Recommendations to Reduce the Risk of Transmission of Hepatitis C Virus (HCV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
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Table of Contents

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I. INTRODUCTION

We, FDA or Agency, are issuing this guidance to assist you, establishments making donor eligibility determinations,[1] in understanding the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps).[2]

This guidance applies to human cells and tissues recovered on or after May 25, 2005, the effective date of the regulations contained in 21 CFR part 1271, subpart C, and provides recommendations to reduce the risk of transmission of hepatitis C virus (HCV) by HCT/Ps. This guidance updates information regarding HCV risk included in the guidance entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry," dated August 2007 (August 2007 HCT/P DE Guidance), by revising recommendations for: 1) donor screening that includes reducing certain time-based risk factors and conditions, and 2) assessing every HCT/P donor for HCV risk using the same individual risk-based questions for every donor regardless of sex.

When finalized, this guidance will provide, specific recommendations for HCT/P donor testing and screening for risk associated with HCV infection and supersede information regarding HCV risk in the August 2007 HCT/P DE Guidance.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic

[1] See 21 CFR 1271.50.

[2] HCT/Ps are defined in 21 CFR 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."

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

Hepatitis C virus (HCV) is a single-stranded ribonucleic acid (RNA) enveloped virus and HCV infection is a major global public health problem (Refs. 1-5). According to the World Health Organization (WHO), 50 million people are chronically infected with HCV worldwide and approximately 242,000 died in 2022, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer), as a result of their HCV infection (Ref. 1).

During 2022, in the United States (U.S.), a total of 4,828 cases of acute hepatitis C were reported to the Centers for Disease Control and Prevention (CDC) by 46 states. After adjusting for under-ascertainment and under-reporting, CDC estimated there were 67,400 HCV infections in 2022 (Ref. 6). Between the years 2017 and 2020, an estimated 2.4 million people were living in the U.S. who were infected with HCV (Ref. 7).

Extrahepatic diseases, such as cryoglobulinemia, renal disease, lymphoma, diabetes, cardiovascular and dermatologic disorders, have been associated with chronic HCV infection and can range from mild to severe and life-threatening (Refs. 8-18). Although the frequency of such findings is uncertain, they are not uncommon. In one small study of 321 HCV patients, extrahepatic diseases were seen in 38% of those infected with HCV (Ref. 8). The annual mortality rate has been calculated at roughly 4% among patients with HCV-related cirrhosis and 30% in patients with HCV who subsequently developed hepatocellular carcinoma (Ref. 18).

III. DISCUSSION

In the Federal Register of May 25, 2004 (69 FR 29786), FDA issued a final rule entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (21 CFR part 1271, subpart C), which took effect on May 25, 2005. In this final rule, FDA identified HCV as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(1). Thus, for donors of HCT/Ps recovered on or after May 25, 2005, screening and testing for HCV is required (21 CFR 1271.75(a)(1)(iii) and 1271.85(a)(4)). Specific tests for HCV, and donor screening for specific risk factors and conditions associated with HCV infection, have been recommended for HCT/P donors in order to adequately and appropriately reduce risk of transmission. Specific recommendations for donor testing and screening for risk associated with HCV were issued in the August 2007 HCT/P DE Guidance.

A. Risk of Transmission

There is a risk of transmission of HCV by HCT/Ps. This is supported by reported cases of HCV transmission via transfusion of blood products, by organ transplantation, and from the use of HCT/Ps.

HCV is transmitted primarily through parenteral exposure to infectious blood or body fluids that contain blood. Possible exposures include injection-drug use, which is currently the most common mode of HCV transmission in the U.S., but other routes of exposure include birth to an HCV-infected mother, sex with an HCV-infected person, sharing personal items contaminated with infectious blood (e.g., razors or toothbrushes), health-care procedures that involve invasive procedures, such as injections where there have been breakdowns in infection control practices, unregulated tattooing or ear/body piercing, receipt of infected donated blood or blood products, needlestick injuries in healthcare settings, and intranasal drug use (Refs. 19-49). HCV transmission has also occurred through transplantation of solid organs (Refs. 50-58) and the transplantation, implantation, or infusion of various types of human cells or tissues (Refs. 55-57, 59-62). Although the prevalence rate of HCV in U.S. tissue donors has been estimated to be lower than in the general population, the estimated probability of undetected viremia at the time of donation is higher among tissue donors than among first-time blood donors (Ref. 63).

1. Potential for Transmission of HCV by Blood Products and Solid Organs

HCV can be transmitted by blood, blood products and solid organs (Refs. 32-33, 50-58). Now that more advanced screening tests for HCV are used by blood establishments, the risk of transmission to a recipient of blood or blood products is considered extremely low, with an estimated risk of less than or equal to one per 1 million donors for undetected HCV infection (Ref. 64).

Beginning in September 1985, FDA recommended that blood establishments indefinitely defer male donors who have had sex with another male, even one time, since 1977, because of the strong clustering of AIDS and the subsequent discovery of high rates of HIV infection among MSM (Ref. 15). FDA subsequently concluded that the available evidence supported a change from the indefinite deferral for MSM, and in December 2015, recommended the 12-month deferral for MSM.

While the studies used to support blood donor deferral recommendations (e.g., ADVANCE study, risk assessments) are not specific to HCT/Ps, they are nonetheless relevant beyond blood donation. These studies considered certain risk factors associated with blood donors acquiring HIV, which are also risk factors for acquiring HCV.

In 2014, FDA launched the Transfusion Transmissible Infections Monitoring System (TTIMS), - a program implemented in the U.S. in order to facilitate monitoring blood safety, particularly in the context of changes in blood collection policy and practice. Following implementation of a 12-month blood donor deferral policy in December 2015 for men who have sex with men (MSM), four years of data from TTIMS indicated there had been no increase in risk to the blood supply from the policy change (Refs. 64-67). Additionally, other countries, including the United Kingdom and Canada moved to a 3-month deferral period for MSM, after which, there were no reports from these countries suggesting safety concerns following the implementation of this change. Thereafter, FDA reduced the recommended blood donor deferral period to 3 months for MSM, through recommendations published in guidance in April 2020 (Ref. 67).

In addition to shortening the recommended deferral period for MSM, FDA concurrently 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 NAT noted above, in April 2020, FDA also revised the recommended deferrals for individuals who exchange sex for money or drugs or engage in non-prescription injection drug use from indefinite to 3-month deferrals. In addition, for similar reasons, the recommended 12-month deferral for other risk factors, including contact with another person's blood, receipt of a blood transfusion or a recent tattoo or piercing, was revised to 3 months.

FDA subsequently helped facilitate and fund the ADVANCE (Assessing Donor Variability and New Concepts in Eligibility) study, a pilot study intended to evaluate individual risk assessment strategies as an alternative to time-based deferrals for MSM (Ref. 68). The ADVANCE study examined a number of HIV risk factors, such as anal sex and rates of HIV infection among MSM study participants.

FDA also recognized that other countries with similar HIV epidemiology as the U.S. revised their donor eligibility criteria for MSM, based on risk assessments performed in these countries. Notably, the United Kingdom in 2021 and Canada in 2022 introduced a new approach for donor questioning based on individual risk factors (Refs. 69-73). The approach is based on surveillance, epidemiology, and risk assessments that demonstrate that new or multiple sexual partners, and for those with new or multiple partners, anal sex, are the most significant risk factors that increase the likelihood of HIV infection (Refs. 69-74). The United Kingdom and Canada have adopted an individual risk-based approach that asks all presenting blood donors (regardless of sex), if they have had a new sexual partner or more than one sexual partner in the last 3 months, and if so, they are asked if they had anal sex (Refs. 71, 75). Individuals who report having a new sexual partner and anal sex or having more than one sexual partner and anal sex in the

last three months are deferred from blood donation. The United Kingdom and Canada have not reported safety concerns following the implementation of this individual risk-based deferral policy.

Subsequently, FDA concluded that implementing an individual risk-based approach will maintain the safety of the blood supply and in May 2023, FDA issued guidance that (1) recommends eliminating the blood donor screening questions specific to MSM and women who have sex with MSM; and (2) recommends assessing blood donor eligibility using the same individual risk-based questions relevant to HIV risk for every donor regardless of sex (Ref. 67).

Other federal agencies have also reconsidered the transmission risk of HCV through solid organs because transmission of HCV infection has been reported after solid organ transplantation (Refs. 50-58). When quantifying risk of transmission of an undetected HCV infection from an organ donor with an HCV risk factor, the probability has been estimated to be fewer than one per 1 million when the donor was additionally screened by testing using a nucleic acid test (NAT) for HCV at least 7 days after the donor's most recent exposure (Ref. 76). In addition, guidelines for assessing solid organ donors and monitoring transplant recipients for risk of HCV (as well as human immunodeficiency virus (HIV), and hepatitis B virus (HBV)) infection have evolved (Ref. 77). An evidence-based process was used to update guidelines that included developing key questions to evaluate behavioral and non-behavioral risk factors associated with transmission of these viruses, and an exhaustive literature review was undertaken where they were categorized according to strength and data quality, and evidence was graded. Organ donor screening guidelines were revised to identify donors at risk for acquiring a recent HIV, HBV, or HCV infection (Ref. 78).

2. Potential for Transmission of HCV by HCT/Ps

HCV has been transmitted by HCT/Ps, including from frozen bone, frozen tendon, cryopreserved blood vessels (i.e., saphenous vein), cryopreserved non-valved cardiac tissue (a patch), hematopoietic stem cell products (Refs. 55-57, 59-62), and has been detected in semen (Ref. 79).

Advances in HCV donor testing (e.g., HCV antibody assays, and HCV NATs) have reduced the "window period" when HCV RNA and/or HCV antibody are not detectable by screening tests (Refs. 77-78, 80-86). Using NAT, HCV RNA is generally detected in blood approximately 1 to 3 weeks after infection but may be detected in as little as 3 to 5 days (Refs. 7, 33, 77, 81-83, 87-91).

Formal studies and collection of data specific to HCT/P donors are lacking, however, many of the studies used to support blood donor deferral recommendations (e.g., ADVANCE study, risk assessments, etc.) are relevant beyond blood donation. These studies considered certain risk factors associated

with donors acquiring HIV, and the same risk factors associated with acquiring HIV are relevant to screening not only blood donors but also donors of HCT/Ps. Further, many of the key risk factors for acquiring HIV are also risk factors for acquiring HCV. In addition, the evidence-based process used to update organ donor screening guidelines that evaluated behavioral and non-behavioral risk factors associated with transmission of HIV, HBV, or HCV, for which a number of risk factors overlap, provides substantial support to identify donors at risk for acquiring a recent infection. Having a recent infection is relevant to risk of transmission presented by HCT/P donors in addition to organ donors. Given these data, experience with a 3-month blood donor deferral in other countries, and the uniform use of HCV NAT for testing HCT/P donors (which can detect HCV well within a 3-month period following initial infection), the Agency concludes, at this time, that a change to a recommended 3-month risk period as detailed below is scientifically supported for certain risk factors and conditions associated with HCV for donors of HCT/Ps (Refs. 77-78).

Additionally, based on our review of the available science, adequacy of available test methods, studies used to evaluate risk behaviors, and experiences with updated blood donor screening questions, FDA also recommends eliminating the HCT/P donor screening questions specific to MSM and women who have sex with MSM and, instead, recommends assessing every HCT/P donor for HCV risk using the same individual risk-based questions relevant to HCV risk regardless of sex.

B. Severity of Effect

Acute hepatitis C is rarely fulminant or fatal; many cases are asymptomatic and go undetected (Refs. 3, 6, 32, 80, 92). Approximately 50-80% of those infected will develop chronic hepatitis C whereas 20-50% will spontaneously resolve their illness (Refs. 3, 6, 32, 80, 87).

Chronic infection with HCV can lead to severe liver disease and complications such as advanced fibrosis, cirrhosis, hepatocellular carcinoma, and death. As a result, HCV infection is the most common indication for liver transplantation in the U.S. (Refs. 3-4, 80, 92). In 2017, there were an estimated 17,253 HCV-associated deaths reported from among 325.7 million U.S. residents correlating to an age-adjusted, HCV-associated death rate of 4.13 (95% CI, 4.07–4.20) deaths per 100,000 population (Ref. 6).

C. Availability of Appropriate Screening and/or Testing Measures

As described above, appropriate donor screening measures have been developed for HCV and specific details are listed below for screening a donor for clinical and physical evidence, and risk factors and conditions to reduce the risk of transmission of HCV.

FDA-licensed donor screening tests to detect antibodies to HCV (anti-HCV) and to detect HCV viral nucleic acid (using NAT) are available for screening cadaveric (non-heart-beating) and/or living donors of HCT/Ps.

The addition of NAT to screen HCT/P donors significantly reduces the risk of transmission of HCV (Refs. 63, 77, 81-83, 94-95). The probability of detecting HCV viremia at the time of tissue donation has been estimated to be reduced from 1 in 42,000 to 1 in 421,000 when individual HCV NAT is used (Ref. 63). An FDA-licensed donor screening NAT for HCV can detect an earlier stage of HCV infection than hepatitis C antibody tests. HCV RNA may be detected within 1 to 3 weeks after HCV infection, whereas HCV antibodies are detected by enzyme linked immunoassay (EIA) in a blood specimen 8 to 12 weeks after infection (Refs. 7, 33, 58, 77, 81-83, 87-96). Some of the FDA-licensed NAT assays are multiplex assays that can simultaneously detect HIV, HCV, and HBV in a single blood specimen, thereby improving the feasibility of using NAT routinely for HCV (Refs. 48, 95).

IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions of HCV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records (21 CFR 1271.3(s)) and ask questions about the donor's medical history and relevant conditions and behavioral risks, including risk factors for RCDADs (21 CFR 1271.75(a)).

The list below provides risk factors and conditions for which we recommend screening in order to reduce the risk of transmission of HCV infection. Except as noted in this section, and in accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for HCV. The following conditions or behaviors should be considered risk factors for HCV:

1. Persons who have ever had a positive or reactive screening test for HCV (Refs. 55-57, 59-62, 79).

2. Persons who have engaged in non-prescription injection drug use in the preceding 3 months, including intravenous, intramuscular, or subcutaneous injections (Refs. 22-23, 38-41, 77-78).

3. Persons who have had sex[3] in exchange for money or drugs or other payment[4] in the preceding 3 months (Refs. 38-42, 51, 77-78, 97-101).

[3] Throughout this guidance, unless specified as "anal sex," the term "sex" or "sexual contact" refers to vaginal, anal, or oral sex, regardless of whether a condom or other protection is used.

[4] https://www.unaids.org/sites/default/files/media_asset/2024-terminology-guidelines_en.pdf

4. Persons who have had sexual contact in the preceding 3 months with any individual who has ever had a positive test for HCV infection (Refs. 34-43, 76-77).

5 Persons who have had sexual contact in the preceding 3 months with any individual who has exchanged sex for money, drugs or other payment. If there is any uncertainty about when their sexual partner exchanged sex for money, drugs or other payment, the person is ineligible for 3 months (Refs. 22-23, 34-43, 51, 76-78).

6. Persons who have had sexual contact in the preceding 3 months with any individual who has engaged in non-prescription injection drug use. If there is any uncertainty about when their sexual partner engaged in non-prescription injection drug use, the person is ineligible for 3 months (Refs. 34-43, 76-77).

7. Persons who have had a new sexual partner[5] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 15, 30, 38, 59-61, 77-78, 80).

   Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[6] If a directed semen donor reports this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

8. Persons who have had more than one sexual partner[7] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 15, 30, 38, 59-61, 77-78, 80).

   Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the

[5] For the purposes of this guidance, the following examples would be considered having sex with a new partner: having sex with someone for the first time; or having had sex with someone in a relationship that ended in the past and having sex again with that person in the last 3 months.

[6] In accordance with 21 CFR 1271.60(a), you must quarantine semen from anonymous donors until the retesting required under § 1271.85(d) is complete. In accordance with 21 CFR 1271.85(d), at least 6 months after the date of donation of semen from anonymous donors, you must collect a new specimen from the donor and test it for evidence of infection due to the communicable disease agents for which testing is required under paragraphs (a), (b), and (c) of 1271.85(d).

[7] See footnote 5.

results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[8] If a directed semen donor reports this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

9. Persons who have been exposed in the preceding 3 months to known or suspected HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 44-46).

10. Persons who have been in lock up, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 3 months (Refs. 70, 105-107).

11. Persons who have lived with (resided in the same dwelling) another person who has clinically active (symptomatic) HCV infection in the preceding 3 months (Refs. 47-49).

12. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 3 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment (Refs. 67, 108-119).

13. Children 1 month of age or younger born to a mother with, or at risk for, HCV infection; see risk factors above (Refs. 6, 102-105).

B. Screening a Donor for Clinical Evidence of HCV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (21 CFR 1271.75). In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who exhibits clinical evidence of HCV (Refs. 5, 30-31, 87-88, 120-122). Examples of clinical evidence of HCV may include:

- A prior positive or reactive screening test for HCV;
- Unexplained jaundice;
- Unexplained hepatomegaly;
- Generalized lymphadenopathy; and/or

[8] See footnote 6.

- Unexplained generalized rash or fever.

Records of the following laboratory data might assist you in making the donor eligibility determination when there is an inconclusive history of hepatitis infection, however, these test results should not be used alone to determine donor eligibility:

- alanine aminotransferase (ALT);
- aspartate aminotransferase (AST);
- bilirubin; or
- prothrombin time.

C. Screening a Donor for Physical Evidence of HCV Infection

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric donor (21 CFR 1271.3(o)) or the physical examination of a living donor.

Some of the following observations are not physical evidence of HCV, but rather are indications of high-risk behavior associated with the disease and would increase the donor's relevant communicable disease risk. Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential donor who has risk factors or clinical evidence of HCV. The following are examples of physical evidence of HCV or high-risk behavior associated with HCV:

1. Physical evidence for risk of sexually transmitted diseases and infections, such as perianal lesions, genital ulcerative disease, herpes simplex, or chancroid (when making a donor eligibility determination, you should consider these findings in light of other information obtained about the donor) (Refs. 34-43, 123-128).

2. Physical evidence of nonmedical percutaneous drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (Refs. 5, 22-23, 68, 108-111).

3. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 3 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment. (Refs. 67, 108-119).

4. Unexplained jaundice, hepatomegaly, or icterus. Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed (Refs. 5, 30-31, 87-88, 129-130).

5. Generalized lymphadenopathy (Refs. 131-132).

6. Unexplained generalized rash or fever (Refs. 5, 30-31, 87-88, 122, 129-130).

D. Testing a Donor for Evidence of HCV Infection

You must test all donors of HCT/Ps for HCV as required under 21 CFR 1271.85(a), unless an exception under 21 CFR 1271.90(a) applies, and as required by 21 CFR 1271.80(c), you must use appropriate FDA-licensed, approved, or cleared screening tests in accordance with the manufacturer's instructions.[9]

The following donor screening tests adequately and appropriately reduce the risk of transmission of HCV (Refs. 63, 76-77, 81-86). Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. FDA-licensed donor screening test for antibody to hepatitis C virus (anti-HCV); and

2. FDA-licensed donor screening Nucleic Acid Test for HCV (HCV NAT); or a combination or multiplex NAT that includes HCV.

Any HCT/P donor whose specimen tests negative (or non-reactive) for both assays (i.e., anti-HCV and HCV NAT) is considered to be negative (or non-reactive) when making a donor eligibility determination. Note that a negative (or non-reactive) test does not necessarily mean that a donor is eligible; donor screening also applies as described above.

Any HCT/P donor whose specimen tests positive (or reactive) using either of the assays (i.e., anti-HCV or HCV NAT) is considered ineligible (21 CFR 1271.80(d)(1)).

[9] The following Center for Biologics Evaluation and Research (CBER) website includes a list of FDA-licensed, approved, or cleared donor screening tests (including manufacturers and tradenames): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

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