



Advancing Transfusion and  
Cellular Therapies Worldwide

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852-1448

**Docket No. 2005D-0261, 27 July 2005, draft “Guidance for Industry-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”**

Dear Docket Manager:

AABB and the American Red Cross (ARC) wish to commend FDA for providing straightforward algorithms that will allow blood centers to clear out a backlog of old deferrals related to HIV and HCV. As stated in the draft guidance document “...some establishments are not attempting to reenter donors because of the complexity of the current reentry algorithms and concerns about inappropriately reentering a donor.”

Listed below are several areas of concern, or areas that need further clarification.

Waiting Period for Reentry Testing

**IV. RECOMMENDATIONS - 7. Reentry for donors Deferred Because of HIV-1 Test Results and 8. Reentry for Donors Deferred Because of HCV Test Results - a.i.(2)**

NOTE: [For purposes of donor notification and counseling, the deferred donor may be tested prior to the 8 week (HIV) or 6 month (HCV) waiting period, but if the NAT results are reactive, or serologic results are repeatedly reactive, the donor is not eligible for reentry and must be permanently deferred].

*COMMENT – We disagree with this provision and note that it is inconsistent with IV.7.a.ii.3 and IV.8.a.ii.3, which allow for a second cycle of reentry testing following a reactive result on the first attempt at reentry. This is further defined in Figures 7 and 8 which specify a second round of “reentry” testing when the EIA is repeat reactive (Western Blot Negative or Indeterminate with a blot pattern that is not progressing or the*

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*RIBA is Negative). Consistent with this provision, we believe that when testing is performed during the 8 week (or 6 month) waiting period for purposes of donor counseling and is again reactive, a second waiting period for purposes of donor reentry should be allowed. Persistent unconfirmed serologic reactivity detected for purposes of donor counseling should not disqualify the donor from the opportunity for reentry as it is common that the same reagent lot numbers that generated the donor's first reactive donation result may still be in use to test the donor counseling follow-up specimen.*

#### Investigation of Unexplained Discrepancy in Testing

#### **IV. RECOMMENDATIONS - 3. Testing, Product Disposition, and Donor Management for a Master Pool that is Reactive on a Multiplex NAT: Resolution by Testing Individual Donor Samples - a. To reenter a donor...**

- i. “If all individual donor samples are Non-Reactive, you may release from quarantine all individual donations (if serologic tests on those donor samples are Negative and the donations are otherwise suitable for release). However, you must investigate the unexplained discrepancy in testing (§ 211.192). Laboratory control procedures must make adequate provisions for monitoring the reliability, accuracy, precision, and performance of laboratory test procedures and instruments, and must include adequate identification and handling of all test samples (§ 606.140(b), (c)). Use of supplies and reagents must be in a manner consistent with the instructions provided by the manufacturer (§§ 606.65(e), 610.40(b)). In addition, as part of an overall Quality Assurance program, we recommend that you conduct additional investigation to determine the cause of the initial reactivity of the Master Pool.”

*COMMENT—There is a baseline level of false reactivity in licensed NAT assay systems even when the testing processes are in control. The rate of false positivity for minipool NAT by the licensed HIV-1/HCV assay ranges between 0.08-0.18% (ARC personal communication) which is very similar to serologic initial reactive rates. If reactivity rises above this background level, facilities have policies in place to further investigate.*

*We believe that it is not appropriate to require that a special investigation be performed for each occurrence in which a reactive master pool result does not resolve to an individual donation. We note that such a requirement is not in place for initially reactive serologic results that do not repeat as reactive. As acknowledged by FDA in BPAC discussion, when testing the individual donations from a NAT reactive pool, the undiluted sample used is 16-24 times more concentrated than the diluted sample, and hence a nonreactive result in this vastly more sensitive test is enough evidence to indicate that the original NAT reactive pool was a false positive. Analogous to serologic results, a NAT reactive pool is simply an initial reactive that does not repeat.*

#### HIV Reentry

#### **IV. RECOMMENDATIONS - 7. Reentry for donors Deferred Because of HIV-1 Test Results - FDA has approved a method or process for reentry of deferred donors in the following classes:**

“...Donors who were NAT-Non-Reactive (or NAT was not performed) and who were Repeatedly Reactive on a screening test for HIV-1 antibody, with an HIV-1 Western Blot or IFA that was Negative (or was not performed), or an HIV-1 Western Blot result that was Indeterminate (viral bands may be present). This includes donors previously deferred because of Repeatedly Reactive HIV serologic test results prior to the initiation of testing by NAT.

These donors may be eligible for reentry only if the HIV-1 p24 antigen EIA (if done) was Negative and if a second, different, licensed HIV-2 EIA was Negative, or, if the second HIV-2 EIA was Repeatedly Reactive, an investigational HIV-2 supplemental test was not Positive. Currently, we have not approved a supplemental (additional, more specific) test for HIV-2.

Donors who were NAT Non-Reactive and who were Negative on a screening test for HIV-1 antibody, but who were Repeatedly Reactive on an HIV-1 p24 antigen EIA with a Positive or an Indeterminate (that is, an Invalid or a Non-Neutralized) result on the Neutralization test.”

*CLARIFICATION REQUEST - It appears that donors previously deferred for HIV-2 reactivity can be offered reentry if their specimen is tested by an investigational HIV-2 supplemental test and gives a Negative result. Please clarify if there are any existing investigational supplemental HIV-2 assays that can be used for reentry testing. If not, please clarify that this provision is being offered in the event such a test becomes available. It is our understanding that the only supplemental testing for HIV-2 currently available is an HIV-2 research test performed by the State of California. Would donations tested by this test be considered for reentry? What about the use of licensed diagnostic tests for HIV-2? Blood donors who are deferred for HIV reactivity would be considered part of the diagnostic testing population if followed and tested by their personal physician, and hence might be receiving test results using licensed diagnostic assays.*

*COMMENT - The written explanation (page 19, last bullet) for reentry of donors does not require that an Additional NAT be performed. However, Figure 7 and Table 7 appear to indicate that only donors with an Additional NAT that is Non-Reactive are eligible for reentry.*

*Figure 7 and Table 7 should be modified to explain that the Additional NAT is not required. However, they should indicate that if an Additional NAT was done, the result must be Negative in order for the donor to be eligible for reentry.*

**IV. RECOMMENDATIONS - 7. Reentry for donors Deferred Because of HIV-1 Test Results - a. To reenter a donor** who meets FDA eligibility criteria (i.e., the donor is otherwise eligible to donate again), we recommend that you do the following (See **Figure 7** and **Table 7**):

- i. “At least 8 weeks after the original donation obtain a new sample from the donor (no donation is made at this time) and perform follow-up testing using:

- (1) a licensed HIV-1 NAT that is the same as the NAT (i.e., the Discriminatory NAT for HIV-1) that was run on the original donor sample or a licensed HIV-1 NAT that is labeled as sensitive for HIV-1 group O and HIV-1 group M variants;” **This equates to Note 7 on Table 7 and Figure 7.**

*CLARIFICATION REQUEST – It is our understanding that there currently are no NAT tests licensed for HIV Group O claims. Information may be included in the package insert that mentions Group O antigens or indicates that the test is designed to be group O sensitive, but this does not constitute a labeling claim for Group O. We believe that this statement is included to indicate requirements in the event such a test is available. This intent should be stated more clearly.*

AND

- (2) “a licensed anti-HIV-1/2 EIA. If the original donor sample was Repeatedly Reactive on the anti-HIV-1/2 EIA, we recommend that you use that same EIA to test this follow-up sample. If the original donor sample was Negative on the anti-HIV-1/2 EIA, we recommend that you use an Alternate EIA that is labeled as sensitive for HIV-1 Group O.” **This equates to note 8 on Table 7 and /Figure 7.**

*CLARIFICATION REQUEST – Currently, there is only one EIA test licensed for Group O claims. Is it correct that donors who enter the reentry algorithm due to NAT reactivity arm will need to be tested by this EIA (or in the future by another serologic test with an HIV Group O claim)?*

*Secondly, what provision has been made for those donors who enter the reentry algorithm due to EIA reactivity on an EIA assay that is no longer available? We suggest that they should be allowed to be tested by any serologic test licensed for anti-HIV-1/2.*

**IV. RECOMMENDATIONS - 7. Reentry for donors Deferred Because of HIV-1 Test Results**, page 20, “...Donors who were NAT-Non-Reactive (or NAT was not performed) and who were Repeatedly Reactive on a screening test for HIV-1 antibody, with an HIV-1 Western Blot or IFA that was Negative (or was not performed), or an HIV-1 Western Blot result that was Indeterminate (viral bands may be present). This includes donors previously deferred because of Repeatedly Reactive serologic test results prior to the initiation of testing by NAT.”

*CLARIFICATION REQUEST – This section should clarify that this statement also applies to a Western Blot that is classified as Invalid or Unreadable.*

**IV. RECOMMENDATIONS - 7. Reentry for donors Deferred Because of HIV-1 Test Results – a. To reenter a donor...**

ii. Evaluate the results of the follow-up testing on the donor’s new sample as follows:

- (3) If the NAT is Non-Reactive and the anti-HIV-1/2 EIA is Repeatedly Reactive, you may reconsider the donor for reentry by additional follow-up testing after a second waiting period of 8 weeks.

When there is a persistent anti HIV-1/2 EIA Repeatedly Reactive result, you may wish to further test the donor's new sample using an HIV-1 Western Blot. If the Western Blot test result is Negative, or an Indeterminate blot pattern has not progressed, you may reconsider the donor for reentry by additional follow-up testing after a second waiting period of 8 weeks. If the Western Blot result is Positive, we recommend that you defer the donor permanently." **This equates to note 9 on Table 7 and Figure 7.**

*CLARIFICATION REQUEST – This section should also clarify that this reentry pathway is acceptable if the Western Blot is classified as Invalid or Unreadable. In addition, IFA, as well as Western Blot, should be considered acceptable to test persistently reactive donors.*

#### HCV Reentry

#### **IV. RECOMMENDATIONS - 8. Reentry for Donors Deferred Because of HCV Test Results - FDA has approved a method or a process for reentry of deferred donors in the following classes:**

“Donors who were NAT-Reactive and seronegative. This includes donors previously deferred because of Reactive test results on an investigational HCV NAT. The HCV Discriminatory NAT may have been either Positive or Negative. If an Additional NAT for HCV (validated for use with individual donor samples) was performed, it must have been Non-Reactive.

...Donors who were NAT-Non-Reactive (or NAT was not performed) and who were Repeatedly Reactive on a screening test for HCV antibody, with an HCV RIBA that was Indeterminate or Negative (or was not performed). This includes donors previously deferred because of Repeatedly Reactive HCV serologic test results prior to the initiation of testing by NAT.”

a. **“To reenter a donor who meets FDA eligibility criteria (i.e., the donor is otherwise eligible to donate again), we recommend that you do the following (See **Figure 8** and **Table 8**):**

- i. At least six months after the original donation, obtain a new sample from the donor (no donation is made at this time) and perform testing using:

(1) a licensed HCV NAT

AND

(2) a licensed HCV EIA.”

*COMMENT - The recommendation should address the sensitivity of the licensed HCV EIA to be performed. It is our understanding that some facilities may be using HCV 2.0 for routine testing, but we believe reentry testing should be performed using an assay with sensitivity equivalent to or greater than HCV 3.0.*

#### **IV. RECOMMENDATIONS - 8. Reentry for Donors Deferred Because of HCV Test Results - a. To reenter a donor...**

ii. “Evaluate the results of the follow-up testing on the donor's new sample as follows:

(3) If the NAT is Non-Reactive and the anti-HCV EIA is Repeatedly Reactive, you may reconsider the donor for reentry by additional follow-up testing after a second waiting period of 6 months.

When there is a persistent anti-HCV EIA Repeatedly Reactive result, you may wish to further test the donor's new sample using an HCV RIBA. If the RIBA test result is Negative, you may reconsider the donor for reentry by additional follow-up testing after a second waiting period of 6 months. If the RIBA test result is Positive or Indeterminate, we recommend that you defer the donor permanently.” **This equates to note 5 on Table / Figure 8.**

*CLARIFICATION REQUEST – Please explain the rationale for not allowing RIBA Indeterminate donors to be retested for reentry purposes after an additional 6 month period. This is allowed for HIV donors with an Indeterminate blot pattern that has not progressed.*

#### Lookback for NAT Reactive Donors that are EIA Negative

*CLARIFICATION REQUEST - The draft guidance does not indicate the time period for which lookback must be performed in this circumstance. We recommend that lookback be based on the estimated duration of an antibody negative phase of infection. One year prior to the NAT reactive, antibody negative donation should provide an acceptable margin of safety.*

AABB and ARC strongly support initiatives that improve the safety of blood donors and transfusion recipients and stand ready to interact with the FDA as necessary.

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

The American Red Cross, through its 36 Blood Services Regions and nine National Testing Laboratories, supplies approximately half of the nation's blood supply. Over six million units of Whole Blood were collected from more than four million Red Cross volunteer donors, separated into 12 million components, and supplied to over 3000 hospitals to meet the transfusion needs of patients last year. Over one million liters of plasma from volunteer blood donations are

recovered annually by the American Red Cross, further processed into numerous plasma derivatives, and distributed to healthcare providers.

Questions concerning these comments may be directed to M. Allene Carr-Greer, Deputy Director Regulatory Affairs at [acarrgreer@aabb.org](mailto:acarrgreer@aabb.org) or 919-658-1689.