Toolkit: HCV Testing, Lookback and Reentry

06/21/22

AABB would like to acknowledge Jenn Vrieze of the Mayo Clinic for her assistance in developing the flowcharts.

PURPOSE:

In response to member requests, this is the second in a series of resources developed as a resource for actions following positive testing for an RTTI.

- The Flowcharts in this Toolkit have been developed to assist with compliance efforts but not replace your review of the recommendations found in FDA's Dec 2017 Guidance, 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 and the regulations in 21 CFR 610.47.
- The Flowcharts are based on the current recommendations in the Dec 2017 Guidance and include references to specific regulations and recommendations for cross-checking information.
    - The guidance includes a number of useful tables and figures to review.

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FLOWCHART 1: HCV TESTING and LOOKBACK REQUIREMENTS, *including quarantine and discard*

1) **All blood donors must be tested for RTTIs**, including HCV, under **21 CFR 610.40** and HCV Lookback must be completed as required by **§610.47 Hepatitis C virus (HCV) "lookback" requirements.**
2) **21 CFR 610.40(a)(1) requires you to "Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(i) through (iii) of this chapter (HIV, HBV, and HCV).**
3) In the **December 2017 Guidance, 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, Section III, Background and Discussion, A.** on p. 6, **FDA clarifies** that: "Under 21 CFR 610.40(b) you must use screening tests that FDA has licensed, approved, or cleared for such use."

When tested as required by **§610.40(a) and (b), and as described in 1, 2 and 3 above, were the donor's test results reactive for evidence of HCV infection?**

No: You may release donations testing nonreactive for HCV by licensed donor screening tests **if all other donation suitability requirements are met** [21 CFR 630.30].

Yes: **You must follow §§610.47(a)(1) and (a)(2)**

§610.47(a)(1): Within 3 calendar days after a donor tests reactive for evidence of HCV infection when tested under **§610.40(a) and (b)** ***or*** *when you are made aware of other reliable test results or information indicating evidence of HCV infection*, you must review all records required under **§606.160(d)** of this chapter, to identify blood and blood components previously donated by such a donor.

Did you find blood and blood components collected twelve months and less before the donor's:
-most recent nonreactive screening tests [**§610.47(a)(1)(i)**]
or
-reactive direct viral detection test, e.g., nucleic acid test or and nonreactive **antibody screening test, whichever is the lesser period?** [**§610.47(a)(1)(ii)**]

§610.47(a)(2): You must perform further testing for HCV on the reactive donation as required under **§610.40(e)** which states:

Further testing. You must further test each donation, including autologous donations, found to be reactive by a donor screening test performed under paragraphs (a) and (b) of this section using a licensed, approved, or cleared supplemental test, when available. If no such supplemental test is available, you 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. Except as described in (e)(1) for autologous donations.

No: No prior collections in 12-month time frame. No Lookback required.

Yes: **§610.47(a)(1)(ii)(A): You must, within that 3 days:**
- Quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures.

§610.47(a)(3): You must notify consignees of:

the results of further testing for HCV,

OR the results of the reactive screening test if further testing is not available,

OR if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA, **within 45 calendar days after the donor tests reactive for evidence of HCV infection.**

Notification must include the test results for blood and blood components identified under paragraph (a)(1) of this section that were previously collected from donors who later test reactive for evidence of HCV infection.

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§610.47(a)(1)(ii)(B): You must, within those 3 days:
-Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) if intended for use in another person or for further manufacture into injectable products, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures.

§610.47(a)(4)
When results of further testing required in §610.47(a)(2) **are negative → Release from quarantine**

OR

When the results of further testing required in §610.47(a)(2) are **positive for evidence of HCV→ destroy or relabel quarantined in-date blood and blood components** consistent with the results of the further testing performed under paragraph (a)(2) of this section, **or the results of the reactive screening test if further testing is not available, or if under an IND or IDE,** exempted for such use by FDA.

NOTIFIED CONSIGNEE §610.47(b):
If you are a consignee of Whole Blood or blood components, including Source Plasma and Source Leukocytes, you must establish, maintain, and follow an appropriate system for the following actions:

(1) You must quarantine all previously collected in-date blood and blood components identified under paragraph (a)(1) of this section, except pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures, when notified by the collecting establishment.

CONSIGNEE is notified of results of further testing based on §610.47(b)(2)
IF NEGATIVE: When notified that further testing required in §610.47(a)(2) was **negative → Release from quarantine**

OR

IF POSITIVE: When notified that further testing required in §610.47(a)(2) is **positive for evidence of HCV→ destroy or relabel quarantined in-date blood and blood components** consistent with the results of the further testing performed under paragraph (a)(2) of this section, or the results of the reactive screening test if further testing is not available, or if under an IND or IDE, is exempted for such use by FDA.

If result of **Further Testing is POSITIVE or not done,** §610.47(b)(3) applies.

CONSIGNEE must notify transfusion recipient /physician of record /legal representative - §610.47(b)(3)
When further testing for HCV is positive or when the screening test is reactive and further testing is not available, or if under an IND OR IDE is exempted for such use by FDA, you must notify transfusion recipients of previous collections of blood and blood components at increased risk of transmitting HCV infection, or the recipient's physician of record, of the need for recipient HCV testing and counseling.

You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, adjudged incompetent by a State court, or if the recipient is competent but State law permits a legal representative or relative to receive information on behalf of the recipient.

You must make reasonable attempts to perform the notification within 12 weeks:
- after receiving the results of further testing for evidence of HCV infection from the collecting establishment, **OR**
- after receiving the donor's reactive screening test result for HCV if further testing is not available, or if under an IND or IDE is exempted for such use by FDA.

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FLOWCHART 2: DONOR DEFERRAL/REENTRY- Based on the Dec 2017 Guidance, 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

Donor deferral and reentry recommendations in FDA's 2017 Guidance, beginning with: **Did the donor initially test NAT HCV non-reactive or test not done?**

No

The donor initially tested **NAT HCV Reactive*** **and also tested**

- **V.B** [pg 33, bullet 1]
  - Anti-HCV Test Reactive (regardless of historical HCV RIBA result)
  - → **V.B.** [pg 33] *Currently, FDA has not found acceptable a process for reentry of deferred donors* with these HCV test results.
- **V.B.1 Group A** [page 33, of guidance]
  - Anti-HCV Test Negative (includes donors previously deferred because of reactive test results on an investigational HCV NAT)

Yes

The donor initially tested **NAT HCV Non-reactive or not done**

- **V.B.1 Group B** [page 34, of guidance]
  - Anti-HCV Test RR (includes deferred donors with an historical HCV RIBA that was indeterminate, negative or not performed. Donors can be RR on a second, different licensed screening test for HCV antibody if it was used in further testing of the index donation in accordance with 21 CFR 610.40(e))
- **V.B** [pg 33, bullet 2]
  - NAT HCV Non-reactive or not done
  - Anti-HCV Tests RR
  - Historical HCV RIBA positive
  - → **V.B.** [pg 33] *Currently, FDA has not found acceptable a process for reentry of deferred donors* with these HCV test results.

After 6 months, test a new follow-up sample using HCV ID-NAT and two different, licensed Anti-HCV screening tests. **No donation is made at this time.** *

Is the HCV ID-NAT non-reactive and are the two different, licensed screening tests negative?

Yes → • Reenter Donor • Donor is eligible for future donations if all other donation eligibility criteria are met.

No, the follow-up sample tested:

- ID-NAT HCV Reactive • Regardless of Anti-HCV results
- ID-NAT HCV Non-Reactive • Both Anti-HCV results RR
- ID-NAT HCV Non-Reactive • One Anti-HCV results RR and one Anti-HCV test negative

Defer donor permanently

After one additional 6 month waiting period, test a new follow-up sample using HCV ID-NAT and two different, licensed Anti-HCV screening tests. **No donation is made at this time.** *

Is the HCV ID-NAT non-reactive and are the two different, licensed screening tests negative?

No → Defer donor permanently

Yes → • Reenter Donor • Donor is eligible for future donations if all other donation eligibility criteria are met.

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1- V. "Donor reentry **does not affect the status of previous collections** from that donor, including donations subject to lookback."
2- HCV ID-NAT, if performed prior to 6 months, must be negative for the donor to be eligible for reentry.
3- If the original sample was HCV NAT reactive, it is recommended to use the same ID-NAT, or if no longer available, a NAT that has the same sensitivity claims as the original NAT or greater sensitivity claims.
4- If the original sample was RR on the anti-HCV test, it is recommended to use the same anti-HCV test that was run on the original donor sample or a more sensitive version as one of the two licensed anti-HCV screening tests used.