

Further Testing of Donations that are Reactive on a Licensed Donor Screening Test for Antibodies to Hepatitis C Virus

Draft Guidance for Industry

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Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://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 the docket number listed in the notice of availability that publishes in the *Federal Register*.

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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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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, the Food and Drug Administration (FDA), are providing you, blood establishments that collect Whole Blood and blood components, including Source Plasma, with recommendations for further testing of donations that are reactive on a licensed donor screening test for antibodies to hepatitis C virus (anti-HCV), as required under 21 CFR 610.40(e). We are also providing guidance to blood establishments on how to report the implementation of these recommendations.

In accordance with 21 CFR 610.40(e), each donation, including autologous donations¹, found to be reactive by a donor screening test must be further tested using a licensed, approved or cleared supplemental test, when available. If no such supplemental test is available, blood establishments must perform one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor's infection status (21 CFR 610.40(e)).

Currently, certain hepatitis C virus (HCV) nucleic acid tests (NAT) licensed for donor screening are also licensed for use as a supplemental test to confirm HCV infection for specimens that are repeatedly reactive on a licensed donor screening test for anti-HCV. We have referred to this indication as a "limited supplemental claim" because a reactive HCV NAT result on a donation that is repeatedly reactive for anti-HCV confirms HCV infection and fulfills the further testing requirement in 21 CFR 610.40(e) (Ref. 1). In contrast, a nonreactive HCV NAT result on a donation that is repeatedly reactive for anti-HCV in a screening test does not provide adequate information about the donor's infection status. This guidance provides recommendations for adequate and appropriate testing of donors with repeatedly-reactive anti-HCV screening results under 21 CFR 610.40(e), using the licensed HCV NAT and licensed anti-HCV donor screening tests that are currently available, to provide additional information about the donor's infection status.

¹ Exceptions to this requirement for autologous donations are found in 21 CFR 610.40(e)(1)(i) – (ii).

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This guidance does not address the requirements to test each donation for evidence of HCV (21 CFR 610.40(a) and (b)) or to perform lookback based on reactive screening test results (21 CFR 610.47(a)(1)). This guidance also does not provide recommendations for product disposition, donor deferral, or reentry. You should refer to previously published guidance documents for these recommendations (Refs. 1-3). However, when finalized, the recommendations in this guidance will update the recommendations related to the use of an appropriate multiantigen supplemental test² contained in “Guidance for Industry: ‘Lookback’ for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV,” dated December 2010 (December 2010 Guidance) (Ref. 1). FDA intends to update the December 2010 Guidance as appropriate subject to finalization of this guidance document.

FDA guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the 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 word *should* in FDA guidance documents means that something is suggested or recommended, but not required.

II. BACKGROUND

Hepatitis C is a blood borne disease caused by acute or chronic infection with HCV. Approximately 75-85% of newly infected adults and adolescents develop chronic HCV infection.

A survey of the general United States (U.S.) population during 2003-2010 estimated that 1.3% or about 3.6 million persons had antibodies to HCV, indicating past or present infection; of whom, about 1% or 2.7 million persons are HCV RNA-positive, indicating chronic infection (Ref. 4). As a group, persons born during 1945-1965 demonstrate a 3.25% prevalence of anti-HCV and account for approximately three fourths of all chronic HCV infections among adults in the U.S. (Ref. 5). Many individuals living with HCV are unaware of their infection status (Ref. 5). NAT is necessary to identify active HCV infection among persons who have tested anti-HCV positive (Ref. 5). Current public health initiatives aim to identify actively infected individuals to prevent and control HCV infection and associated chronic disease, cirrhosis, and hepatocellular carcinoma.

The prevalence of HCV infection is substantially lower among blood donors than in the general population. Based on the federally-funded Transfusion-Transmissible Infections Monitoring System (TTIMS) that collated infectious disease test results on about 14 million blood donations, or about half of the U.S. blood supply in 2015 to 2017, the prevalence of HCV in blood donations was 0.02% overall and 0.1% among first-time donors (Ref. 6). Blood donor testing

² The Chiron RIBA™ HCV 3.0 assay (HCV RIBA) was used as the supplemental test for donations found to be reactive on a licensed screening test for anti-HCV before it was discontinued in February 2013.

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allows for the appropriate identification of donors infected with the virus so that they can be deferred from donation, notified, and counseled of their results. Studies have demonstrated the utility of HCV NAT in an HCV supplemental testing algorithm for the purposes of donor notification and counseling. Among anti-HCV repeatedly reactive donations, about 40% were reactive by individual donation HCV NAT demonstrating acute or chronic HCV infection in these donors (Ref. 7). In this scenario, supplemental testing for anti-HCV is not necessary. The counseling message to donors with these results is that they have ongoing HCV infection, are potentially infectious to others, and need further medical evaluation for liver disease, monitoring and possible treatment (Refs. 7, 8). In contrast, donors with a repeatedly reactive anti-HCV screening test and nonreactive HCV NAT may have a false-reactive screening test and be uninfected, may have a chronic persistent infection with transient or intermittent low-level viremia, or may have a resolved infection (Refs. 7, 9). Further testing is necessary to clarify the donor's HCV infection status.

The Chiron RIBA™ HCV 3.0 assay (HCV RIBA) had been used as the supplemental test for donations found to be repeatedly reactive on a licensed screening test for anti-HCV before it was discontinued in February 2013. Upon discontinuation of the HCV RIBA, FDA posted information on its website to assist blood establishments in managing donations that are repeatedly reactive on an anti-HCV screening test. In the web posting, FDA advised blood establishments that they could use licensed HCV NAT tests labeled with a “limited supplemental claim,” because a reactive NAT acts as a positive supplemental test and confirms HCV infection. FDA did not provide recommendations for further testing when donations are repeatedly reactive on an anti-HCV screening test and nonreactive on HCV NAT.

In 2015, FDA issued a final rule that revised the requirement for further testing under 21 CFR 610.40(e).³ Consistent with the previous regulation, under the final rule, establishments must perform further testing using an approved supplemental test when one is available. When a supplemental test is not available, the rule now requires the use of other tests as adequate and appropriate to provide additional information concerning the reactive donor's infection status.

In this guidance, we are providing recommendations for further testing under 21 CFR 610.40(e) of donations that are repeatedly reactive on a licensed screening test for anti-HCV. Blood establishments must use the results of this further testing performed under 21 CFR 610.40(e) to notify donors who have been deferred based on the testing results (21 CFR 630.40), and to take the actions based on further testing described in the lookback requirements, including notifying consignees (21 CFR 610.47(a)(3)), notifying transfusion recipients (21 CFR 610.47(b)(3)) and determining disposition of quarantined, in-date blood, and blood components (21 CFR 610.47(a)(4) and (b)(2)).

³ See Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (80 FR 29842, May 22, 2015). The rule became effective May 23, 2016.

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III. RECOMMENDATIONS FOR FURTHER TESTING OF DONATIONS THAT ARE REPEATEDLY REACTIVE ON A LICENSED SCREENING TEST FOR ANTI-HCV

We recommend further testing of donations, including autologous donations, which are repeatedly reactive for anti-HCV on a licensed donor screening test, using a licensed HCV NAT test that is labeled with the supplemental indication, according to the manufacturer's instructions in the package insert.

1. If NAT is reactive for HCV, the result confirms HCV infection and no additional testing is necessary. The donor should be counseled as HCV infected. The test results for the donation should be regarded as positive for the actions based on further testing under the lookback requirements found in 21 CFR 610.47(a)(3) and (4) and (b)(2) and (3).
2. If NAT is nonreactive for HCV, further testing is necessary. You should perform a second, different licensed donor screening test for anti-HCV.
 - a. If the result is negative, the donor should be counseled that HCV infection was not confirmed and is unlikely. The test results for the donation may be regarded as negative for the actions based on further testing under the lookback requirements found in 21 CFR 610.47(a)(3) and (4) and (b)(2) and (3).
 - b. If the result is repeatedly-reactive for anti-HCV, the donor should be counseled appropriately. The test results for the donation are considered positive for the actions based on further testing under the lookback requirements found in 21 CFR 610.47(a)(3) and (4) and (b)(2) and (3).

A list of tests licensed for use in blood donor screening and supplemental testing is available on the FDA website, available at <https://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/BloodDonorScreening/InfectiousDisease/ucm080466.htm>

If additional supplemental test(s) for anti-HCV are licensed, approved, or cleared in the future, FDA may update these recommendations as warranted.

IV. IMPLEMENTATION AND REPORTING

We propose that once finalized, blood establishments implement and report to FDA the recommendations in this guidance as follows:

1. Blood establishments that implement the recommendations in this guidance without modification and in their entirety:
 - a. We consider the implementation of the recommendations in this guidance without modification and in their entirety to be a minor change. Licensed blood

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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.

- b. Unlicensed blood establishments are not required to report this change to FDA.
2. Blood establishments that wish to implement an alternative algorithm for further testing donations that are repeatedly reactive on a licensed screening test for anti-HCV:
 - a. We consider the implementation of an alternative testing algorithm to be a major change. Therefore, licensed blood establishments must submit a Prior Approval Supplement (PAS) to FDA under 21 CFR 601.12(b). We recommend the supplement include the following:
 - i. 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>.
 - ii. A cover letter describing the request and the contents of the submission.
 - iii. A written SOP describing the testing algorithm or process.
 - b. If an unlicensed blood establishment implements an alternative testing algorithm, it must be adequate and appropriate (21 CFR 610.40(e)). Although the unlicensed blood establishment is not required to report this change to FDA, we recommend the blood establishment submit the contents of the algorithm to FDA for review and comment before implementing.

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V. REFERENCES

1. Guidance for Industry: “Lookback” for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV, updated December 2010.
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM238488.pdf>.
2. Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry; Guidance for Industry, updated December 2017.
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM210270.pdf>.
3. Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components (including Source Plasma and Source Leukocytes) to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV, October 2004.
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080291.pdf>.
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