DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606 and 610

[Docket No. 1999N–2337 (formerly Docket No. 99N–2337)]

RIN 0910–AB76

Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection (''Lookback'')

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is requiring establishments collecting Whole Blood or blood components, including Source Plasma and Source Leukocytes, to establish, maintain, and follow an appropriate system for identifying blood and blood components previously donated by a donor who tests reactive for evidence of hepatitis C virus (HCV) infection on a subsequent donation identified either by current testing or after a review of historical testing records, or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HCV infection. Such collections may be at increased risk of transmitting HCV infection. FDA is requiring collecting establishments to quarantine prior in-date blood and blood components from such a donor, to notify consignees of prior in-date blood and blood components from such a donor for quarantine purposes, and to perform further testing on the donor. FDA is also requiring consignees to notify transfusion recipients of blood and blood components from such a donor, as appropriate. In addition, FDA is revising the human immunodeficiency virus (HIV) ''lookback'' requirements for greater consistency with the HCV ''lookback'' requirements, and extending the record retention period to 10 years. FDA is taking this action to help ensure the continued safety of the blood supply and to help ensure that information is provided to recipients of blood and blood components that may have been at increased risk of transmitting HIV or HCV infection. Elsewhere in this issue of the **Federal Register**, FDA is announcing the availability of a guidance document entitled ''Guidance for Industry: 'Lookback' for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV'' (the ''lookback'' guidance). We are also issuing this final rule in conjunction with a companion interim final rule published by the Centers for Medicare and Medicaid Services (CMS) elsewhere in this issue of the **Federal Register**.

DATES: This rule is effective February 20, 2008.

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I. Introduction

A. Background

As a result of extensive screening and testing procedures and other layers of safety used to help ensure a safe blood supply, the risk of transmitting infection through blood transfusion is very low. Despite the best practices of blood establishments[1], however, a person may donate blood and blood components early in an infection, during the period when the testable marker is not detectable by a screening test, but the infectious agent is present in the donor's blood (a ''window'' period). Such products are considered as having an increased risk of transmitting infection. We are issuing this final rule to help ensure the continued safety of the blood supply and to help ensure that information is provided to recipients of blood and blood components possibly donated during a ''window'' period, which therefore may be at increased risk of transmitting infection.

Chronic hepatitis due to HCV is a major health problem in the United States. The infection is usually asymptomatic for decades despite possible progression. Thus, individuals with chronic, active hepatitis C can remain unaware that they have a serious infection until symptoms develop late in the course of the disease. Five to twenty percent of infected persons might develop cirrhosis of the liver over a period of 20 to 30 years and one to five percent might die from the consequences of long term infection (liver cancer or cirrhosis). As a result, infected people typically are unaware of their disease. Although transfusion-transmitted infections account for only a small proportion of HCV infections, it is possible to identify and ''lookback'' at prior donations collected during the ''window'' period from donors later identified as reactive on a test for evidence of HCV infection. Further information on existing donor screening and testing requirements and a history of HCV testing is provided in the proposed rule entitled ''Current Good Manufacturing Practice for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting HCV Infection ('Lookback')'' (the HCV ''lookback'' proposed rule) (November 16, 2000, 65 FR 69378 at 69379).

In an August 1993 memorandum to all registered blood establishments entitled ''Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV),'' we did not recommend a ''lookback'' program, pending the outcome of discussions on the issue at the December 1993 Blood Product Advisory Committee (BPAC) meeting. Following the discussions on HCV at the meeting in December 1993, the BPAC unanimously recommended product quarantine of prior collections from a donor who later tests repeatedly reactive for antibody to HCV and tests positive or indeterminate on a supplemental (additional, more specific) test.

[1] The term ''establishment'' is defined in FDA's blood regulations at 21 CFR 607.3(c).

However, BPAC only marginally endorsed consignee[2] notification for the purpose of transfusion recipient notification, and reiterated many of the reservations regarding the lack of an established public health benefit in performing this activity. We issued in July 1996 a memorandum to all registered blood establishments entitled ''Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human T-Lymphotropic Virus Type I (HTLV–I)'' (the July 1996 memorandum). The July 1996 memorandum recommended testing, consignee notification, and quarantine of affected products, but did not provide recommendations for the notification of recipients of such donations because the public health benefit of such notification was not clear.

The Department of Health and Human Services Advisory Committee on Blood Safety and Availability (the HHS Advisory Committee) discussed improvements in the treatment and management of HCV infection and improvements in testing for antibody to HCV at public meetings held on April 24 and 25, 1997, and August 11 and 12, 1997. The DHHS Advisory Committee discussed the public health benefits of notification of transfusion recipients receiving prior collections from a donor who subsequently tests reactive for evidence of HCV infection and made recommendations for HCV ''lookback.'' Following acceptance by the Department of Health and Human Services (DHHS) of the DHHS Advisory Committee's recommendations for HCV ''lookback,'' we issued a notice in the **Federal Register** of March 20, 1998 (63 FR 13675), announcing the availability of a document entitled ''Guidance for Industry: Supplemental Testing and the Notification of Consignees of Donor Test Results for Antibody to Hepatitis C Virus (Anti-HCV)'' (the March 1998 guidance) in which we recommended that blood establishments implement HCV ''lookback'' procedures. In the March 1998 guidance, we recommended that donors currently testing repeatedly reactive for antibody to HCV by a licensed test be further tested for antibody to HCV using a licensed, multi-antigen supplemental test. Additionally, we recommended that consignees of certain blood and blood components collected since January 1, 1988, which were anti-HCV negative or untested, be notified when donors subsequently test repeatedly reactive for anti-HCV by a licensed multiantigen-based antibody screening test and reactive by a licensed or investigational supplemental test. This notification would enable consignees to inform recipients that they were transfused with units that may have contained HCV, so that they might obtain further medical counseling and treatment. The March 1998 guidance provided our recommendations for donor screening, a review of past testing records, further testing for antibody to HCV, notification of consignees, and transfusion recipient notification and counseling by physicians regarding transfusion with blood or blood components at increased risk of transmitting HCV. The March 1998 guidance was intended to supplement the July 1996 memorandum.

In response to comments received, the March 1998 guidance was withdrawn on September 8, 1998, and we issued a revised guidance dated September 1998, on October 21, 1998 (63 FR 56198), entitled ''Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Units From Prior Collections From Donors With Repeatedly Reactive Screening Test for Antibody to Hepatitis C Virus (Anti-HCV); (2) Supplemental Testing, and the Notification of Consignees and Blood Recipients of Donor Test Results for Anti-HCV,'' (the September 1998 guidance). The September 1998 guidance provided recommendations to enable quarantine and disposition of blood and blood components from prior collections from donors with repeatedly reactive screening test results.

The September 1998 guidance addressed several significant comments and requests from industry:

- We revised several time periods for ''lookback'' actions in response to concerns about the impact on industry and the need for additional time for testing due to availability problems with certain test kits, and to allow time for the completion of physician education (ensuring that counseling messages would be available for use in notification of recipients);
- We clarified options for further testing with an HCV enzyme linked immunosorbent assay 3.0 (HCV EIA 3.0 screening test);
- We clarified our recommendations on labeling of the blood and blood components released from quarantine and for consistency with existing regulations on product labeling;
- We provided flow chart diagrams to assist industry in implementing procedures contained in the guidance; and
- We recommended the option of transfusion services notifying the transfusion recipient directly as an alternative to notifying the transfusion recipient's physician of record, to permit easier, more rapid notification of the recipient.

At public meetings on November 24, 1998, and January 28, 1999, the DHHS Advisory Committee reconsidered the issue of recipient notification related to repeatedly reactive results by the single antigen-based antibody screening test. The DHHS Advisory Committee recommended that targeted ''lookback'' be initiated based on a repeatedly reactive HCV EIA 1.0 screening test result on a repeat donor except in the following conditions: (1) A supplemental (additional, more specific) test was performed and the result did not indicate increased risk of HCV infection; (2) in the absence of a supplemental test result, the signal to cut-off (S/CO) value of the repeatedly reactive HCV EIA 1.0 screening test was less than 2.5; or (3) followup testing of the donor was negative. We published a notice in the **Federal Register** of June 22, 1999 (64 FR 33309), announcing the availability of a draft guidance entitled ''Draft Guidance for Industry: Current Good Manufacturing Practice for Blood and Blood Components: (1) Quarantine and Disposition of Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis C Virus (HCV); (2) Supplemental Testing, and the Notification of Consignees and Transfusion Recipients of Donor Test Results for Antibody to HCV (Anti-HCV)'' (the June 1999 draft guidance). Consistent with the recommendations of the DHHS Advisory Committee, this revised draft guidance addressed ''lookback'' actions related to donor screening by HCV EIA 1.0 and also recommended that the search of historical test records of prior donations from donors with repeatedly reactive EIA 1.0, EIA 2.0, or EIA 3.0 screening tests for HCV should extend back indefinitely to the extent that electronic records exist. In addition, we revised the flowchart diagrams to reflect the changes to the guidance. We added specific recommendations for prior collections from a repeatedly reactive autologous donor and clarified recommendations on implementing ''lookback'' for repeatedly reactive plasma donations.

On November 16, 2000, FDA and the Health Care Financing Administration, now known as the Centers for Medicare and Medicaid Services (CMS), issued proposed rules that would further

[2] We use the term ''consignee'' to refer to the person or entity to whom the blood is shipped.

protect the blood supply and notify recipients of the possibility that they may have received blood or blood components with an increased risk of transmitting HCV. FDA's HCV ''lookback'' proposed rule, along with CMS's companion proposed rule (November 16, 2000, 65 FR 69416), proposed to require establishments involved in the collection, processing, and distribution of blood and blood components to quarantine certain blood and blood components and to inform the consignee. The consignee, as appropriate, would inform the recipient's physician of record or the recipient of the possibility that blood used for transfusion was obtained from a donor who subsequently tested repeatedly reactive for antibody to HCV.

Elsewhere in this issue of the **Federal Register**, we are announcing the availability of a guidance document entitled ''Guidance for Industry: 'Lookback' for Hepatitis C Virus (HCV): Product Quarantine, Consignee Notification, Further Testing, Product Disposition, and Notification of Transfusion Recipients Based on Donor Test Results Indicating Infection with HCV'' (the ''lookback'' guidance). We prepared the ''lookback'' guidance based on comments received on the June 1999 draft guidance and comments received on the HCV ''lookback'' proposed rule and issued the guidance document for implementation by the agency. The guidance document does not create or impose any legal rights or requirements, rather, it represents our current thinking on methods for satisfying the requirements now imposed by this rule and addresses actions that could be taken based on results of screening and supplemental testing. It supercedes the September 1998 guidance and the HCV sections of the July 1996 memorandum.

B. Legal Authority

We are issuing this final rule under the authority of sections 351 and 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262 and 264) and the provisions of the Federal Food, Drug, and Cosmetic Act (the act), which apply to drugs (section 201 of the act *et seq.* (21 U.S.C. 321 *et seq.*)). Under section 361 of the PHS Act, by delegation from the Secretary of Health and Human Services, we may make and enforce regulations necessary to prevent the introduction, transmission, and spread of communicable disease between the States or from foreign countries into the States. Intrastate transactions may also be regulated under section 361 of the PHS Act. (See *Louisiana* v. *Mathew*, 427 F. Supp. 174, 176 (E. D. La. 1977).) Because a major purpose of the HCV ''lookback'' final rule is to prevent the introduction, transmission, and spread of HCV, a communicable disease, section 361 of the PHS Act provides the primary legal authority for this final rule, including the rule's provisions on standard operating procedures, records, donor deferral, and ''lookback'' requirements, for manufacturers, including collecting establishments, and consignees.

All blood and blood components introduced or delivered for introduction into interstate commerce also are subject to section 351 of the PHS Act. Section 351(a) requires that manufacturers of biological products, which include blood and blood components intended for further manufacture into injectable products, have a license, issued upon a demonstration that the product is safe, pure, and potent and that the manufacturing establishment meets all applicable standards, including those prescribed in the FDA regulations, designed to ensure the continued safety, purity, and potency of the blood. Moreover, section 351(a)(2)(A) of the PHS Act gives us, by delegation from the Secretary of Health and Human Services, authority to establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses. This final rule establishes such requirements for blood and blood components intended for further manufacture into injectable products.

Our license revocation regulations provide that we may initiate revocation proceedings, among other reasons, if an establishment or product fails to conform to the standards in the license application or in the regulations designed to ensure the continued safety, purity, or potency of the product (21 CFR 601.5). The requirements of this final rule are designed to ensure the continued safety, purity and potency of donated blood and blood products. Section 351 of the PHS Act also provides for civil and criminal penalties for violation of the laws governing biological products. Violations can be punishable by fines, imprisonment, or both.

Section 351(j) of the PHS Act states that the Federal, Food, Drug, and Cosmetic Act also applies to biological products. Blood and blood components for transfusion or for further manufacture into injectable products are drugs, as that term is defined in section 201(g)(1) of the act. (See *United States* v. *Calise*, 217 F. Supp. 705, 709 (S.D.N.Y. 1962)). Because blood and blood components are drugs under the act, blood and plasma establishments must comply with the substantive provisions and related regulatory scheme of the act. For example, under section 501 of the act (21 U.S.C. 351), drugs are deemed ''adulterated'' if the methods used in their manufacturing, processing, packing, or holding do not conform to current good manufacturing practice (CGMP). Under this final rule, the CGMP regulations for manufacturers of blood and blood components are amended to require those establishments to develop standard operating procedures (SOPs) for HCV ''lookback,'' identification, quarantine of affected blood and blood components, and consignee and transfusion recipient notification. A blood or plasma establishment that fails to comply with HCV ''lookback'' procedures would not be in compliance with CGMP requirements and, therefore, would be subject to the act's enforcement provisions.

II. Highlights and Summary of the Final Rule

We are issuing this final rule in conjunction with a companion interim final rule published by CMS elsewhere in this issue of the **Federal Register**. This final rule and the CMS interim final rule provide steps designed to further protect the blood supply and to notify recipients of the possibility that they may have received blood or blood components at increased risk of transmitting HIV or HCV. The phrase ''blood and blood components,'' as used in this rulemaking, includes Source Plasma and Source Leukocytes.

A. Restructuring of the Proposed Rule

After careful review of the proposed rule, and in response to comments submitted to the docket, we have revised the codified section of the proposed rule as follows:

- We combined proposed §§ 610.46 and 610.47 into requirements under new § 610.46 for prospective HIV ''lookback.''
- We combined proposed §§ 610.48 and 610.49 into requirements under new § 610.47 for prospective HCV ''lookback.''
- We removed the requirements for retrospective HCV ''lookback'' from proposed §§ 610.48 and 610.49 and placed them under new § 610.48.
- Each section separates provisions for collecting establishments and for consignees.
- The codified section lists objective actions and eliminates the prescriptive language in the proposed rule.
- The sections for prospective HIV and HCV ''lookback'' (§§ 610.46 and 610.47) are analogous in their requirements.

• The final rule establishes a ''cut-off'' date for retrospective HCV ''lookback.''

B. Summary of the Final Rule

1. HIV and HCV ''Lookback'' (§§ 610.46 and 610.47, respectively)

a. *Responsibilities of the collecting establishment*. In §§ 610.46 and 610.47, respectively, the final rule requires collecting establishments to establish, maintain, and follow an appropriate system for performing HIV and HCV prospective ''lookback'' when a donor tests reactive for evidence of HIV or HCV infection (see § 610.40(a) and (b) (21 CFR 610.40(a) and (b))), or when the collecting establishment becomes aware of other reliable test results or information indicating evidence of HIV or HCV infection (''prospective lookback'') (§§ 610.46(a)(1) and 610.47(a)(1)). The requirement for ''an appropriate system'' states the intention of the requirement and replaces the more prescriptive language of the proposed rule. This provision requires the collecting establishment to design SOPs to identify and quarantine all blood and blood components previously collected from a donor who later tests reactive for evidence of HIV or HCV infection, or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection (see section II.C.4 of this document for further discussion of the term ''reactive''). Within 3 calendar days of the donor testing reactive by an HIV or HCV screening test or the collecting establishment becoming aware of other reliable test results or information, the collecting establishment must take the following actions:

• Review all records, required to be maintained under § 606.160(d), to identify blood and blood components previously donated by such a donor. For those blood and blood components collected 12 months and less before the donor's most recent nonreactive screening tests for HIV or HCV, or 12 months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test (NAT) (HIV and HCV) or HIV p24 antigen test (HIV), and a nonreactive antibody screening test for HIV or HCV, whichever is a lesser period (§§ 610.46(a)(1)(i) and (a)(1)(ii), and 610.47(a)(1)(i) and (a)(1)(ii)), the collecting establishment must do the following:

• Quarantine all identified previously collected in-date blood and blood components if intended for use in another person or for further manufacturing into injectable products (§§ 610.46(a)(1)(ii)(A) and 610.47(a)(1)(ii)(A)). Pooled blood components solely intended for further manufacturing into products that are manufactured using validated clearance (i.e., inactivation and removal) procedures are not subject to quarantine; and

• Notify consignees to quarantine all identified previously collected in-date blood and blood components (§§ 610.46(a)(1)(ii)(B) and 610.47(a)(1)(ii)(B)). The consignee's pooled blood components solely intended for further manufacturing into products that are manufactured using validated viral clearance (i.e., inactivation and removal) procedures also are not subject to quarantine.

Within 45 calendar days of the reactive screening test, the collecting establishment must perform a supplemental additional, more specific) test on the reactive donation (§ 610.40(e)) for HIV (§ 610.46(a)(2)) or HCV (§ 610.47(a)(2)), and must notify the consignees of the supplemental test results, or the results of a reactive screening test if there is no available supplemental test that is approved for such use by FDA (§§ 610.46(a)(3) and 610.47(a)(3)). Thus, if we have not approved a supplemental test for a required screening test, you must notify consignees of the results of the reactive screening test. Similarly, if there is a shortage of an approved supplemental test such that they are not available for commercial purchase, you must notify consignees of the results of the reactive screening test. By adding the term ''available'' to the codified language, we are not authorizing blood establishments to simply choose to notify consignees of the result of a reactive screening test if the establishment has simply run out of the approved supplemental test. Rather, the test must be unavailable commercially. We are also adding ''or if under an IND or IDE, is exempted for such use by FDA'' so that we have the ability to authorize the use of a supplemental test under an investigational new drug application (IND) or an investigational device exemption (IDE) under certain circumstances. In such cases, we will issue guidance on alternative product use under conditions where approved supplemental tests are unavailable, or when a product under IND or IDE is exempted for such use. Currently, there are FDA-approved supplemental tests for all antibody and antigen screening tests for HIV and HCV, except NAT. Therefore, if a donor tests reactive by NAT and nonreactive by an antibody screening test, the results would be reported to the consignee without further testing. Notification must include the supplemental test results for all identified blood and blood components previously collected from donors who later test reactive for evidence of HIV or HCV infection.

Once the collecting establishment receives the supplemental test results and notifies the consignees, then the collecting establishments must release, destroy, or relabel quarantined in-date blood and blood components consistent with the supplemental test results or a reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA (§§ 610.46(a)(4) and 610.47(a)(4)). Our current thinking on the appropriate actions of releasing, destroying, and relabeling is discussed in the ''lookback'' guidance.

b. *Responsibilities of the consignees*. The consignee must also establish, maintain, and follow an appropriate system (as described in section II.B.1.a of this document) for performing HIV and HCV ''lookback'' when notified by the collecting establishment that they have received blood and blood components previously collected from donors who later tested reactive for evidence of HIV or HCV infection, or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection in a donor (§§ 610.46(b) and 610.47(b)). This provision for a system requires the consignee to establish SOPs for the following actions:

• Quarantining consigned in-date blood and blood components when notified by the collecting establishment (§§ 610.46(b)(1) and 610.47(b)(1)).

• Releasing, destroying, or relabeling quarantined in-date blood and blood components consistent with the supplemental test results or a reactive screening test if there is no available supplemental test that is approved for such use by FDA or exempted for such use by FDA (§§ 610.46(b)(2) and 610.47(b)(2)).

• Notifying transfusion recipients of blood and blood components, or the recipient's physician of record or legal representative, when such action is indicated by the results of the supplemental (additional, more specific) tests or a reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA. The consignee must make reasonable attempts to perform the notification within 12 weeks of receipt of the supplemental test result or receipt of a reactive screening test result when

there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA. Notification of the recipient is necessary in order to permit testing, counseling, and (if necessary) treatment for recipients who received blood or blood components potentially at risk of transmitting HIV or HCV (§§ 610.46(b)(3) and 610.47(b)(3)).

c. *No recall action*. We have added a statement in §§ 610.46(c), 610.47(c), and 610.48(d) that ''lookback'' does not constitute a recall as defined in 21 CFR 7.3. Discussion of the differences between a recall action and a ''lookback'' action may be found in the HCV ''lookback'' proposed rule (65 FR 69378 at 69391). FDA recognizes that a ''lookback'' action does not mean that an establishment has erred or that it did not meet its obligations under the regulations and the statute in assuring the safety of the blood supply. However, failure to comply with the ''lookback'' regulations is a regulatory violation and may merit enforcement action.

2. HCV ''Lookback'' Requirements Based on Review of Historical Testing Records (§ 610.48)

As previously described, we have removed the requirements for the review of historical testing records from proposed §§ 610.48 and 610.49 and placed them under final § 610.48 *Hepatitis C virus (HCV) ''lookback'' requirements based on review of historical testing records*. It is important to identify and notify recipients previously transfused with blood or blood components at increased risk of transmitting HCV infection because HCV is a chronic, often asymptomatic disease that may ultimately have serious consequences. Therefore, we are requiring the review of historical HCV testing records of donors so that blood and blood components previously collected from donors who later test reactive for evidence of HCV infection are identified, and recipients of such blood and blood components are notified of the possibility of being infected with HCV. With this information, the recipients can be tested and, if infected, pursue treatment and counseling, and take preventive measures to avoid transmitting HCV to others. The requirements for historical review of HCV testing records or ''retrospective review'' are the same as the requirements for the prospective review of HCV testing records, except for variations in the required time for completion of the actions, the extent of record review, and a distinction regarding the specimen that may be used for further testing (either a frozen sample from the same reactive donation or a fresh sample from the same donor).

a. *Completion of required actions*. To permit adequate time to perform the requirement for the review of historical HCV testing records, § 610.48(a) requires that the collecting establishments complete the actions prescribed in § 610.48(b) within 1 year of the effective date of this final rule. Consignees must complete the actions prescribed in § 610.48(c) within 1 year of the date of notification by the collecting establishment.

We have also established a date for the conclusion of historical record review of HCV testing in § 610.48(b)(1)(i). The historical record review must include all HCV testing performed before February 20, 2008, the effective date of this rule. The requirements under § 610.48 will remain in effect for 8 years after the date of publication in the **Federal Register**.

b. *Extent of record review*. When performing the historical record review, under § 610.48(b)(1)(i), the establishment must review all HCV testing from February 20, 2008 back indefinitely for computerized electronic records, and to January 1, 1988, for all other records. Once a reactive screening test is found, you must identify for further action blood and blood components collected 12 months and less before the donor's most recent nonreactive screening tests, or 12 months and less before the donor's reactive direct viral detection test and nonreactive antibody screening test, whichever is the lesser period (§ 610.48(b)(1)(ii) and (b)(1)(iii)).

To prevent unnecessary repetition of already completed ''lookback'' actions, we have added an exemption stating that any ''lookback'' action performed before the effective date of the final rule that otherwise satisfies the requirements for prospective ''lookback'' in final § 610.47, is exempt from the retrospective ''lookback'' requirements in final § 610.48. We recognize that, without this exemption, when this final rule becomes effective, collecting establishments that already performed prospective ''lookback'' actions that comport with the recommendations set forth in the ''lookback'' guidance could face a situation in which they would be compelled under the final rule to repeat these already completed ''lookback'' actions under the retrospective ''lookback'' provisions. As this would mandate an obvious waste of effort and would penalize establishments that conducted expeditious prospective ''lookback'' actions guided by our recommendations in the ''lookback'' guidance, we have added the exemption for completed adequate ''lookback.''

c. *Further testing*. Under § 610.48(b)(1)(ii), quarantine and consignee notification are not required when donors, who tested reactive by a screening test, test negative on the same donation by an appropriate supplemental (additional, more specific) test for evidence of HCV infection. In the context of this rule, an appropriate supplemental test for a reactive antibody screening test is a test for antibody, i.e., the recombinant immunoblot assay (RIBA). At this time, an appropriate supplemental test for NAT does not exist. However, when a supplemental test becomes appropriate for NAT, we will notify the public on its use through guidance.

Under § 610.48(b)(2), if a supplemental (additional, more specific) test for HCV is not performed on the same donation at the time of the reactive screening test, the collecting establishment may choose to perform the supplemental test or a licensed screening test (e.g., an EIA 3.0) with known greater sensitivity than the test of record (e.g., an EIA 2.0) on a frozen sample from the same reactive donation, or may collect and test a fresh sample from the same donor, if obtainable. If a supplemental test for a reactive screening test is not approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA, a suitable test is unavailable, or the collecting establishment does not perform further testing due to the unavailability of a sample, then the collecting establishment must proceed with quarantine and consignee notification under § 610.48(b)(3), (b)(4), and (b)(5).

A variation between §§ 610.47(a)(3) (prospective review) and 610.48(b)(4) (retrospective review) is the event initiating the notification of the consignee of the test results within 45 calendar days. Under § 610.47(a)(3), the collecting establishment must notify the consignee of the supplemental test results within 45 calendar days after the donor tests reactive for evidence of HCV infection. Under § 610.48(b)(4), the collecting establishment must notify the consignee of the supplemental test results within 45 calendar days of completing the supplemental tests.

d. *Notification of transfusion recipients*. Under § 610.48(c)(3), the consignee is required to notify the transfusion recipient under any of the following conditions:

- The supplemental (additional, more specific) test for HCV is positive; or
- The supplemental test is indeterminate, but the supplemental test

is know to be less sensitive than the screening test; or

- The screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA; or
- The supplemental testing is not performed.
- Transfusion recipients do not need to be notified if there is a negative result by an alternative licensed screening test with known greater sensitivity than the test of record, and that the alternative screening test was performed on the original reactive donor sample or a fresh sample from the same donor.

C. Changes to Related Regulations

1. Standard Operating Procedures (§ 606.100(b)(19))

We are requiring that collecting establishments and consignees establish, maintain, and follow procedures:

- For identifying previously donated blood and blood components from a donor who later tests reactive for evidence of infection with HIV or HCV, or when the collecting establishment becomes aware of other reliable test results or information indicating evidence of infection;
- For quarantining such in-date blood and blood components, intended for use in another person or for further manufacture into injectable products, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance (i.e., inactivation and removal) procedures;
- For notifying consignees to quarantine such in-date blood and blood components, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance (i.e., inactivation and removal) procedures;
- For determining the suitability of the quarantined blood or blood components for release, destruction, or relabeling;
- For notifying the consignees of the test results for HIV or HCV performed on donors of such blood and blood components; and
- For notifying the recipient of such blood or blood components, the recipient's physician of record, or the recipient's legal representative by the consignee that the recipient received blood or blood components which may have been at increased risk of transmitting HIV or HCV, respectively.

2. Recordkeeping (§ 606.160(b)(1)(viii))

Collecting establishments and consignees must keep records concerning the requirements of this final rule. This includes any records relating to quarantine; notification of consignees; testing; notification of the transfusion recipient, the recipient's physician of record, or the recipient's legal representative; and disposition of the identified blood and blood components.

3. Retention of Records (§ 606.160(d))

Current § 606.160(d) requires the retention of records no less than 5 years after the records of processing are completed or 6 months after the latest expiration date for the individual product, whichever is the latest date. In § 606.160(d), we are changing the requirement for record retention from 5 years to 10 years. There can be a prolonged time between exposure to an agent and development of symptoms, as is the case for HIV and HCV. A longer record retention time will allow establishments to trace recipients of blood from donors who had not been regular donors. This change is also consistent with industry standards for record retention by blood establishments for ''lookback'' to identify recipients who may have been infected with HIV or HCV (AABB Standards for Blood Banks and Transfusion Services; 23rd edition). Because of the widespread use of electronic recordkeeping, it is now practical to search records for up to 10 years.

This change accommodates the advances in medical diagnosis and therapy that have created opportunities for disease prevention or treatment many years after recipient exposure to a donor later determined to be at increased risk of transmitting disease by transfusion.

4. Donor Deferral (§ 610.41(c))

In the **Federal Register** of June 11, 2001 (66 FR 31146), we published a final rule entitled ''Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents'' (the June 2001 final rule). Under § 610.41(a), any donor of blood and blood components who tests reactive for a communicable disease agent described in § 610.40(a) or reactive with a serological test for syphilis must be deferred from donation. Section 610.41(b) permits the reentry of a deferred donor into the donor pool when the donor is requalified by a process or method approved for such use by FDA.

We have moved proposed § 610.40(g) to § 610.41(c) in this final rule. Section 610.41(c) requires collecting establishments to perform ''lookback'' when a donor tests reactive by a screening test for HIV or HCV, or when the establishment becomes aware of other reliable tests results or information indicating evidence of infection with HIV or HCV.

To be consistent with the language used in the June 2001 final rule, we refer in this final rule to screening tests as ''reactive'' instead of ''repeatedly reactive,'' to accommodate the different testing algorithms established for NAT and other screening tests. In cases where the testing algorithm requires initial and repeat testing as part of a single screening procedure, we would interpret the term ''reactive'' to mean ''repeatedly reactive.''

III. Comments on the Proposed Rule and FDA's Responses

Twelve blood establishments, i.e., blood banks, blood centers, and blood industry trade associations, submitted comments raising multiple issues with the proposed rule. The following comments and responses are grouped by subject matter rather than by sections of the proposed rule because many comments generally relate to both HIV and HCV prospective review (§§ 610.46 and 610.47, respectively), and HCV retrospective review (§ 610.48). When the comment or response is particular to HIV, HCV, prospective review, or retrospective review, we specify it when we describe the comment.

Five comments expressed general approval of the proposed rule. Another comment noted that the proposed rule was in keeping with the commenter's mission to provide the best possible health care. One comment stated that the proposed rule goes beyond the current guidance issued in September 1998, i.e., to include the prior donations from individuals identified as HCV-infected through their reactivity on the HCV screening test by EIA 1.0, and extending multi-antigen ''lookback'' further back in time. Another comment supported extending the requirement for HCV ''lookback'' beyond the September 1998 guidance.

We also received comments on the specific prescriptive language of the proposed rule for quarantining, releasing from quarantine, relabeling, appropriate algorithms for proceeding with HCV ''lookback'' resulting from the historical record review, the interpretation of the signal to cutoff values used in interpreting the results of

the EIA 1.0 test, and the use of unlicensed tests in the algorithms. However, because in preparing this final rule, we opted to set forth requirements rather than specific procedures for achieving those requirements, we have not responded specifically to comments on prescriptive language that is not in the final rule. We reviewed and considered all comments in preparing the ''lookback'' guidance. Although the ''lookback'' guidance does not prescribe the sole means to comply with this final rule, it does discuss measures that would satisfy the final rule's requirements. A summary of the comments and our responses follows.

A. General Comments

(Comment 1) Several comments stated that the proposed rule is too long and complex, making it difficult to find cross-referenced relevant provisions within the proposed rule, and that a flowchart or table would make the requirements easier to follow and understand. Many comments pointed out that certain testing outcomes are not adequately addressed in the proposed rule's prescriptive language. One comment urged FDA to create an appropriate mechanism, allowing blood establishments to modify ''lookback'' timeframes and procedures as new tests or new generations of viral tests become available. One comment suggested that FDA modify the proposed rule by issuing requirements that would apply to donors who test reactive by screening tests for HCV (prospective ''lookback'') as of the effective date of the final rule, and that the September 1998 guidance would apply to all other ''lookback'' actions (retrospective ''lookback'').

(Response) We agree that the proposed rule was long, complex, and difficult to understand. When we issued the proposed rule, we provided reference tables to help readers understand the proposed requirements due to the complexity of the codified section. The tables showed the various tests performed for HCV, steps of the ''lookback'' process, and applicable provisions of proposed §§ 610.48 and 610.49. As described in section II.A of this document, and in response to the comments, we have restructured the codified section of the final rule to make it easier to understand and follow. We have constructed the requirements by listing the objective actions that must be performed and by eliminating the prescriptive language in the final rule. In other words, the regulation now tells you what to do, not how to do it.

We considered the comments on testing outcomes in the proposed rule when revising the September 1998 guidance document. We are issuing the ''lookback'' guidance, which represents our current thinking on how to conduct HCV ''lookback.'' We have not prescribed specifically how you must comply with the final rule's requirements, though the guidance discusses the agency's current thinking and offers an explanation of some satisfactory approaches. We provide flowcharts and tables in the guidance document to assist you in performing the ''lookback'' actions. As new tests or new generations of viral tests become available, we can revise or modify the companion guidance to assist you in complying with the required ''lookback'' actions.

As requested, we have provided a date in § 610.48(b)(1)(i), which defines the period of record review under § 610.48. Consistent with the ''lookback'' guidance, establishments could already be performing the review now required under §§ 610.47 and 610.48 by the time this final rule becomes effective. However, we want to reiterate that, whereas the ''lookback'' guidance offers only our current thinking on some satisfactory approaches, it is this final rule that imposes a date to define record review and creates an enforceable requirement.

(Comment 2) Another comment expressed concern regarding the adverse consequences of informing donors of potential HCV infected status when such a donor tests reactive by a screening test for HCV. The comment pointed out the scientific uncertainty in treating HCV-infected individuals and asked FDA to be mindful of these facts when issuing the final rule. The comment further explained that treatment protocols are ambiguous for many infected individuals and response rates are variable. The comment was concerned that the donor's infectious status may not result in high risk behavior change, especially where no clinical symptoms are present, and that there may be personal ramifications of informing a donor of an infectious status, i.e., personal disruption or trauma and potential for discrimination against the donor.

(Response) Although this rulemaking does not address notification of donors at increased risk of transmitting HCV, we are very aware of the consequences of informing donors (required under 21 CFR 630.6), as well as recipients, of their increased risk of being infected with HCV. However, in the interest of protecting individual and public health, we believe it is imperative that such individuals be informed so that they may pursue further testing and counseling. Through such means the recipient can monitor the disease process, if infected, and can take precautions to prevent infecting others. Notification of the individual also is necessary because some infected individuals with a progressive, but treatable liver disease, remain asymptomatic for many years and are not being treated because of a lack of awareness of their condition. The agency cannot regulate the behavior of the individual if infected, nor eliminate the trauma of notification, but notifying the individual, recommending further testing, and permitting an opportunity for counseling and treatment can help minimize any adverse outcome and is necessary to protect the health of others.

B. Records

Proposed § 606.160(d) would require that blood establishments keep records no less than 10 years after the completion of the processing of records or 6 months after the latest expiration date for the individual product, whichever is later.

(Comment 3) One comment agreed with the proposed requirement. The comment further suggested that prospective ''lookback'' be confined to a ''rolling'' 10-year period, which would be consistent with the CMS companion interim final rule requiring transfusion services to maintain records of disposition for 10 years. The comment also requested that FDA establish an expiration date for recovered plasma to prevent the retention of records indefinitely as required for such products in current § 606.160(d).

(Response) We agree that the 10-year recordkeeping period should be a ''rolling'' 10-year period. The final rule requires collecting establishments to retain records for 10 years from the date of completion of the processing records or 6 months after the latest expiration date for the individual product, whichever is later (§ 606.160(d)). A ''rolling'' 10-year record retention period is described as the establishment increasing the record retention period yearly until 10 years of records from the date of disposition have accrued. For example, if you currently have records dating back 5 years, then the first year after the effective date of this regulation you must have 6 years of records, the second year after the effective date, you must have 7 years of records, etc., until 10 years have been reached. However, if you already retain 10 years of records, then the 10-year record retention period is immediately satisfied.

As for the comment's suggestion regarding an expiration date for recovered plasma, the comment raises significant issues beyond the scope of

this rulemaking. We decline to establish an expiration date for recovered plasma at this time, but we will take the comment's suggestion under consideration.

C. HIV and HCV ''Lookback''

1. Initiation of Record Review

Proposed §§ 610.46(a) and 610.48(a) would require that the collecting establishment initiate HIV or HCV ''lookback,'' respectively, when a donor tests reactive by a screening test for evidence of HIV or HCV infection. Collecting establishments would also initiate record review when the establishment becomes aware of other test results indicating evidence of HIV or HCV infection, provided that the testing was performed by a laboratory certified under the Clinical Laboratories Improvement Amendments of 1988 (CLIA), using a test approved by FDA.

(Comment 4) One comment suggested deleting from proposed §§ 610.46(a) and 610.48(a), the requirement to conduct prospective record review when a blood establishment is ''made aware of other test results'' indicating evidence of HIV or HCV infection. The comment explained that the language is too vague as to the nature, source, and reliability of the information, and requested clarification of what constitutes ''made aware'' and ''evidence.'' The comment also considered determining a lab's CLIA certification status as problematic because there is no available database for searching such information.

(Response) We decline to delete the requirement. In the preamble of the proposed rule (65 FR 69378 at 69383), we explained that this provision clarifies the existing language in § 610.46, which requires HIV ''lookback'' when the donor is determined otherwise to be unsuitable when tested under 21 CFR 610.45.

However, we added the term ''reliable'' as describing other test results that initiate record review. We consider other ''reliable'' test results to be information that, if known to the collecting establishment, would indicate that the donor is unsuitable or should be deferred from donation.

A collecting establishment does not routinely receive information that a donor is unsuitable for donation unless the screening and testing occurs in the same collecting establishment. However, we are aware that donors may inform collecting establishments when they test reactive for evidence of HIV or HCV as a result of a physical examination or if they donate at another collecting establishment. In the final rule, therefore, we have removed the provision from proposed §§ 610.46(a) and 610.48(a) for the testing laboratory to be certified under CLIA and for the other information to be based on a test approved by FDA, and have described our thoughts about the relevant laboratory qualification information in the ''lookback'' guidance. These qualifications are already required under § 610.40(f). Such qualifying information can be obtained by asking if the laboratory is a Medicare participant.

2. Extent of Record Review

Proposed §§ 610.46(a) and 610.48(a) would require that the collecting establishment review HIV or HCV testing records and identify blood and blood components previously collected from a donor who subsequently tests reactive for evidence of infection with HIV or HCV. Record review would include all available records.

Proposed § 610.48(c) would require collecting establishments to perform a review of records for HCV testing prior to the effective date of the final rule. These records would date back indefinitely for computerized electronic records, and to January 1, 1988, for all other readily retrievable records, or to the date 12 months before the most recent negative screening test for HCV, whichever is the lesser period.

(Comment 5) Several comments asked for revisions to the codified section to clarify the extent of prospective record review. One comment requested a fixed date for ''lookback'' regardless of the establishment's method of recordkeeping. The comment stated that the proposed rule penalizes establishments that keep records longer and agreed that the rule is a deterrent for keeping good computerized records. The other comment interpreted the language of the proposed prospective HIV and HCV record review, i.e., ''whenever records are available,'' as resulting in an open-ended, continuous search. The comments preferred the description of the retrospective HCV record review and suggested modifying the prospective HIV and HCV record review language to reflect similar language, or, as one comment suggested, changing the record review period to 10 years for transfusable products and 6 months for recovered plasma intended for further manufacturing use. The comment reasoned that, because recovered plasma does not have an expiration date, the blood establishment would have to search records that are 20 to 30 years old. Another comment recommended limiting the record review to computerized electronic records.

For retrospective review, one comment recommended that we base the ''lookback'' on a record review that extends as far back as computerized records exist for donation and distribution, or back to January 1, 1988, whichever is longer.

(Response) In regards to the extent of record review required under final §§ 610.46(a)(1) and 610.47(a)(1) (prospective review), we recognize the difficulty in interpretation and we have eliminated the phrase ''whenever records are available.'' In its place, we have inserted a reference to the requirements under § 606.160(d) for the record retention period (10 years). Any affected blood or blood components collected before the required record retention period will most likely be outdated; or collected more than 12 months before the donor's most recent nonreactive screening tests for HIV or HCV, or more than 12 months before the donor's reactive direct viral detection test, e.g., NAT (HIV and HCV) or HIV p24 antigen test (HIV), and nonreactive antibody screening test for HIV or HCV, and will not need to be quarantined. If the establishment retains records beyond the required retention period, we suggest that the establishment search such records as appropriate in the ''lookback'' requirements to identify blood and blood components previously collected from a donor who later tests reactive for evidence of HIV or HCV infection. Our intention is not to penalize those establishments that keep records longer than required, but to help ensure that recipients are notified that they may have received blood or blood components at increased risk of transmitting infection so that they may seek testing, counseling, and (if necessary) treatment.

We decline to make the suggested change for retrospective record review because not all establishments' records are computerized.

(Comment 6) Three comments requested clarification of certain terms used in the proposed rule. One comment requested that the prospective and retrospective ''lookback'' be consistent with regard to the form and content of the reviewed records, i.e., ''computerized electronic records'' and ''readily retrievable records.'' The comment also suggested defining ''available'' in the prospective ''lookback'' as synonymous with ''computerized electronic'' in the retrospective ''lookback.'' Another comment contended that nonconformity in such language might lead to different interpretations between the blood establishments and FDA investigators. A

third comment requested clarification of the term ''readily.''

(Response) We acknowledge that the descriptive terminology used in the proposed codified section relating to the extent of record review could lead to differences in interpretation. However, we decline to use the same terms for prospective review and retrospective review due to the different events initiating the review, i.e., a donor's reactive screening test for HIV or HCV in prospective review or the final rule's requirement for historical HCV testing record review. However, to lessen confusion, we are changing the description of the prospective record review in §§ 610.46(a)(1)(i) and 610.47(a)(1)(i) from ''whenever records are available'' to ''records required under § 606.160(d).'' In this final rule, records must be available for 10 years after the records of processing are completed or 6 months after the latest expiration date for the individual product, whichever is later. Because the current regulation requires a 5-year record retention period, the 10-year record retention period is a ''rolling'' 10 years, as previously discussed in comment 3 of this document. Prospective record review must include all records required under § 606.160(d), including computerized electronic records. We have removed the term ''readily retrievable'' from the final rule.

3. Quarantine

Proposed §§ 610.46(a) and 610.48(a) and (c) would require the collecting establishment to quarantine in-date blood and blood components identified during the record review. Because the identified in-date blood and blood components are considered at risk for transmitting HIV or HCV infection and are still in inventory, they would be required to be removed from inventory and isolated in quarantine so that they may not be transfused or used for further manufacture into injectable products. The proposal would require collecting establishments to notify consignees to quarantine such blood and blood components, removing the possibility of infecting others. The proposed rule would require the collecting establishment to complete these actions within 3 calendar days of the donor testing reactive for evidence of HIV or HCV infection. We specifically requested comments on the appropriateness of 3 calendar days to complete quarantine and notification of consignees.

(Comment 7) Several comments requested that FDA revise § 610.46(a) to be consistent with § 610.48(a) by limiting quarantine and notification of consignees to in-date products, and that the retrospective review in proposed § 610.48(e) be limited to in-date products only. Another comment suggested eliminating the action of quarantine for outdated products for both prospective and retrospective record review. The same comment asked whether in-date and outdated products are to be treated identically.

(Response) We agree with the comment that the requirements for HIV ''lookback'' in proposed § 610.46(a) and the requirements for HCV ''lookback'' in proposed § 610.48(a) should be consistent and have made the change. The action of quarantining identified blood and blood components by the collecting establishment and the initial notification of the consignees to quarantine such products is limited to in-date blood and blood components because they are available for transfusion or use for further manufacturing into injectable products if they remain in inventory. Quarantine by the collecting establishment or consignee does not apply to outdated blood and blood components because they should no longer be in the establishment's releasable inventory. However, we want to clarify that the prospective HIV and HCV ''lookback'' (final §§ 610.46 and 610.47) must identify both in-date and outdated blood and blood components previously donated by a donor with a reactive screening test for HIV or HCV. This identification is necessary so that recipients of such blood and blood components can be notified for the purpose of testing, counseling, and treatment if indicated by the supplemental (additional, more specific) test results. These actions also apply to the requirements of historical HCV testing record review under final § 610.48.

(Comment 8) One comment urged FDA to modify the time period of 12 months for the quarantine of identified prior collections of blood and blood components from the most recent reactive screening test for evidence of HIV infection in proposed § 610.46(c). The comment suggested changing the time period from 12 to 3 months to remain consistent with current guidance for donors testing reactive for HIV–1 antigen in a Blood Memorandum to All Registered Blood and Plasma Establishments entitled ''Recommendations for Donor Screening with a Licensed Test for HIV–1 Antigen'' (August 1995 memorandum).

(Response) We understand the comment's request for consistency with existing guidance. However, we decline to make the change for the following reason. Since 1995, industry has collected additional scientific information showing that donors infected with HIV may experience intermittent viremias for a variable period of time prior to a persistently detectable viremia or an antibody response. Because these episodes of transient viremia may extend over a longer window period than previously estimated, we are requiring a record review period of 12 months before the donor's reactive direct viral detection test with a nonreactive antibody screening test or 12 months prior to the most recent nonreactive screening tests, whichever is the lesser period. A 12-month timeframe is necessary to encompass with sufficient confidence the window period for HIV prior to the detection of antibody. We have elected not to address an alternative (possibly shorter) ''lookback'' period based on the last negative direct viral test in order to minimize operational complexity and because the appropriate period has not been well established scientifically. This requirement supersedes the 3-month ''lookback'' recommendation for donors testing reactive for HIV p24 antigen in the August 1995 memorandum and is for prospective application. However, we recommend that collecting establishments ''lookback'' 12 months before the few previously identified reactive HIV p24 antigen tests with a nonreactive antibody screening test that were confirmed as infected with HIV.

(Comment 9) One comment interpreted ''quarantine'' as gaining control of distributed prior collections of blood and blood components from a donor who subsequently tests reactive by a screening test for evidence of HIV or HCV infection.

(Response) We disagree with the comment's interpretation of ''quarantine.'' The requirement for ''quarantine'' simply means the removal of the identified in-date blood and blood components from the collecting establishment's or consignee's inventory and their placement into isolation to prevent transfusion or use for further manufacture into injectable products. It is not intended to require the collecting establishment to physically retrieve the identified blood and blood components from the consignee, though such action is permissible. It also is permissible for the consignee to return to the collecting establishment any in-date blood and blood components identified for quarantine.

(Comment 10) Five comments considered the timeframe of 3 calendar days in proposed §§ 610.46 and 610.48 to be inadequate for the quarantine of all

prior collections of blood and blood components from donors testing reactive by a screening test for evidence of HIV or HCV infection, and for consignee notification, especially if the quarantine action is initiated by information from an outside source (prospective record review). Another comment stated that 3 calendar days is appropriate for quarantining in-date blood and blood components, but that additional time is needed for consignee notification. Several comments suggested 7 calendar days, 3 working days, or 5 business days as alternative timeframes for quarantine and consignee notification. Two comments suggested that the time period start once the prior collections of the donor with the reactive screening test are identified, not when the reactive screening test occurs.

(Response) We decline to change the timeframe. Our objective is to minimize the possibility of transmitting an HIV or HCV infection to an individual due to his or her exposure to blood and blood components at risk of transmitting HIV or HCV. It is important that consignee notification and quarantine of such blood and blood components be performed expeditiously within a reasonable timeframe and we believe that 3 calendar days is reasonable. We define ''3 calendar days'' as the period ending at the close of business 3 full days after a donor tests reactive. So, for example, if a donor testing reactive by a screening test for HIV or HCV on the first day (e.g., Friday), then quarantine by the collecting establishment and notification of consignees to quarantine must occur by close of business on the fourth day (e.g., Monday).

(Comment 11) Several comments suggested adjusting the time period for quarantine and notification for the HCV retrospective review requirements in proposed § 610.48(e) and (f). Suggested changes ranged from 3 working days, to 7 calendar or 5 business days, to 1 year for quarantine of prior collections and consignee notification. Another comment requested a change from 3 calendar days to 3 working days for outdated products. One comment suggested deleting proposed § 610.48(f)(2), which addresses the review of historical records based on screening performed using a single antigen-base antibody screening test during 1990 to 1992. The comment said that there would be few in-date products that would necessitate immediate quarantine and notification of the consignee.

(Response) We decline to make the suggested changes for the reason stated in response to comment 10 of this document. We want to clarify that these actions are initiated by the identification of a reactive screening test on a donor upon review of historical records. The 3-calendar day timeframe is required only when in-date blood and blood components are identified. If the review does not identify in-date blood and blood components, then the quarantine and notification of consignees to quarantine is unnecessary.

We agree with the comment to delete proposed § 610.48(f)(2) based on the reason that there would be few in-date products that would necessitate quarantine and notification of consignees. This revision is not necessary because of our restructuring of the codified section.

4. Exemptions From Quarantine

Proposed §§ 610.46(c) and 610.48(g) would permit exemption from quarantine of blood and blood components collected more than 12 months before the donor's most recent negative screening test for HIV or HCV infection.

(Comment 12) One comment suggested that FDA make an exception to HIV and HCV ''lookback'' for autologous donations that have a reactive screening test for HIV or HCV if the donor did not make any prior donations for allogeneic use, and if the blood establishment receiving those prior autologous donations from the donor did not have a crossover program, i.e., unused autologous donations put into inventory for allogeneic use.

(Response) We agree that such autologous donations should be exempt from ''lookback'' because the risk of transmitting HIV and HCV infection to a recipient does not exist because the autologous donor has not donated blood or blood components that will be used by others. We have clarified in the final rule that ''lookback'' applies to blood and blood components ''intended for use in another person.''

(Comment 13) One comment requests that we exempt products previously quarantined under FDA guidance and other existing regulations for ''lookback'' from new quarantine requirements. The comment suggested that we consider previous ''lookback'' actions as prospective and not impose further review requirements on these cases that would make the same reviews retrospective. The comment also claimed that retrospective record review is a one-time process and that it is too cumbersome to have retrospective requirements intertwined with the continuous process of prospective records review requirements.

(Response) If actions performed pursuant to the ''lookback'' guidance or requirements for quarantine fulfill the requirements of this final rule, then they are considered completed. As discussed in section II.B.2.b and comment 1 of this document, we established a date distinguishing the end of the retrospective review period and an exemption in certain circumstances, thereby eliminating any overlap of retrospective review and prospective review.

(Comment 14) Four comments asked us to include blood and blood components already pooled for further manufacturing use in the exception to quarantine in proposed §§ 610.46 and 610.48. The comments also asked if these sections include historical or retrospective record review in addition to the prospective record review.

(Response) We agree with the comment and have added the exemption from quarantine for pooled blood components intended solely for further manufacturing into products that are manufactured using validated viral clearance (i.e., inactivation and removal) procedures in the requirements for prospective review, in final §§ 610.46(a)(1)(ii), 610.47(a)(1)(ii), and in the requirement for retrospective record review in final § 610.48(b)(3)(i) and (c)(1). Pooled components intended solely for further manufacturing are exempted because it is impractical to retrieve such pools and, additionally, the manufacturing process is designed to remove or inactivate HIV and HCV.

5. Notification of Consignee

Proposed §§ 610.46(a)(1)(ii), 610.48(a)(1)(ii), and 610.48(e)(2) and (f)(2) would require the collecting establishment to notify the consignee to quarantine in-date blood and blood components previously collected from a donor who later tested reactive for evidence of HIV or HCV infection. Notification would be required to occur within 3 calendar days after the date a donor tests reactive by a screening test for HIV or HCV, or after the date of identification of the donor's reactive screening test for HCV.

In proposed §§ 610.46(b) and 610.48(b) (prospective review), the collecting establishment would notify the consignee of the results of further testing within 45 days after the donor tested reactive by a screening test for HIV or HCV. Under proposed § 610.48(h)(3) (retrospective review), the collecting establishment would notify the consignee of the results of further testing within 45 days following completion of further testing and prior

to 1 year after the effective date of the final rule.

(Comment 15) Two comments requested clarification of the notification responsibilities in general. One comment suggested listing all the conditions that trigger quarantine and consignee notification in one section of the codified section of the final rule. The comment also requested clarification of the different criteria that trigger consignee notification versus recipient notification. The second comment recommended that the consignee be notified after the confirmatory test is completed to make the notification more effective by supplying all the necessary information and to reduce the number of contacts.

(Response) We agree with the comment to group separately the requirements specific to consignee notification and recipient notification. Consequently, we have restructured the final rule into specific actions for the collecting establishment, which is responsible for consignee notification, and the consignee, who is responsible for the recipient notification. However, we do not agree with the recommendation that the collecting establishment limit notifying the consignee until after all the testing is completed. We clarified that the collecting establishment must notify the consignee when in-date blood and blood components distributed to the consignee are identified for the purpose of quarantine, and notify the consignee again with the results of the completed further testing. The consignee must notify the transfusion recipient if indicated by the results of the supplemental tests for HIV or HCV infection or when the donor's screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(Comment 16) One comment suggested that we create an exemption for notifying the consignee when the consignee gives documentation to the blood establishment showing that records no longer exist for products during a specified time period. The comment said that if the blood establishment knows that records do not exist, then it would be ineffective to notify the consignee to quarantine the products.

(Response) We agree that it would be ineffective to notify the consignee to quarantine blood and blood components if records do not exist. However, initial notification of the consignee is for the purpose of quarantining in-date blood and blood components. Such consignees of blood and blood components must have existing records under § 606.160(d). The final rule requires the collecting establishment to notify the consignee of further testing results for both in-date and outdated blood and blood components identified as at increased risk of transmitting HIV or HCV infection for the purpose of recipient notification.

(Comment 17) A few comments asked that we clarify, in proposed § 610.48(g), that it is not necessary to notify the consignee when prior collections from a donor with a reactive screening test for HCV are exempt due to the supplemental test results.

(Response) In the preamble to the proposed rule (65 FR 69378 at 69387), we explained that when an appropriate supplemental (additional, more specific) test for HCV is negative and is completed within the 3 calendar days provided for the completion of quarantine and consignee notification, consignee notification is not necessary. In the final rule, if the supplemental test is negative within the provided 3 calendar days, then the reactive screening test result is interpreted as a ''false reactive,'' HCV infection is not indicated, and the identified blood and blood components are considered not at increased risk of transmitting HCV. If, however, the supplemental test is completed more than the provided 3 calendar days after the date of the reactive screening test for HCV infection, the collecting establishment must quarantine identified in-date blood and blood components, and notify consignees to quarantine identified in-date blood and blood components, but may release the blood and blood components from quarantine if the supplemental test is negative. This applies to a donor testing reactive by a screening test for HIV infection as well.

For retrospective record review, when a collecting establishment identifies a donor testing reactive by a HCV screening test, and if an appropriate supplemental test is negative, then quarantine and consignee notification is unnecessary. However, if additional supplemental testing or testing with a licensed screening test with known greater sensitivity than the test of record is necessary to establish the infectious status of the identified blood and blood components, then quarantine and consignee notification of in-date blood and blood components must occur within the provided 3 calendar days until further testing is completed.

6. Further Testing and Consignee Notification of Test Results

In the case of prospective record review, proposed §§ 610.46(b) and 610.48(b) would require that the collecting establishment perform further testing on the donor's blood and notify the consignee of the results within 45 calendar days after the date on which the donor tested reactive by a screening test for evidence of HIV or HCV infection.

While performing retrospective record review, proposed § 610.48(h) and (i) would require the collecting establishment to perform further testing, if not previously performed. The collecting establishment would perform the further testing either on a frozen sample from the reactive donation, if available, or on a fresh specimen from the donor, if obtainable. The collecting establishments would then notify the consignees of the results within 45 calendar days following the completion of further testing and prior to 1 year after the effective date of the final rule.

(Comment 18) One comment suggested changing ''shall'' to ''may'' in proposed § 610.48(h)(1) and (i)(1) to give the establishment the option of immediately performing quarantine and notification rather than locating the donor for further testing.

(Response) We agree with the comment and have revised final § 610.48(b)(2) by changing ''shall'' to ''may'' to permit the collecting establishment to choose between either immediate quarantine and consignee notification, or obtaining a sample for further testing from the donor. However, we emphasize the benefit of further testing when recipient notification is indicated, and reiterate that every effort should be made to complete further testing.

(Comment 19) One comment suggested alternatives for the 45-calendar day time period for notifying consignees of the results of further testing in both prospective and retrospective review. For proposed §§ 610.46(b) and 610.48(h)(3)(i), the comment suggested exempting completely the requirement of notifying the consignee of further HIV or HCV testing results within 45 days when prior collections are returned to the blood establishment or destroyed. The comment suggested extending the time period to 90 days in proposed § 610.48(b) for notifying consignees of further HCV testing results when the products from prior collections of the donor are outdated. The 90-day time period would permit the blood establishment to retrieve records that are stored offsite and in varying forms, or to give additional search and review efforts to records not as readily accessible for in-date products. The comment further suggested that

notification for outdated products made from prior collections should occur within 1 year of the effective date of the final rule and only if the test results indicate that consignees must take action to notify the recipients.

(Response) We agree that it is not necessary to notify the consignee of the results of further testing within 45 calendar days if the blood and blood components previously collected from a donor who later tests reactive for evidence of HIV or HCV infection are returned to the collecting establishment or destroyed by the consignee.

We decline to extend the time period of 45 calendar days to 90 calendar days in final § 610.48(b) as suggested by the comment. Although the comment reasoned that a longer time period would enable the collecting establishment to retrieve records that are stored offsite and in varying forms or enhance additional search and review efforts to records not as readily accessible as those for in-date products, we believe that 45 calendar days is adequate for such purposes and that it is imperative that consignees obtain such information, which may necessitate recipient notification, in a reasonable time period.

7. Notification of Transfusion Recipient

Proposed §§ 610.47 and 610.49 would require consignees (transfusion services) to notify recipients that they received blood and blood components previously collected from a donor later determined to be unsuitable when tested for evidence of infection with HIV or HCV. The transfusion service would notify the recipient's physician of record (i.e., physician of record or physician who ordered the blood or blood component) and ask the physician to inform the recipient of the need for HIV or HCV testing and counseling. If the physician is not available or declines to notify the recipient, the transfusion service would be required to notify the recipient and inform the recipient of the need for HIV or HCV testing and counseling. The notification process would include a minimum of three attempts within a maximum of 12 weeks of receipt of the result of the supplemental test. If the recipient is adjudged incompetent by a State court, or the recipient is competent but State law permits notification of a legal representative or relative, or if the recipient is a minor, then the transfusion service would notify the legal representative, relative, or recipient's physician of record. If the recipient is deceased, proposed § 610.47(c) for HIV would have the notification process continue, and the transfusion service or the recipient's physician of record would notify the legal representative or relative. Under proposed § 610.49(c) for HCV, if the recipient were deceased, then the notification process would be terminated.

(Comment 20) One comment urged FDA to remove the exceptions for recipient notification by the transfusion service/consignee in proposed § 610.49(a) and place them in the section that pertains to the blood establishment. The comment stated that the requirement, as proposed, would require the blood establishment to notify the consignee even when the further testing results show that the donor is not at increased risk of transmitting HCV. The comment said that the suggested change would allow blood establishments to avoid notification of the consignees in cases that require no recipient notification, would streamline the final rule, and would have no ill effect on public health.

(Response) We have accommodated the comment's request by restructuring the codified section, requiring objective actions for collecting establishments and consignees, and removing the prescriptive language. In this process, we removed proposed § 610.49.

(Comment 21) Several comments sought changes to proposed § 610.49(b). One comment interpreted the proposed section as requiring concurrent notification of the recipient's physician of record and the recipient. Some comments stated that the recipient's physician of record at a transfusion service often does not have an ongoing relationship with the recipient and that the most common reason for notifying the recipient directly is because the physician of record refuses to notify the recipient. The comments would revise proposed § 610.49(b) to require the recipient's physician of record, not the transfusion service, to notify the recipient and would make the transfusion service responsible for notification only if the recipient's physician requests it or is unavailable. One comment said that the transfusion services are not in the position to provide patient counseling and further testing of the recipient for diagnostic purposes, and that the physician's decision should not be overridden by the transfusion service.

(Response) The comments misread the proposed rule. Proposed § 610.49(b) stated that ''[T]he transfusion service shall either notify the recipient directly or notify the recipient's physician of record * * * and ask him or her to inform the recipient of the need for HCV testing and counseling.'' The proposal, therefore, did not propose concurrent notification of the recipient's physician and the recipient. In the final rule we require that the transfusion service notify the transfusion recipient of blood and blood components at increased risk of transmitting HCV, or the recipient's physician of record (§ 610.47(b)(3)). Whether the transfusion service or the recipient's physician of record notifies the recipient, the recipient must be informed of the need for testing and counseling. At a minimum, the notifying party should inform the recipient of his or her increased risk of HCV infection and advise the recipient to seek testing, counseling, and treatment if necessary.

(Comment 22) Several comments expressed concern regarding the requirement in proposed § 610.49(b) that would require a minimum of 3 attempts to notify the recipient. The comments asked for the flexibility to discontinue the attempts once the transfusion service has obtained solid information indicating that further attempts are not necessary or would not be fruitful, and documentation is kept. Two comments would revise proposed § 610.49(b) to require only one attempt at notification using a traceable method, i.e., certified mail, return receipt. The comments asserted that there is a tremendous cost associated with more than one attempt and that we should permit the transfusion services to show good faith effort at notification if they use the information available in the patient record.

(Response) The final rule clarifies, in § 610.47(b)(3), that a consignee must make reasonable attempts to notify the recipient or the recipient's physician of record. We eliminated the requirement for three attempts; however, we emphasize that a consignee should continue attempting to notify the recipient or the recipient's physician of record until it is clear that further attempts would not be successful. If the initial attempt or attempts are unsuccessful, a consignee may need to try other methods to contact the recipient or the recipient's physician of record. If a consignee is successful in notifying a recipient or physician of record, then, obviously, no other attempts are necessary. We have also clarified this requirement in §§ 610.46(b)(3) and 610.48(c)(3). Consignees, under § 606.160(b)(1)(viii), must document their attempts to notify recipients or physicians of record and maintain a record of these attempts, whether successful or not.

(Comment 23) Two comments requested consistency in proposed §§ 610.47(c) (HIV ''lookback'') and

610.49(c) (HCV prospective ''lookback'') regarding the notification of the legal representative or relative when a transfusion recipient is deceased. Proposed § 610.47(c) for HIV would require notification to continue if the transfusion recipient is deceased, and proposed § 610.49(c) for HCV would discontinue the process if the transfusion recipient were deceased. Another comment requested that we eliminate the requirement in proposed § 610.49(c) to notify the legal representative or relative of a recipient who is incompetent or deceased. The comment said the risk of secondary transmission under such circumstances is slim and such notification wastes resources.

(Response) The final rule, in § 610.46(b)(3), continues to require the consignee to notify the legal representative or relative of a deceased recipient who received blood and blood components determined to be at risk of transmitting HIV infection. Requiring notification of the legal representative or relative when the recipient is deceased may help prevent the further spread of HIV, which the donor may have spread to a spouse or significant other before death. With this information, the spouse or significant other may be tested for the communicable disease, receive counseling, and take precautions not to spread it to others, if infected. We do not believe that the notification requirement is necessary in §§ 610.47(b)(3) and 610.48(c)(3) for HCV ''lookback'' because direct percutaneous exposure to infectious blood, particularly in the setting of drug abuse, accounts for the majority of HCV infections acquired in the United States; secondary transmission of HCV to sexual partners, care providers, or others with close contact is very unlikely.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is an economically significant regulatory action under section 3(f)(1) of the Executive order, since it may lead to impacts of greater than $100 million in any one year.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the average annualized costs for small entities will be less than 0.3 percent of average annual revenues, the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing ''any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year.'' The current threshold after adjustment for inflation is $122 million, using the most current (2005) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

The final rule will provide information to consignees and recipients of blood and blood components that may be at increased risk of transmitting HCV infection. Based on the following analysis, FDA projects that one-time costs will total approximately $73.5 million and annual costs will be approximately $1.7 million. Benefits of the final rule are measured as the gains in quality-adjusted life years (QALYs) of blood transfusion recipients who receive treatment for newly-identified post-transfusion hepatitis C virus infections that would otherwise go untreated in the absence of ''lookback.'' The value of this potential one-time gain in quality-adjusted life years ranges from $264 million to $1,228 million depending on the societal value of a quality-adjusted life year, or from $30.9 million to $143.9 million when annualized over 10 years with a 3 percent discount rate. Benefits could not be estimated with a 7 percent discount rate. With total annualized costs of $10.3 million, the net annualized benefits of the final rule are between $20.6 million and $133.6 million with a 3 percent discount rate over 10 years. Thus, FDA has determined that the final rule will be economically significant as defined by the Executive Order, because the final rule might generate benefits that exceed $100 million in a single year.

A. Economic Impact[3]

The purpose of the final rule is to ensure the continued safety of the Nation's blood supply by removing blood previously donated by individuals who test reactive for evidence of the HCV infection and by notifying recipients that these blood and blood components are at increased risk of transmitting the infection. Although blood is screened for several infectious diseases, including HCV, it is possible for a donor to give blood in the early stages of an infection before a screening test can detect its presence. Blood given during this window period has an increased risk of transmitting disease. The need for this final rule stems from the information failure caused by the inability of screening tests to identify infections in the early stages. HCV ''lookback'' will ensure that blood transfusion recipients be notified in the rare event that they receive at-risk blood.

In addition to the proposed rule, the agency has issued several draft guidances on HCV ''lookback.'' The final rule, however, outlines the set of actions blood collection establishments and consignees (i.e., transfusion service establishments) must follow when tests show that an allogeneic blood donation from a repeat donor may be at increased risk for HCV infection. Because industry guidance can be updated more quickly as technologies advance, much of the prescriptive language in the proposed rule has been removed from the final rule. In response to the agency's guidance documents, much of the blood industry has voluntarily adopted HCV ''lookback'' as a standard business practice. Nevertheless, some establishments have not implemented all elements of ''lookback,'' specifically recipient notification. Without the final rule, partial implementation of ''lookback'' would likely persist with some blood transfusion recipients not being notified that they received blood components at increased risk for HCV infection. The agency further notes that the costs and benefits of the FDA and CMS interim final rule are not additive, as the impacts considered in the CMS interim final rule are also accounted for in the FDA final rule.

[3] The final rule revises the HIV ''lookback'' requirements to make them consistent with the HCV ''lookback'' requirements. Because these revisions do not change the level of effort required for HIV ''lookback,'' an economic impact for the HIV ''lookback'' is not provided. The economic analysis for the HIV ''lookback'' requirements is addressed in the **Federal Register** issued September 9, 1996 (61 FR 47420).

1. Annual Number of Blood Donations and Blood Components Affected

a. *Number of donations from repeat donors confirmed HCV positive.* At a May 2, 2003, meeting of the DHHS Advisory Committee, the agency reported that previously unpublished American Red Cross (ARC) data show the HCV prevalence rate for repeat donors was 0.007 percent in 2000 (Ref. 1). This estimate implies that with approximately 11.2 million donations annually from repeat donors (14 million donations x 80 percent of donations from repeat donors), blood banks will find an estimated 780 donations from HCV-infected donors (11.2 million donations x 0.007 percent infected with HCV) per year. We note the reported prevalence rate has declined since 1997 when the ARC reported an HCV prevalence rate of 0.03 percent for repeat donors (Ref. 2). If prevalence rates continue to decline, we would expect even fewer donations from HCV-infected donors in the future.

b. *Number of previously donated components.* A blood donation is normally separated into multiple components. Based on 1999 Center for Disease Control and Prevention (CDC) survey findings, we initially estimated that an average of 1.1 previously donated components would be found for each donor triggering ''lookback'' (Ref. 3). Several comments from blood banks affiliated with the America's Blood Centers (ABC) disagreed with the CDC survey findings and cited their experience that a review of donation records for a donor testing reactive to evidence of HCV infection can uncover up to 10 previously donated components.

The wording of some survey questions may partially explain why CDC found fewer components. Blood banks reported the number of repeat donors who triggered ''lookback'' according to the type of screening test used, and the total number of blood components for these donors that had been previously shipped to transfusion services. However, some blood banks may have held or destroyed donations with abnormal surrogate markers for HCV even though the blood screened negative for HCV. These blood banks would report fewer components previously shipped to transfusion services (Ref. 3, p. 1180).

The agency accepts that some collecting establishments may have more previously donated components than suggested by the CDC data. However, ABC establishments receive only about half of the annual donations in the United States. We assume that the CDC survey findings are representative of the remaining blood donations. Taking the average of the midpoint of the range reported in comments on the proposed rule (i.e., 5 components) and the CDC survey findings (i.e., 1.112 components), we increase the estimated average number of previously donated components for each donation from 1.1 to 3.1 (3.06 = (5 + 1.112) / 2).

2. The Number and Type of Entities Affected

The final rule will affect establishments that collect, process, and ship blood and blood components, and establishments that transfuse those products. The affected entities include commercial plasma centers, regional and community blood collection or donation centers, hospitals that operate blood collection centers, and facilities that transfuse blood products. In the United States, there are 981 registered blood collection establishments and 60 licensed plasma collection establishments listed with FDA's Office of Blood Research and Review (OBRR) (i.e., a total of 1,041 establishments). CMS has records of another 4,980 establishments that transfuse blood and blood components.

With the exception of hospitals that both collect and transfuse blood products, establishments affected by the final rule will either act as a blood collection establishment or as a consignee (i.e., a transfusion service), but not both. To distinguish the impact of the requirements on blood collection establishments and consignees, the final rule provisions affecting each type of establishment will be treated separately in the analysis that follows.

3. Estimated Impact on Blood and Plasma Collection Establishments

First, we present the costs that are the same for all collection establishments, regardless of the number of ''lookbacks'' performed. Second, we discuss the costs that vary according to how many ''lookbacks'' occur.

a. *Fixed costs—Standard operating procedures and record retention.* Each blood or plasma collection establishment must perform a one-time review and reconcile its current SOPs with the requirements of the final rule. In the analysis for the proposed rule, FDA estimated a staff medical technologist will need an additional 40 hours to review and update SOPs for the following actions: (1) Record review; (2) product quarantine; (3) consignee notification to quarantine identified products; (4) consignee notification of supplemental (additional, more specific) test results; (5) release, destruction, or relabeling of quarantined products; and (6) donor and blood product recordkeeping. No comments on this estimate were submitted to the agency. Using the original time burden and the revised loaded hourly wage of $33.84 (Ref. 4), each establishment will incur one-time costs of $1,354, resulting in an industry-wide cost of approximately $1.4 million (40 hours x $33.84 per hour x 1,041 establishments).

The final rule requires that blood and plasma collection establishments extend the length of time they keep individual product records from 5 to 10 years after the records of processing have been completed, or 6 months after the expiration date for the individual product, whichever is the later date. According to the AABB (formerly known as the American Association of Blood Banks), all establishments collecting blood in the United States, including the American Red Cross and America's Blood Centers, are accredited by their organization and comply with their standards. Current AABB standards require that establishments retain records 10 years. Because the final rule will not affect current industry practices, the blood collection industry will incur no additional compliance costs for this provision.

b. *Variable costs—HCV ''lookback.''* The agency has issued several draft guidances describing the specific actions blood collection establishments should take when a donor's screening test is reactive for HCV or if the blood collection establishment becomes aware of other reliable test results or information indicating evidence of HCV infection. When these activities are initiated by a current blood donation, the current donation is destroyed and the set of actions required of the collection establishment is called a prospective ''lookback.'' However, when ''lookback'' is triggered by an historical review of blood donor testing records, the set of actions is called an historical or retrospective ''lookback.''

Although the actions required by the prospective and retrospective ''lookback'' provisions of the final rule are similar, the timing of these actions differs between the two ''lookbacks.'' In general, for donors with reactive test results for HCV, the collection establishment must take the following actions: (1) Review records to identify any other blood donations from these donors, (2) quarantine all previously collected in-date components from the donors that were intended for use in another person or for further manufacture into injectable products, and (3) notify consignees to quarantine all previously collected in-date

components at increased risk of transmitting the virus.

A collection establishment must perform a supplemental test (i.e., a test more specific than the screening test as described in the current industry guidance) for HCV on the current reactive blood sample. For reactive donations identified by an historical review of donor testing records, if no supplemental test was performed when the donation was collected, a collection establishment may perform a supplemental test on a frozen sample from the same reactive donation or a fresh sample from the same donor. If no further supplemental testing is possible for the retrospective ''lookback'', a blood collection establishment must send the reactive test results to the consignee. Once supplemental or other required test results are received, both types of ''lookback'' require that the collecting establishment do the following: (1) Notify consignees of these test results for both in-date and outdated previously collected components, (2) identify quarantined in-date components, and (3) take the appropriate action (i.e., release from quarantine, destroy the quarantined components, or relabel the components) indicated by the test results. However, collections taken more than 12 months before the donor's most recent nonreactive screening tests, or 12 months before the donor's reactive direct viral detection test and nonreactive antibody screening test for HCV are exempt from the required record review.

Some comments requested that FDA specify how the final rule will affect plasma establishments because HCV is inactivated when pooled plasma is further manufactured. The ''lookback'' requirements of the final rule will only affect plasma establishments that store and distribute unpooled units to consignees. The number of firms in this category is expected to be small. Comments from a plasma industry trade organization support the agency's initial analysis that plasma establishments will only be minimally affected by these requirements.

i. *Prospective HCV ''lookbacks.''* At the May 2003 DHHS Advisory Committee meeting, the agency reported that FDA-inspected blood collection establishments voluntarily follow the agency's draft guidance and perform prospective ''lookback'' as part of their standard business practices (Ref. 1). No parties present at the meeting dissented from this statement. Because these provisions of the final rule will not require blood collection establishments to change their current practices, the blood collection industry will not incur any additional compliance costs for prospective ''lookback.''

ii. *Retrospective HCV ''lookback.''* The final rule requires a review of historical testing records for donations collected prior to the effective date of the final rule. Within 1 year of the effective date of the final rule, blood establishments must complete the retrospective ''lookback'' as described previously in this document. Because industry did not comment on the agency's initial estimate of the compliance costs for the retrospective ''lookback,'' the cost per consignee notification remains unchanged from the initial analysis (65 FR 69378 at 69396).

Published and unpublished data from CDC suggest that 188,448 components from donors screened with single-antigen screening tests and 105,706 components from donors screened with multi-antigen screening tests require retrospective ''lookback'' by blood collection establishments (Ref. 3). In their survey of the blood industry, CDC found that by 1999, blood collection establishments had completed about 85 percent of the retrospective ''lookback'' based on reactive multi-antigen tests or approximately 30 percent of the entire retrospective ''lookback'' (Ref. 3). Adjusting our initial estimate to account for completion of 85 percent of blood collection establishments' ''lookbacks'' based on reactive multi-antigen test results, blood collection establishments must conduct no more than 204,000 ''lookbacks'' [188,448 components screened with single-antigen tests + ((100 percent - 85 percent) x 105,706 components screened with multi-antigen tests)]. At the estimated cost of $113 per notification, blood collection establishments will spend about $23 million (i.e., $22.9 million = 203,775 components x $112.50) to comply with the retrospective ''lookback'' provisions of the final rule, or $2.7 million per year when annualized for 10 years at a 3 percent discount rate and $3.3 million when annualized at 7 percent. Furthermore, ''lookback'' efforts have continued since the CDC survey was conducted. Although CDC has not conducted a follow-up survey, informal contacts with the blood collection industry have indicated that a substantial portion of the retrospective ''lookback'' has already been completed. Thus, $23 million represents an upper bound for the compliance costs of the retrospective ''lookback.'' If, for example, ''lookback'' based on multi-antigen screening tests has been completed, the one-time cost for ''lookback'' based on the older single-antigen screening test will be $21 million (188,448 components x $112.50 per component), or $2.5 million annualized for 10 years at a 3 percent discount rate and $3.0 million annualized at 7 percent.

c. *Total costs for blood collection establishments.* The costs of the final rule for blood collection establishments are shown in table 1 of this document. FDA estimates that the blood collection industry will incur total one-time costs to revise SOPs and complete the retrospective ''lookback'' of up to $24.3 million. Over 10 years, the annualized costs equal about $2.9 million at a 3 percent discount rate and $3.5 million at a 7 percent discount rate.

TABLE 1.—COSTS OF THE FINAL RULE FOR BLOOD COLLECTION ESTABLISHMENTS[1]

	Number Affected	Current Compliance Rate (percent)	One-Time Costs ($ million)	Annualized Costs ($ million)	
				3 percent	7 percent
Review and revise SOPs	1,041	0	1.4	0.2	0.2
Retain records for 10 years	1,041	100	—	—	—
Prospective ''lookback''	981	100	—	—	—
Retrospective ''lookback''[2]	981	30+	22.9	2.7	3.3
Total			24.3	2.9	3.5

[1] Numbers may not sum due to rounding.

[2] This upper bound estimate assumes that at least 30 percent of the retrospective ''lookback'' has been completed, including 85 percent of the ''lookback'' based on the multi-antigen screening test and no ''lookbacks'' based on the single-antigen screening test.

4. Estimated Impact on Blood Product Consignees (Transfusion Services)

Similar to the analysis for blood and plasma collection establishments, we focus first on the costs that are independent of the number of ''lookbacks'' conducted and then on the costs that vary according to how many ''lookbacks'' consignees perform.

a. *Fixed costs—Standard operating procedures and record retention.* Similar to blood collection establishments, consignees must also review and adapt their current SOPs to the requirements of the final rule. Specifically, consignees must have procedures for the required set of actions to take when notified by a blood collection establishment that the consignee received blood products at increased risk of transmitting HCV infection. These actions include the following: (1) Identifying and quarantining affected in-date unpooled blood components, and (2) processing quarantined in-date unpooled blood components according to the results of a supplemental test. Moreover, when the supplemental test for HCV is positive or there is no available supplemental test for a reactive screening test, the consignee must notify blood transfusion recipients that they received blood products at increased risk of transmitting the HCV infection. Because consignees already have SOPs in place for HIV ''lookback,'' FDA estimated that an average of 16 additional hours would be needed by each consignee to adapt or modify current procedures. We did not receive any comments on the estimate of this time burden; therefore it remains unchanged for the final analysis. At the revised hourly wage of $33.84 with benefits for a staff medical technologist (Ref. 4), each consignee will incur one-time costs of $541, or about $2.7 million for the entire industry ($33.84 per hour x 16 hours x 4,980 consignees).

The final rule requires that consignees increase the time they keep records from 5 to 10 years. Although the agency did not include the annual cost of keeping records for a longer period in the analysis for the proposed rule, it may take 40 hours for a computer programmer to perform routine maintenance of these additional records. At a wage of $34.00 per hour including benefits (Ref. 5), a consignee would spend an additional $1,360 annually to conform to this provision of the final rule. However, according to the AABB, 80 percent of the consignees are accredited by the AABB and already comply with their standards, including retaining records for 10 years. Taking AABB compliance into account, the final economic analysis includes additional costs of maintaining records for 20 percent of the consignees, a total annual cost of $1.4 million ($34.00 per hour x 40 hours x 4,980 consignees x 20 percent).

b. *Variable costs—HCV ''lookback.''* The prospective and retrospective provisions of the final rule require a similar set of actions by the consignee, although the amount of time a consignee may take to complete an action varies. The HCV ''lookback'' provisions of the final rule require that upon notification that a consignee was shipped blood or blood components at increased risk of transmitting HCV infection, the consignee must quarantine all identified in-date unpooled blood components, and make a reasonable effort to notify any recipients of blood components from donors confirmed HCV positive of the increased risk posed by these products. The consignees may notify the recipient's physician of record or notify the recipient directly. If the transfusion recipient is a minor or adjudged incompetent by a State court, the consignees would be required to notify the recipient's legal representative or the recipient's physician of record. Once supplemental test results on quarantined in-date unpooled products are received, the consignee must take the appropriate action indicated by those results (i.e., release from quarantine, destruction, or relabeling of affected blood products).

Consignee costs can be separated into product quarantine costs and recipient notification costs. Based on the amount of time required to complete the different actions, the agency estimates that the product quarantine accounts for about 40 percent of the unit cost ($66 = 40 percent x $165) while the recipient notification accounts for the other 60 percent of the unit cost ($99 = 60 percent x $165). Although consignees did not comment on the agency's initial estimate that it would cost $165 to comply with all of the ''lookback'' provisions for each affected component, Los Angeles County recently reported that a vendor was paid $118 per patient to abstract health records, locate and notify transfusion recipients, and give pretest counseling (Ref. 6). Without other data, for both the prospective and retrospective ''lookbacks,'' we continue to use $66 as the cost of product quarantine, but increase the cost of recipient notification from $99 to $118, based on the experience of the Los Angeles County.

i. *Prospective HCV ''lookback.''* According to agency inspectors, FDA-inspected consignees voluntarily follow the agency's draft guidance and currently comply with all requirements of prospective ''lookback.'' Although we have no data that directly measure the number of ''lookbacks'' FDA-inspected establishments conduct, we expect the number will be proportional to the number of transfusions given in these establishments. Using data from the American Hospital Association, Healthcare Cost and Utilization Project, and FDA's Center for Biologics Evaluation and Research's registration list, we estimate that FDA-inspected establishments give between 25 percent and 35 percent of all transfusions (Refs. 7 and 8). We assume for this analysis that CMS-inspected establishments account for between 65 percent and 75 percent of all transfusions. Some CMS-inspected establishments currently conduct prospective ''lookback;'' in the absence of data on the actual number, we assume for this analysis that all CMS-inspected establishments will need to comply with the requirements of prospective ''lookback.'' This assumption may overstate the actual costs of prospective ''lookback'' by no more than $120,000 annually.

Consignees will quarantine blood components when notified that they received components from a donor who subsequently tested reactive on a screening test for HCV. All other ''lookback'' actions would be triggered when the consignee receives supplemental test results for the donor. When notified that they received blood components from donors who are confirmed HCV positive with a supplemental test, consignees must attempt to notify recipients of those blood components. The proposed rule would have required consignees make at least three attempts to notify a transfusion recipient. Several comments expressed concern that it would be costly to continue attempts to contact an individual who no longer resides at the last known address in the recipient's medical records. In response to these comments, the final rule removes the prescriptive language concerning the number of notification attempts. Under the final rule, consignees must make a reasonable attempt to contact any affected transfusion recipient within 12

weeks of receipt from the collecting establishment of the donor's supplemental test results indicating evidence of HCV infection, or receipt of the reactive screening test if a supplemental test result is not available.

Based on the HCV prevalence levels reported by the American Red Cross for 2000, about 2,400 components could trigger ''lookback'' (780 donations from HCV-infected donors x 3.1 components per donation) (Ref. 1). The CDC survey found that on average about 85 percent of the at-risk components sent to consignees were transfused (Ref. 3). For the analysis of the proposed rule, we assumed that no patient would receive more than one affected component. This assumption suggests that consignees will quarantine about 2,400 components and attempt about 2,050 recipient notifications (780 HCV positive donors x 3.1 components per donor x 85 percent transfused).

Because CMS-inspected consignees account for about 65 percent to 75 percent of the number of transfusions, the annual costs for consignees to conduct the prospective ''lookback'' actions range from $260,000 to $300,000 [65 percent by CMS-inspected establishments x (2,400 components annually triggering quarantine x $66 per component quarantine + 2,050 components annually triggering recipient notification x $118 per recipient notification) to 75 percent by CMS-inspected establishments x (2,400 components annually triggering quarantine x $66 per component quarantine + 2,050 components annually triggering recipient notification x $118 per recipient notification)].[4]

ii. *Retrospective HCV ''lookback.''* Retrospective ''lookback'' will be triggered when a blood collecting establishment notifies a consignee that a review of historical records for blood donations screened with multi-antigen or single-antigen tests shows that an at-risk blood component may have been sent to the consignee. For consignees that also collect blood, it is likely that these consignees will identify additional at-risk components among their historical donor testing records. Once the consignee becomes aware that it received an at-risk blood component, it must complete the required ''lookback'' actions within 1 year.

From their interim survey findings published in 1999, CDC estimated that 115,228 components screened with multi-antigen tests will trigger retrospective ''lookback'' by consignees. However, CDC also estimated that consignees had completed 80 percent of retrospective ''lookback,'' including recipient notification, for these components[5] (Ref. 3). According to unpublished CDC data, an additional 188,448 components from donors screened with the single-antigen tests could trigger ''lookback'' by consignees. We lack information to estimate the total number of ''lookbacks'' that will be based on single-antigen tests and thus retain the number of components screened with single-antigen tests (i.e., 188,448 components) used in the analysis of the proposed rule. Adjusting our initial estimate of the number of components screened with multi-antigen tests by 80 percent to account for ''lookbacks'' completed by 1999, consignees have no more than 212,000 components [188,448 components screened with single-antigen tests + ((100 percent - 80 percent completion rate) x 115,228 components screened with multi-antigen tests)] requiring action. At a total unit cost of $184 ($66 + $118) per component triggering ''lookback'', the estimated one-time cost associated with the review of historical testing records is about $39 million (211,494 components x $184 / component). If all retrospective ''lookbacks'' based on the multi-antigen screening test have been completed, consignees will only incur additional one-time costs of $35 million (188,448 components x $184 / component).

c. *Total costs for consignees.* Table 2 of this document shows the costs of the final rule for blood product consignees. Industry will incur up to $1.7 million in annual costs for the prospective ''lookback'' provisions and to retain records for 10 years, and up to $42 million in one-time costs for SOPs and the retrospective ''lookback'' based on historical review of records. The annualized costs of the final rule over 10 years at 3 and 7 percent interest rates will be $6.5 and $7.6 million.

TABLE 2.—COSTS OF THE FINAL RULE FOR CONSIGNEES (TRANSFUSION SERVICES)[1]

	Current Compliance Rate (percent)	One-Time Costs ($ million)	Annual Costs ($ million)	Annualized Costs ($ million)	
				3 percent	7 percent
Review and revise SOPs	0	2.7		0.3	0.4
Retain records for 10 years	80		1.4	1.4	1.4
Prospective ''lookback''	25 to 35		0.3 - 0.3	0.3 - 0.3	0.3 - 0.3
Retrospective ''lookback''[2]	30+	38.9		4.6	5.5
Total		41.6	1.6 - 1.7	6.5 - 6.5	7.5 - 7.6

[1] Numbers may not add due to rounding.

[2] This upper bound estimate assumes that at least 30 percent of the retrospective ''lookback'' has been completed, including 80 percent of the ''lookbacks'' based on the multi-antigen screening test and no ''lookbacks'' based on the single antigen screening test.

5. Summary of SOP, Record Retention and ''Lookback'' Costs

Table 3 of this document summarizes the estimated costs of the final rule for blood collection establishments and consignees. The one-time costs for retrospective ''lookback'' and to revise procedures will be $65.9 million. Because blood collecting establishments have 1 year after the effective date of the final rule to complete their review of historical records and consignees have 1 year after being notified by collecting establishments to complete their recipient notifications, we expect that

[4] With 10 components, we estimate that consignees attempt from 4,350 to 5,020 recipient notifications at an annual ''lookback'' cost from $800,000 to $925,000.

[5] This differs from the 105,706 components that CDC estimated for collection establishments because some consignees identified, among their own collections, additional at-risk components that had been screened with multi-antigen tests. Moreover, CDC found that completion rates for retrospective ''lookback'' based on multi-antigen tests varied for blood collection establishments (i.e., 85 percent completion rate) and consignees (i.e., 80 percent completion rate).

the one-time costs will be incurred over a 2 year period. Over 10 years, the total annualized costs of these activities will range from $9.3 million to $9.4 million for a 3 percent discount rate and $11.0 million for a 7 percent discount rate. We estimate the testing and treatment costs for transfusion recipients in the benefits section.

TABLE 3.—SOP, RECORD RETENTION AND "LOOKBACK" COSTS OF THE FINAL RULE[1]

	One-Time Costs ($ million)	Annual Costs ($ million)	Annualized Costs ($ million)	
			3 percent	7 percent
Review and revise SOPs	4.1		0.5	0.6
Retain records for 10 years		1.4	1.4	1.4
Prospective "lookback"		0.3 - 0.3	0.3 - 0.3	0.3 - 0.3
Retrospective "lookback"	61.8		7.2	8.8
Total	65.9	1.6 - 1.7	9.3 - 9.4	11.0 - 11.0

[1] Numbers may not add due to rounding.

B. Benefits of the Final Rule

1. Overview

The final rule will help ensure the continued safety of the blood supply. FDA is requiring specific blood safety procedures designed to minimize risk to the blood supply and, in the rare cases that patients receive at-risk blood or blood components, to inform those recipients.

Prior to 1990, with no reliable test licensed to screen blood donations for HCV, the risk of transmission from blood transfusion was 1:200 according to CDC. Improvements in test accuracy have reduced these risks dramatically so that current repeat donor screening tests based on nucleic acid amplification technology are associated with a less than a 1:1.6 million risk of transfusion-related transmission of HCV (Ref. 9). Even though transfusion of HCV-infected blood components is no longer one of the primary ways people acquire the infection, HCV can still go undetected in blood collected from donors during the window period before screening tests can detect the presence of the virus. Because 70 to 75 percent of HCV infections are asymptomatic, if recipients of blood products at increased risk of HCV transmission become infected, most would not show any symptoms of the infection for several years and would not know to seek treatment in the early stages of the infection.

Once information becomes available that blood from an infected donor may have entered the blood supply, it is medically ethical to inform identified transfusion recipients of their HCV risk. Timely notification of possible HCV infection gives recipients the chance to be tested and, if infected, obtain treatment and counseling, and take preventive measures to avoid transmitting HCV to others. When treatment is initiated early in an infection, the best and most cost effective outcomes are achieved. For example, Bennett and others showed that the years of life gained and cost effectiveness of interferon-alpha2b treatment decreased as the age of the patient increased, from 3.1 years at $500 per year of life extended (YLE) for 20-year-old patients to 22 days at $62,000 per YLE for 70-year-old patients (Ref. 10). Moreover, because HCV infection may be associated with chronic liver disease, cirrhosis and hepatocellular carcinoma, an informed recipient can take steps to protect his or her liver function, such as decreasing or eliminating alcohol consumption and carefully monitoring the hepatic effects of any prescription or over-the-counter drugs and herbal supplements.

Notification will cause some recipients to seek testing and medical advice. Once diagnosed with HCV infection, some people will obtain treatment that would otherwise not have been received in the absence of "lookback." These treatments lead to the health benefits from this final rule. In what follows, we have estimated these benefits, and the medical and other health-care costs.

2. Estimate of Improved Patient Outcomes: Gains in Quality-Adjusted Life Years

Newly identified recipients who test positive for HCV may receive drug therapy for the previously unknown HCV infection. Markov models based on the results of clinical trials suggest that, in many cases, drug therapy will improve patient outcomes, measured as a gain in quality-adjusted life years.[6] However, drug therapy is not recommended for all patients with chronic HCV infection. Most clinical trials exclude up to two-thirds of the patients with an HCV infection (Ref. 11). We expect that newly identified recipients infected with HCV would not differ from HCV-infected individuals in the general population. Therefore, in contrast to the initial estimate, this analysis assumes that only 33 percent of the newly identified recipients would receive drug therapy.

For the proposed rule we used the Markov model from Kim and others that predicted a gain of 0.25 quality-adjusted life years with 6 months of interferon monotherapy (Ref. 12).[7] No comments

[6] A cost-effectiveness model (i.e., Markov model) of a drug therapy begins at a defined health state and follows how a drug therapy affects patient outcomes and lifetime health care costs. Models use transitional probabilities between health states to simulate the timing of patient outcomes. Each health state is assigned a (1) health care cost per unit of time and (2) quality of life utility between 0 and 1. The quality-adjusted life years are defined as the number of years that a patient remains in a particular health state, adjusted by the quality of life utility for that health state. Summing the quality-adjusted life years for all health states totals the quality-adjusted life years for a particular drug therapy. The health care costs for a particular health state are the product of the health care costs per unit time and the amount of time the patient remains in the health state. Summing the health care costs for all health states totals the health care costs for a particular drug therapy. The cost per quality-adjusted life year is the total health care costs divided by the number of quality-adjusted life years. Treatment costs and changes in quality-adjusted life years associated with different therapies can be used to compare the cost-effectiveness of different drug therapies for the same condition.

[7] Kim and others developed a Markov model that compares the long-term outcomes for treatment of HCV between: (1) No treatment and (2) treatment with interferon-alpha for 6 months. Beginning with a state of chronic HCV infection, patients may be cured or transition to other health states including compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, orthotopic liver transplantation, and death. Each simulation run includes 4,000 patients, stratified by age (30, 40, 50 and 60 years old). Age cohorts were further divided

Continued

were received on the method we used to estimate the gain in quality-adjusted life years. However, newer studies have found that treatment with interferon and ribavirin yield better outcomes than treatment with interferon alone. Because the Kim model only examines gains from treatment with now-obsolete therapies, our initial analysis predicts lower benefits than would be achieved with current treatment regimes.

Models on the effects of combination therapy predict gains ranging from 0.3 to 2.8 quality-adjusted life years per person treated (Ref. 13). Differences in how models simulate the progression of chronic HCV infection make comparison of published models difficult. For this analysis, we have selected the model by Younossi and others (Ref. 14) because it estimates a disease progression similar to that used by Kim and others (Ref. 12).[8]

3. Costs of Diagnostic Testing

a. *Cost of screening tests.* Screening recipients for HCV infection would cost about $49 for the screening test, including $30 for the laboratory test (Ref. 15), and $19 for 15 minutes of a physician's time at hourly wages plus benefits of $77 ($30 + (0.25 hours x $59.04 per hour x 1.3)). Although it is uncertain how much time consumers will lose taking this test, we estimate about 1 hour with an average value of $22.61.

b. *Cost of supplemental tests.* Because about 35 percent of reactive screening results are false positives, the cost of the supplemental test will vary depending on whether medical counseling is provided. When a test result is positive, supplemental testing costs about $158, including $81 for the laboratory test (Ref. 15), and about $77 for 1 hour of a physician's time ($81+ (1 hour x $59.04 per hour x 1.3)). With the additional time for counseling, a patient might lose up to 2 hours valued at $45.22 (2 hours x $22.61 per hour). With a negative supplemental test result (i.e., a false positive reactive screening result), medical counseling is unnecessary, reducing the cost to about $100, including $81 for the laboratory test and $19 for 15 minutes of a physician's time ($81 + (0.25 hours x $59.04 per hour x 1.3)). Moreover, patients would lose about 1 hour for a cost of about $22.61.

c. *Cost of HCV genotype testing.* Accounting for about 75 percent of all chronic HCV infections, genotype 1 HCV is more difficult to treat than other genotypes and requires a longer course of drugs. Viral genotyping will cost about $486 for the laboratory test. Similar to other diagnostic blood work, patients can lose up to $22.61 for 1 hour of time.

d. *Cost of liver biopsy.* A liver biopsy can measure whether an HCV infection has progressed to liver disease. Needle biopsies account for about 95 percent of the diagnostic liver biopsies associated with HCV infection. In about 5 percent of cases, a more invasive procedure such as a wedge biopsy may be required. The needle biopsy costs about $560, including $455 for the facilities and $105 for the physician's time (82 minutes / 60 minutes per hour x $59.04 per hour x 1.3). In addition, patients might lose up to 2.5 hours with a value of $56.50 ($22.61 per hour x 2.5 hours). In contrast to the needle biopsy, the wedge biopsy requires a median stay of 4 days in the hospital and can cost about $10,280, including $9,858 for hospital charges (Ref. 16) and about $422 for a physician to follow-up after the biopsy (5.5 hours x $59.04 per hour x 1.3) (Ref. 17). Moreover, because some mortality risk exists with this procedure, patients and their families may experience anxiety before the surgery. However, we have no data quantifying the value to avoid this anxiety or any pain associated with the biopsy.

e. *Summary of testing costs.* Table 4 of this document summarizes the costs of the diagnostic tests used in the benefits analysis. The table also includes the average number of hours that patients lose for each test.

TABLE 4.—COSTS OF DIAGNOSTIC TESTS AND LOST TIME[1]

Type of Test	Laboratory Cost	Physician Time (minutes)	Cost of Physician Time[2]	Lost Patient Time	Value of Lost Time[3]	Total Cost
HCV screening test	$30	15	$19	1 hr	$23	$72
Supplemental test:						
Negative results	$81	15	$19	1 hr	$23	$123
Positive results	$81	60	$77	2 hr	$45	$203
HCV genotyping	$486	0	0	1 hr	$23	$509
Liver biopsy:						
Needle biopsy	$455	82	$105	2.5 hr	$57	$616
Wedge biopsy	$9,858	330	$422	4 days	$2,224[4]	$12,504

[1] Numbers may not sum or multiply due to rounding.
[2] Valued at a loaded hourly wage of $76.75 ($59.04 per hour with 30 percent benefits).
[3] Valued at $22.61 per hour.
[4] This includes the willingness to pay to avoid a 0.03 percent mortality risk, using $5 million as the value of a statistical life.

equally by: (1) Gender, and (2) virulence of the infection. Quality of life utilities for each health state were elicited from medical professionals with a generic instrument.

[8] Although the Younossi model simulates long-term outcomes of six drug treatment regimes compared with the no treatment option, for this analysis we only compare the results of: (1) No treatment, and (2) combination treatment with interferon and ribavirin following virus genotyping. Similar to the Kim model, the Younossi model begins with chronic HCV infection. Some transitional probabilities differ between the two models, because Younossi and others based their probabilities on different published findings. The Younossi model simulates outcomes for cohorts of identical patients, using a 45-year-old man as the reference patient. Sensitivity analyses using two alternate ages for the reference patient (30 and 60 years of age) had relatively little effect on the outcomes of the model. Similar to Kim's parameter for infection virulence, genotyping of the hepatitis C virus introduces a variation in treatment response into the model. When possible, Younossi and others used quality of life utilities elicited directly from patients using the Health Utility Index Mark III, a multi-attribute health status classification system (Ref. 18). Costs and health states of the model were discounted at 3 percent. Our assumption about the proportion of newly identified recipients who would seek treatment accounts for potential gender differences between the Kim and Younossi models. Moreover, since ''lookback'' will only identify living recipients, presumably those healthy or young enough to survive the medical condition requiring the transfusion, the Younossi model is likely to be representative of those newly identified recipients with asymptomatic chronic hepatitis C.

4. Benefits of Prospective ''Lookback''

The economic benefit of a public health action normally relates to the risk reduction associated with that action. Because the current risk of transfusion-transmitted HCV infection is already very low (i.e., less than 1:1.6 million), we anticipate that prospective ''lookback'' will occur infrequently. However, in the rare case when ''lookback'' is necessary, this action will be relatively cost-effective. To assess the cost-effectiveness of prospective ''lookback,'' we first estimate the number of transfusion recipients that would be newly identified, then estimate the testing costs associated with ''lookback.''

a. *The number of HCV positive transfusion recipients identified by ''lookback.''* FDA cannot precisely determine the number of HCV positive individuals who could be newly identified by ''lookback,'' although this analysis suggests that it would vary from one-half dozen to two dozen per year. As discussed in the section on the costs of prospective ''lookback'' (i.e., section IV.A.4.b.i of this document), about 2,050 affected components may trigger recipient ''lookback'' each year. Taking into account notifications already being made by FDA-inspected consignees, the final rule will require that consignees attempt from approximately 1,330 (2,050 x 65 percent noncompliance) to 1,540 (2,050 x 75 percent noncompliance) recipient notifications.[9]

For the analysis of the proposed rule, we based the probability of finding a newly infected transfusion recipient on the CDC survey findings for recipients transfused within 3 years of the survey (i.e., 1996 to 1999) (Ref. 3). Therefore, using these CDC findings, we estimate that from 568 recipients (1,330 x 48 percent living x 89 percent successfully notified) to 656 recipients (1,540 x 48 percent living x 89 percent successfully notified) will be successfully notified by ''lookback.'' Once recipients are successfully notified that they received at-risk blood, about 307 (568 recipients x 54 percent tested) to 354 (656 recipients x 54 percent tested) will decide to seek testing to determine if they are infected with HCV. We predict that about 35 percent of the reactive screening tests will have false positive results. As shown in table 5 of this document, the estimated number of negative supplemental test results varies from 107 (307 x 35 percent) to 124 (354 x 35 percent), depending on the current noncompliance rate.

Because NAT pooled testing has reduced the risk of transfusion-related HCV infection, the HCV positive rate of recipients notified by ''lookback'' may be lower than the 10 percent suggested by the CDC survey findings for 1996—1999 (table 2 in Ref. 3). In table 5 of this document, therefore, we present upper and lower bound estimates of the number of individuals that would potentially test HCV positive. As discussed earlier, the CDC survey found that about one-third of the HCV positive recipients will already know about their infection (Ref. 3). Therefore, fewer infected individuals will be newly identified by ''lookback'' than test positive for HCV. The possible range of newly identified recipients that would be expected from prospective ''lookback'' each year extends from 6 to 24, depending on the noncompliance rate and the HCV positive rate.

TABLE 5.—ESTIMATED ANNUAL NUMBER OF DIAGNOSTIC TESTS AND NEWLY IDENTIFIED RECIPIENTS WITH PROSPECTIVE ''LOOKBACK''[1]

	65 Percent CMS-Inspected		75 Percent CMS-Inspected	
HCV screening tests	307		354	
Negative supplemental tests (i.e., false positive screening result)	107		124	
	HCV Positive Rate			
	2.7 percent[2]	10 percent[3]	2.7 percent[2]	10 percent[3]
Positive supplemental tests	8	31	10	35
Newly identified HCV infected recipients[4]	6	21	7	24

[1] Recipient estimates are rounded to the nearest integer; numbers may not sum or multiply due to rounding.
[2] Derived as the ratio of the ''window'' period and the inter-donation period. For this example we assume a 10-day window period with NAT screening and a 365-day median inter-donation interval (0.027 = 10/365).
[3] Based on the CDC survey findings that 10 percent of the newly identified blood recipients transfused in 1996–1999, were confirmed HCV antibody-positive with the third generation serological tests (see table 2 in Ref. 3).
[4] Sixty-eight percent of the recipients that test HCV positive do not already know about their infection.

b. *Testing costs of prospective ''lookback.''* Even though some individuals contacted by ''lookback'' will already know about their HCV positive status, for this analysis we assume that all recipients successfully contacted will receive diagnostic testing. Because Younossi and others found negative incremental treatment costs (i.e., a lifetime cost savings over the no treatment option), we exclude all treatment costs from this analysis (Ref. 14). Table 6 of this document summarizes the total testing costs of prospective ''lookback'' for all recipients.

[9] We note that if there are 10 affected components for each donor triggering ''lookback,'' consignees would attempt from 4,350 to 5,020 recipient notifications and might newly identify from 14 to 59 HCV positive recipients, of which from 4 to 20 could seek treatment and potentially gain from 3 QALYs to 56 QALYs.

TABLE 6.—TOTAL COSTS OF TESTING AND LOST PATIENT TIME OF PROSPECTIVE ''LOOKBACK''[1,2]

	65 Percent CMS-Inspected		75 Percent CMS-Inspected	
HCV screening tests	$22,049		$25,442	
Negative supplemental tests (i.e., false positive screening result)	$13,199		$15,230	
	HCV Positive Rate			
	2.7 percent	10 percent	2.7 percent	10 percent
Positive supplemental tests	$1,708	$6,233	$1,970	$7,192
Total testing costs	$36,956	$41,482	$42,642	$47,864

[1] Numbers may not sum due to rounding.
[2] Derived from tables 4 and 5 of this document.

c. *Cost-effectiveness of prospective ''lookback.''* Because the costs of ''lookback'' and the number of newly identified infected recipients are essentially proportional, the cost-effectiveness of recipient notification does not vary with changes in the number of prospective ''lookbacks.'' Total annual ''lookback'' and testing costs for the prospective ''lookback'' range from $300,000 to $350,000 (see sections IV.A.4.b.i and IV.B.4.b) of this document), depending on the proportion of CMS-inspected consignees already performing prospective ''lookback'' (i.e., 65 to 75 percent). As shown in table 7 of this document, the cost per newly identified transfusion recipient infected with HCV ranges from about $14,400, if the HCV positive rate is 10 percent and to about $51,900, if the HCV positive rate is 2.7 percent. We note again that these cost-effectiveness ratios hold regardless of the number of donations from repeat donors that trigger prospective ''lookback.''

TABLE 7.—COST-EFFECTIVENESS OF RECIPIENT NOTIFICATION FOR PROSPECTIVE ''LOOKBACK''[1]

	65 Percent CMS-Inspected		75 Percent CMS-Inspected	
	HCV Positive Rate			
	2.7 percent	10 percent	2.7 percent	10 percent
Costs of Testing & Lost Patient Time	$36,956	$41,482	$42,642	$47,864
''Lookback'' costs	$260,006	$260,006	$300,007	$300,007
Total costs	$296,963	$301,488	$342,649	$347,871
Newly identified HCV infected recipients[2]	6	21	7	24
Cost per newly identified recipient[3]	$51,897	$14,435	$51,897	$14,435

[1] Numbers may not sum or multiply due to rounding.
[2] Recipient estimates are rounded to the nearest integer.
[3] Calculated with the non-rounded number of newly identified recipients (i.e., 5.7, 20.9, 6.6, and 24.1).

5. Benefits of Retrospective ''Lookback''

Because the one-time retrospective ''lookback'' has the potential to newly identify thousands of infected transfusion recipients, the key benefit of ''lookback'' is the health improvement that newly identified individuals would enjoy as a result of timely treatment. We estimate this benefit by looking first at the number of newly identified recipients chronically infected with the hepatitis C virus. Using the published Younossi model of disease progression, we then estimate the number of quality-adjusted life years that each person could gain from interferon and ribavirin treatment of their HCV infection. Then we estimate the value that society might place on this health improvement. Next we quantify the potential costs of diagnostic testing and treatment. Finally we report the cost-effectiveness of this one-time public health initiative.

a. *The number of HCV positive transfusion recipients identified by ''lookback.''* For the analysis of the proposed rule, we estimated that about 2 percent (30 percent living x 74 percent successfully notified x 51 percent tested x 25 percent positive for HCV x 68 percent unknown infection) of the 258,125 recipient notifications[10] performed under retrospective ''lookback'' (i.e., about 5,000 recipients) would newly identify individuals who test positive for the hepatitis C virus. As discussed previously, consignees completed at least 80 percent of the retrospective ''lookback'' based on multi-antigen screening by 1999. Subtracting the recipient notifications

[10] ''Lookback'' actions for consignees include product quarantine and recipient notification. Based on their interim survey findings, CDC estimated that only about 85 percent of the components received by consignees are transfused. Based on this CDC data, consignees will perform product quarantine for about 269,100 components and perform about 258,100 recipient notifications.

that have been completed (i.e., 80 percent), table 8 of this document shows the potential number of HCV-positive recipients that retrospective ''lookback'' might newly identify, and the corresponding number of diagnostic tests that might be performed.

TABLE 8.—ESTIMATED ONE-TIME NUMBER OF DIAGNOSTIC TESTS AND NEWLY IDENTIFIED RECIPIENTS WITH RETROSPECTIVE ''LOOKBACK''[1]

	Multi-Antigen Screening Results[2]	Single-Antigen Screening Results[3]	Total
HCV screening tests	2,353	17,819	20,172
Negative supplemental tests (i.e., false positive screening result)[4]	824	6,237	7,060
Positive supplemental tests	447	5,168	5,615
Newly identified HCV-positive recipients[5]	304	3,514	3,818

[1] Recipient estimates are rounded to the nearest integer; numbers may not sum or multiply due to rounding.
[2] Adjusting the number of components triggering ''lookback'' based on multi-antigen tests (i.e., 115,228 components) by the transfusion rate (i.e., 85 percent transfused) and the completion rate (80 percent of completed), consignees will attempt about 19,674 transfusion recipient notifications. Estimates were derived using the findings in table 3 of Ref. 3: 31 percent would be living, 78 percent would be successfully notified, 50 percent would be tested, and a 19 percent HCV positive rate.
[3] Adjusting the number of components triggering ''lookback'' based on single-antigen tests (i.e., 188,448) by the transfusion rate (i.e., 85 percent transfused), consignees will attempt about 160,879 transfusion recipient notifications. Estimates were derived using the findings in table 2 for transfusions in 1988–1989 of Ref. 3: 30 percent would be living, 72 percent would be successfully notified, 52 percent would be tested, 29 percent HCV positive rate.
[4] Based on 35 percent false positive rate for screening tests.
[5] Based on CDC survey findings that 68 percent of the HCV positive recipients did not already know about their infection.

b. *Number of Quality-Adjusted Life Years gained.* Benefits of the retrospective ''lookback'' come from treating post-transfusion hepatitis C virus infections, and in doing so, delaying or reducing adverse health outcomes from illnesses that would be caused by untreated hepatitis C virus infections. We use a quality-adjusted life year as the measure of this gain in health outcomes and estimate the number of quality-adjusted life years that newly identified infected recipients can gain from treatment of their chronic HCV infections. Adjusting for the 75 percent chronic infection rate, about 2,865 chronically infected recipients would be newly identified by retrospective ''lookback'' (3,818 newly identified recipients x 75 percent chronic infection rate).

As noted previously, to estimate the gain in quality-adjusted life years, we selected the Markov model of Younossi and others (Ref. 14). Their findings predict that patients receiving combination therapy with standard interferon could gain 2.8 quality-adjusted life years, compared with receiving no treatment for the infection. For this analysis, we assume that newly identified transfusion recipients are similar to the general population in terms of genotype of the hepatitis C virus (i.e., 75 percent are infected by genotype 1 HCV) and suitability for treatment (33 percent of HCV positive individuals would receive drug therapy). Accounting for these factors, an estimated 945 individuals (2,864 patients x 33 percent treated) would gain 2,640 quality-adjusted life years (2.79 quality-adjusted life years/patient x 945 patients).

c. *The societal value of ''lookback''.* The preferred measure of the value of the benefit of retrospective ''lookback'' is the average willingness to pay to reduce the probability of adverse health outcomes from untreated post-transfusion HCV infections. Such measures are not readily available for most illnesses, including those caused by hepatitis C virus infection. In the absence of the direct measures recommended in the literature (Ref. 18), we assign a monetary value to a quality-adjusted life year as a proxy for willingness to pay. We recognize, however, that there is no unique, accepted societal monetary value for a quality-adjusted life year gained, and some economists are skeptical that this measure of public health improvement is even sufficiently consistent with consumer preferences to permit systematic estimates of its monetary value. To reflect the uncertainty about the value of a quality-adjusted life year, FDA uses a range of dollar amounts.

As a lower bound, FDA uses $100,000 per quality-adjusted life year, an amount similar to that used by Cutler and Richardson (Ref. 19). We derive other values for a quality-adjusted life year from estimates of the value of a statistical life. A number of empirical studies indicate a societal willingness to pay from $1.6 million to $11.6 million to avoid a statistical death. Although there is not necessarily a direct link between the willingness to pay to reduce the probability of a particular illness (or set of symptoms) and the willingness to pay to reduce the probability of death, the value of a statistical life—the sum of individual willingness to pay to avoid small risks of premature death that together add up to one expected life saved—bounds the value of a quality-adjusted life year, which is used in this analysis as a proxy for the sum of individual willingness to pay to avoid small risks of being undiagnosed as HCV positive and suffering additional morbidity impacts.

Current estimates of the value of a statistical life run from $1 million to $11 million (Ref. 20). In recent regulatory analyses, we have used values of $5 million and $6.5 million, which fall within that range. Because the Younossi model was developed with a 3 percent discount rate, we use this discount rate to estimate the value of a statistical life year. Annualizing $6.5 million over 35 years at 3 percent implies a value of $300,000 for an additional statistical life year and to develop an upper bound, annualizing $10 million over 35 years at 3 percent discount rates implies a value of $465,000 for an additional statistical life year.[11] We therefore calculate estimated benefits from this final rule with three possible values of a quality-adjusted life year: $100,000, $300,000 and $465,000. This range of values is consistent with a reasonable interpretation of studies of willingness

[11] We could, however, generate these same two values with many different combinations of values of a statistical life, discount rates, and years.

to pay to reduce mortality risks (Ref. 20).

At $100,000 per quality-adjusted life year gained, the retrospective ''lookback'' would yield one-time benefits to society of $264 million (2,640 quality-adjusted life years x $100,000 per quality-adjusted life year). At $300,000 per quality-adjusted life year gained, the retrospective ''lookback'' would yield one-time benefits to society of $792 million (2,640 quality-adjusted life years x $300,000 per quality-adjusted life year). At $465,000 per quality-adjusted life year gained, the retrospective ''lookback'' would yield one-time benefits to society of $1,228 million (2,640 quality-adjusted life years x $465,000 per quality-adjusted life year).

d. *Testing costs of retrospective ''lookback.''* Table 9 of this document summarizes the potential diagnostic testing costs associated with retrospective ''lookback.'' Diagnostic costs are based on the number of newly identified recipients with a hepatitis C virus infection, the related testing frequencies, and the unit costs for diagnostic tests and lost time for patients. As noted previously, we selected the Markov model of Younossi and others for our analysis (Ref. 14). Because Younossi's simulation begins after a patient has received a liver biopsy and uses HCV genotype to determine the duration of therapy, we also estimate these costs. All recipients infected with the hepatitis C virus would receive genotyping, however, only those infected with the genotype 1 virus (i.e., 75 percent) would undergo a liver biopsy. We exclude all treatment costs from this analysis because Younossi and others found negative incremental treatment costs (i.e., a lifetime cost savings over the no treatment option) (Ref. 14).

TABLE 9.—TOTAL COSTS OF DIAGNOSTIC TESTING AND LOST PATIENT TIME OF RETROSPECTIVE ''LOOKBACK''[1]

Type Diagnostic Tests	Cost of Diagnostic Tests[2] ($ mil)
HCV screening tests[3]	1.4
Negative supplemental tests (i.e., false positive screening result)[3]	0.9
Positive supplemental tests[3]	1.1
Hepatitis C virus genotype tests[4]	1.5
Liver biopsy[5]	2.6
Total	7.5

[1] Numbers may not sum or multiply due to rounding.
[2] Unit costs for diagnostic tests are from table 4 of this document.
[2] Unit costs for diagnostic tests are from table 4 of this document.
[3] Number of diagnostic tests are from table 8 of this document.
[4] We assume that seventy-five percent of the recipients with positive supplemental tests are chronically infected with the hepatitis C virus and have HCV genotype testing.
[5] The prevalence rate for hepatitis C virus genotype 1 is approximately 75 percent; ninety-five percent of recipients infected with genotype 1 have a needle biopsy, and 5 percent of recipients infected with genotype 1 have a wedge biopsy.

e. *Cost-effectiveness of retrospective ''lookback.''* The cost-effectiveness of retrospective ''lookback'' can be expressed as the cost per newly identified transfusion recipient or as the cost per quality-adjusted life year gained. Compliance with the retrospective ''lookback'' will cost about $61.8 million (see table 3 of this document). Accounting for these compliance costs and the screening and supplemental test costs in table 9 of this document, the one-time retrospective ''lookback'' will cost about $17,100 per newly identified HCV positive person (($1.4 million screening tests + $0.9 million negative supplemental tests + $1.1 million positive supplemental tests + $61.8 million compliance costs) / 3,818 recipients).

Including all testing costs, the retrospective ''lookback'' provisions of the final rule would cost approximately $69.4 million ($61.8 million ''lookback'' costs + $7.5 million total testing costs) with a cost-effectiveness of $26,300 per quality-adjusted life year gained ($69.4 million/2,640 quality-adjusted life years). Younossi's article reports an incremental treatment cost savings, but we do not have sufficient information to include these savings in the cost per quality-adjusted life year (Ref. 14) and therefore ignore all treatment costs in our analysis. To the extent that we exclude these cost savings, the cost-effectiveness ratio is overstated.

6. Summary of Benefits and Costs of the Final Rule

Recent public reviews of blood supply issues have recognized the importance of ensuring safety. Although the current risk of transfusion-transmitted HCV infection is already very low (i.e., less than 1:1.6 million), one-time retrospective ''lookback'' has the potential to newly identify thousands of infected transfusion recipients. In contrast, because we anticipate that prospective ''lookback'' will occur infrequently, in most years, between 0 and 5 newly identified recipients might seek treatment and benefit from a gain in quality-adjusted life years. The size of this gain is so small, however, that it is captured in the rounding for the retrospective ''lookback'' analysis. Therefore, we exclude these gains from this analysis of the final rule and quantify only the benefits of gains in quality-adjusted life years from the retrospective ''lookback.'' The final rule can be expected to gain a one-time total of 2,640 quality-adjusted life years with an estimated discounted value that ranges from $264 million to $1,228 million. As presented in table 10, over 10 years the annualized net benefits of all provisions of the final rule, including direct and diagnostic costs for both retrospective ''lookback'' and prospective ''lookback,'' will range from about $20.6 million ($31.0 million annualized benefits–$10.3 million annualized costs) to $133.6 million ($143.9 million annualized benefits–$10.3 million annualized costs). For all provisions of the final rule, the present value of all costs equals $87.6 million and is the sum of (1) The one-time ''lookback'' costs ($65.9 million) and one-time diagnostic costs ($7.5 million) for the retrospective ''lookback'', and (2) the present value of the annual direct and diagnostic costs for the prospective ''lookback'' over 10 years at a 3 percent discount rate ($13.8 million in direct costs + $0.4 million in diagnostic costs). The cost-effectiveness of the entire final rule equals $33,200 per quality-adjusted life year ($87.6 million / 2,640 quality-adjusted life years) as shown in table 10.

TABLE 10.—SUMMARY OF NET BENEFITS AND COST PER QALY[1]

Annualized Costs[2]:	
Prospective and Retrospective ''Lookback''	$9.4
Testing and Lost Patient Time	$0.9
Total Annualized Costs	$10.3

TABLE 10.—SUMMARY OF NET BENEFITS AND COST PER QALY[1]—Continued

	Low value of QALY	Medium value of QALY	High value of QALY
Annualized Benefits[3]:			
Value of QALYs gained	$31.0	$92.9	$143.9
Total Annualized Net Benefits	$20.6	$82.5	$133.6
Cost-Effectiveness:			
Present Value of Total Costs[4]		$87.6	
Number of QALYs gained[5]		2,640	
Cost per QALY ($)		$33,200	

[1] Some numbers are rounded. Unless noted, all dollar amounts are $ million. Costs and benefits annualized over 10 years at 3 percent discount rate.
[2] Includes costs to comply with all provisions of the final rule, all costs associated with the gain in QALYs from the retrospective ''lookback,'' and the costs of screening and confirmatory tests to newly identify HCV positive recipients with prospective ''lookback.''
[3] Includes only quantifiable benefits of retrospective ''lookback.'' QALYs are valued at $100,000, $300,000 and $465,000.
[4] Includes one-time costs and the present value of annual costs over 10 years at 3 percent.
[5] Because so few individuals would be newly identified from prospective ''lookback,'' the summary benefits equal the gains through retrospective ''lookback.'' Note that prospective effects, should they exist, unambiguously increase benefits but the size of this gain would be so small that it is captured in the rounding for the retrospective ''lookback'' analysis.

7. Alternatives Considered for HCV ''Lookback''

FDA finds that the targeted ''lookback'' approach is the most effective alternative when evaluated in terms of ethical, cost, and effectiveness criteria. The following provides a discussion of the baseline for the analysis and the alternatives that have been considered.

a. *Baseline: No regulatory action.* FDA has already issued an industry guidance concerning HCV ''lookback.'' Because FDA can only recommend a process and timeframe with a guidance, with no means of enforcing it, some establishments might decide not to perform ''lookback'' or to adopt a more extended timeframe to perform the ''lookback'' based on the review of historical testing records to spread the costs of this effort. Such delay, however, would increase each recipient's risk of serious disease complications.

b. *Alternative: Use of general ''lookback.''* General ''lookback'' is an alternative approach that has the potential to reach all patients who received transfusions during the period covered by ''lookback.'' The cost and ultimate effectiveness of general ''lookback'' would vary depending on the program structure and the risk message. Because general ''lookback'' would not be based on identification of at-risk donations, the risk message would communicate the average risk of HCV infection from a blood transfusion. To be effective, the risk message should reach those recipients who would have been contacted by targeted ''lookback'' and motivate them to seek testing, but not to unnecessarily alarm and burden the majority of recipients who would never be contacted by targeted ''lookback'' and who face an extremely low risk of being infected by HCV from a transfusion. Compared with targeted ''lookback,'' general ''lookback'' programs shift costs from blood collection establishments and consignees to: (1) The entity conducting the general ''lookback'' program; and (2) recipients, health-care providers and payers.

No nationwide general ''lookback'' campaign has been conducted in the United States, although some limited programs have been initiated. For example, a CDC Web site offers educational materials about hepatitis C (*www.cdc.gov/hepatitis*). In 1999, CDC pilot-tested an HCV general ''lookback'' with public service announcement posters in the public transit systems of two cities, and also distributed an audio- and videotaped general ''lookback'' message by the surgeon general to radio and television stations in 2000. The effectiveness of these programs is unknown.

In the United States, few articles have been published on the outcomes of general ''lookback'' programs. Although several general and targeted ''lookback'' programs have been conducted in Canada, there has been no standardization of outcomes or cost estimates in that country. The authors of an article reviewing general ''lookback'' programs in Canada concluded that without standardized data, it is impossible to compare the cost-effectiveness of Canadian targeted and general ''lookback'' programs (Ref. 21). Moreover, it is uncertain whether the Canadian experience would be comparable to what would happen in the United States. Nevertheless, in Canada, general ''lookback'' programs missed some recipients that were identified by targeted ''lookback.'' For example, a Canadian hospital had completed a general letter ''lookback'' for HCV when the Canadian Red Cross Society began targeted ''lookback'' in 1995. By April of 1998, at least 13 new seropositive recipients had been identified by targeted ''lookback'' who were missed by general ''lookback'' (Ref. 22). As a result, targeted ''lookback'' raised the number of HCV-positive recipients tested at that hospital by at least 9 percent over general ''lookback.''

In 2000, the Alaska Native Medical Center—a hospital providing services to Alaska Natives—began a general ''lookback'' program to contact adults and children who had received transfusions between January 1980 and July 1992 (Ref. 23). Patients identified by the record review were sent letters notifying them of their transfusion history and encouraged them to seek testing for HCV infection. In a study of that program, the study's authors estimate that the entire program cost $129,000, a total that includes $56 for each patient notification. They note that a similar program in a private sector health care setting would cost substantially more than their results suggest.

Another general ''lookback'' program conducted in Alaska notified patients who had received transfusions in a neonatal intensive care unit between January 1975 and July 1992. These patients may have been unaware of the previous transfusion event. As a regional referral center located in Anchorage, the neonatal intensive care unit provided care for patients from the Alaska Native Medical Center (i.e., integrated health-care setting) and for

patients of private sector health-care providers.

Results of general ''lookback'' varied significantly between the two health-care settings, with a higher percentage of patients identified and screened in the integrated health care setting than in the private sector setting (Ref. 24). As shown in table 11 of this document, 63 percent of the patients in the integrated health-care setting sought testing for hepatitis C virus infection, compared with 17 percent of the patients in the private sector health-care setting. This difference illustrates the uncertainty about the yield of a general ''lookback'' program in the United States. Characteristics of each health-care setting might explain some of the differences in yields between health-care settings. For example, patient records in the integrated health-care setting contain the results of hepatitis C tests. In contrast, private sector patients had to report the results of their hepatitis C tests on an anonymous questionnaire.

With the results of the two Alaskan programs we provide a rough estimate of the potential costs and outcomes of a nationwide general ''lookback'' program for patients who received transfusions between 1988 and mid-1992 (i.e., a similar timeframe to the retrospective targeted ''lookback'' based on single-antigen tests). Published data suggests that about 15.2 million patients received red blood cell or whole blood transfusions during this period (Refs. 25, 26, and 27). We apply the transitional probabilities from the two Alaskan ''lookback'' programs, shown in table 11 of this document, to the total number of patients transfused, to estimate the number of patients that might be identified at each stage of the general ''lookback'' program. With this information, we estimate a type of general ''lookback'' program similar to the recipient notification programs conducted in Canada and calculate an estimate of the total potential ''lookback'' and diagnostic costs.

TABLE 11.—YIELDS OF THREE ''LOOKBACK'' PROGRAMS[1]

Percentage of Patients from the Prior Stage of ''Lookback'' (number of patients)	Published Results of General ''Lookback'' Programs		Targeted ''Lookback''[4]
	Integrated Health Care Setting[2]	Private Sector Health Care Setting[3]	
Transfused	100% (3,169)	100% (1,396)	100% (160,879)
Sent notice	38% (1,213)	27% (374)	21% (34,267)
Notified who were screened	63% (764)	17% (64)	52% (17,819)
Screened who tested HCV+	2% (19)	2% (1)	29% (5,168)

[1] Numbers may not sum or multiply due to rounding.
[2] Based on the results from Ref. 23.
[3] Based on the results from Ref. 24.
[4] Based on the CDC interim survey results for transfusions from 1988 to 1989 (Ref. 3).

Comparing the yield of a nationwide general ''lookback'' program in a private sector health care setting to the yield of a nationwide general ''lookback'' program in an integrated health care setting gives us a range of potential outcomes for a general ''lookback'' program for recipients who received transfusions between 1988 and mid-1992. It should be noted that the Alaskan programs include some recipients who received blood transfusions prior to 1988, before blood donations were routinely screened for HCV. In addition, applying the transitional probabilities from the Alaskan programs to recipients transfused between 1988 and mid-1992, when the risk of transfusion-related HCV infection was falling, overestimates the potential yield of general ''lookback.''

A general ''lookback'' program with recipient notification requires far more resources than targeted ''lookback.'' As shown in Table 12 of this document our analysis suggests that a general transfusion recipient notification program could cost more than $500 million and newly identify between 3,600 and 30,000 recipients of tranfusions who are infected with the hepatitis C virus and who choose to receive treatment. However, these results should be interpreted with caution. CDC estimated that about 300,000 people might have been infected by blood transfusions in the 20 years prior to donor screening for HCV (Ref. 3). Our analysis suggests that general ''lookback'' might newly identify from 1.2 percent to 10 percent of those people who were infected with HCV from a blood transfusion even though we only include transfusion recipients between 1988 and mid-1992. However, in the United States, about 3.9 million people are infected with the hepatitis C virus (Ref. 28). Because general ''lookback'' contacts more persons than targeted ''lookback,'' the program might identify persons who were infected with the hepatitis C virus by other routes than transfusions. Thus, general ''lookback'' is likely to generate benefits not directly related to at-risk transfusions.

''Lookback'' programs can take many forms and target different at-risk populations. General ''lookback'' activities, such as those tested by CDC, can play an important role in efforts to reach the population at risk due to parental drug use or other risk behaviors not involving blood transfusion (Ref. 3). We have considered an Alaskan-type general ''lookback'' here as a potential alternative to a targeted ''lookback.'' If further evidence or analysis shows that the yield of the Alaskan-type program is representative of the potential yield of a nationwide general ''lookback'' program, then a general ''lookback'' program might be a cost-effective public health initiative to complement a targeted ''lookback'' and notify a subset of transfusion recipients who might be missed by the targeted ''lookback'' (e.g. patients who received transfusions before blood donations were screened for HCV; patients who were transfused as infants but who are unaware of the transfusion event and who respond only after receiving the second ''lookback'' notification).

To understand the potential yield of a general ''lookback'' that complements targeted ''lookback,'' we use the numbers shown in table 12 to adjust our estimate of the total costs and number of quality-adjusted life years gained. This approach assumes that the targeted ''lookback'' program is completed before the general ''lookback'' program begins. We also assume that all of the infected persons identified by the targeted ''lookback'' would be included within the set of infected persons identified by general ''lookback'' programs. To adjust the yields, we subtract the diagnostic costs and quality-adjusted life years gained from targeted ''lookback'' from the diagnostic costs and quality-adjusted life years gained from general ''lookback.'' The adjusted total costs for a general recipient notification ''lookback'' that complements the targeted ''lookback'' range from $487.3 million (= $494.1 million - $6.8 million) to $735.1 million (= $741.9 million - $6.8 million), and the adjusted gain in quality-adjusted life years range from 7,567 quality-adjusted life years (= 9,992 quality-adjusted life years - 2,425 quality-adjusted life years) to 81,205 quality-adjusted life years (= 83,630 quality-adjusted life years - 2,425 quality-adjusted life years). Thus, the potential cost per quality-adjusted life year for a general ''lookback'' program that complements targeted ''lookback'' range from $9,050 to $64,400. We therefore conclude that the targeted ''lookback'' analyzed here is the preferred alternative for this final rule, but an Alaskan-type general ''lookback'' could be a cost-effective HCV policy.

c. *Final: Use of targeted ''lookback.''* The ''lookback'' provisions of the final rule can be characterized as a targeted ''lookback'' program, meaning that the notification of infection risk is limited to, or targeted at, individuals identified as recipients of blood from donors subsequently found to be infected with HCV. Targeted ''lookback'' requires that the transfusion service be aware that the donor subsequently tested positive, donor and product disposition records be available to link blood components with the identified donors, and the physician or transfusion service know the recipient's current whereabouts. Blood consignees would locate recipient records for all transfused units from an affected donor, and send out notifications to the most recent address. Ideally, the recipient will still be alive and be able to receive testing and treatment, if appropriate.

Despite the difficulties of implementing targeted ''lookback,'' FDA concludes that this alternative remains the most reliable means of reaching people at increased risk of HCV infection from a transfusion. However, in response to comments on the proposed rule, some of the more prescriptive language was moved from the codified section to the accompanying guidance for industry. Therefore, the final rule lists the objective actions required of industry, and the timeframe in which they must be taken to give individual establishments the flexibility to accomplish these actions in the most cost effective manner.

d. *Limited comparison of regulatory alternatives.* The purpose of this final rule is to contact recipients who received transfusions of blood or blood components that were at risk of transmitting the hepatitis C virus. Table 12 of this document presents a comparison of the retrospective targeted ''lookback'' based on single-antigen tests and possible general ''lookback'' programs for recipients of transfusions between 1988 and mid-1992. The two general ''lookback'' estimates illustrate the uncertainty of general ''lookback'' and the likelihood that this program would identify people who were infected by other routes than transfusion events. The cost-effectiveness of the targeted ''lookback'' program falls in between the cost-effectiveness of the two general programs. The estimated effectiveness of targeted ''lookback'' is less uncertain than the estimated effectiveness of general ''lookback'', and is therefore more likely to achieve the goals of this final rule.

TABLE 12.—COMPARISON OF THE TARGETED ''LOOKBACK'' PROGRAM BASED ON SINGLE-ANTIGEN SCREENING TESTS AND TWO GENERAL ''LOOKBACK'' PROGRAMS FOR RECIPIENTS WHO RECEIVED TRANSFUSIONS BETWEEN 1988 AND MID-1992[1]

	Targeted ''Lookback'' for donations screened with single antigen test	Estimate of a Nationwide General ''Lookback'' Program for Recipients Transfused Between 1988 and mid-1992	
		Private sector health care setting	Integrated health care setting
Number of patients transfused	160,879	15.2 million	15.2 million
Number of ''lookback'' notifications	34,267	4,058,811	5,798,974
Number of screening tests	17,819	694,556	3,652,446
Number of supplemental tests	11,405	10,852	181,666
Number of HCV+ patients	5,168	10,852	90,833
Number of HCV+ patients treated	869	3,581	29,975
''Lookback'' costs ($ mil)	$55.9[2]	$426.2[3]	$324.7[4]
Diagnostic costs[5] ($ mil)	$6.8	$67.9	$417.2
Total costs ($ mil)	$62.7	$494.1	$741.9
Number of QALYs gained	2,425	9,992	83,630
Cost per QALY gained ($)	$25,862[6]	$49,449	$8,871
Incremental cost per QALY gained between targeted and the upper and lower bounds of general ''lookback''	—	*$57,011*	*$8,364*

[1] Unless noted, all dollar amounts are $ million.
[2] ''Lookback'' costs of $113 for blood collection establishments and $184 for transfusion establishments.
[3] ''Lookback'' costs of $105 based on Ref. 24.
[4] ''Lookback'' costs of $56 based on Ref. 23.
[5] Unit costs for diagnostic tests are shown in table 4 of this document.
[6] For this example, we report the cost-effectiveness of the retrospective ''lookback'' based on single-antigen tests. This differs from the cost-effectiveness of the entire retrospective ''lookback'' reported in section 6.e. of this document.

C. Impact on Small Entities

No comments were received on the initial regulatory flexibility analysis or the agency's request for specific information essential to estimate the final rule's impact on small entities. Because information on the affected industries is limited, the agency cannot predict the extent of the economic impact of the final rule on small entities and, therefore, performed a final regulatory flexibility analysis.

The final rule will help ensure the continued safety of the blood supply and will help ensure that consignees and recipients who received blood and blood components at increased risk of transmitting HCV are informed. Affected entities include commercial plasma centers, community and hospital blood banks, and hospital transfusion services that collect or receive blood and blood components. For the regulatory flexibility analysis affected firms are considered small if they are: (1) A for-profit firm with annual receipts or revenue less than the current Small Business Administration (SBA) industry size standards; (2) an independently owned and operated, not-for-profit enterprise which is not dominant in its field; or (3) operated by a small governmental jurisdiction with a population of less than 50,000 individuals. Aggregate information about hospitals and blood banks are available under SIC (Standard Industrial Classification) group 80 for health services. However, the North American Industry Classification System (NAICS) reports information at the blood and organ banks level. Similarly, more detailed general medical and surgical hospital information is available with NAICS than with the SIC system. To estimate the economic impact of the final rule on these different types of small entities, the costs per firm shown in table 13 of this document are expressed as a percentage of average annual revenue in tables 14, 15, and 16 of this document.

TABLE 13.—ESTIMATED PER FIRM REGULATORY COSTS BY TYPE OF SMALL ENTITY[1]

Type of Small Entity	Share of "Lookback" Costs	Annual Costs[2]	One-Time Costs[3]	Total Annualized Costs	
				3 percent	7 percent
Plasma collection	N/A	—	$1,350	$160	$190
Blood collection	0.04%	—	$10,210	$1,200	$1,450
For-profit hospital	0.02%	$1,410	$7,370	$2,270	$2,460
Not-for-profit hospital	0.02%	$1,410	$7,060	$2,240	$2,420
Government hospital	0.00%	$1,370	$1,420	$1,540	$1,570

[1] Numbers may not add due to rounding.
[2] Although 80 percent of hospitals already retain records for 10 years, this analysis assumes small hospitals are not in compliance with this provision of the final rule. Blood collection establishments currently comply with these provisions of the final rule.
[3] Includes one-time cost for SOPs and historical "lookback" actions.

In the United States, most plasma establishments are owned by large, for-profit companies, whereas almost all blood collection establishments are not-for-profit organizations. The SBA size standards in effect since December 6, 2005, define as small any blood and organ bank (NAICS 621991) with an annual income of less than $9 million. Although the 1997 Economic Census lists 449 blood and organ banks (including plasma collection establishments) owned by 173 for-profit firms and 721 blood and organ banks owned by 300 not-for-profit firms (NAICS 621991), this data has limited use because it includes organ banks, excludes any blood collection establishment operating as part of a hospital, and uses different receipt sizes than the SBA.

FDA estimates the final rule will affect 60 commercial plasma collection establishments and 981 blood collection establishments. The FDA registry of blood establishments does not provide an indication of the size of the registered entities. However, previously the agency estimated that 37 small plasma establishments collect approximately 8 percent of the plasma and 906 small blood banks collect 35 percent of the donated blood (66 FR 31146 at 31159).

Each affected establishment will incur the one-time cost to revise SOPs. Blood and plasma collection establishments have had procedures in place for HIV "lookback" for years. Thus, no additional skills are required because each establishment has existing personnel experienced in preparation of SOPs and the establishment would update existing SOPs by including HCV into the "lookback" procedures. Using 1997 Economic Census data on for-profit firms included in NAICS 621991, table 14 of this document illustrates that the annualized costs of the SOPs will be less than 0.5 percent of average receipts for all small plasma entities, illustrating that the average impact of the final rule will not be significant for small plasma entities.

TABLE 14.—ONE-TIME AND ANNUALIZED COSTS OF THE FINAL RULE ON FOR-PROFIT PLASMA CENTERS OPERATING ALL YEAR[1]

Receipts Size of Firm[1]	Number of Firms[1]	Receipts[1] ($1,000)	Average Receipt per Firm[1] ($1,000)	Per Firm One-Time Costs as Percent of Average Receipts[2]	Per Firm Annualized Costs as Percent of Average Receipts[2]	
					3 percent	7 percent
< $100,000	28	1,714	61.2	2.2%	0.3%	0.3%
$100,000 to $249,999	21	3,257	155.1	0.9%	0.1%	0.1%

TABLE 14.—ONE-TIME AND ANNUALIZED COSTS OF THE FINAL RULE ON FOR-PROFIT PLASMA CENTERS OPERATING ALL YEAR[1]—Continued

Receipts Size of Firm[1]	Number of Firms[1]	Receipts[1] ($1,000)	Average Receipt per Firm[1] ($1,000)	Per Firm One-Time Costs as Percent of Average Receipts[2]	Per Firm Annualized Costs as Percent of Average Receipts[2]	
					3 percent	7 percent
$250,000 to $499,999	16	5,737	358.6	0.4%	0.0%	0.1%
$500,000 to $999,999	30	21,626	720.9	0.2%	0.0%	0.0%
$1,000,000 to $2,499,999	37	56,837	1,536.1	0.1%	0.0%	0.0%
$2,500,000 to $4,999,999	16	55,677	3,479.8	0.0%	0.0%	0.0%
$5,000,000 to $9,999,999	5	37,124	7,424.8	0.0%	0.0%	0.0%
$10,000,000 +	20	804,559	NA	NA		NA
Total	173	986,531				

[1] Source: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau, ''1997 Economic Census, Health Care and Social Assistance, Subject Series: Establishment and Firm Size,'' EC97S62S–SZ, October 2000, table 4a, NAICS 621991 (blood and organ banks).
[2] Per firm costs from table 13 of this document.

In addition to the cost of revising SOPs, the one-time costs of the retrospective ''lookback'' will be proportional to the volume of blood collected by blood establishments. Therefore, small entities collecting few donations will incur the lowest ''lookback'' costs. Because 906 small entities collect about 35 percent of the blood, the proportion of ''lookback'' costs for each entity will be small. For example, if blood donations are distributed evenly among small blood collection establishments, each small organization would incur only 0.04 percent (0.04 percent = 35 percent / 906) of the ''lookback'' costs and collect approximately 5,400 donations each year (5,408 donations / establishment = 14 million donations x 35 percent / 906 establishments). Using $96 as the price for a unit of red blood cells, small blood collection establishments average a minimum annual revenue of approximately $520,000 (Ref. 29). Table 15 of this document summarizes the one-time and annualized costs of the final rule as a percentage of this minimum average revenue for small blood collection organizations.

TABLE 15.—ONE-TIME AND ANNUALIZED COSTS OF THE FINAL RULE ON NOT-FOR-PROFIT BLOOD COLLECTION ORGANIZATIONS

Number of Small Organizations	Average Annual Revenue[1]	Per Firm One-Time Costs as Percent of Average Revenue[2]	Per Firm Annualized Costs as Percent of Average Revenue[2]	
			3 percent	7 percent
906	$519,200	2.0%	0.2%	0.3%

[1] 5,370 units x $96/unit of red blood cells = $515,520. A unit of whole blood can be separated into non-red blood cell components that yield additional revenues in excess of $135.
[2] Per firm costs from table 13 of this document.

An estimated 4,980 hospitals perform transfusion services in the United States. The SBA defines as small any general medical and surgical hospital (NAICS 622110) with annual receipts less than $31.5 million. Similar to blood banks, the census uses receipt sizes that differ from those of the SBA. Therefore, in this analysis, for-profit hospitals with annual receipts less than $25 million are treated as small businesses. Furthermore, not-for-profit, non-government hospitals that have no more than one establishment are treated as small organizations. Similarly, the number of government hospitals (NAICS 6221101) classified as single-unit firms, or firms with one establishment, provides an estimate of the number of small government hospitals. This approach most likely overestimates the number of hospitals operated by small government jurisdictions, because many urban county hospitals (i.e., with populations greater than 50,000) may have only one establishment.

In contrast to blood banks, the 1997 Economic Census reports data separately on 774 for-profit hospitals (NAICS 622110), 1,571 government hospitals (NAICS 6221101), and 3,076 non-government, not-for-profit hospitals (NAICS 6221102). Each hospital transfusion service will incur the cost of preparing SOPs and 20 percent will spend more to retain records an additional 5 years. Hospitals have experience preparing SOPs and have already been performing an historical ''lookback'' under an agency guidance to industry. Thus compliance with the final rule requires no new skills.

Similar to blood banks, ''lookback'' costs are proportional to transfusion volume. Unlike blood banks, however, data from several sources provides sufficient information to distribute transfusion volume to different types of small entities. National statistics from the Healthcare Cost and Utilization Project (HCUP) on in-hospital blood transfusions in 1997 (i.e., clinical classifications software procedure category 222) give a reasonable estimate of the volume of blood transfused by hospitals categorized by ownership (i.e., government; private, not-for-profit; and private, for-profit) (Ref. 8). Furthermore, HCUP provides data on the number of transfusions by ownership category and

bed size. In 1997, HCUP defined bed size category based on location and teaching status of the hospital. Thus small bed size refers to the following: (1) 1 to 49 beds for rural hospitals; (2) 1 to 99 beds for urban, non-teaching hospitals; and (3) 1 to 299 beds for urban, teaching hospitals. However, most teaching hospitals are affiliated with public or private, not-for-profit colleges or universities which would be considered organizations. Using the HCUP definition, small for-profit hospitals are assumed to have no more than 99 beds. Data from a 1998 American Hospital Association (AHA) survey on hospitals in the United States shows that hospitals with less than 100 beds had average revenues of $27.7 million or less (Ref. 7). The HCUP data on the number of transfusions given in small, for-profit hospitals is used, therefore, to estimate the share of total transfusion for small businesses. In contrast, small not-for-profit or government hospitals may not necessarily be classified as small based on HCUP bed size. Thus for these small entities, revenue shares calculated from the 1997 Economic Census data serve as proxies for transfusion volume.

Table 16 of this document shows the average one-time and annual costs incurred by small hospitals as a percentage of annual receipts or revenue. In all cases, one-time costs are less than one percent of average revenue or receipts and annualized costs are less than 0.2 percent of average revenue or receipts. Therefore, the final rule does not have a significant economic impact on these small entities.

TABLE 16.—HOSPITAL INDUSTRY ONE-TIME AND ANNUAL COSTS AS A PERCENTAGE OF AVERAGE ANNUAL REVENUE BY SIZE AND TYPE OF FIRM[1,2]

Receipt Size of Firm	Number of Firms	Receipts ($1,000)	Average Receipt Per Firm ($1,000)	Per Firm One-Time Costs as Percent of Average Receipts	Per Firm Annualized Costs as Percent of Average Receipts	
					3 percent	7 percent
For-Profit Hospitals Operating All Year:[3]						
$0 to $999,999	0					
$1,000,000 to $2,499,999	6	9,737	1,622.8	0.5%	0.1%	0.2%
$2,500,000 to $4,999,999	21	73,777	3,513.2	0.2%	0.1%	0.1%
$5,000,000 to $9,999,999	43	316,631	7,363.5	0.1%	0.0%	0.0%
$10,000,000 to $24,999,999	38	630,189	16,583.9	0.0%	0.0%	0.0%
$25,000,000 +	66	NA	NA			NA
Total	174	33,782,805				
Size Category (share of total revenue)	Number of Firms	Revenue ($1,000)	Average Revenue Per Firm ($1,000)	Per Firm One-Time Costs as Percent of Average Revenue	Per Firm Annualized Costs as Percent of Average Revenue	
					3 percent	7 percent
Not-For-Profit Hospitals Operating All Year:[4]						
Single-unit firm (14%)	918	44,832,121	48,836.7	0.0%	0.0%	0.0%
One establishment (23%)	813	74,651,556	91,822.3	0.0%	0.0%	0.0%
Total	2,034	242,896,322				
Government Hospitals Operating All Year:[5]						
Single-unit firm (7%)	994	23,175,491	23,315.4	0.0%	0.0%	0.0%
One establishment (14%)	515	43,739,763	84,931.6	0.0%	0.0%	0.0%
Total	1,537	77,024,061				

[1] Source: U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau, ''1997 Economic Census, Health Care and Social Assistance, Subject Series: Establishment and Firm Size,'' EC97S62S–SZ, October 2000.

[2] Per firm costs from table 13 of this document.

[3] 1997 Economic Census, table 4a, NAICS 622110. Based on 1997 HCUP data, small private for-profit hospitals account for approximately 2 percent of the annual transfusion volume (1.8% = 23,182 / 1,296,723).

[4] 1997 Economic Census, table 3b, NAICS 6221102. HCUP data shows private, not-for-profit hospitals account for 71% of all transfusions (= 924,730 / 1,296,723). According to 1997 Economic Census data, hospitals with less than two establishments account for 37% of total revenues for all private, not-for-profit hospitals. Therefore small, private, not-for-profit hospitals will incur about 27% (27% = 71% x 37%) of the consignee ''lookback'' costs. Costs as a percent of revenue less than 0.05 percent are rounded to 0.0 percent.

[5] 1997 Economic Census, table 3b, NAICS 6221101, HCUP data shows government hospitals account for 15% of all transfusions (= 193,679 / 1,296,723). According to 1997 Economic Census data, government hospitals with less than two establishments account for 21% of total revenues for all government hospitals. Therefore, small government hospitals will incur about 3% (3% = 15% x 21%) of the consignee ''lookback'' costs. Costs as a percent of revenue less than 0.05 percent are rounded to 0.0 percent.

As described earlier, FDA has considered several alternatives, and considers that a targeted ''lookback'' will be the most effective approach to inform recipients of HCV-infected blood products. Because ''lookback'' costs are proportional to blood collection or transfusion volume, the smallest entities will incur the lowest costs. Furthermore, the agency allows for flexibility in an establishment's individual approach to compliance by moving the prescriptive language of the proposed rule to an industry guidance document and specifying only the objective actions required by an establishment in the final rule. This will enable each entity to develop procedures that are most appropriate and cost-effective given the particular situation and the resources available. In addition, the agency has specified a limited time frame for notification to provide a clear endpoint to facilitate efforts related to the historical ''lookback.'' The agency concludes that this final rule will ensure the safety of

the blood supply and meet public health goals in the least intrusive and most cost-effective way. Therefore, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

V. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these provisions, with an estimate of the annual reporting and recordkeeping burden, follows. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Current Good Manufacturing Practices for Blood and Blood Components; Notification of Consignees and Transfusion Recipients Receiving Blood and Blood Components at Increased Risk of Transmitting Hepatitis C Virus Infection (''Lookback'').

Description: This final rule requires collecting establishments and consignees to prepare and follow written procedures when a donor who tests reactive for evidence of HIV or HCV infection either on a repeat donation or after a review of historical testing records (recordkeeping burden in § 606.100(b)(19)). Such collections may be at increased risk of transmitting HIV or HCV infection. We are requiring collecting establishments to review testing records, to quarantine prior in-date blood and blood components from such a donor, to perform further testing on the donor, and to notify consignees of prior in-date blood and blood components from such a donor for quarantine purposes (reporting burden in §§ 610.46(a)(1)(ii)(B), 610.47(a)(1)(ii)(B), and 610.48(b)(3)(ii) and (b)(3)(iii)) and to notify consignees of further testing results (reporting burden in §§ 610.46(a)(3), 610.47(a)(3), and 610.48(b)(4)). We also are requiring consignees to notify transfusion recipients, the recipients' physicians of record, or the recipients' legal representatives that the recipient received blood and blood components at increased risk of transmitting HIV or HCV (reporting burden in §§ 610.46(b)(3), 610.47(b)(3), and 610.48(c)(3)). Records of these actions must be kept (recordkeeping burden in § 606.160(b)(1)(viii)). We also are extending record retention under § 606.160(d) from 5 to 10 years.

Description of Respondents: Collecting establishments (business and not-for-profit) and consignees of collecting establishments, including hospitals, transfusion services, and physicians.

As required by section 3506(c)(2)(B) of the PRA, we provided an opportunity for public comment on the information collection requirements of the HCV ''lookback'' proposed rule (65 FR 69378). In accordance with the PRA, OMB reserved approval of the information collection burden in the proposed rule, stating it will make an assessment in light of public comments received on the proposed rule. No comments on the information collection requirements were submitted to OMB or the docket.

The total reporting and recordkeeping burden for the first year is estimated to be 495,309.5 hours. However, of this total approximately 456,280 hours would be expended on a one-time basis for establishing the written procedures and doing the one-time retrospective review of historical HCV testing records. Therefore, 39,029.5 hours is estimated as the ongoing annual burden related to these regulations. The total ongoing annual burden for collecting establishments under §§ 610.46(a)(1)(ii)(B), 610.46(a)(3), 610.46(b)(3), and 606.160(b)(1)(viii) for HIV ''lookback'' is estimated to be 12,763 hours. The total ongoing annual burden for collecting establishments under §§ 610.47(a)(1)(ii)(B), 610.47(a)(3), 610.47(b)(3), and 606.160(b)(1)(viii) for HCV ''lookback'' is estimated to be 26,266.5 hours.

Based on information retrieved from FDA's registration database and as discussed in section IV of this document, there are approximately 1,041 FDA registered establishments (60 licensed plasma establishments and 981 registered collecting establishments) in the United States that collect approximately 27 million donations annually: 13 million donations of Source Plasma and 14 million donations of Whole Blood, including approximately 695,000 autologous units. As calculated in section IV of this document, there are approximately 11.2 million donations of Whole Blood from repeat donors per year. As previously discussed in section IV.A.3.b of this document, the Source Plasma industry will only be minimally affected by these requirements. Therefore, we are only estimating burden for Source Plasma collecting establishments in regards to § 606.100(b)(19). The following reporting and recordkeeping estimates are based on information provided by industry and FDA experience.

A. Annual Reporting Burden

1. HIV Reporting Burden

In table 17 of this document, we estimate that approximately 3,500 repeat donors will test reactive on a screening test for HIV. We estimate that an average of three components were made from each donation. Under § 610.46(a)(1)(ii)(B) and 610.46(a)(3), this estimate results in 10,500 (3,500 x 3) notifications of the HIV screening test results to consignees by collecting establishments for the purpose of quarantining affected blood and blood components, and another 10,500 (3,500 x 3) notifications to consignees of subsequent test results. We estimate an average of 10 minutes per notification of consignees. The estimate for consignee notifications in the final rule is higher than the estimate in the proposed rule because we based our calculations in the final rule on the number of components at risk of transmitting HCV infection rather than the number of reactive donors. We also have increased the number of components per donation from two to three.

In addition, we estimate that § 610.46(b)(3) will require 4,980 consignees to notify transfusion recipients or physicians of record an average of 0.35 times per year resulting in a total number of 1,755 (585 confirmed positive repeat donors x 3) notifications. In the proposed rule, we estimated 0.5 hours as the average time for a reasonable attempt to notify recipients by consignees. However, under § 610.46(b)(3), we are increasing the estimate to 1 hour to accommodate the time to gather test results and the recipient's records and to accommodate multiple attempts to contact the recipient.

2. HCV Reporting Burden

We estimate that approximately 7,800 repeat donors per year would test reactive for antibody to HCV (780 repeat donors confirmed HCV positive / 0.1 rate for repeat donors confirmed HCV positive / repeat donors with reactive tests = 7,800 repeat donors with reactive tests). Under §§ 610.47(a)(1)(ii)(B) and 610.47(a)(3), collecting establishments would notify the consignee two times for each of the 23,400 (7,800 x 3 components) components prepared from these donations, once for quarantine purposes and again with additional HCV test results for a total of 46,800 notifications as an annual ongoing burden. Under § 610.47(b)(3), we estimate that approximately 4,980 consignees would notify approximately 2,050 recipients (calculated in section IV.A.4.b.i of this document) or their

physicians of record annually. The estimated average 1 hour to complete notification is based on the criteria discussed in the previous section on HIV Reporting Burden.

B. Estimated One-Time Reporting Burden

Based on estimates from CDC, we expect that for the one-time retrospective review of historical testing records, as many as approximately 212,000 blood components (calculated in section IV.A.4.b.ii of this document) would be at increased risk for transmitting HCV. For each of these products, under §§ 610.48(b)(3)(ii) and (b)(3)(iii), and 610.48(b)(4) collecting establishments would notify consignees to quarantine these products and report additional HCV test results to consignees, and, under § 610.48(c)(3), consignees would notify transfusion recipients or recipients' physicians of record. CDC estimated that there could be approximately 212,000 transfusion recipients that would be notified after a one-time retrospective review of historical test results for HCV screening. The numbers in the ''Hours per Response'' column of table 18 of this document are the same as the burden for table 7 of this document.

C. Estimated Annual and One-Time Recordkeeping Burden

In the recordkeeping tables (tables 19 and 20 of this document), the numbers in the ''Hours per Record'' column are based on our estimate of the time to complete one record. We also estimate that each documentation of consignee and recipient notification takes approximately 5 minutes. In table 20 of this document, we estimate that it will take collecting establishments approximately 40 hours to establish the written procedures required under § 606.100(b)(19) and consignees approximately 16 hours to establish written procedures under § 606.100(b)(19). In table 19 of this document, the estimate for annual recordkeeping is based on the estimate that it takes approximately 10 minutes to document and maintain the records to relate the donor with the unit number of each previous donation for both the collecting establishment and the consignee. The time required for recordkeeping under § 606.160(b)(1)(viii) is estimated to be approximately 10 minutes for each HIV or HCV reactive donation record and approximately 10 minutes per transfusion recipient record required under §§ 610.46(b)(3), 610.47(b)(3), and 610.48(c)(3).

Because the final rule will not affect current industry practice of retaining ''lookback'' records for 10 years, no burden is calculated for § 606.160(d). We estimate the burden for this collection of information as follows:

TABLE 17.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
610.46(a)(1)(ii)(B)	981	10.7	10,500	0.17	1,785
610.46(a)(3)	981	10.7	10,500	0.17	1,785
610.46(b)(3)	4,980	0.35	1,755	1.0	1,755
610.47(a)(1)(ii)(B)	981	23.85	23,400	0.17	3,978
610.47(a)(3)	981	23.85	23,400	0.17	3,978
610.47(b)(3)	4,980	0.41	42,050	1.0	2,050
Total					15,331

[1] There are no capital or operating and maintenance costs associated with this collection of information.

TABLE 18.—ESTIMATED ONE-TIME REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
610.48(b)(3)(ii) and (b)(3)(iii)	981	216.1	212,000	0.17	36,040
610.48(b)(4)	981	216.1	212,000	0.17	36,040
610.48(c)(3)	4,980	42.57	212,000	1.0	212,000
Total					284,080

[1] There are no capital or operating and maintenance costs associated with this collection of information.

TABLE 19.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
606.160(b)(1)(viii)					
HIV consignee notification	981	21.4	21,000	.17	3,570
	4,980	4.2	21,000	.17	3,570
HCV consignee notification	981	47.71	46,800	.17	7,956

TABLE 19.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]—Continued

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
	4,980	9.4	46,800	.17	7,956
HIV recipient notification	4,980	0.35	1,755	.17	298
HCV recipient notification	4,980	0.41	2,050	.17	348.5
Total					23,698.5

[1] There are no capital or operating and maintenance costs associated with this collection of information.

TABLE 20.—ESTIMATED ONE-TIME RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
606.100(b)(19)	1,041	1	1,041	40	41,640
606.100(b)(19)	4,980	1	4,980	16	79,680
606.160(b)(1)(viii)	1,041	203.65	212,000	.08	16,960
606.160(b)(1)(viii)	4,980	42.57	212,000	.08	16,960
610.48(c)(3)	4,980	42.57	212,000	.08	16,960
Total					172,200

[1] There are no capital or operating and maintenance costs associated with this collection of information.

The information collection provisions of this final rule have been submitted to OMB for review.

Before the final rule becomes effective, we will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment, nor an environmental impact statement is required.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive Order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web sites after this document publishes in the **Federal Register**.)

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Lists of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 610

Biologics, Labeling, Reporting and recordkeeping requirements.

■ Therefore, under the Federal Food, Drug, and Cosmetic Act, and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 606 and 610 are amended as follows:

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

■ 1. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

■ 2. Section 606.100 is amended by revising paragraph (b)(19) to read as follows:

§ 606.100 Standard operating procedures.

* * * * *

(b) * * *

(19) Procedures under §§ 610.46, 610.47, and 610.48 of this chapter:

(i) To identify previously donated blood and blood components from a donor who later tests reactive for evidence of human immunodeficiency virus (HIV) infection or hepatitis C virus (HCV) infection when tested under § 610.40 of this chapter, or when a blood establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection;

(ii) To quarantine in-date blood and blood components previously donated by such a donor that are intended for use in another person or further manufacture into injectable products, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(iii) To notify consignees to quarantine in-date blood and blood components previously donated by such a donor intended for use in another person or for further manufacture into injectable products, except pooled components intended solely for further manufacturing into products that are manufactured using validated viral clearance procedures;

(iv) To determine the suitability for release, destruction, or relabeling of quarantined in-date blood and blood components;

(v) To notify consignees of the results of the HIV or HCV testing performed on the donors of such blood and blood components;

(vi) To notify the transfusion recipient, the recipient's physician of record, or the recipient's legal representative that the recipient received blood or blood components at increased risk of transmitting HIV or HCV, respectively.

* * * * *

■ 3. Section 606.160 is amended by revising paragraph (b)(1)(viii) and the second sentence of paragraph (d) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(1) * * *

(viii) Records concerning the following activities performed under §§ 610.46, 610.47, and 610.48 of this chapter: Quarantine; consignee notification; testing; notification of a transfusion recipient, the recipient's physician of record, or the recipient's legal representative; and disposition.

* * * * *

(d) * * * You must retain individual product records no less than 10 years after the records of processing are completed or 6 months after the latest expiration date for the individual product, whichever is the later date.

* * *

* * * * *

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

■ 4. The authority citation for 21 CFR part 610 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

■ 5. Section 610.41 is amended by adding paragraph (c) to read as follows:

§ 610.41 Donor deferral.

* * * * *

(c) You must comply with the requirements under §§ 610.46 and

610.47 when a donor tests reactive by a screening test for HIV or HCV required under § 610.40(a) and (b), or when you are aware of other reliable test results or information indicating evidence of HIV or HCV infection.

■ 6. Section 610.46 is revised to read as follows:

§ 610.46 Human immunodeficiency virus (HIV) ''lookback'' requirements.

(a) If you are an establishment that collects 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) Within 3 calendar days after a donor tests reactive for evidence of human immunodeficiency virus (HIV) 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 HIV 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. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test or HIV p24 antigen test, and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) 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; and

(B) Notify consignees to 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;

(2) You must perform a supplemental (additional, more specific) test for HIV as required under § 610.40(e) of this chapter on the reactive donation.

(3) You must notify consignees of the supplemental (additional, more specific) test results for HIV, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, 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 HIV infection under § 610.40(a) and (b) of this chapter. Notification of consignees 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 HIV infection.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, exempted for such use by FDA.

(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.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HIV is positive or when the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, 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 HIV infection, or the recipient's physician of record, of the need for recipient HIV testing and counseling. You must notify the recipient's physician of record or a legal representative or relative if the recipient is a minor, deceased, 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 supplemental (additional, more specific) test results for evidence of HIV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HIV if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

■ 7. Section 610.47 is revised to read as follows:

§ 610.47 Hepatitis C virus (HCV) ''lookback'' requirements.

(a) If you are an establishment that collects 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) Within 3 calendar days after a donor tests reactive for evidence of hepatitis C virus (HCV) infection when tested under § 610.40(a) and (b) of this chapter 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. For those identified blood and blood components collected:

(i) Twelve months and less before the donor's most recent nonreactive screening tests, or

(ii) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test and nonreactive antibody screening test, whichever is the lesser period, you must:

(A) 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; and

(B) Notify consignees to 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;

(2) You must perform a supplemental (additional, more specific) test for HCV as required under § 610.40(e) on the reactive donation.

(3) You must notify consignees of the supplemental (additional, more specific) test results for HCV, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, 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 under § 610.40(a) and (b). Notification of consignees 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.

(4) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, exempted for such use by FDA.

(b) If you are a consignee of Whole Blood or blood components, including Source Plasma or 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.

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the supplemental (additional, more specific) test performed under paragraph (a)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HCV is positive or when the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, 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 supplemental (additional, more specific) test results for evidence of HCV infection from the collecting establishment, or after receiving the donor's reactive screening test result for HCV if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA.

(c) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

■ 8. Section 610.48 is added to subpart E to read as follows:

§ 610.48 Hepatitis C virus (HCV) ''lookback'' requirements based on review of historical testing records.

(a) Establishments that collect Whole Blood or blood components, including Source Plasma and Source Leukocytes, must complete the following actions by February 19, 2009.

(b) If you are an establishment that collects 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:

(i) Review all records of donor testing for hepatitis C virus (HCV) performed before February 20, 2008. The review must include records dating back indefinitely for computerized electronic records, and to January 1, 1988, for all other records. Record review, quarantine, testing, notification, and disposition performed before February 20, 2008 that otherwise satisfy the requirements under § 610.47, are exempt from this section.

(ii) Identify donors who tested reactive for evidence of HCV infection. Donors who tested reactive by a screening test and negative by an appropriate supplemental (additional, more specific) test under § 610.40(e) for evidence of HCV infection on the same donation are not subject to further action.

(iii) Identify the blood and blood components previously collected from such donors:

(A) Twelve months and less before the donor's most recent nonreactive screening tests, or

(B) Twelve months and less before the donor's reactive direct viral detection test, e.g., nucleic acid test and nonreactive antibody screening test, whichever is the lesser period.

(2) If you did not perform a supplemental (additional, more specific) test at the time of the reactive donation, you may perform a supplemental test or a licensed screening test with known greater sensitivity than the test of record using either a frozen sample from the same reactive donation or a fresh sample from the same donor, if obtainable. If neither is available, proceed with paragraphs (b)(3), (b)(4), and (b)(5) of this section.

(3) You must, within 3 calendar days after identifying the blood and blood components previously collected from donors who tested reactive for evidence of HCV infection:

(i) Quarantine all previously collected in-date blood and blood components identified under paragraph (b)(1)(iii) of this section if intended for use in another person or for further manufacture into injectable products, except pooled components solely intended for further manufacturing into products that are manufactured using validated viral clearance procedures.

(ii) Notify consignees to quarantine all previously collected in-date blood and blood components identified under paragraph (b)(1)(iii) 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; and

(iii) Notify consignees of the donor's test results, including the results of a supplemental (additional, more specific) test or a licensed screening test with known greater sensitivity than the test of record, if available at that time.

(4) You must notify consignees of the results of the supplemental (additional, more specific) test or the licensed screening test with known greater sensitivity than the test of record for

HCV, if performed, within 45 calendar days of completing the further testing. Notification of consignees must include the test results for blood and blood components identified under paragraph (b)(1)(iii) of this section that were previously collected from a donor who later tests reactive for evidence of HCV infection.

(5) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components consistent with the results of the further testing performed under paragraph (b)(2) of this section or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an investigational new drug application (IND) or investigational device exemption (IDE), is exempted for such use by FDA.

(c) 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, which you must complete within 1 year of the date of notification by the collecting establishment:

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

(2) You must release from quarantine, destroy, or relabel quarantined in-date blood and blood components, consistent with the results of the further testing performed under paragraph (b)(2) of this section, or the results of the reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE is exempted for such use by FDA.

(3) When the supplemental (additional, more specific) test for HCV is positive; or the supplemental test is indeterminate, but the supplemental test is known to be less sensitive than the screening test; or the screening test is reactive and there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA; or if supplemental testing is not performed, you must make reasonable attempts to 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.

(d) Actions under this section do not constitute a recall as defined in § 7.3 of this chapter.

(e) This section will expire on August 24, 2015.

Dated: July 5, 2007.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. E7–16607 Filed 8–23–07; 8:45 am]

BILLING CODE 4160–01–S