Addendum for:
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Screening Blood Donors with the Donor History Questionnaire, 2nd edition
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Update on US FDA Guidance Documents, March 2020-May 2023

This addendum to *Screening Blood Donors with the Donor History Questionnaire*, which was published in 2019, serves to update several of the chapters with the changes in donor eligibility recommendations that occurred in the ensuing 3 years.

During the unprecedented COVID-19 public health emergency (PHE) in March 2020, the US FDA released several guidance documents that provided revised recommendations on donor eligibility assessment, to address the serious disruptions caused by the SARS-CoV-2 pandemic and immediate need for blood donations, while simplifying the screening process and maintaining the safety of the blood supply.

In April 2020, the following guidance documents were released for immediate implementation:

- Revised recommendations to reduce the risk of transfusion-transmitted malaria (April 2020, reissued in December 2022 to continue after the PHE)
- Revised recommendations for reducing the risk of human immunodeficiency virus (HIV) transmission by blood and blood components (April 2020 and updated August 2020)

Also in April 2020, FDA finalized the following guidance document, and provided a further update in May 2022, to remove the geographic deferrals for possible risk of vCJD:

- Recommendations to reduce the possible risk of transmission of Creutzfeldt-Jakob disease and variant Creutzfeldt-Jakob (vCJD) disease by blood and blood components (May 2022)

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This addendum reflects the views of A. Eder and M. Goldman and should not be construed to represent views or policies of the FDA or Canadian Blood Services.

In December 2020, FDA updated the 2014 syphilis guidance, to shorten the recommended deferral period following treatment for syphilis or gonorrhea to 3 months, for consistency with the 3-month deferral for behavioral risk factors in the aforementioned 2020 HIV guidance. In addition, the guidance added a recommendation for reentry of donors with false positive screening test results who are subsequently determined to have never had a diagnosis of syphilis and removed the recommendation for donors to provide written evidence of completion of syphilis treatment prior to reentry.

In January 2023, FDA issued draft guidance entitled "Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products" that eliminates the specific questions for men who have sex with men (MSM) and for women who have sex with MSM and introduces individual, risk-based assessment regardless of the donors' gender. Donors who report a history of having a new sexual partner, or more than one sexual partner, and anal sex in the last 3 months would be deferred. Finalized in May 2023, this guidance supersedes the aforementioned 2020 HIV guidance, issued in April 2020 and updated in August 2020.

Also of note during this period, although unrelated to the DHQ,, FDA eliminated the requirement to test all donations for Zika virus in May 2021.

Herein, is a brief summary and comparison tables of the revised recommendations for donor eligibility assessment that changed over 2020-2023, in the order of the book chapters in which they appear.

Chapter 7 Update: HIV Risk Factors and Individual Risk-based Assessment

FDA revised the recommendations to reduce the risk of transfusion-transmitted HIV (Table 7-1) in 2020, as summarized in the updated Table, below. The changes in this guidance also address risks of transfusion-transmitted hepatitis, previously covered in Chapter 8 (Table 8-1).In addition, FDA issued a draft guidance in January 2023, that was finalized in March 2023, with recommendations to eliminate the gender-specific questions for men who have sex with men (MSM) and women who have sex with MSM, and replace them with questions based on individual, risk-based assessment regardless of sex or gender, for having a new sexual partner, or more than one sexual partner, and anal sex in the last 3 months.

In the May, 2023 Guidance, FDA evaluated the available scientific information to inform the individual risk-based recommendations, including the following sources:

- Surveillance of blood supply by the Transfusion-transmissible Infection Monitoring System (TTIMS)
- Experience in United Kingdom (UK) and Canada with risk-based assessment
- Data from PrEP randomized clinical trials on breakthrough HIV infections and delayed detection
- Performance characteristics of nucleic acid testing for HIV

- Information from the ADVANCE study (Assessing Donor Variability and New Concepts in Eligibility)

FDA concluded that the totality of the surveillance information and the experience with a 3-month deferral in the U.K., Canada, and other countries, combined with the uniform use of nucleic acid testing for HIV, HBV, and HCV, which can detect each of these viruses within a 3-month period following initial infection, supported the recommendations (Updated Table 7-1, below).

In addition, in the May, 2023 guidance FDA recommended deferral of any individual taking medications to treat or prevent HIV infection (i.e., pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and antiretroviral therapy (ART)). This deferral is already in place in most U.S. blood centers and in many other countries. The antiretroviral drugs can reduce the HIV viral load of individuals to levels that are undetectable by nucleic acid testing. Although "undetectable equals untransmissible" for sexual transmission, this does not apply to transfusion transmission of HIV. The antiretroviral drugs do not fully eliminate the virus from the body, and donated blood from individuals infected with HIV taking ART can potentially still transmit HIV to a transfusion recipient. Further, the available data demonstrate that the use of PrEP and PEP may delay detection of HIV by currently licensed screening tests for blood donations, potentially resulting in false negative results.

FDA expects implementation of these revised recommendationswill maintain the safety of the blood supply without appreciably affecting the available donor base. Specifically, a statistical model estimated the effect of the risk-based deferral policy on current donor base will resultin less than 2% additional deferrals (Whitaker et al., ISBT abstract, 2023).

Updated Table 7-1: FDA Recommended deferrals to Reduce the Risk of HIV Transmission Through Blood and Blood Components

Risk Category	**Deferral Recommendations[1] in FDA Guidance**			
	Memorandum April 23, 1992	**December 2015**	**April 2020 (Updated August 2020)**	**May 2023**
Clinical or laboratory evidence of AIDS (HIV infection)	Permanent	Positive test for HIV, Permanent	No change[2]	No change
Taken medication to treat an HIV infection (i.e., antiretroviral therapy)	N/A[3]	N/A	N/A	Permanent
(For Men): Sex with another man	Indefinite, for MSM even once since	12 months	3 months	Removed

	1977			
More than one sexual partner in the last 3 months and anal sex	N/A	N/A	N/A	3 months
New sexual partner in the last 3 months and anal sex	N/A	N/A	N/A	3 months
Taken any medication by mouth (oral) to prevent HIV infection (i.e., short-acting PrEP or PEP)	N/A	N/A	N/A	3 months
Taken any medication by injection to prevent HIV infection (i.e., long-acting PrEP or PEP)	N/A	N/A	N/A	2 years
Engaged in non-prescription injection drug use	Indefinite	No change	3 months	No change
Exchanged sex for money or drugs	Indefinite, since 1977	No change	3 months	No change
Recipient of clotting factor concentrates	Indefinite	No deferral, unless underlying hematologic condition is a cause for deferral	No change	No change
Sexual contact with a person who has ever had a positive test for HIV	12 months	12 months	3 months	No change
(For women): Sexual contact with a man who had sex with another man	12 months	12 months	3 months	Removed
Sexual contact with person who engaged in non-prescription injection drug use	12 months	No change	3 months	No change
Sexual contact with person who has exchanged sex for money or drugs	12 months	No change	3 months	No change
Sexual contact with recipient of clotting factor concentrates	12 months	Removed (no deferral)	N/A	N/A
Treatment for syphilis or gonorrhea	12 months	No change	3 months	No change
Recipient of allogeneic blood transfusion	12 months	No change	3 months	No change

Contact with someone else's blood through percutaneous inoculation (e.g., needlestick) or through mucous membrane contact	12 months	No change	3 months	No change
Tattoo, unless applied by a state-regulated entity with sterile needles and single use ink; Ear and body piercing, unless applied with single use equipment	N/A	12 months	3 months	No change
Institutionalization for at least 72 hours consecutively in an institutional facility4	12 months[4]	No change	No change	No change

[1] All deferral periods are from date of the most recent exposure or risk behavior.
[2] No change from previous guidance
[3] N/A, – not addressed [4] The requirement for a 12-month deferral was introduced in a Memorandum to All Registered Blood Establishments on June 8, 1995, because "incarceration in a correctional institution is associated with behaviors, such as intravenous drug abuse that indicate an increased risk of transfusion transmitted disease"; in 2015, the requirement was codified under 21 CFR 630.10 (e)(1)(iv).

Chapter 9 Update: Travel and Related Health History:
Malaria and variant Creutzfeldt-Jakob Disease

A. Malaria:

FDA revised the recommendations to reduce the risk of transfusion-transmitted malaria (Chapter 9, page 169) in April 2020 during the COVID-19 public health emergency and reissued the recommendations in December 2022 to continue after the public health emergency, as summarized in the Table 1, below.

The recommendation for a shorter 3-month deferral, instead of a 12-month deferral, for a donor who is a resident of a country in which malaria is not endemic (non-endemic country) and who has traveled to a malaria-endemic area is largely based on the small likelihood of asymptomatic infection. CDC surveillance data demonstrates that more than 90% of imported malaria cases develop clinical symptoms within 3 months and only a small percentage remain asymptomatic beyond 3 months.

The recommendations also describe an alternative procedure to donor deferral. Blood establishments can collect components from otherwise eligible donors who are residents of malaria non-endemic countries and have traveled to a malaria-endemic area, provided the establishments use an FDA-approved pathogen reduction device that demonstrate effective reduction of *Plasmodium falciparum* for plasma or platelet components, according to the instructions for use of the device.

The guidance also recommended a 3-month deferral, instead of a 12-month deferral from the time of return to a non-endemic country, for a donor who was a prior resident of a malaria-endemic country and who had not traveled to a malaria-endemic area for *3 or more consecutive years* preceding the most recent travel to a malaria-endemic area. This recommendation is based on the available information that clinical immunity wanes after 3 or more continuous years of residence in a non-endemic country, such that a prior resident of a malaria-endemic country may be considered to be a resident of a non-endemic country for the purposes of screening blood donors.

Table 1: Comparison of Recommendations in 2013 (Updated 2014) and 2020 to Reduce the Risk of Transmission of Malaria through Blood and Blood Components

Risk Category	**Deferral [1] Recommendations in FDA Guidance**	
	August 2013 Updated August 2014	**April 2020 (PHE guidance) December 2022**
Resident of a country that is non-endemic for malaria, who travels to a malaria-endemic area	1 year	3 months (or pathogen reduction for platelets and plasma)
Resident[2] of a malaria-endemic country	3 years	3 years
Prior resident[2] of a malaria-endemic country (who has spent less than 3 consecutive years in non-endemic countries), who travels to a malaria-endemic area	3 years	3 years
Prior resident[2] of a malaria-endemic country (who has spent 3 or more years consecutively in non-endemic countries), who travels to a malaria-endemic area	1 year	3 months (or pathogen reduction for platelets and plasma)
Diagnosis of malaria[3]	3 years	3 years

[1] Deferral is from date of departure from malaria-endemic area or malaria-endemic country
[2] Residence is defined as a continuous stay of longer than 5 years in a country or countries having any malaria-endemic area
[3] Deferral after history of malaria provided donor has been free from malaria for at least 3 years while residing in malaria non-endemic country

B. CJD and vCJD

FDA revised the recommendations to reduce the possible risk of transfusion transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) (Chapter 9, page 177) in April 2020 (updated in August 2020). FDA subsequently issued another guidance in May 2022 with revised recommendations, as summarized in Table 2, below.

FDA's decision in 2022 to eliminate the geographic-based deferrals was based on its assessment of new data and mathematical models regarding the effect of donor deferral for geographic risk in the UK, France, and Ireland on blood safety. FDA concluded that the new policy would expose transfusion recipients to no or minimal additional risk of vCJD in the future; for blood components that are leukocyte reduced, the possible risk is even further reduced. Consequently, FDA removed the geographic deferral recommendations from the guidance.

Table 1: Comparison of Recommendations in 2016, 2020, and 2022 Guidance Documents

May 2010 (Updated January 2016)	**April 2020 (Updated August 2020)**	**May 2022**
Defer permanently donors who have been diagnosed with vCJD or any other form of CJD. [1]	No change[2]	No change
Defer permanently donors if they have received: • A dura mater transplant.	Revised to clarify the source of tissue that is a cause for deferral:	No change

• an injection of human cadaveric pituitary-derived growth hormone (hGH).	• Defer permanently a donor who has received a human cadaveric (allogeneic) dura mater transplant. • Defer permanently a donor who received cadaveric pituitary hGH [3].	
Defer indefinitely donors with one or more blood relatives diagnosed with CJD.	Defer permanently a donor who has a blood relative diagnosed with familial prion disease (e.g., fCJD, GSS, or FFI). [1]	No change
Defer indefinitely donors who have spent 3 months or more in U.K. from 1980-1996.	No change	Removed
Defer indefinitely donors who have spent 5 years or more cumulatively in France from 1980 – present.	Defer indefinitely a donor who has spent 5 or more years cumulatively in France or Ireland from the beginning of 1980 to the end of 2001.	Removed
Defer indefinitely former or current U.S. military personnel, civilian military personnel, and their dependents, for residence on: • U.S. military bases in Northern Europe (Germany, U.K., Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or • U.S. military bases elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996.	Removed	No change
Defer indefinitely donors with a history of transfusion in the U.K. or France from 1980 – present.	Defer indefinitely a donor with a history of transfusion in the U.K. (i.e., England, Northern Ireland, Scotland, the Isle of Man, the Channel Islands, Gibraltar, or the Falkland Islands), France, or Ireland from the beginning of 1980 to present.	Removed

Defer indefinitely donors who have injected bovine insulin since 1980, unless you can confirm that the product was not manufactured after 1980 from U.K. cattle.	Removed	No change
Defer indefinitely donors who have spent 5 years or more in Europe from 1980 - present.	Removed	No change

[1] FDA does not recommend questioning donors for vCJD, CJD, or any other TSE or for blood relatives with familial prion disease (e.g., fCJD, GSS, or FFI) because of the inability to identify asymptomatic individuals harboring TSEs, the rarity of the conditions, and the available evidence from lookback studies that have not identified a case among recipients of blood from infected donors. However, individuals that volunteer such information should be permanently deferred.
[2] No change from prior guidance

[3] The prevalence of individuals who might have been exposed to cadaveric pituitary hGH is very low among blood donors, and the transmission risk of CJD by blood components remains theoretical. However, individuals that volunteer such information should be permanently deferred.

Chapter 11 Update: Deferral and Reentry recommendations for Reactive Screening Tests for Syphilis

FDA updated the 2014 syphilis guidance in December 2020 to shorten the recommended deferral period following treatment for syphilis or gonorrhea to 3 months, making it consistent with the 3-month deferrals for risk factors in the August 2020 HIV guidance.

In addition, the December 2020 guidance added a recommendation for reentry of donors with false positive screening test results who are subsequently determined to have never had a diagnosis of syphilis and removed the recommendation for donors to provide written evidence from a physician or public health clinic of completion of known, effective treatment for syphilis prior to reentry.

We have provided the recommendations for reentry of donors after reactive screening test results in the Updated Table 11-2.

Updated Table 11-2 Reentry after Reactive Syphilis (*Treponema pallidum*) Screening Tests

Screening Test Result Index Donation	**Eligible for Reentry**	**Required for Reentry**	
	Test results on index donation or follow-up sample collected at a later date	**Minimum interval**	**2020 Criteria or Recommendation**

Nontreponemal screening test - REACTIVE[1]	Treponemal test – NEGATIVE	N/A	Donor may be reentered[3]
	Treponemal test – POSITIVE	3 months after completion of treatment for syphilis	Donor may be reentered if : • the donor subsequently reports being treated for syphilis, provided that the treatment was successfully completed at least 3 months before the next donation and the donor meets all donor eligibility criteria OR • the blood center's responsible physician determines that the donor never had syphilis, based on subsequent medical evaluation and diagnostic testing for syphilis (i.e., previous test results were falsely positive) and the donor meets all eligibility criteria.
Treponemal screening test-REACTIVE[2]	• Different FDA-cleared treponemal screening test – NEGATIVE	N/A	Donor may be reentered[3]
	• Different FDA-cleared treponemal screening test – POSITIVE • Non-treponemal test – NEGATIVE (consistent with recovery or cure from a previous syphilis infection)	3 months after completion of treatment for syphilis	Donor may be reentered if : • the donor subsequently reports being treated for syphilis, provided that the treatment was successfully completed at least 3 months before the next donation and the donor meets all donor eligibility criteria [4] OR • the blood center's responsible physician determines that the donor never had syphilis, based on subsequent medical evaluation and diagnostic testing for syphilis (i.e., previous test results were falsely positive) and the donor meets all eligibility criteria.

	• Different FDA-cleared treponemal screening test – POSITIVE • Non-treponemal test – POSITIVE (consistent with an active or recently treated syphilis infection)	3 months after completion of treatment for syphilis	Donor may be reentered if : • the donor subsequently reports being treated for syphilis, provided that the treatment was successfully completed at least 3 months before the next donation and the donor meets all donor eligibility criteria[4] OR • the blood center's responsible physician determines that the donor never had syphilis, based on subsequent medical evaluation and diagnostic testing for syphilis (i.e., previous test results were falsely positive) and the donor meets all eligibility criteria.

[1]Nontreponemal screening tests include rapid plasma reagin (RPR) test, venereal disease research laboratory (VDRL) test. The term "reactive" includes "repeatedly reactive results," as defined in the manufacturer's instructions in the package insert.
[2]Treponemal screening tests include enzyme immunoassay (EIA); fluorescent treponemal antibody absorbed (FTA-ABS) assays, *T. pallidum* microhemagglutination (MHA-TPA) assays; *T. pallidum* particle agglutination (TP-PA) assays. The term "reactive" includes "repeatedly reactive results," as defined in manufacturer's instructions in package insert.
[3]Test the reentered donor's next donation and subsequent donations with FDA-cleared treponemal or nontreponemal screening test.
[4] If the donor was not treated for syphilis or was not medically evaluated for reentry, they remain indefinitely deferred.

References

All FDA blood guidance documents are available on the FDA website at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/blood-guidances, including the following:

- Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products; Draft Guidance for Industry
  1/2023

- Recommendations to Reduce the Risk of Transfusion-Transmitted Malaria; Guidance for Industry
  12/2022
- Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components; Guidance for Industry
  (Updated May 23, 2022) - 5/2022
- Information for Blood Establishments Regarding FDA's Determination that Zika Virus is no Longer a Relevant Transfusion-Transmitted Infection, and Withdrawal of Guidance titled "Revised Recommendations for Reducing the Risk of Zika Virus Transmission by Blood and Blood Components"
  5/2021
- Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis; Guidance for Industry
  12/2020
- Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products - Guidance for Industry
  (Updated August 27, 2020) - 8/2020