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

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions concerning labeling, reporting or licensing issues, contact the Division of Blood Applications at 301-827-3543. For questions regarding testing issues, contact the Division of Emerging Transfusion Transmitted Diseases at 301-827-3008.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
October 2004

Table of Contents

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

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

FDA's blood testing rule requires you, an establishment that collects blood and blood components (e.g. Whole Blood and blood components including Source Plasma and Source Leukocytes), to test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare a medical device, for evidence of infection due to specific communicable disease agents(21 CFR 610.40(a)). This rule also requires you to use one or more approved screening tests as necessary to reduce adequately and appropriately the risk of transmission of communicable disease. (21 CFR 610.40(b)) In the preamble to this final rule, we discussed the approved donor screening tests that we believed were necessary to reduce adequately and appropriately the risk of transmission of Human Immunodeficiency Virus type 1 (HIV-1) and hepatitis C virus (HCV). We also stated that as technology advances, we would issue guidance describing those tests that we believe would adequately and appropriately reduce the risk of transmission of communicable disease agents. (66 FR 31146, 31162 June 11, 2001).

The purpose of this guidance is to inform you that:

1) FDA has licensed nucleic acid tests (NAT) as tests to screen blood donors for HIV-1 ribonucleic acid (RNA), and HCV RNA; and

2) these licensed tests can detect evidence of infection at a significantly earlier stage than is possible under previously approved tests using antibody or antigen detection technology; including the HIV-1 p24 antigen test.

We believe that these newly licensed tests are now widely available, and that these tests meet the criteria for screening tests that are necessary to reduce adequately and appropriately the risk of transmission of communicable disease through blood products.

The biologics regulations require licensed blood and Source Plasma manufacturers to report manufacturing changes, such as a change in donor testing, to FDA (§ 601.12). We further explain those reporting requirements in Section V of this guidance.

This guidance combines and finalizes the draft guidance "Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV" dated December 2001 (January 31, 2002, 67 FR 4719) and the draft guidance "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" dated March 2002 (April 9, 2002, 67 FR 17077).

II. BACKGROUND

Transmission of HIV and HCV by blood and blood components has been dramatically reduced as a result of implementation of sensitive tests for viral antibody and antigen. The major sources of remaining risk of transmission of HIV and HCV by blood and blood components include window period donations (donations that occur when the donor is infectious, but before the infection can be detected using approved tests), viral variants (which may not be detectable using tests designed to identify the common forms of a virus), atypical seroconversion as indicated by an unusually prolonged window period or lack of seroconversion, and laboratory testing error **(Ref. 1, 2**). In addition, initiatives by the Source Plasma industry, including the study of NAT performed under an investigational new drug application (IND), have greatly reduced the frequency of infectious units entering plasma pools for further manufacturing **(Ref. 3**). Although effective viral clearance methods are in place for almost all plasma derivatives, measures to reduce the occurrence of window period donations are expected to further reduce the residual risk of HIV or HCV infectious units entering plasma pools, and enhance the overall safety of blood products.

In 1994, we held a workshop to explore the potential application of nucleic acid based methods to screen samples from blood donors for HIV. At that time, it was thought that although these methods were clearly sensitive, they were not ready for implementation on a large scale. However, the workshop fueled interest in developing systems for implementing nucleic acid methodology for testing blood and plasma donations, since the methodology might be used to identify earlier stages of infection, and therefore reduce the window period for donations.

Subsequently, test kit manufacturers and blood organizations, in collaboration with the government (The National Institutes of Health (NIH) and FDA), actively pursued development of NAT assays for HIV-1 RNA and HCV RNA. The sensitivity of NAT on pooled samples and labor intensiveness of testing individual donations made testing pooled samples more efficient than testing individual donations.

Clinical studies to evaluate NAT were initiated in 1997 under INDs. Large-scale studies were necessary to demonstrate the efficacy of NAT as a donor screening method, primarily because the frequency of window period donations is low. We have worked with manufacturers to validate NAT assays for donor screening through review of their Biologics License Applications (BLAs) **(Ref. 4)**. In December 1999, we provided industry with guidance on manufacturing and assay validation for licensure of NAT.

By 1997, some manufacturers in Europe had voluntarily instituted NAT on pooled samples of plasma. At about that time, the European Union issued a directive requiring HCV RNA testing for all plasma fractionated in Europe by July 1, 1999, and stated that HIV-1 RNA testing would be required at a later date. The European directive, which applied to both Source Plasma and recovered plasma, provided further impetus to the rapid development of NAT for blood and plasma donations in the United States.

Since September 2001, we have licensed several NAT assays for the detection of HIV-1 RNA and HCV RNA in Whole Blood and blood components including Source Plasma. Validation data submitted by manufacturers support replacement of currently licensed assays for HIV-1 p24 antigen by both pooled and individual NAT.

FDA has previously issued guidance on Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV) (Memorandum to All Blood Establishments, April 23, 1992, http://www.fda.gov/cber/bldmem/hcv042392.pdf) and Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products (Memorandum to All Blood Establishments, April 23, 1992, http://www.fda.gov/cber/bldmem/hiv042392.pdf).

III. RECOMMENDATIONS FOR DONOR SCREENING

Under 21 CFR 610.40(b), you must perform one or more screening tests approved by the FDA as necessary to reduce adequately and appropriately the risk of transmission of communicable disease agents, including HIV-1 and HIV-2, and, HCV. Note that the regulation requires testing for all of these agents, and does not provide an exemption from the requirement to test for all named agents if a donation will be discarded on the basis of reactive tests for a single disease agent such as HIV-1.

We recommend that you meet the requirement for conducting adequate and appropriate testing for HIV and HCV, as required by 21 CFR § 610.40(b), in accord with points 1 and 2 below. Note that, although we recommend the use of HIV-1 NAT and HCV NAT on units that are not reactive on a donor screening test for the detection of antibodies to HIV or HCV, respectively, we do not believe that HIV-1 NAT and HCV NAT are necessary in all instances. We do not believe that a licensed HIV-1 NAT is part of the adequate and appropriate testing required under 610.40(b) for donations that are reactive on a test for the detection of antibodies to HIV-1 and are to be discarded or used in the manufacture of non-injectable products. Similarly, we do not believe that a licensed HCV NAT is part of the adequate and appropriate testing required under 610.40(a) for donations that are reactive on a donor screening test for the detection of antibodies

to HCV and are to be discarded or used in the manufacture of non-inject able products. Nevertheless, you may decide to perform HIV-1 and HCV NAT in order to obtain useful information regarding the donor's infection status. This information may be useful as part of donor notification.

1) For HIV-1: To meet the requirement to use one or more approved screening tests, as necessary to adequately and appropriately reduce the risk of transmission of communicable disease, we recommend that you use an FDA licensed donor screening test for the detection of antibodies to HIV-1 (either a stand alone HIV-1 test or a combination HIV-1/HIV-2 test). If the FDA licensed test for detection of antibodies to HIV-1 is negative or non-reactive, we recommend that, as part of adequate and appropriate screening, you test the donation further using an FDA licensed HIV-1 NAT. Testing using the tests for the antibodies to HIV-1 and HIV-1 NAT may be performed concurrently.

   If that FDA licensed test for the detection of antibodies to HIV-1 is reactive and the donation will be discarded or used in the manufacture of non-injectable products, we believe that you have met the standard for adequate and appropriate screening for HIV-1. Although you may choose to test such a reactive donation by using an FDA licensed HIV-1 NAT, and although additional testing may provide information that would be useful to the donor, we do not believe that it is necessary to perform this additional test. However, you must proceed to supplemental testing for HIV-1 using an additional, more specific test, as required by 21 CFR § 610.40(e).

   Conversely, if a donation that is reactive on a test for the detection of antibodies to HIV-1 will be used for autologous transfusion or for further manufacturing into injectable products, we recommend that you test the donation using an FDA licensed HIV-1 NAT.

   We believe that, when HIV-1 NAT is used in accordance with these recommendations, the use of the HIV-1 p24 test (previously recommended by FDA) is not necessary to reduce adequately and appropriately the risk of transmission of HIV-1.

2) For HCV: To meet the requirement to use one or more approved screening tests, as necessary to adequately and appropriately reduce the risk of transmission of communicable disease, we recommend that you use an FDA licensed donor screening test for the detection of antibodies to HCV. If the FDA licensed test for detection of antibodies to HCV is negative or non reactive, we recommend that, as part of adequate and appropriate screening, you test the donation further using an FDA licensed HCV NAT. Testing using a test for antibodies to HCV and the HCV NAT test may be performed concurrently.

   If that FDA licensed test for the detection of antibodies to HCV is reactive and the donation will be discarded or used in the manufacture of non-injectable products,

we believe that you have met the standard for adequate and appropriate screening for HCV. Although you may choose to test such a reactive donation by using an FDA licensed HCV NAT, and although additional testing may provide information that would be useful to the donor, we do not believe that it is necessary to perform this additional test. However, you must proceed to supplemental testing for HCV using an additional, more specific test, as required by 21 CFR § 610.40(e).

Conversely, if a donation that is reactive on a test for the detection of antibodies to HCV will be used for autologous transfusion or for further manufacturing into injectable products, we recommend that you test the donation using an FDA licensed HCV NAT.

IV. ADDITIONAL TESTING CONSIDERATIONS

You must defer a donor who tests reactive by a donor-screening test (§ 610.41), you must perform a supplemental (additional, more specific) test on donations that test reactive on an initial screening test (§ 610.40(e)), and you must make reasonable attempts to notify a donor who has been deferred based on the results of tests for communicable diseases (§ 630.6).

V. REQUIREMENTS FOR REPORTING IMPLEMENTATION OF HIV-1 AND HCV NAT FOR LICENSED BLOOD AND PLASMA ESTABLISHMENTS (21 CFR 601.12)

Under 21 CFR 601.12, biologics license applicants are required to inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved application(s). Before distributing a product made using a change (including instrumentation), an applicant must demonstrate, through appropriate validation and/or studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product (21 CFR 601.12(a)). The type of notification to FDA required under this section varies according to the potential of the change to have an adverse effect on the identity, strength, quality, purity, or potency of the product, as they may relate to the safety or effectiveness of the product. Notification may be by annual report (when there is a minimal potential for adverse effect, 21 CFR 601.12(d)), changes being effective supplement (when there is a moderate potential for adverse effect and particular assurances are provided to FDA, 21 CFR 601.12(c)(5)), changes being effective in 30 days supplement (when there is a moderate potential for adverse effect, 21 CFR 601.12(c)), or prior approval supplement (PAS) (when there is a substantial potential for adverse effect, 21 CFR 601.12(b)). Labeling changes are addressed in 21 CFR 601.12(f).

In section V.A. below, we describe our recommendations for reporting your implementation of a licensed NAT kit.

In section V.B., below, we describe our recommendations for reporting implementation of NAT using a licensed NAT assay test facility approved for use on pools of samples from Source

Plasma donors. In addition, if you intend to use a licensed NAT test facility, and you or your contract laboratory intend to use instruments and software for sample pooling that have not previously been validated using these assays, we believe this manufacturing change would present a substantial potential for adverse effect. We recommend that you submit the change in a PAS, and include validation data, information on the instruments and software used, the procedure/algorithm for pooling and the number of samples in the master pool

A. Implementation of a licensed NAT kit for Whole Blood and blood components including Source Plasma and Source Leukocytes for which instruments and software for pooling of samples are referenced in the product insert and are validated as part of the test procedure

The following recommendations for reporting manufacturing changes under 601.12 apply when implementing a licensed NAT (with the particular test to be used identified in your submission) according to the manufacturer's instructions (see Table 1).

Table 1. Implementation of a Licensed NAT Kit

If you…	***And…***	***Then we recommend that you:***
will perform licensed NAT in your facility	you are already FDA approved to perform infectious disease testing for your Whole Blood and blood components	report in your next annual report (AR) (§ 601.12(d)). Submit an instruction circular and revised labeling, as described in section VI. (§ 601.12(f))
	testing is new at your facility	submit a prior approval supplement (PAS) to your BLA (§ 601.12(b)). Include an instruction circular and revised labeling, with your supplement (see section VI.)
will use an FDA registered contract laboratory to perform licensed NAT	you have already supplemented your BLA to use this laboratory for infectious disease testing for your Whole Blood and blood components	report in your next AR (§ 601.12(d)). Submit an instruction circular and revised labeling, as described in section VI.
	you have not used the laboratory before and they already perform infectious disease testing for Whole Blood and blood components	submit a changes being effected in 30 days (CBE-30) supplement to your BLA (§ 601.12(c)). Submit an instruction circular and revised labeling, as described in section VI.
	the laboratory has not previously performed infectious disease testing for Whole Blood and blood components	submit a PAS to your BLA (§ 601.12(b)). Include an instruction circular and revised labeling, with your supplement. (see section VI.)
will concurrently discontinue testing for HIV-1 p24 antigen		include this information in the submission described above, and submit revised labeling as described in section VI.

B. Implementation of NAT using a licensed NAT assay test facility approved for use on pools of samples from Source Plasma donors

If a licensed NAT assay test facility will perform testing or testing and pooling of the samples, we recommend that you submit a CBE-30 to supplement your BLA (§ 601.12(c), and revised labeling to supplement your BLA as described in section VI. If you intend to discontinue testing for HIV-p24 antigen, we recommend that you include this information in your CBE-30 supplement.

Table 2. Implementation of NAT using a Licensed NAT Assay Test Facility

If you…	***and…***	***Then we recommend that you:***
will perform sample pooling at your facility	you already perform infectious disease testing on your Source Plasma	submit a CBE-30 supplement to your BLA (§601.12(c)), including information on the procedure/algorithm for pooling and the number of samples in the master pool. This information may be included in the CBE-30 supplement for implementing NAT.
	infectious disease testing is new at your facility	submit a PAS to your BLA (§ 601.12(b)), including SOPs, validation data on pooling, storage, sample shipment, and information on software and data management systems.
will use a registered contractor to perform pooling in support of licensed NAT	the contractor is already registered to perform infectious disease testing for a. Whole Blood and blood components or b. pooling of Source Plasma donor samples for NAT	submit a CBE-30 supplement to your BLA (§ 601.12 (c)) including information on the procedure/algorithm for pooling and the number of samples in the master pool. This information may be included in your CBE-30 supplement for implementing NAT.
	the contractor is already registered but has not previously performed infectious disease testing for a. Whole Blood and blood components or b. pooling of Source Plasma donor samples for NAT testing	submit a PAS to your BLA (§601.12) and additional information described above for PAS submissions.

VI. PRODUCT LABELING AND DISPOSITION

A. Whole Blood and blood components for transfusion

Consistent with the labeling for other infectious disease markers, nonreactive NAT results need not appear on the container label. We recommend that you include these test results in the instruction circular. Upon implementation of a licensed NAT, we recommend that you use an instruction circular that reflects the results of NAT, and the discontinuation of HIV-1 p24 antigen testing, if applicable, and that you submit a revised instruction circular incorporating the results of NAT for HIV-1 and HCV, as well as discontinuation of HIV-1 p24 antigen testing as a changes being effected supplement under § 601.12(f)(2)(i)(E). In a Final Guidance for Industry, An Acceptable Circular of Information for the Use of Human Blood and Blood Components, December 2003

http://www.fda.gov/cber/gdlns/circbld.htm, FDA recognized "as acceptable for use by manufacturers of blood and blood components intended for transfusion subject to United States statutes and regulations, the instruction circular entitled 'Circular of Information for the Use of Human Blood and Blood Components' (Circular)" dated July 2002, http://www.fda.gov/cber/gdlns/crclr.pdf. This circular has incorporated the results of NAT and the discontinuation of HIV-1 p24 antigen testing.

B. Blood components intended for further manufacture

Upon implementation of a licensed NAT, we recommend that you include NAT results on the labeling for blood components intended for further manufacture into injectable or non-injectable products. We recommend that you use the following statement on the labeling for donations that test nonreactive:

"Nonreactive for HIV-1 RNA and HCV RNA."

Alternatively, you may report NAT results in combination with the results of other infectious disease testing.

If you wish to use a statement regarding NAT results that is consistent with the recommendations above, we recommend that you submit this labeling change as a changes being effected supplement under § 601.12(f)(2)(i)(E).

NOTE: For section B (above), we do not recommend that you submit an additional labeling supplement if you have already received approval for an alternate test statement.

C. Reactive units and product disposition

NAT reactive units must not be shipped or used, except as provided in § 610.40(h)(2). If released for these uses, the units must be relabeled consistent with the labeling requirements in §§ 606.120, 610.40, and 640.70.

Additionally, under § 610.40(h)(2)(ii)(B), (C), and (E), you must label the reactive unit with the "Biohazard" legend and with the following cautionary statements as applicable:

"Reactive for HIV-1 RNA",

or

"Reactive for HCV RNA",

or

"Reactive for HIV-1 RNA and HCV RNA",

and either

"Caution: For Further Manufacturing into In Vitro Diagnostic Reagents for Which There Are No Alternative Sources",

or

"Caution: For Laboratory Research Use Only".

VII. IMPLEMENTATION

HIV-1 and HCV NAT for testing samples from donors of Whole Blood and blood components (including Source Plasma and Source Leukocytes) may involve the use of complex pooling and testing systems. We recognize that it may require time to implement these systems. We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than six months after the guidance issue date.

VIII. REFERENCES

1. M.P. Busch and S. H. Kleinman, Nucleic Acid Amplification Testing of Blood Donors for Transfusion- Transmitted Infectious Diseases, Transfusion 2000; 40:143-159.
2. S.H. Kleinman and M.P. Busch, The Risks of Transfusion-Transmitted Infection: Direct Estimation and Mathematical Modeling. Bailliere's Clinical Hematology 2000; 13:631-649.
3. General Accounting Office, Blood Plasma Safety: Plasma Product Risks Are Low If Good Manufacturing Practices Are Followed, GAO/HEHS-98-205.
4. Guidance for Industry: In the Manufacture and Clinical Evaluation of In Vitro Tests to Detect Nucleic Acid Sequences of Human Immunodeficiency Viruses Type 1 and 2. December 1999 (December 14, 1999; 64 FR 71147) (http://www.fda.gov/cber/gdlns/hivnas.htm).