potential donors, and
- deferral based upon individual risk assessment.

Although not making a change would maintain the current level of safety of the blood supply, as noted above, there is evidence that the indefinite deferral policy is becoming less effective over time. In addition, the indefinite policy is perceived by some as discriminatory. The data that a five-year deferral would be safer than a one-year deferral are not compelling. However, some have argued that a five-year deferral would, in theory, add a safeguard by allowing time for intervention against an emerging infectious disease that might spread rapidly among MSM and be transmitted through blood transfusion. Sufficient data are not available to assess the effectiveness of selecting MSM with low HIV risk based on deferral times of less than one year since last exposure. The individual risk-based options were not determined to be viable options for a policy change at this time for a number of reasons: pretesting would be logistically challenging, and would likely also be viewed as discriminatory by some individuals, and individual risk assessment by trained medical professionals would be very difficult to validate and implement in our current blood donor system due to resource constraints. Additionally, the available epidemiologic data in the published literature do not support the concept that MSM who report mutual monogamy with a partner or who report routine use of safe sex practices are at low risk for HIV. Specifically, the rate of partner infidelity in ostensibly monogamous heterosexual couples and same-sex male couples is estimated to be about 25%, and condom use is associated with a 1 to 2% failure rate per episode of anal intercourse (Refs. 38, 39, 40, 41). In addition, the prevalence of HIV infection is significantly higher in MSM with multiple male partners compared with individuals who have only multiple opposite sex partners (Ref. 28).

Change to a one-year deferral is also supported by other evidence, including the experience in countries that have already changed their policies to a one-year deferral (Argentina, Australia, Brazil, Hungary, Japan, Sweden and United Kingdom). In addition, this change would potentially better harmonize the deferral for MSM with the one-year deferral in place for both men and women who engage in certain other sexual behaviors associated with an increased risk of HIV exposure (e.g., sex with an HIV-positive partner, sex with a commercial sex worker). Thus, following careful review, the BOTS Working Group was supportive of a policy change to a one-year deferral for MSM.

E. Outcome of Advisory Committee Meetings

Following deliberation of the BOTS Working Group, two advisory committee meetings were held. The Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA) met on November 13, 2014, to review the MSM deferral policy (Ref. 33). The scientific information described in sections II.C. and D. was presented to the ACBTSA members along with the BOTS Working Group recommendation. Additionally, the meeting included an open public hearing session. The ACBTSA voted 16 to 2 to recommend a policy change to a one-year MSM deferral. It also recommended that this change be accompanied by establishment of a robust system to monitor the safety of the blood supply and a communication plan on the policy change targeted to all stakeholders.

Subsequently, on December 2, 2014, the BPAC met to consider measurement of HIV incidence in blood donors as an additional method to assess transfusion risk, and the potential value of laboratory tests to detect recently acquired HIV infections in seropositive donors as part of a Transfusion Transmissible Infections Monitoring System (TTIMS) (Ref. 42). An open public hearing was also held. At that meeting, FDA noted that it intended to establish in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), NIH, a general program to monitor the safety of the blood supply for a number of different transfusion-transmitted viral infections. FDA also noted that it intended to explore options and engage in public discussions of issues such as enhancements to education about the donation of safe blood and further evaluation of the effectiveness of the blood donor history questionnaire. In their comments, some BPAC committee members indicated support for a change in MSM deferral policy to one year, and most members noted that they considered concomitant establishment of a blood donor monitoring program a prerequisite for any policy change. On the topic of testing for recency of HIV infection, several BPAC committee members commented that tests looking at how recently HIV infection had been contracted (recency tests[2]) could potentially be very useful additions to the established measures of incidence for monitoring the safety of the blood supply.

F. Evaluating Alternative Policy Options Using Available Evidence

FDA is responsible for maintaining the safety of the blood supply in the U.S. FDA recognizes that the current indefinite deferrals for certain groups are not optimal. However, changes to the existing deferral policies must be made in the context of maintaining the high level of safety of the U.S. blood supply achieved to date.

[2] HIV recency tests typically involve detailed assessment of the strength and characteristics of antibody profiles that develop and change over time in response to HIV infection. Thus, it appears to be technically feasible that a serologically-based HIV recency test, once validated in a blood donor setting, could reflect a high likelihood that an HIV infection occurred within a certain interval of time (e.g., in the past six months). While such tests are not yet FDA-approved for this purpose, this additional measure of new HIV infection may increase the statistical power to assess whether HIV incidence in the blood donor pool changed significantly after a change in the deferral recommendations.

The safety of the blood supply rests upon the practical implementation of a combination of screening measures that are based upon the best available scientific evidence. The following is a summary of the practical and scientific considerations associated with various potential options regarding changing the blood donor deferral policy for reducing the risk of HIV transmission.

1. **No change in policy, continue indefinite deferral.** Evidence indicates that the indefinite deferral policy for men who have had sex with other men, even once, since 1977 has become less effective over time. Similar data are not available for CSW and IDU. The rate of non-compliance of MSM under the indefinite deferral policy appears to be increasing because the percentage of male donors estimated to be MSM has risen from 0.6% in 1993, to 1.2% in 1998, and to 2.6% in 2013. Therefore, it is appropriate to consider alternatives.

2. **Eliminate any deferral related to HIV for all donors and rely on laboratory testing alone.** HIV testing on blood donated in the United States is currently implemented by assays including nucleic acid testing. Nucleic acid testing is generally performed on pools of 6 to 16 donor samples. Pooling of samples both markedly reduces the cost of testing and is associated with a reduced number of false positive samples. The window period when recent HIV infection might be missed using this testing strategy is approximately 9 days. Given this, it has been suggested that no donor deferral is necessary, given the relatively low likelihood that a recently infected individual would give blood. However, in the setting of the approximately 50,000 new HIV infections per year in the United States, conservative calculations performed by FDA estimate that this approach could potentially be associated with an approximately four-fold increase in HIV transmissions resulting from blood transfusions each year. Such a policy, increasing the potential for the transmission of HIV infection, is not aligned with maintaining or improving the safety of the blood supply in the U.S.

3. **Eliminate any deferral related to HIV for all donors and implement laboratory pre-testing.** Rapid tests for HIV infection have been approved, and could potentially be used at blood collection centers to pre-screen potential donors in order to reduce collection of HIV-positive units. However, such tests do not address the problem of identifying recently infected donors. Testing individuals 10 to 14 days in advance of blood donation and then retesting them on the day of donation could theoretically reduce the potential for window period transmission of HIV without the need for a prolonged period of sexual abstinence, so long as individuals refrain from sexual activity between the time that the initial testing is performed and the time of blood donation, when such testing would be performed again. However, retesting donors for the millions of donations made each year would add significant burden to donors to

appear for donation on two separate occasions and would add very significant logistic complexity to the blood donor system. For example, initial testing would need to be completed and the results would need to be available for review at the time individuals returned to donate during the specific time interval during which the results would be valid. An alternative, pre-testing those individuals identified through certain screening questions as potentially being at increased risk of HIV, would first require validation of the questions posed and would have similar logistic complexity.

4. **Individually assess donor risk.** Although individual donor assessment for risk of HIV and other infections has been implemented in a few countries, significant differences exist regarding the situation in those countries and the situation in the United States. For example, in South Africa, HIV transmission is primarily heterosexual and every unit is screened individually for HIV, given the epidemiology affecting all available blood donors. Individual risk assessment presents significant challenges in the United States for a number of reasons. At this time there are inadequate data to support the effectiveness of the use of donor educational materials and questionnaires on safe sexual practices for the prevention of transfusion-transmitted infections through donated blood. In addition, self-report of monogamy cannot be relied upon because of the relatively high rate of infidelity between partners in any type of sexual relationship (Ref. 38). Even if a potential donor is truthful in providing responses regarding his or her own behavior, the response may not be meaningful if a partner has not been monogamous. Although the effectiveness of individual assessment of donor risk can be explored in the future, currently there is no validated and accepted individual risk assessment tool or questionnaire.

5. **Implement a time-based deferral.** Although it might seem that any deferral longer than the 9 day window period would be effective, this assumption is incorrect because of recall bias, non-compliance, and other behavioral factors. As a group, in the United States, MSM have the highest HIV risk: according to CDC, two-thirds of new HIV infections occur in the approximately 2% of the population who are MSM (Ref. 27). The risk of HIV among MSM is more than twenty-fold higher than that of men who have sex with multiple female partners and women who have sex with multiple male partners (Ref. 32). Thus, absent another scientifically-validated way of identifying individuals at highest risk of transmitting HIV, a time-based deferral for MSM since last sexual encounter is the one deferral policy that has been demonstrated to be effective in a setting with similar HIV epidemiology to the United States. The data available from the transition to a one-year deferral policy in Australia are particularly compelling because it monitored the effect of the change using a national blood surveillance program. Data for the five

years preceding and following the change from an indefinite to a one-year deferral showed no detectable decrease in safety of the blood supply. Twenty-four HIV-positive donations were identified among 4,025,571 donations prior to the change in policy compared with 24 among 4,964,628 donations following it. Scientifically robust data are not available for time-based deferral periods of less than one year.

FDA concludes that the available evidence most strongly supports a change from the indefinite deferral to a one year blood donor deferral policy for MSM, and FDA expects that this change will maintain or improve blood safety with respect to HIV. FDA will continue to monitor the safety of the blood supply, including the effect of a change to a one year deferral.

G. Status of Other Deferral Categories

In addition to the behavioral deferrals noted for MSM, CSW and IDU, the 1992 blood memo addressed several other deferrals that had been recommended in order to reduce the risk of HIV transmission through the blood supply (Ref. 1). For most of these deferrals, directly applicable data are not available at this time to support a change in the existing deferral policies.

In the case of the deferral for persons with hemophilia or related clotting disorders who have received clotting factor concentrates, the rationale for deferral has changed from prevention of HIV transmission to that of ensuring that donors are not harmed by the use of large bore needles used during the donation process. Given the enhanced safety measures now used in the manufacture of clotting factor concentrates (Ref. 16), FDA does not consider the receipt of FDA-licensed clotting factor concentrates or sex with a person that has received clotting factor concentrates to be a risk factor for HIV or hepatitis. Therefore, we no longer recommend deferral for individuals who have had sex with an individual with hemophilia or related clotting factor deficiencies who has used clotting factor concentrates. Further, FDA has not recommended a deferral for the receipt of other FDA-licensed plasma-derivatives because of HIV or hepatitis risk[3].

H. Blood Safety Monitoring

A Transfusion Transmissible Infections Monitoring System (TTIMS) is being implemented in the United States in order to facilitate monitoring of the safety of the U.S. blood supply for a variety of different pathogens. FDA will use TTIMS to further investigate and refine blood safety screening measures over the coming years. Through this monitoring system a variety of donor risk factors can also be evaluated, based in part upon further investigation of units donated that are detected upon screening to contain infectious agents. Based upon the information obtained from TTIMS and other sources,

[3] Consistent with the donor history questionnaires and accompanying materials prepared by AABB and Plasma Protein Therapeutics Association (PPTA) and found acceptable by FDA, a voluntary donor deferral exists for the receipt of Hepatitis B Immune Globulin because the donor had been recently exposed to hepatitis B virus.

additional studies may be undertaken in the future in order to further assess the effectiveness of alternatives to time-based donor deferral strategies, including such approaches as individual risk assessments. As part of its ongoing efforts to ensure the safety of the blood supply, FDA intends to routinely review information from the TTIMS along with emerging scientific evidence to reevaluate its donor deferral policies.

III. RECOMMENDATIONS

The following sections summarize the revised recommendations related to blood donor deferral and requalification related to reducing the risk of HIV transmission by blood and blood products. Given the passage of time, and in order to simplify practical application of these criteria for donors and blood collection establishments, reference made previously in some criteria to "since 1977" has been dropped as the period of time during which individuals are assessed to be at risk of transmitting HIV.

A. Donor Educational Material and Donor History Questionnaire

1. We recommend that donors be provided donor educational material before each donation explaining the risk of HIV transmission by blood and blood products and certain behaviors associated with the risk of HIV infection so that donors can self defer. We recommend the donor educational materials explain that individuals with risk factors for HIV need to be aware of the signs and symptoms associated with acute HIV infection, namely fever, enlarged lymph nodes, sore throat and rash.[4] FDA currently recommends, and under 21 CFR 630.10(b), effective May 23, 2016, FDA will require that donor educational material be presented to donors in a manner they will understand, which may include oral, written, or multimedia formats, and must instruct the donor not to donate when a risk factor for HIV infection is present. The donor educational material should indicate that individuals who have engaged in any activity or who have any risk factor that would result in a deferral (see section III.B. of this guidance) should not donate blood or blood components.

2. We recommend that blood collection establishments update their donor educational material, DHQ, including full-length and abbreviated DHQs, and accompanying materials (e.g., flow charts) and processes to incorporate the recommendations provided in this guidance.

[4] See CDC website at http://www.cdc.gov/hiv/basics/whatishiv.html.

3. We recommend that the updated DHQ include the following elements to assess donors for risk:

   a. A history ever of a positive[5] test for HIV,
   b. A history ever of exchanging sex[6] for money or drugs,
   c. A history ever of non-prescription injection drug use[7],
   d. A history in the past 12 months of sex with any of the following individuals: a person with a history ever of positive test for HIV, a person with a history ever of exchanging sex for money or drugs, or a person with a history ever of non-prescription injection drug use,
   e. A history in the past 12 months of receiving a transfusion of Whole Blood or blood components such as packed red blood cells, platelets, or plasma,
   f. A history in the past 12 months of contact with blood of another individual through percutaneous inoculation such as a needle stick or through contact with a donor's open wound or mucous membranes,
   g. A history in the past 12 months of a tattoo, ear or body piercing,
   h. A history in the past 12 months of syphilis or gonorrhea, or treatment for syphilis or gonorrhea,
   i. For male donors: a history in the past 12 months of sex with another man,
   j. For female donors: a history in the past 12 months of sex with a man who has had sex with another man in the past 12 months.

Note: In the context of the donor history questionnaire, FDA recommends that male or female gender be taken to be self-identified and self-reported.

[5] In this context, "positive" includes reactive test results on an HIV diagnostic assay and repeatedly reactive or reactive results on antibody or NAT blood donor screening assays, respectively.

[6] Throughout this guidance the term "sex" refers to having anal, oral, or vaginal sex, regardless of whether or not a condom or other protection is used.

[7] Non-prescription injection drug use includes not only the injection of non-prescription drugs, but also includes the improper injection of legally-prescribed drugs, such as injecting a prescription drug intended for oral administration or injecting a prescription drug that was prescribed for another individual.

B. Donor Deferral

We recommend that you defer as follows:

1. Defer indefinitely an individual who has ever had a positive test for HIV[8].
2. Defer indefinitely an individual who has ever exchanged sex for money or drugs.
3. Defer indefinitely an individual who has ever engaged in non-prescription injection drug use.
4. Defer for 12 months from the most recent sexual contact any individual who has a history of sex with a person who: has ever had a positive test for HIV, ever exchanged sex for money or drugs, or ever engaged in non-prescription injection drug use.
5. Defer for 12 months from the most recent allogeneic transfusion any individual who has a history of receiving an allogeneic transfusion of Whole Blood or blood components.
6. Defer for 12 months from the most recent exposure, any individual who has a history of contact with blood of another individual through percutaneous inoculation such as a needle stick or through contact with a donor's open wound or mucous membranes.
7. Defer for 12 months from the most recent tattoo, ear or body piercing, an individual who has a history of tattoo, ear or body piercing. However, individuals who have undergone tattooing within 12 months of donation are eligible to donate if the tattoo was applied by a state regulated entity with sterile needles and non-reused ink. Individuals who have undergone ear or body piercing within 12 months of donation are eligible to donate if the piercing was done using single-use equipment.
8. Defer for 12 months after completion of treatment, an individual with a history of syphilis or gonorrhea, or an individual with a history of diagnosis or treatment for syphilis or gonorrhea in the past 12 months.
9. Defer for 12 months from the most recent sexual contact, a man who has had sex with another man during the past 12 months.

[8] A donor deferred because of a repeatedly reactive or reactive result on an antibody or a NAT blood donor screening assay, respectively, may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 610.41(b)). Current FDA recommendations are found in "Guidance for Industry: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry, dated May 2010. Under 21 CFR 630.35(b), effective May 23, 2016, deferred donors with a previously false-positive result on an HIV diagnostic test may be considered for re-entry by a requalification method or process found acceptable for such purposes by FDA (21 CFR 630.35(b)). We recommend that you contact FDA for recommendations on a case by case basis for an acceptable requalification method or process.

10. Defer for 12 months from the most recent sexual contact, a female who has had sex during the past 12 months with a man who has had sex with another man in the past 12 months.

We recommend that you defer indefinitely an individual with hemophilia or related clotting factor deficiencies requiring treatment with clotting factor concentrates for reasons of donor safety, rather than based upon the risk of HIV infection. Accordingly, we no longer recommend deferral for individuals who have had sex with an individual with hemophilia or related clotting factor deficiencies requiring treatment with clotting factor concentrates.

Notes:

1. Additional recommendations for donor deferral to reduce the risk of HIV transmission by blood and blood products have been established in other FDA guidance documents, including:

    - "Guidance for Industry: Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis," dated September 2014;

    - "Guidance for Industry - Recommendations for Management of Donors at Increased Risk for Human Immunodeficiency Virus Type 1 (HIV-1) Group O Infection," dated August 2009; and,

    - "Memorandum to All Registered Blood Establishments - Recommendations for the Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma," dated June 8, 1995.

2. Collections from donors at risk of HIV infection must be approved by CBER under 21 CFR 640.120, consistent with the "Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors)," dated September 1989.

3. FDA currently recommends, and under 21 CFR 630.5 and 630.10(a), effective May 23, 2016, FDA will require the responsible physician of a blood collection establishment to determine the eligibility of a donor, and

to defer any donor if the donation could adversely affect the health of the donor or the safety of the blood or blood component.[9]

C. Donor Requalification

1. Donors deferred because of a history of sex during the past 12 months with any of the following individuals: a person who has a positive test for HIV; a person with a history of exchanging sex for money or drugs; or a person with a history of non-prescription injection drug use, may be eligible to donate provided that 12 months since the last sexual contact have passed and they meet all other donor eligibility criteria.

2. Donors deferred because of a history of receiving an allogeneic transfusion of Whole Blood or blood components such as packed red blood cells, platelets, or plasma during the past 12 months may be eligible to donate if 12 months have passed since their last allogeneic transfusion and they meet all other donor eligibility criteria.

3. Donors deferred because of a history of contact with blood of another individual through percutaneous inoculation such as a needle stick or through contact with a donor's open wound or mucous membranes during the past 12 months may be eligible to donate if 12 months have passed since their last exposure and they meet all other donor eligibility criteria.

4. Donors deferred because of a history of tattoo, ear or body piercing in the past 12 months may be eligible to donate if 12 months have passed since their last tattoo, ear or body piercing and they meet all other donor eligibility criteria.

5. Donors deferred because of a history of syphilis or gonorrhea, or treatment for syphilis or gonorrhea in the past 12 months may be eligible to donate if 12 months have passed since diagnosis and completion of treatment and they meet all other donor eligibility criteria.

6. Male donors previously deferred because of a history of sex with another man, even one time, since 1977, may be eligible to donate provided that they have not had sex with another man during the past 12 months and they meet all other donor eligibility criteria.

7. Male donors deferred because of a history of sex with another man in the past 12 months may be eligible to donate provided they have not had sex

[9] See "Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use" final rule (80 FR 29842, May 22, 2015) https://www.federalregister.gov/articles/2015/05/22/2015-12228/requirements-for-blood-and-blood-components-intended-for-transfusion-or-for-further-manufacturing. The final rule is effective May 23, 2016.

with another man during the past 12 months and they meet all other donor eligibility criteria.

8. Female donors deferred because of a history of sex in the past 12 months with a man who has had sex with another man in the past 12 months may be eligible to donate provided that during the past 12 months the female donors have not had sex with a man who has had sex with another man in the past 12 months and the female donors meet all other donor eligibility criteria.

D. Product Retrieval and Quarantine; Notification of Consignees of Blood and Blood Components

If you collected blood or blood components from a donor who tests reactive for HIV on that donation, or when you are made aware of other reliable test results or information indicating evidence of HIV infection, you must follow the HIV "lookback" requirements in 21 CFR 610.46.

In addition, we recommend that you take the following actions if you determine that blood or blood components have been collected from a donor who should have been deferred according to the recommendations in section III.B. 2-10 of this guidance, for reasons other than a positive HIV test result.

1. If you collected blood or blood components from a donor who should have been deferred according to the recommendations in section III.B. of this guidance, we recommend that you quarantine and destroy any undistributed in-date blood or blood components collected from that donor.

2. If you distributed blood or blood components collected from a donor who should have been deferred according to the recommendations in section III.B. of this guidance, we recommend that you notify consignees of the in-date blood and blood components collected from the donor during the period that he or she should have been deferred. We recommend that the consignee retrieve and quarantine the in-date blood and blood components collected from that donor during the period he or she should have been deferred. We do not recommend retrieval and quarantine of plasma pooled for further manufacturing into products that are manufactured under processes that include validated viral clearance steps, which have been shown to be robust in the clearance of lipid-enveloped viruses.

E. Product Disposition and Labeling

1. We recommend that you destroy or re-label blood or blood components that were collected from a donor who should have been deferred based on risk factors for HIV infection in accordance with the recommendations in

section III.B. of this guidance. If you re-label the blood or blood components as described in this section, they may be released for research or for manufacture into noninjectable products or in vitro diagnostic reagents when no other suitable sources are available.

a. You must use the following statement to prominently re-label the blood or blood components originally collected for transfusion in accordance with 21 CFR 606.121(f):

"NOT FOR TRANSFUSION: Collected From a Donor Determined To Be At Risk For Infection With HIV"

In addition, you should include one of the following cautionary label statements, as applicable:

"Caution: For Laboratory Research Only"

or

"Caution: For Further Manufacturing into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"Caution: For Use in Manufacturing Noninjectable Products Only"

And, for recovered plasma:

"Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act"

b. You should use the following statements to prominently re-label the un-pooled blood or blood components originally collected or intended for further manufacture:

"Collected from a Donor Determined to be at Risk for Infection with HIV"

And

"Caution: For Laboratory Research Only"

or

"Caution: For Further Manufacturing into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"Caution: For Use in Manufacturing Noninjectable Products Only"

And, for recovered plasma:

"Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act"

2. You must destroy or re-label blood or blood components, including Source Plasma, collected from a donor who currently tests reactive for HIV or collected from a donor deferred for reactive HIV testing (21 CFR 610.40(h)). If you re-label the blood or blood components, including Source Plasma, in accordance with 21 CFR 610.40(h) and 606.121, the blood or blood components may be released for research or for manufacture into noninjectable products or in vitro diagnostic reagents when no other suitable sources are available. You must label the reactive unit with the "BIOHAZARD" legend (21 CFR 610.40(h)(2)(ii)(B)), and:

   a. You must use the following statement to prominently re-label the blood or blood components originally collected for transfusion (21 CFR 606.121(f)):

      "NOT FOR TRANSFUSION: Collected From a Donor Determined To Be Reactive for HIV"

      In addition, you should use one of the following cautionary label statements, as applicable:

      "Caution: For Laboratory Research Only"

      or

      "Caution: For Further Manufacturing into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

      or

      "Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources"

   b. You must use the following statement to prominently re-label the un-pooled blood or blood components, including Source Plasma, originally collected or intended for further manufacture (21 CFR 610.40(h)(2)(ii)(C)):

"Collected from a Donor Determined to be Reactive for Infection with HIV"

In addition, you should use one of the following cautionary label statements, as applicable:

"Caution: For Laboratory Research Only"

or

"Caution: For Further Manufacturing into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources"

or

"Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources"

F. Biological Product Deviation Reporting

If you have distributed blood or blood components for transfusion or for further manufacturing, collected from a donor who should have been deferred according to section III.B. of this guidance, you should report a biological product deviation as soon as possible, but you must report within 45 calendar days from the date you acquire the information reasonably suggesting that a reportable event has occurred (21 CFR 606.171).

G. Testing Requirements and Considerations

Section 610.40(a) (21 CFR 610.40(a)) requires establishments that collect blood or blood components to test each donation intended for use in preparing a product, for evidence of infection due to HIV type 1 (HIV-1) and HIV type 2 (HIV-2). In addition, 21 CFR 610.40(b) requires you to use one or more approved screening test as necessary to reduce adequately and appropriately the risk of transmission of HIV-1 and HIV-2. FDA has considered the use of approved donor screening tests for antibodies to both HIV-1 and HIV-2 as necessary to reduce adequately and appropriately the risk of transmission of HIV. In addition, FDA recommendations on the use of approved HIV-1 nucleic acid donor screening tests to meet the requirements under 21 CFR 610.40(b) are found in, "Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV," dated October 2004.

You must defer a donor who tests reactive by a donor-screening test for HIV-1 or HIV-2 (21 CFR 610.41), you must perform further testing using a supplemental test on

donations that test reactive on a screening test, when available. If no supplemental test is available, you must perform one or more licensed, approved or cleared test as adequate and appropriate to provide additional information regarding the donor's infection status. (21 CFR 610.40(e)). You must make reasonable attempts to notify a donor who has been deferred based on the results of tests for communicable diseases (21 CFR 630.6). Where appropriate, donors who are deferred because of reactive test results should be provided information about the need for medical follow-up and counseling.

Current FDA recommendations are found in "Guidance for Industry: Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry," dated May 2010. In addition, for the purpose of donor counseling, if a donation tests repeatedly reactive for antibodies to HIV-1/HIV-2 or for HIV-2 on an approved donor screening test, but HIV-1 positivity is not confirmed on an approved supplemental test, further testing may be performed using licensed or approved tests to diagnose HIV-2 infection and clarify the donor's infection status.

IV. IMPLEMENTATION

You may implement these recommendations once you have revised your donor educational material, DHQ, including full-length and abbreviated DHQs, and accompanying materials to reflect the new donor deferral recommendations. Licensed blood establishments must report the indicated revisions to FDA in the following manner (21 CFR 601.12):

1. Revision of your own donor educational materials, DHQ and accompanying materials must be submitted to FDA as a prior approval supplement (PAS) under 21 CFR 601.12(b).

2. Revision of a previously FDA accepted DHQ and accompanying materials must be reported as a major change if you are revising the FDA accepted DHQ and accompanying materials to implement these new recommendations. Report such a change to FDA as a prior approval supplement (PAS) under 21 CFR 601.12(b).

3. If the current version of the donor educational materials, DHQ and accompanying materials prepared by the AABB Donor History Task Force or PPTA are revised to contain the recommendations in this guidance and are found acceptable by FDA, we would consider the implementation of the donor educational materials, DHQ and accompanying materials to be minor changes, if implemented without modification and in their entirety as a complete process for administering questions to donors. Report such a change to FDA in your annual report under 21 CFR 601.12(d), noting the date the process was implemented.

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