

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

Guidance for Industry

This guidance is for immediate implementation.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at <https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances> or <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Preface

Public Comment

Given the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2015-D-1211 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "Coronavirus Disease 2019 (COVID-19)," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and the FDA webpage titled "Search for FDA Guidance Documents" available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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Questions

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This revised 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 supersedes the December 2015 guidance of the same title (Notice of Availability, 80 FR 79913 (December 17, 2015)). The recommendations contained in this guidance apply to the collection of blood and blood components, including Source Plasma.

The recommendations in this revised guidance reflect the Agency's current thinking on donor deferral recommendations for individuals with increased risk for transmitting HIV infection. Based on the Agency's careful evaluation of the available data, including data regarding the detection characteristics of nucleic acid testing, FDA expects implementation of these revised recommendations will not be associated with any adverse effect on the safety of the blood supply. Furthermore, early implementation of the recommendations in this guidance may help to address significant blood shortages that are occurring as a result of a current and ongoing public health emergency. In particular, there is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating

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Divisions of HHS.¹ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.²

As a result of this public health emergency, there is a significant shortage in the supply of blood in the United States, which early implementation of the recommendations in this guidance may help to address (even though the recommendations in this guidance are broadly applicable beyond the COVID-19 public health emergency). For this reason, this revised guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C)(i) of the FD&C Act and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices. Because this revised guidance is being issued without prior public comment in light of the COVID-19 public health emergency, it is intended to remain in effect for the duration of this public health emergency, including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)). However, as noted, FDA expects that the recommendations set forth in this revised guidance will continue to apply outside the context of the current public health emergency. Therefore, within 60 days following the termination of the public health emergency, FDA intends to revise and replace this guidance with an updated guidance that incorporates any appropriate changes based on comments received on this guidance and the Agency's experience with implementation.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

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. 1, 2, 3). 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. 4, 5). Subsequently, AIDS was also found to be associated with heterosexual transmission through commercial sex work and with intravenous drug use (Refs. 6, 7). 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

¹ Secretary of Health and Human Services Alex M Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx>).

² President Donald J. Trump, Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>).

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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.

Beginning in 1983, 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. 1, 8, 9, 10). 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. 11). 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. 1, 3, 9).

From September 1985 to December 2015, FDA 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. 12). 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)) then 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. 13, 14). 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. 15).

During the period from 1997 to 2010, FDA and HHS held several 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. 16, 17, 18, 19, 20). 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. 21), 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

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review the studies that had been initiated and to consider other study designs or interventions. The following information became available by mid-2014 and was subsequently reviewed by the BOTS Working Group, the Advisory Committee on Blood and Tissue Safety and Availability (ACBTSA), which met on November 13, 2014, and the BPAC, which met on December 2, 2014:

1. An operational assessment that 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 described several measures that could be taken to characterize and prevent such errors (Ref. 22). Quarantine release errors now appear to contribute minimally to the risk of HIV transmission through the blood supply (Ref. 23).
2. The Donor History Questionnaire (DHQ) Study, which 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. 24). 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 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.
3. The REDS-II Transfusion-Transmitted Retrovirus and Hepatitis Virus Rates and Risk Factors Study 2011-2013, which was a pilot blood donor surveillance study that evaluated four viral markers (HBV, HCV, human T cell lymphotropic virus (HTLV), and HIV) in just over 50% of the nation’s blood supply (Ref. 25). 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. Key findings from this study included that for each of these viral infections, the primary behavioral risk factors were consistent with the known epidemiology for each infection in the U.S. 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. The Blood Donation Rules Opinion Study (BloodDROPS), which 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

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(Ref. 26). A key finding was that MSM, who comprise approximately 7% (Ref. 27) of the U.S. male population, represented an estimated 2.6% of male blood donors. Although the data were determined by different methodologies, they suggested an increase in the proportion of blood donors reporting MSM behavior from 0.6% in 1993 and 1.2% in 1998. In the male blood donor survey, 83 of 3,183 respondents reported donating after male-to-male sexual contact. However, 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 those reporting regular MSM behavior (Ref. 28). This indicates that considerable self-selection likely took place in individuals who presented to donate.

5. Epidemiologic data from countries that had changed their deferral policy for MSM indicated no safety concerns (Refs. 29, 30). The most robust data measuring the impact of these policy changes came from Australia (Ref. 30). Australia has a voluntary blood donor system and a similar percentage of men reporting male-to-male sexual contact at some time during their lives as in the U.S. (5% compared with 7%) (Ref. 27). 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. 31).

Other information was considered in 2014 regarding alternatives to time-based deferral strategies, such as individual risk assessment. Data of concern at the time were that the rate of partner infidelity in ostensibly monogamous heterosexual couples and same-sex male couples was estimated to be about 25%, and that condom use was associated with a 1 to 2% failure rate per episode of anal intercourse (Refs. 32, 33, 34, 35). In addition, prevalence of HIV infection was significantly higher in MSM with multiple male partners compared with individuals who have only multiple opposite sex partners (Ref. 36).

Following careful review of all the options, it was ultimately determined that the available information was not sufficiently compelling to adopt the approach of individual risk assessment without further scientific evaluation of the validity of asking questions regarding monogamy or the use of safe sexual practices. Instead, the BOTS Working Group and ACBTSA and BPAC advisory committee opinions agreed that the available scientific evidence supported a move to a 12-month deferral period. At the same time, they recommended further study of alternatives to time-based deferrals. FDA subsequently also concluded that the available evidence strongly supported a change from the indefinite deferral to a 12-month blood donor deferral policy for MSM. This change was implemented in December 2015.

Even before the change in the blood donor deferral policy for MSM was made, the Transfusion Transmissible Infections Monitoring System (TTIMS) was implemented in the United States in order to facilitate monitoring of the safety of the U.S. blood supply for a variety of different

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pathogens following changes in donor deferral criteria that might be made (Ref. 37). FDA has used TTIMS to further investigate and develop information to facilitate the refinement of blood safety screening measures over the past several years.

Data from the two years following effective implementation of the 12-month donor deferral criteria for MSM comparing the rates of HIV in those donating blood indicate that there has been no increase in risk to the blood supply from the change that was made. Additionally, other countries, including the United Kingdom and Canada have moved to a 3-month deferral period for MSM, and to date, there have been no reports from these countries suggesting safety concerns following the implementation of this change. In fact, preliminary information communicated to FDA by foreign regulators indicates that compliance of MSM with the donor deferral criteria may be increased. The totality of the surveillance information and the experience with a 3-month deferral in other countries, combined with the uniform use of nucleic acid testing for HIV, HBV, and HCV, which can detect each of these viruses well within a 3-month period following initial infection, leads the agency to conclude that at this time a change to a recommended 3-month deferral is scientifically supported. FDA expects that this change will not be associated with any adverse effect on the safety of the blood supply, and it will continue to monitor the safety of the blood supply using the TTIMS.

In addition to the deferrals noted above for MSM, FDA has evaluated the available scientific evidence that could support modification of several other blood donor deferrals related to risk for HIV. Based on the experience in the United Kingdom and Canada, along with the detection characteristics of the nucleic acid testing noted above that has been implemented for HIV, HBV, and HCV, the agency has determined that the recommended deferrals for commercial sex work (CSW) and injection drug use (IDU) can be changed from indefinite deferrals to 3-month deferrals. In addition, for similar reasons, the 12-month deferral for a recent tattoo or piercing can be reduced to 3 months. FDA also believes that by aligning many of the deferrals to asking about a 3-month period, donor recall of events will be enhanced, and this could potentially enhance the safety of the blood supply.

To comply with global regulatory requirements on deferral policies, it is acknowledged that 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 all of FDA's recommended shortening of deferral policies noted in this guidance, and instead may elect to maintain longer deferral policies.

Finally, FDA remains committed to further investigating individual risk assessment as an alternative to time-based deferrals. A study of this approach is currently be initiated and should provide valuable information regarding the feasibility of implementing this approach in the future.

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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.

A. Donor Educational Material and Donor History Questionnaire

1. Blood establishments must provide donors educational material before each donation explaining the risk of HIV transmission by blood and blood products and risk factors associated with HIV infection so that donors can self-defer (see 21 CFR 630.10 (b)). 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.³ The educational material must 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 (see 21 CFR 630.10(b)). 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.
3. We recommend that the updated DHQ include the following elements to assess donors for risk:
 - a. A history ever of a positive⁴ test for HIV,
 - b. A history in the past three months of exchanging sex⁵ for money or drugs,
 - c. A history in the past three months of non-prescription injection drug use⁶,
 - d. A history in the past 3 months of sex with any of the following individuals: a person with a history ever of a positive test for HIV, a person with a history ever of exchanging sex for money or drugs,

³ See CDC website at <https://www.cdc.gov/hiv/basics/whatishiv.html>.

⁴ 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.

⁵ 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.

⁶ 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.

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- or a person with a history ever of non-prescription injection drug use,
- e. A history in the past 3 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 3 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 3 months of a tattoo, ear or body piercing,
 - h. A history in the past 3 months of syphilis or gonorrhea, or treatment for syphilis or gonorrhea,
 - i. For male donors: a history in the past 3 months of sex with another man,
 - j. For female donors: a history in the past 3 months of sex with a man who has had sex with another man in the past 3 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.

B. Donor Deferral

We recommend that you defer as follows:

1. Defer indefinitely an individual who has ever had a positive test for HIV⁷.
2. Defer for 3 months from the most recent event, an individual who has exchanged sex for money or drugs.
3. Defer for 3 months from the most recent event, an individual who has engaged in non-prescription injection drug use.
4. Defer for 3 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 3 months from the most recent allogeneic transfusion, any individual who has a history of receiving an allogeneic transfusion of Whole Blood or blood components.

⁷ 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)). Under 21 CFR 630.35(b), 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.

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6. Defer for 3 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 3 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 3 months of donation are eligible to donate without deferral 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 3 months of donation are eligible to donate without deferral if the piercing was done using single-use equipment.
8. Defer for 3 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 3 months.
9. Defer for 3 months from the most recent sexual contact, a man who has had sex with another man during the past 3 months.
10. Defer for 3 months from the most recent sexual contact, a female who has had sex during the past 3 months with a man who has had sex with another man in the past 3 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.

Note: Under 21 CFR 630.5 and 630.10(a), FDA requires 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.

C. Donor Requalification

1. A donor deferred for any of the factors in section III.B. 2-10 of this guidance may be eligible to donate after the 3-month deferral period, provided the donor meets all other donor eligibility criteria.
2. A donor previously deferred indefinitely for: exchanging sex for money or drugs, for engaging in non-prescription injection drug use, or, for a male donor, having sex with another man, may be eligible to donate, provided the donor meets all donor eligibility criteria.

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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.
 - 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”

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And,

“Caution: For Laboratory Research Only”

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:

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“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. 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 transfusion or for use in manufacturing 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 tests as necessary to reduce adequately and appropriately the risk of transmission of HIV-1 and HIV-2. FDA has considered the use of licensed 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 recommends the use of licensed HIV-1 nucleic acid donor screening tests to meet the requirements under 21 CFR 610.40(b).

You must defer a donor who tests reactive by a donor screening test for HIV-1 or HIV-2 (21 CFR 610.41) and 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 tests 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.

IV. IMPLEMENTATION

You may implement the recommendations once you have revised your DHQ, including the full-length and abbreviated DHQ, and accompanying materials to reflect the new donor deferral recommendations.

Licensed blood establishments must report changes to their approved application to FDA in accordance with 21 CFR 601.12.

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1. Licensed blood establishments that revise their DHQs and accompanying materials must report the change to FDA in a Changes Being Effected (CBE) Supplement under 21 CFR 601.12(c)(5) (see 21 CFR 601.12(a)(3)). The blood and blood components collected using the change may be distributed immediately upon receipt of the supplement by FDA. Include the following information in your CBE Supplement:
 - a. Form FDA 356h “Application to Market a New or Abbreviated New Drug, or Biologic for Human Use.”
 - b. Cover letter describing the request and contents of the supplement.
 - c. The DHQ and accompanying document(s). Please highlight the modifications.
2. Licensed blood establishments that implement a revised version of the DHQ and accompanying materials prepared by the AABB Donor History Task Force or the Plasma Proteins Therapeutic Association (PPTA) found acceptable by FDA must report the changes to FDA in an annual report under 21 CFR 601.12(d), noting the date the process was implemented.
3. Unlicensed establishments are not required to report this change to FDA.

Contains Nonbinding Recommendations

V. REFERENCES

1. Epstein JS, Jaffe HW, Alter HJ, Klein HG, Blood system changes since recognition of transfusion-associated AIDS, *Transfusion* 2013, 53:2365-2374.
2. Stramer SL, Dodd RY, Transfusion-transmitted emerging infectious disease: 30 years of challenges and progress, *Transfusion* 2013, 53:2375-2383.
3. Dubin C, Francis D, Closing the circle: a thirty-year retrospective on the AIDS/blood epidemic, *Transfusion* 2013, 53:2359-2364.
4. Centers for Disease Control and Prevention, Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A, *MMWR* 1982, 31:365-367.
5. Centers for Disease Control and Prevention, Epidemiologic Notes and Reports Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS)—California, *MMWR* 1982, 31:652-654.
6. Ginzburg HM, Intravenous drug users and the acquired immune deficiency syndrome, *Public Health Rep* 1984, 99:206-212.
7. Van de Perre P, Clumeck N, Carael M, Nzabihimana E, Robert-Guroff M, De Mol P, Freyens P, Butzler JP, Gallo RC, Kanyamupira JB, Female prostitutes: a risk group for infection with human T-cell lymphotropic virus type III, *The Lancet* 1985, 8454:524-527.
8. FDA Memorandum: Recommendations to Decrease the Risk of Transmitting Acquired Immune Deficiency Syndrome (AIDS) from Blood Donors, March 24, 1983.
9. Leveton LB, Sox Jr HC, Stoto MA, eds, *HIV and The Blood Supply: An Analysis of Crisis Decision Making*, Institute of Medicine, National Academy Press, Washington DC 1995.
10. Centers for Disease Control and Prevention, Current Trends Prevention of Acquired Immune Deficiency Syndrome (AIDS): Report of Inter-Agency Recommendations, *MMWR* 1983, 32:101-103.
11. Perkins HA, Busch MP, Transfusion-associated infections: 50 years of relentless challenges and remarkable progress, *Transfusion* 2010, 50:2080-2099.
12. Centers for Disease Control and Prevention, Update: Revised Public Health Service Definition of Persons Who Should Refrain from Donating Blood and Plasma – United States. *MMWR* 1985, 34(35); 547-548.
13. Ward JW, Grindon AJ, Feorino PM, Schable C, Parvin M, Allen JR, Laboratory and epidemiologic evaluation of an enzyme immunoassay for antibodies to HTLV-III, *JAMA* 1986, 256:357-361.

Contains Nonbinding Recommendations

14. Zou S, Stramer SL, Dodd RY, Donor testing and risk: current prevalence, incidence, and residual risk of transfusion-transmissible agents in US allogeneic donations, *Transfus Med Rev* 2012, 26:119-128.
15. Klamroth R, Gröner A, Simon TL, Pathogen inactivation and removal methods for plasma-derived clotting factor concentrates, *Transfusion* 2014, 54:1406-1417.
16. FDA Blood Products Advisory Committee Meeting, December 11-12, 1997, <https://wayback.archive-it.org/7993/20170403222342/https://www.fda.gov/ohrms/dockets/ac/cber97t.htm>.
17. FDA Workshop on Donor Suitability, 1998, <https://www.govinfo.gov/content/pkg/FR-1998-11-10/pdf/98-30006.pdf>.
18. FDA Blood Products Advisory Committee Meeting, September 14-15, 2000, <https://wayback.archive-it.org/7993/20170403222326/https://www.fda.gov/ohrms/dockets/ac/cber00.htm#Blood%20Prducts>.
19. FDA Workshop on Behavior-Based Donor Deferral in the NAT Era, 2006, <https://www.federalregister.gov/documents/2006/02/07/E6-1588/behavior-based-blood-donor-deferrals-in-the-era-of-nucleic-acid-testing-public-workshop-request-for>.
20. HHS Advisory Committee on Blood Safety and Availability Meeting, 2010, https://wayback.archive-it.org/3919/20140402193351/http://www.hhs.gov/ash/bloodsafety/advisorycommittee/recommendations/06112010_recommendations.pdf.
21. *Federal Register* Notice, “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) <https://www.federalregister.gov/articles/2012/03/13/2012-6091/request-for-information-rfi-on-design-of-a-pilot-operational-study-to-assess-alternative-blood-donor>.
22. AABB on Quarantine Release Errors, White Paper 2013, <https://www.aabb.org/research/whitepapers/Documents/quarantine-release-errors-white-paper.pdf#search=qre>.
23. FDA workshop on Quarantine Release Errors in Blood Establishments, September 2011, <https://www.federalregister.gov/documents/2011/07/19/2011-18093/quarantine-release-errors-in-blood-establishments-public-workshop>.
24. Advisory Committee on Blood and Tissue Safety and Availability, Results from the Uniform Donor History Questionnaire, December 2013, https://www.hhs.gov/ash/bloodsafety/advisorycommittee/acbtsa_201312meeting_agenda.html.
25. Custer B, Kessler D, Vahidnia F, Leparc G, Krysztof DE, Shaz B, Kamel H, Glynn S, Dodd RY, Stramer SL; NHLBI Retrovirus Epidemiology Donor Study-II (REDS-II),

Contains Nonbinding Recommendations

- Risk factors for retrovirus and hepatitis virus infections in accepted blood donors, *Transfusion*. 2015; 55:1098-1107.
26. Custer B, Sheon N, Siedle-Khan B, Pollack L, Spencer B, Bialkowski W, D'Andrea P, Sullivan M, Glynn S, Williams A, for the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) Blood donor deferral for men who have sex with men: the Blood Donation Rules Opinion Study (Blood DROPS). *Transfusion*. 2015; 55:2826-2834.
 27. Purcell DW, Johnson CH, Lansky A, Prejean J, Stein R, Denning P, Gaul Z, Weinstock H, Su J, Crepaz N, Estimating the population size of men who have sex with men in the United States to obtain HIV and syphilis rates, *Open AIDS J* 2012, M6:98-107.
 28. Benjamin RJ, et al, Deferral of males who had sex with other males, *Vox Sanguinis* 2011, 101:339-367.
 29. Offergeld R, et al, Sexual risk behavior and donor deferral in Europe, *Vox Sanguinis* 2014, 107:420-427.
 30. Seed CR, Kiely P, Law M, Keller AJ, No evidence of a significantly increased risk of transfusion-transmitted human immunodeficiency virus infection in Australia subsequent to implementing a 12-month deferral for men who have had sex with men, *Transfusion* 2010, 50:2722-2730.
 31. Lucky TTA, Seed CR, Waller D, Lee JF, McDonald A, Wand H, Wroth S, Shuttleworth G, Keller AJ, Pink J, Wilson DP, Understanding noncompliance with selective donor deferral criteria for high-risk behaviors in Australian blood donors, *Transfusion* 2014, 54:1739-1749.
 32. Mark KP, Janssen E, Milhausen RR, Infidelity in heterosexual couples: demographic, interpersonal, and personality-related predictors of extradyadic sex, *Arch Sex Behav* 2011, 40:971-982.
 33. Stone E, Heagerty P, Vittinghoff E, Douglas JM Jr, Koblin BA, Mayer KH, Celum CL, Gross M, Woody GE, Marmor M, Seage GR III, Buchbinder SP, Correlates of condom failure in a sexually active cohort of men who have sex with men, *J Acquir Immune Defic Syndr Hum Retrovirol* 1999, 20:495-501.
 34. Weller S, Davis-Beaty K, Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database of Systematic Reviews* 2002. (1):CD003255.
 35. Smith DK, Herbst JH, Zhang X, Rose CE, Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States, *J Acquir Immune Defic Syndr* 2015, 68(3):337-344.
 36. CDC, Estimated HIV incidence in the United States, 2007–2010. *HIV Surveillance Supplemental Report* 2012; 17(No. 4). Published December 2012.

Contains Nonbinding Recommendations

37. Custer B, Stramer SL, Glynn S, Williams AE. Transfusion-transmissible infection monitoring system: a tool to monitor changes in blood safety. *Transfusion*. 2016; 56:1499-1502.