

October 24, 2005

To FDA Dockets Manager:

**RE 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”**

Thank you for the opportunity to comment on this draft guidance. I would like to offer the following comments and requests for clarification.

1. Lookback for NAT reactive/antibody negative donors: how far back?

The draft guidance mentions in several places that lookback (recipient notification) is recommended if the donor tests reactive for HIV or HCV NAT. However, there are no existing guidance documents or regulations that define how far back lookback should extend in the case of a donor who is NAT reactive but antibody negative. For these donors, whose test results indicate recently acquired infection, it would be medically and scientifically reasonable to limit lookback to those products donated within the estimated duration of the antibody negative phase of infection, or some small multiple of this time period. The agency previously acknowledged this in its 1995 guidance for HIV p24 antigen, which required lookback only for those products donated within 3 months prior to an antigen positive/antibody negative donation. Similarly, lookback for HIV or HCV NAT positive/antibody negative donors could and should be limited to a short period of time that would encompass the duration of the infectious/antibody negative phase of infection, for example, 8 weeks for HIV and 6 months for HCV. Certainly, lookback for NAT reactive/antibody negative donors should not extend further than one year prior to the (current) NAT POSITIVE/antibody negative donation.

2. Permanent deferral for donors EIA reactive on early retesting: why?

For both HIV and HCV, the draft guidance indicates that a recurrent false positive EIA would not permanently exclude the donor if this result is obtained on a sample drawn after the required waiting time (8 weeks for HIV and 6 months for HCV). However, Sections IV.7.a.i and IV.8.a.i. of the draft guidance inexplicably state that a recurrent false positive EIA on a sample obtained before the end of the waiting period would result in permanent deferral of the donor. There is no scientific or medical justification for considering a recurrent false positive EIA on an early sample to be more worrisome than a false positive EIA on a later sample. The permanent deferral of donors with early recurrent false positive EIA reactions was not recommended by BPAC. In fact, in June 2001 BPAC agreed to permit future consideration of reentry for any donor with recurrent false positive EIA results. There is no medical or scientific rationale to differentiate between early false positive vs. later false positive EIA results in terms of future donor eligibility. The permanent exclusion of donors

with early recurrent false positive EIA results would lead donors to fear retesting at the time of counseling and would constitute poor medical service to our donors. Recurrent false positive EIA reactions are common on samples obtained soon after a false positive donation. This is because the same test kit involved in the initial reaction is likely to still be in use, and any biologic factors that contributed to the initial false positive result (for example, flu vaccine) might still be having an effect on the donor. There is no medical or scientific reason to consider these early reactions to be more indicative of infection than later reactions, and no medical or scientific justification for permanent deferral of these donors. BPAC did not recommend such a policy. This requirement should be deleted from the above noted sections of the guidance. Donors with recurrent false positive EIA on a sample drawn within the waiting period should be eligible again for re-entry testing after another waiting period (8 weeks for HIV and 6 months for HCV) has elapsed from the date of the most recent reactive specimen.

3. Reentry for HCV antibody reactive donors: Section IV.8.a.i. should take into account the differential sensitivity of HCV 2.0 vs. 3.0 EIA assays

At the June 2001 BPAC meeting, data were presented that described the finding, during the Roche HCV NAT trial, of individuals who were HCV NAT reactive/EIA 3.0 reactive/EIA 2.0 non-reactive/RIBA indeterminate for prolonged periods of time. These findings were subsequently published (Comparative yield of HCV RNA testing in blood donors screened by 2.0 versus 3.0 antibody assays. *Transfusion* 2002;42:1507-13). This failure of HCV 2.0 to detect, for prolonged periods of time, some infected individuals detected by HCV 3.0 has also been reported by other investigators. Because of the differential sensitivity of the two HCV EIA assays, it would seem prudent to require that the EIA used for HCV reentry testing should be EIA version 3.0 or above. At a minimum, it should be specified in Section IV.8.a.i that re-entry testing of donors whose donations were HCV EIA reactive must be performed using an EIA of at least the same version as the one that was reactive initially. Specifically, if the index donation was reactive on EIA 3.0, then re-entry testing should be performed using EIA version 3.0 or above.

4. Section IV.7: Please clarify that HIV IFA indeterminate donors are eligible for reentry:

Table 7, Figure 7, and Section III.B.2 indicate that it is the intention of the agency that HIV IFA indeterminate donors should be eligible for reentry. However, Section IV.7 (Page 20, second paragraph) does not explicitly state that HIV IFA indeterminate donors are eligible for reentry. Please revise Section IV.7 (page 20, paragraph 2) to clarify that these donors are eligible for consideration for reentry.

5. Unreadable HIV-1 Western blots

Please revise Section IV.7, Table 7 and Figure 7 to clarify that donors with unreadable HIV-1 Western Blot are eligible for consideration for reentry.

Alternatively, please clarify that unreadable blots may be considered “Western blot not done” for the purpose of this guidance.

6. Selection of tests for HIV re-entry testing (Section IV.7.a.i):

The selection of the assay to be used for testing the follow-up specimen seems unnecessarily complex, as the recommendation varies from situation to situation. This will make it very difficult for blood centers to correctly select the appropriate assays for performing re-entry testing. The follow-up testing algorithm could be greatly simplified by stating the following for every situation:

- The assay used to perform follow-up testing for the previously reactive test may be either the same assay that was reactive, or another assay with at least the same sensitivity claims as the test that was reactive on the donation.
- The follow-up testing for the test that was non-reactive on the donation should be performed using an assay with HIV 1, 2, and HIV-1 Group O claims (in the case of EIA) or HIV-1 Group O claims (in the case of NAT).

The above considerations apply to the following sections of the guidance:

- a. Section IV.7.a.i.(2) states that if the original donor sample was repeatedly reactive on the HIV1/2 EIA, the same EIA should be used to test the follow-up specimen. There is no recommendation for the situation where the original EIA is not available. Please permit reentry testing with EITHER the original EIA that was reactive OR another EIA with at least the same sensitivity claims as the test that was reactive.
- b. Section IV.7.a.i.(2) states that for donors who were originally NAT reactive but EIA1/2 non-reactive, follow-up EIA testing should be performed using an “Alternate EIA labeled as sensitive for HIV-1 Group O”. Why does the follow-up EIA test have to be an “Alternate” EIA? Any EIA labeled as sensitive for HIV-1 Group O should suffice. Additionally, the test used for re-entry should be specified to include a claim for HIV-2. Accordingly, please change the wording of this section to specify that re-entry testing of donors whose donations were HIV 1/2 non-reactive may be performed using any licensed EIA(s) with HIV 1, 2, and HIV-1 Group O claims. Also, please clarify that “labeled as sensitive for HIV-1 Group O” refers to an intended use claim that includes detection of HIV-1 Group O.
- c. Reentry testing for donors with reactive HIV NAT or non-discriminated multiplex NAT is recommended to be performed with either the same test that was reactive or a test with HIV Group O and M variant claims. Why would Group O and M variant testing be required if the initial test that was reactive did not include these sensitivities? It should be sufficient to require that for

NAT reactive donors, the test used for re-entry testing must include at least the same claims as the reactive test.

7. HIV-2 investigational supplemental testing: please clarify that blood centers are not required to perform this investigational testing as a prerequisite for re-entry

In Section IV.7, Figure 7 footnote 4, and Table 7 footnote 4, please change the wording to “or, if Repeatedly Reactive, an investigational HIV-2 supplemental test, *if performed*, was not positive.” Investigational supplemental testing for HIV-2 should not be required as these tests have not been adequately validated for use in the donor population.

8. Permanent deferral for RIBA indeterminates on follow-up testing: why?

Section IV.8.a.ii.(3) states that a RIBA indeterminate result on the follow-up testing would result in permanent deferral of the donor. This was not recommended by BPAC which recommended that donors indeterminate on follow-up should remain eligible for future consideration for re-entry. This draft guidance does permit ongoing consideration for re-entry for HIV indeterminate donors. Please similarly permit donors with indeterminate HCV RIBA to remain eligible for future re-entry as recommended by BPAC.

9. Request for clarification: “Western Blot pattern has not progressed”

Section IV.7.a.ii., Figure 7, and Table 7, permit consideration of future re-entry for donors whose follow-up specimen has a “Western Blot pattern [that] has not progressed”. This wording will cause difficulty in interpretation for eligibility, for example, a donor whose follow-up blot has bands not seen on the initial Blot but who does not meet the criteria for positive. Please note that Indeterminate Western Blots are extremely common in uninfected individuals. It would be very common, therefore, to find an uninfected donor with a negative Western Blot on the donation but an indeterminate Western Blot on the follow-up specimen. This should not necessarily be considered “progression” because of the high frequency of indeterminate blots in healthy, uninfected individuals. It would be clearer, and medically justifiable, to state in this guidance that as long as the follow-up Western Blot is either negative or indeterminate the donor would remain eligible for future reconsideration for re-entry. This was the stated recommendation of the BPAC in June 2001.

10. Request for clarification: Section IV.7.a.i(1), Figure7, and Table 7: “(i.e., the Discriminatory NAT for HIV-1)”

This phrase which refers to a “discriminatory NAT” appears to exclude the possibility of re-entry testing using the single target (Roche) HIV-1 NAT which is not called a “discriminatory NAT”. Please change the wording of this phrase to the wording used in earlier sections of this guidance that takes into account both of the current

manufacturer platforms, specifically: “(i.e., *the separate NAT for HIV-1 RNA or the Discriminatory NAT for HIV-1*) that was run on the original donor sample or ...”.

11. Request for clarification: NAT testing of follow-up specimens must be run unpooled

Please clarify that the NAT testing on the follow-up specimens should be run on the individual sample, and not as part of a pool.

Thank you again for the opportunity to comment on this guidance document.