

# Requalification of Donors Previously Deferred for a History of Viral Hepatitis after the 11<sup>th</sup> Birthday

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## Guidance for Industry

**This guidance is for immediate implementation.**

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with docket number FDA-2017-D-5152.

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](mailto:ocod@fda.hhs.gov), or from the Internet at

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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U.S. Department of Health and Human Services  
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**Contains Nonbinding Recommendations**

**Table of Contents**

**I. INTRODUCTION..... 1**

**II. BACKGROUND ..... 2**

**III. DISCUSSION ..... 3**

**IV. RECOMMENDATIONS..... 4**

**A. Standard Operating Procedures for Requalification of Donors Previously  
    Deferred for a History of Viral Hepatitis ..... 4**

**B. Requalification of Donors Previously Deferred for a History of Viral  
    Hepatitis ..... 4**

**V. IMPLEMENTATION ..... 5**

**A. Implementation without Modification or with More Restrictive Criteria ..... 5**

**B. Implementation with Modification..... 6**

**VI. REFERENCES..... 7**

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## Guidance for Industry

*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

We, FDA, are issuing this guidance to provide you, establishments that collect Whole Blood or blood components intended for transfusion or for further manufacture, including Source Plasma and Source Leukocytes, with recommendations for a requalification method under Title 21 of the Code of Federal Regulations (CFR) 630.35(b) (21 CFR 630.35(b)) for donors who had been indefinitely deferred for a history of viral hepatitis after the 11<sup>th</sup> birthday, prior to the elimination of the donor suitability requirement under 21 CFR 640.3(c)(1) and 21 CFR 640.63(c)(11).<sup>1</sup>

This guidance also advises licensed manufacturers who choose to implement the recommendations on how to report the manufacturing change to FDA under 21 CFR 601.12.

This guidance does not apply to individuals with reactive donor screening test results for hepatitis B virus (HBV) and hepatitis C virus (HCV) who are deferred under 21 CFR 610.41(a) or to the requalification methods after reactive donor screening test results for HBV and HCV under 21 CFR 610.41(b) recommended in separate guidance documents.

This guidance supersedes the following memoranda to blood establishments: “Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis” dated December 22, 1993 (1993 Memorandum) and “Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven Years to Serve as Donors of Whole Blood and Plasma: Alternative Procedures, 21 CFR 640.120” dated April 23, 1992.

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<sup>1</sup> See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015), effective May 23, 2016. Sections 640.3 and 21 CFR 640.63 were removed in this final rule.

## Contains Nonbinding Recommendations

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 longstanding requirement to evaluate donors for a history of hepatitis was introduced in the 1950's before HBV and HCV were recognized and before specific laboratory tests became available to screen all donations. The regulations, in place until May 23, 2016, precluded donation by individuals with "a history of viral hepatitis after the 11<sup>th</sup> birthday" from Whole Blood and Source Plasma donation (21 CFR 640.3(c)(1) and 21 CFR 640.63(c)(11), respectively). The age-related exception was allowed because most cases of viral hepatitis that occurred in donors when they were younger than 11 years were attributed to hepatitis A virus (HAV). HAV would not have caused a chronic and therefore potentially transfusion-transmissible infection in the donor. The regulations persisted for many years because it was unknown if there were viruses other than HBV and HCV that could cause chronic posttransfusion hepatitis.

FDA provided further recommendations for evaluating donors for a history of hepatitis in a 1993 Memorandum (Ref. 1). FDA advised manufacturers to assess donor suitability by asking the donor about physical signs or symptoms of clinical hepatitis (e.g., jaundice), history of liver disease, viral hepatitis or a positive test for hepatitis. As a result, the deferral captured not only individuals with HBV or HCV, but also those who reported HAV or certain other, common viral infections associated with jaundice, such as cytomegalovirus (CMV) and infectious mononucleosis caused by Epstein-Barr virus (EBV), which do not cause chronic posttransfusion hepatitis. The deferral rate exceeded 1 in 5,000 individuals who presented to donate blood each year (Ref. 2). The policy ultimately resulted in the disqualification of thousands of individuals who did not have HBV or HCV and required blood establishments to maintain their names in donor deferral records (Ref. 3).

In March 2000, FDA held a Blood Products Advisory Committee (BPAC) meeting to consider whether there was sufficient information to eliminate the exclusion of donors with a history of viral hepatitis (Ref. 3). The points that emerged were that the regulations were likely useful in the past to prevent posttransfusion hepatitis, but their contribution to transfusion safety was questionable after the introduction of sensitive donor screening tests for HBV and HCV. In addition, data presented at the BPAC meeting demonstrated the limited utility of asking questions about hepatitis, because most infected individuals did not report a history of hepatitis (Ref. 3). The committee voted unanimously (13-0) that the exclusion of donors with a history of viral hepatitis should be eliminated or modified to exclude donors only for a limited time (e.g., for one year after disappearance of symptoms).

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Since the discovery of HCV as the cause of non-A/non-B transfusion-transmitted hepatitis, no additional viral hepatitis agents have been identified to cause chronic, asymptomatic infections in donors that might pose significant health risks to transfusion recipients based on a prior history of hepatitis (Refs. 4-7). Moreover, public health initiatives to increase awareness have prioritized prevention strategies for HBV and HCV (Ref. 8). Current donor screening tests have reduced the window periods of viral detection to 18.5 – 26.5 days for HBV and 7.4 days for HCV (Refs. 9 and 10). The corresponding calculated transfusion risk of viral transmission per unit is 1:1,149,000 for HCV and 1:843,000 – 1:1,208,000 for HBV based on mathematical models (Refs. 9 and 10).

On May 22, 2015 (80 FR 29842), FDA published revised regulations for the determination of blood donor eligibility and eliminated the requirement to defer donors with a history of viral hepatitis after the 11<sup>th</sup> birthday. The revised regulations also include donor requalification requirements under 21 CFR 630.35. This guidance describes an acceptable process for blood establishments to requalify donors previously deferred for a history of viral hepatitis, as required by 21 CFR 630.35(b).

### **III. DISCUSSION**

Individuals with a history of viral hepatitis after the 11<sup>th</sup> birthday who had been indefinitely deferred prior to the effective date of the revised donor eligibility regulations (80 FR 29842, May 22, 2015, effective May 23, 2016) may be requalified as donors if the reason for the hepatitis-related deferral was not infection with HBV or HCV and all other eligibility requirements are met.

Current regulations require that donors must be in good health and free from transfusion-transmitted infections (21 CFR 630.10(a)). Blood establishments must assess the donor's medical history to identify clinical evidence of a relevant transfusion-transmitted disease (21 CFR 630.10(e)). In the context of this guidance, clinical evidence of HBV or HCV includes a medical diagnosis of HBV or HCV at any age regardless of symptoms, including a history of spontaneous resolution, treatment, or diagnostic test results that indicate current or past HBV or HCV infection.

Individuals are not eligible to donate if the purpose of donating is to obtain test results for a relevant transfusion-transmitted infection (RTTI) (21 CFR 630.10(e)(2)(vi)). Individuals with reactive test results for RTTI including HBV and HCV are deferred under 21 CFR 610.41(a).

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### IV. RECOMMENDATIONS

#### A. Standard Operating Procedures for Requalification of Donors Previously Deferred for a History of Viral Hepatitis

Blood establishments that choose to requalify donors must: a) establish a standard operating procedure (SOP) to include the criteria used to determine donor eligibility for those individuals who were previously deferred for a history of viral hepatitis after the 11<sup>th</sup> birthday (21 CFR 606.100(b)(1)). The SOP should describe processes to evaluate the previous reason for deferral and assess the donor's eligibility for reentry. The process could include but is not limited to reviewing donor records, re-interviewing the donor or obtaining further medical consultation, as appropriate. The blood establishment should have a process to manage information provided by the donor or reliable third party at any stage in the screening process.

With respect to the recommendations for the responsible physician to assess an individual donor's eligibility, as described below in section IV.B.3, the determination cannot be delegated to a trained person or physician substitute. However, the responsible physician may make this eligibility determination by telephonic or other offsite consultation.

Blood establishments must follow their SOPs for documenting the criteria used to determine donor eligibility for those individuals who were previously deferred for a history of viral hepatitis after the 11<sup>th</sup> birthday (21 CFR 606.100(b)). We recommend that requalified individuals be removed from the donor deferral registry.

#### B. Requalification of Donors Previously Deferred for a History of Viral Hepatitis

Individuals who have had HBV or HCV infection at any age, regardless of symptoms, spontaneous resolution or treatment, must be indefinitely deferred (21 CFR 630.10(a)) and are not eligible for reentry.

Currently, FDA has not identified an acceptable method or process for requalification of previously deferred individuals with the following history:

- a. Clinical diagnosis or confirmed laboratory tests for HBV at any age.  
OR
- b. Clinical diagnosis or confirmed laboratory tests for HCV at any age.

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1. History of viral hepatitis or specific diagnosis of hepatitis other than HBV or HCV

The following donors may be eligible for reentry without performing predonation testing if the donor otherwise meets all eligibility criteria:

- a. Previous reason for deferral was for HAV.
  - b. Previous reason for deferral was for infectious mononucleosis or viral hepatitis due to EBV or CMV.
2. History of viral hepatitis with an unknown or uncertain clinical diagnosis

If the deferred donor is uncertain about his or her medical diagnosis, test results or whether they had HBV or HCV, the responsible physician should determine if the donor qualifies for reentry. The responsible physician's assessment may include but is not limited to interviewing the donor, interpreting the results of laboratory testing for HCV and HBV, if available, and/or referring the donor for further evaluation as necessary.

If the blood establishment performs testing for HBV and HCV to obtain additional information about the donor's infection status, a sample should be drawn separate from a donation. The test results should be available and be negative/non-reactive before donations can begin.

If the responsible physician determines that the previously deferred donor does not have evidence of current or past HBV or HCV infection, the donor may be eligible for reentry provided all eligibility criteria are met.

## **V. IMPLEMENTATION**

### **A. Implementation without Modification or with More Restrictive Criteria**

We consider the recommendations in this guidance to be an acceptable method or process within the meaning of 21 CFR 630.35(b), for requalifying donors who were previously deferred for a history of viral hepatitis.

If the recommendations in this guidance are implemented without modification in their entirety or if a more restrictive process is adopted, we consider this to be a minor change. Blood establishments should report the change as follows:

1. Licensed blood establishments must report this change to FDA in the annual report under 21 CFR 601.12(d), noting the date the method or process was implemented. See 21 CFR 601.12(a)(3).
2. Unlicensed blood establishments are not required to report this change to FDA.

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### **B. Implementation with Modification**

Procedures for determining donor eligibility potentially may have an adverse effect on the identity, strength, quality, purity, or potency of blood and blood components, as they may relate to the safety or effectiveness of the product. Therefore, implementing a method or process that is less restrictive than the recommendations in this guidance is a major change.

Therefore, blood establishments must report modified, less restrictive donor requalification processes to FDA as follows:

Licensed blood establishments must report the change as a Prior Approval Supplement (PAS) under 21 CFR 601.12(b). We recommend that the supplement include the following:

- a. Form FDA 356h “Application to Market a New or Abbreviated New Drug or Biologic for Human Use” which may be obtained at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.
- b. A cover letter describing the request and the contents of the submission.
- c. A written SOP describing the requalification method or process.

Similarly, before an unlicensed establishment implements a modified, less restrictive requalification method or process from that described in this guidance, FDA must first find the method or process to be acceptable for such purpose (21 CFR 630.35(b)).



## Contains Nonbinding Recommendations

### VI. REFERENCES

1. Memorandum: Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis, December 22, 1993.
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