

Guidance for Industry

Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components for Transfusion to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV

DRAFT GUIDANCE

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For questions on the scientific content of the draft guidance document contact the Division of Emerging and Transfusion Transmitted Diseases at 301-827-3008. For questions concerning labeling or licensing issues, contact the Division of Blood Applications at 301-827-3524.

U.S. Department of Health and Human Services
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GUIDANCE FOR INDUSTRY

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I. INTRODUCTION

The purpose of this guidance document is to inform you, all establishments engaged in the manufacture of Whole Blood (as defined in 21 CFR 640.1) and blood components: i) that we, the Food and Drug Administration (FDA), have licensed a nucleic acid test (NAT) to identify HIV-1 and HCV in Whole Blood donations and blood components; ii) that we believe that a licensed NAT to identify HIV-1 and HCV in Whole Blood donations and blood components will adequately and appropriately reduce the risk of transmission of these communicable diseases; and iii) that we recommend that blood establishments use a licensed NAT to identify HIV-1 and HCV in Whole Blood donations and blood components within 6 months after a final guidance is issued. We have explained in this document how you should report implementation of a licensed NAT at your facility, or at your contract testing laboratory, as required by 21 CFR 601.12.

II. BACKGROUND

FDA's final rule (66 FR 31146, June 11, 2001) entitled "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents" became effective on December 10, 2001. Section 610.40(b) of the rule requires that manufacturers "perform one or more such [screening] tests as necessary to reduce adequately and appropriately the risk of transmission of communicable disease" (66 FR 31146 at 31162). As we noted in the preamble to this regulation, the standard for adequate and appropriate testing will change as technology and other circumstances change. We explained that, "... we intend to regularly issue guidance describing those tests that we believe would adequately and appropriately reduce the risk of transmission of communicable disease agents" (66 FR 31146 at 31149).

The availability of a licensed NAT to identify HIV-1 and HCV will change the testing protocol for adequately and appropriately reducing the risk of transmission of those diseases. We believe that it is no longer appropriate to rely solely on other tests for HIV-1 and HCV, such as those for antibody and antigen. Transmission of HIV-1 and HCV by blood and blood products has been dramatically reduced as a result of implementation of sensitive tests for viral antibody and antigen, and, in the case of plasma derivatives, the use of effective virus removal and inactivation

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methods. The major sources of remaining risk are window period donations, viral variants, atypical seroconversions and laboratory testing error. According to recent reports, donations during the window period constitute at least 90% of the risk (Ref. 1, 2). Therefore, measures to close the window period were expected to further reduce the low residual risk in HIV-1 and HCV transmission by blood and plasma. In 1994, we held a workshop to explore the potential application of nucleic acid based methods to the screening of donated blood for HIV-1. It was felt that although these methods were clearly sensitive, they were not ready for implementation on a large scale at that time. However, the workshop fueled interest in developing systems for implementation of nucleic acid methodology for testing blood and plasma donations.

Subsequently, test kit manufacturers and blood organizations, in collaboration with the government (NIH, FDA), actively pursued development of NAT systems for HIV-1 and HCV. Because of the cost and labor intensity of NAT, testing of minipools of plasma rather than individual donations seemed to be more feasible. By 1997, some manufacturers in Europe had voluntarily instituted NAT on pooled samples of plasma. At about that time, the European Union (E.U.) issued a directive (98/463/EC) that would require by July 1, 1999, HCV RNA testing in Europe for all plasma for fractionation. The E.U. also indicated that the requirement for HIV-1 RNA testing would follow at a later date. The E.U. directive, which applied to both Source Plasma and recovered plasma, provided impetus to the rapid development of NAT for all blood and plasma donations. In the U.S., we issued for public comment a draft guidance entitled "Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma", issued November 1999 (64 FR 66481), stating that all NAT tests used to screen blood and plasma were subject to regulation as biological products under the licensing mechanism.

We permitted the clinical study of this investigational technology on a large scale. Such large-scale studies were thought to be necessary to demonstrate the efficacy of NAT primarily because the frequency of window period donations is low. Clinical studies to evaluate NAT were initiated in 1997 under Investigational New Drug Applications (INDs). Data collected under these INDs would be submitted in support of approval of subsequent Biologics License Applications (BLAs). We have worked with manufacturers towards validation of NAT assays for donor screening. In addition, manufacturers were provided with validation criteria for replacement of currently licensed HIV-1 p24 antigen tests by pooled and/or individual sample NAT.

III. AVAILABILITY OF LICENSED NAT SYSTEM FOR SCREENING OF WHOLE BLOOD DONORS

On February 27, 2002, FDA licensed the first pooled and individual sample NAT system for the detection of HIV-1 and HCV RNA in Whole Blood donations. The Procleix HIV-1/HCV Assay for screening pooled and individual samples from Whole Blood donations was developed by Gen-Probe Inc., and is distributed by Chiron Corporation. The assay meets the current FDA sensitivity standards of 100 copies/ml for the analytical sensitivity of the pool test and 5,000 IU/ml for the original donation when tested in pools. The sensitivity standard of 5,000 IU/ml replaces FDA's previously published standard of 5,000 copies/ml (Ref. 3). Validation data submitted by the manufacturer support replacement of currently licensed assays for HIV-1 p24 antigen by both the pooled and individual sample NAT assay.

IV. IMPLEMENTATION

Nucleic acid testing of Whole Blood and blood components involves the use of defined pooling and testing systems. We recognize that the licensed testing technology is not universally available. We are aware that blood establishments are currently performing nucleic acid testing under IND and that they need time to implement these systems. Because of the complex issues surrounding implementation of nucleic acid testing in the transfusion setting, we are recommending that blood establishments implement a licensed NAT within 6 months of publication of the final guidance.

A. Reporting Requirements for Licensed Blood Establishments (21 CFR 601.12)

If you are a licensed blood establishment and you begin using a licensed NAT according to the manufacturer's test insert at your facility, we recommend that you notify us of the testing change in your Annual Report (AR) (21 CFR 601.12(d)). If you have already supplemented your BLA to use a contract laboratory to perform infectious disease testing for blood products, and the contract laboratory will now perform NAT, you should also report this change in your AR.

If you use a new contract laboratory to perform NAT, and the laboratory already performs infectious disease testing for blood products, then we recommend that you report this change at least 30 days prior to distribution of the product made using the change (CBE-30) (21 CFR 601.12 (c)). If your contract laboratory has not previously performed infectious disease testing for blood products, then you should report this change as a prior approval supplement (PAS) (21 CFR 601.12(b)). Finally, if you or your contract laboratory wishes to discontinue HIV-1 antigen testing upon implementation of this licensed NAT, then we recommend that you notify us of this change in your AR, CBE-30, or PAS submission as referenced above.

We recognize that after licensure of the NAT assay, some establishments that used the now- licensed test under IND may need up to six months to fully implement the licensed test with all approved components, including the licensed test and supporting software cleared as a device. During this transition period, when establishments are using some, but not all, of the licensed or cleared components, establishments should continue their existing INDs and report the use of the licensed assay or the related cleared components as an amendment to their existing INDs. When an establishment implements all licensed or cleared components of the test system, we recommend that you withdraw the IND (21 CFR 312.38).

B. Labeling Requirements (21 CFR 606.122)

1. Whole Blood and blood components for transfusion

Upon implementation of a licensed (pooled or individual sample) NAT, both licensed and unlicensed blood establishments should revise the instruction

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circular (21 CFR 606.122), also known as the “Circular of Information”, for blood products intended for transfusion to include NAT, and delete references to HIV-1 antigen testing, if applicable. If you are a licensed blood establishment, you may submit this labeling as a change being effected immediately, (CBE) (21 CFR601.12 (c)(5)), provided the revision is identical to one of the following statements:

- For pooled sample:
“Licensed Nucleic Acid Tests (NAT) for HCV RNA and HIV-1 RNA have been performed on pooled samples and found to be nonreactive”, or
- For individual sample:
“Licensed Nucleic Acid Tests (NAT) for HCV RNA and HIV-1 RNA have been performed on individual samples and found to be nonreactive”.

If you wish to use a different statement, then you must submit the labeling change as a PAS (21 CFR 601.12(b)). If you are an unlicensed blood establishment, you must revise the instruction circular (21 CFR 606.122), but you are not required to submit it to us.

The revised circular may be used for blood products already tested with IND reagents after licensure of NAT, as the reagents are identical to the licensed reagents.

2. Blood components prepared from Whole Blood or blood components for further manufacture into injectable or non-injectable products

Actual NAT results should be included on the label for blood components intended for further manufacture into injectable or non-injectable products, such as recovered plasma. The recommended test statement is:

- For pooled sample:
“Nonreactive by licensed Nucleic Acid Tests for HCV RNA and HIV-1 RNA performed on pooled samples”, or
- For individual sample:
“Nonreactive by licensed Nucleic Acid Tests for HCV RNA and HIV-1 RNA performed on individual samples”. As noted above, blood components already tested with IND reagents may be relabeled with this statement after licensure of NAT.

V. REFERENCES

1. M.P. Busch and S.H. Kleinman, Nucleic acid amplification testing of blood donors for transfusion-transmitted infectious diseases, *Transfusion* 2000; 40:143-156.
2. S.H. Kleinman and M.P. Busch, The risks of transfusion-transmitted infection: Direct estimation and mathematical modelling, *Baillier's Clinical Haematology* 2000; 13(4):631-649.
3. Guidance for Industry: In the Manufacture and Clinical Evaluation of *In Vitro* Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Viruses Types 1 and 2., December 1999 (64 FR 71147).