American Red Cross

National Headquarters

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

RE: 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") Docket # 99N-2337 [65 Fed. Reg. 69378, November 16, 2000]

Dear Docket Officer:

This letter is to provide public comments on behalf of the American Red Cross (ARC or Red Cross) concerning the Food and Drug Administration's (FDA or Agency) Proposed Rule *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* (proposal) as published on November 16, 2000. The rule provides recommendations for blood establishments and their consignees for following Lookback procedures for donors who test positive for the hepatitis C virus (HCV). The rule also proposes certain changes to the current regulations and guidances for human immunodeficiency virus (HIV) Lookback (CFR 610.46).

Red Cross, through its 36 Blood Services regions, supplies approximately half of the nation's blood component for transfusion needs. Red Cross is following all the instructions in the current HCV Guidance published on September 23, 1998. This proposal contemplates a number of changes from the existing HCV Lookback guidances and from the current HIV Lookback requirements. These changes have an important effect on blood establishments and their consignees. Given the direct and very large impact of the contemplated revisions, Red Cross appreciates the opportunity to provide input to FDA.

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ARC believes that the recommendations contained in this letter and the two accompanying attachments are primarily clarifications and adjustments to allow appropriate scientific and other considerations to be factored into FDA's Lookback requirements. These recommendations will not alter the ultimate objective of informing patients who may be at risk of exposure. Indeed, we believe these clarifications will streamline efforts so that the Lookback process can be completed in the most expeditious manner possible.

Our main recommendations include the following:

- Clarify the descriptions of the records that must be reviewed and the dates going back, particularly with respect to the use of computerized records.

- When establishing the product quarantine requirements for HIV Lookback, retain the currently required three month period prior to the repeat reactive donation as the time frame for determining which products must be quarantined when only the HIV-1 p24 antigen test is positive.

- Apply the rule only to Lookback cases that are opened after the final rule's effective date. Allow blood establishments to retain Lookback decisions (e.g. completed cases) made under the current guidances and prior to the final rule.

- Add to the final regulation the exemptions under existing guidances for those products already pooled for fractionation which inactivates the virus of concern, and when the consignee is unable to notify recipients because records of products distributed for transfusion are no longer in existence.

- Encourage blood establishments to research new testing technologies by allowing them to continue to apply the results of unlicensed or in-house testing services to quarantine, Lookback and notification decisions.

Attachment 1 provides a comprehensive description of the above points as well as additional recommendations. Attachment 2 contains a section-by-section table of ARC's recommendations linked to the individual proposed sections. Also included as Attachment 3 is the Red Cross letter to the FDA regarding the June 22, 1999, Draft HCV Lookback Guidance. As noted in the 1999 letter and accompanying data, the public health benefits of expanding the Lookback prior to January 1, 1988 are, at best, doubtful.

Again, the Red Cross appreciates the opportunity to submit its views and hopes the agency finds these suggestions constructive. If there are any questions on this letter, or if you wish to meet to discuss these concerns in greater detail, please contact Anita Ducca, Director, Regulatory Relations, 703-312-5601 or Linda Chambers, MD, 703-312-5610.

Sincerely,

Glenn M. Mattei, Esq.
Interim Vice President
Quality Assurance and Regulatory Affairs
Biomedical Services
American Red Cross

Attachments

cc: Paul Mied, Ph.D.

Comments by
The American Red Cross
On the Proposed Regulation
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'')
Docket # 99N-2337 65 Fed. Reg. 69378

Introduction

This attachment contains the comments of The American Red Cross (ARC or Red Cross) on the overall policies and Lookback decisions contained in the proposed regulation (proposal). Attachment 2 contains a detailed chart providing additional comments on the specific sections of the proposal. To simplify the discussion, we have used the term "prospective" to indicate the segments of the proposal regarding quarantine and consignee notification based on current testing. The review of historical testing records will be referred to as "retrospective" Lookback.

I. Modify the Descriptions of the Records and Establish Clear Parameters for the Length of the Lookback (HIV and HCV)

a. Prospective Lookback

A primary concern involves the records that must be reviewed during the prospective Lookback. The proposal (§ 610.46(a) and § 610.48 (a)) states that blood establishments must conduct the quarantine and notification activities *"whenever records are available..."*. Because of this description of the records, it is our interpretation that the prospective Lookback will, in effect, become an open ended, continuous search. The Red Cross urges FDA to revise this requirement.

ARC believes that the prospective Lookback should be consistent with the retrospective Lookback with regard to the definition of the form and content of records that must be reviewed. Specifically, § 610.48(c) states that the records reviewed for retrospective Lookback are "computerized electronic records and...readily retrievable records...". This description gives the blood establishments better guidance in determining which records to review and is also more likely to result in streamlining efforts to obtain and review records. While the scope of the review is extensive, the proposal also contains a better definition of the retrospective Lookback dates than the prospective Lookback dates.

Another reason for requesting the clarification of records and dates for review is that the Red Cross and many other blood establishments have already been performing Lookback procedures following the current HIV and HCV Lookback guidances. We have retrieved and reviewed records going back as required under those guidances for HCV[1], the rule for HIV[2] and related FDA memoranda and guidances. If the descriptions of the records and dates of review remain unclear, blood establishments will be required to reopen records of the previously completed and closed Lookback cases in order to be sure to identify all donations "whenever records are available". We believe it appropriate to allow blood establishments to rely on any action performed under an existing regulation or guidance as being sufficient, without changing the rules after completing actions. (ARC describes this concern more fully in Section V below.)

Finally, if the proposal's description of the records that must be reviewed for prospective Lookback remains unclear, there may be differences in interpretations among establishments and between establishments and FDA investigators. The Red Cross and FDA have the common goal of ensuring consistency of inspections and consistency among blood establishments. Clarification will advance that goal.

ARC recommends a solution that will clarify both the date back to which records must be reviewed, and the type of records that must be covered. Specifically, for prospective Lookback, the Red Cross recommends modifying the language of the proposal to read:

> In the absence of an appropriate non-reactive screening test for antibody, conduct a record review going back to the extent that records are computerized such that all donation and shipping information needed to perform a notification is available by computer or 10 years before the repeat reactive screening test whichever is longer, except that the HIV Lookback shall extend back three months from the date of the repeat reactive screening test result if HIV-1 p24 antigen testing was performed.

We believe this definition of the records and the Lookback time frame will clearly state what is meant by records that are "available" or "readily retrievable", will establish deadlines that can be met within reasonable time frames, and allow development of more effective record review processes.

This revision is also consistent with Section II, below, that HIV Lookback does not need to extend back further than the three months prior to the repeat reactive screening test when the HIV-1 p24 antigen test is performed. It is well accepted in the scientific literature that virtually

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[1] HCV - See September 1998 "Guidance for Industry, Current Good Manufacturing Practices for Blood and Blood Components" 63 FR 56198.
[2] HIV - See CFR 610.46.

all such donors will seroconvert within three months, and therefore, the Lookback will cover all donations potentially at risk of HIV transmission.

Finally, the Red Cross also urges FDA to create an appropriate mechanism to modify the time frame for review as new tests that will further close the window become available and allow blood establishments to modify Lookback procedures accordingly.

b. Retrospective Lookback

While the Red Cross prefers the records description contained in the retrospective Lookback, as proposed, to that of the prospective Lookback, there still remains some concerns with the retrospective Lookback records description. For example, the phrase "other readily retrievable records" found in § 610.48(c) and § 610.48(d) is also likely to lead to variable interpretations.

ARC recommends the following revision to the retrospective Lookback sections:

> In the absence of an appropriate non-reactive screening test for antibody, conduct a record review going back to the extent that records are computerized such that all donation and shipping information needed to perform a notification is available by computer or going back to January 1, 1988, whichever is longer.

II. Revision of Quarantine Requirements for Human Immunodeficiency Virus (HIV)

The proposal establishes the quarantine requirements for HIV Lookback, including the product quarantine period for prior collections, as described in § 610.46(c), which states:

> if ...the blood or blood component was collected more than 12 months prior to the donor's most recent negative screening test when tested for HIV...

This is a departure from the current guidance which states:

> For cases in which units were obtained from the donor during the **three month period** prior to the repeatedly reactive donation, blood centers should notify consignees... [emphasis added][3]

Thus, blood establishments have been allowed a three month Lookback time frame for HIV rather than the proposed twelve months. The Red Cross urges a modification of the proposal to

[3] FDA Memorandum to All Registered Blood and Plasma Establishments "Recommendations for Donor Screening with a Licensed Test for HIV-1 Antigen", August 8, 1995.

incorporate a three month time frame into the final rule to remain consistent with current guidance.

Retaining a three month time frame is appropriate because the current testing by blood establishments, including the HIV-1 p24 antigen test and the Nucleic Acid Test (NAT) will ensure that appropriate collections obtained from donors at risk of transmitting HIV and whose exposures occurred within the three month time frame, and will be identified during the testing process.

It is well accepted in the scientific literature that HIV-1 p24 antigen is a transient marker of early HIV infection that is present for only one to two weeks prior to the appearance of HIV Antibody and complete seroconversion. The appearance of HIV-1 p24 antigen correlates with the appearance of HIV-1 RNA as detected by the Nucleic Acid Test (NAT); all studies to date demonstrate that these events (i.e., the detection of RNA followed in five to ten days by HIV-1 p24 antigen and then in another 7 to 14 days by HIV antibody seroconversion) validate the current FDA guidance of a three-month product quarantine, product retrieval and recipient tracing period for prior collections from donors whose samples tested repeat reactive for HIV-1 p24.[4]

III. Exceptions from Notification (HIV and HCV)

Sections 610.47(a) and 610.49(a) contain the requirements for transfusion services/consignees to notify "when a recipient has received prior collections of blood or blood components from a donor later determined to be at increased risk...". Section 610.49(a)(3) continues to define the notification conditions, and also contains exceptions where notification is not required or appropriate.

For example, if the blood establishment has followed the testing algorithm(s) found in section 610.48(h)(2)(i), (h)(2)(ii), or (h)(2)(iii) and the testing has met the defined conditions, then consignees will not need to conduct patient notification.

The Red Cross asks FDA to change the way in which the exceptions are granted and applied. Specifically, we urge FDA to place the exceptions in the section of the final regulation that must be followed by the blood establishment, rather than the transfusion center/consignee. Under the proposal, the blood establishment will need to conduct consignee notification procedures, even when the additional testing reveals that the donor was not at increased risk of transmitting HIV or HCV. Thus, the blood establishments will be required to make notifications to consignees even when the consignee does not need to take action.

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[4] See for example, for HCV: Murthy et al, Transfusion 39;688-693:1999.
for HIV-1 p24: Busch et al, Transfusion 35;91-97:1995.

It is more efficient to place the exceptions under the sections that apply to blood establishments and thereby avoid giving consignees notices that require no action on their part. This change will simplify the process, for both blood establishments and consignees, with no effect on the final results of the rule or public safety.

IV. Additional Quarantine Revisions

ARC recommends reexamining certain quarantining requirements.

a. Timeframes

The proposal establishes a time limit on quarantine and notification. For example, Sections 610.48(e)(1) refers to the retrospective review of historic records and states:

> within 3-calendar days of the date of the identification of the donor's repeatedly reactive multiantigen [and single antigen] screening test for HCV, quarantine all in-date prior collections of blood and blood components....

Currently, the Red Cross requires that for in-date products, quarantine will take place immediately, to avoid a potential transfusion risk. To accomplish this, the regulation would be modified to include the term "in-date", when describing the blood and blood components under review for HIV Lookback (§ 610.46(a)). Alternatively, the Red Cross recommends that FDA indicate a separate requirement for "outdated" products to require quarantine within 3 *working* days.

b. Reduce Unnecessary Quarantines

ARC believes it is unnecessary to quarantine the products or components under the following two circumstances.

The July 19, 1996, FDA memorandum established conditions where a quarantine of products, including those with repeat reactive test results, should be conducted.[5] Under that document, the Red Cross also quarantined those products for which the test results were subsequently 3.0 RIBA indeterminate. The memorandum requires a five year records search, so that at this point in time, products that met the criteria have already been retrieved going back to 1991. By the time this proposal is made final, there will be a full ten year time span for which the requirement has already been met. Additionally, since July, 1998, based on FDA guidances, the Red Cross has conducted a records search back as required. Thus, the Red Cross recommends granting an

[5] IBID

exception to the quarantine requirements, if the quarantine effort has already been conducted under either of these guidances.

In addition, we recommend that FDA remove the quarantine requirements when the Signal to Cutoff Ratio (S/CO) is less than 2.5. The proposal indicates that notification of the transfusion recipient would not be required. However, as we interpret the proposal, we believe it requires us to research records for many donors and to quarantine the product despite this S/CO result. Thus, we ask that FDA to clarify in the rule that if notification of a recipient is not required, then product quarantine will not be required. (This recommendation is discussed more fully in section VIII below.)

V. Retaining Previous Decisions after Promulgation of the Final Rule

a. Prospective Lookback

ARC wishes to point out that what had been "prospective" record review under the March 1998 and September 1998 guidances will become the "retrospective" record review if this rule is finalized and implemented as proposed. We urge FDA to indicate that the prospective Lookback performed under these guidances will not be subject to the retrospective review requirements once the proposal is final.

Subjecting blood establishments to a later regulation with changes in the decision criteria, when guidances have been issued and followed previously, will heavily penalize blood establishments that implemented the guidances and completed the specifications. The blood establishments will have to reopen records to be in compliance with additional requirements set in this proposal. The Red Cross believes it is fair and appropriate to retain and apply only the existing guidances for retrospective Lookback and any prospective Lookback performed up until the implementation date of the rule and eliminate any reference to retrospective Lookback from the final regulation.

In the alternative, we suggest that the final rule clearly state that cases already handled as prospective Lookback retain that assignment, and no additional retrospective research requirements will be applied to those cases. Additionally, the Red Cross urges a change in the structure of the proposed regulation. Currently, the HCV retrospective Lookback requirements are incorporated into § 610.48, which covers all of Hepatitis C Virus Lookback. However, while the prospective Lookback process will be conducted continuously from the time the rule is finalized, the retrospective Lookback is a one-time effort. Tracking both efforts within one section will be cumbersome. Thus, in order to streamline the requirements and simplify blood establishments' efforts to comply, we recommend that FDA consider completely separating prospective from retrospective HCV Lookback, and create two separate sections of regulatory text.

b. Retrospective Lookback

Blood establishments have also taken steps to implement retrospective Lookback under the guidances already issued. Many have made decisions and determinations based on the recommendations in the existing guidances, some of which differ from the instructions in the proposed regulation.

ARC recommends that the final rule clearly state that blood establishments may retain the retrospective Lookback research and decisions made under the current guidance, and no additional requirements will be applied to those cases.

ARC believes it is appropriate to make this clarification since blood establishments have been following FDA published guidances in initiating and performing retrospective Lookback to date. "Mixed signals" can arise when blood establishments are performing functions under one set of criteria (i.e., the final HCV guidance in existence) but another criteria (i.e., the proposed HCV Lookback rule) is superimposed upon their activities. We believe it is fair and appropriate that blood establishments not be expected to backtrack once the rule is finalized and revise Lookback cases which have already been completed.

VI. Recommendations for Additional Exceptions from HIV and HCV Lookback

We have noted that the proposal does not include several exceptions that have been discussed in previous documents or forums. The Red Cross requests that FDA consider including these exceptions. These include:

a. Autologous donations (HIV and HCV)

The Red Cross recommends addressing autologous donations specifically. These donations are not intended to be transfused to any recipient other than the donor. We agree with the point made in the Draft FDA guidance of June, 1999 which indicated that if "the donor made prior donations for allogeneic use or if the blood establishment is involved in a crossover program in which prior autologous collections could be released for allogeneic use" such donations should be subject to the Lookback process. Otherwise, autologous donations should be excluded from the Lookback process.

b. Products already pooled for fractionation (HIV and HCV)

The proposal's preamble states that "The proposal would not require quarantine of products that have already been pooled for further processing because the process of fractionation inactivates or removes HCV" (p. 69382), and the current HIV regulation allows an exception for

fractionation as noted in § 610.46(c) which states: "pooled Source Plasma and Source Leukocytes are exempt from quarantine."

However, there is no mention of this exception in the proposal's regulatory text. The Red Cross agrees with the logic that the processing will inactivate the virus, and requests that FDA specifically include this exemption in both Sections 610.46 and 610.48 so that there is no misunderstanding once the rule is finalized.

c. Availability of consignee records (HIV and HCV)

In many cases, consignees do not have records dating back "indefinitely" or even as far back as ten years. In such cases, the consignee will not be able to notify transfusion recipients even if the blood establishment conducts all appropriate procedures. Thus, the ultimate objective, that of notifying the recipient, will not be met regardless of the steps that the blood establishment will take.

ARC requests that FDA grant an exclusion from Lookback notification for the years for which the consignee does not have records if the consignee provides the blood establishment with documentation that such records no longer exist.

This recommendation is consistent with the Final FDA guidance issued in September of 1998, which stated:

> ...notification of consignees need *not* be done if the consignee can document that records of product distribution for transfusion are no longer available for the time period during which the unit was released for transfusion. [emphasis added]

Note that this comment only applies to outdated products. The Red Cross still intends to retrieve all in-date products and notify consignees of those which may pose a potential risk of transmission, regardless of consignee recipient records.

d. Transfusion Recipient Death (§ 610.47 - HIV)

In some instances, the transfusion recipient may not survive the hospital stay during which they received the component that may pose the risk. If they died after the transfusion and while still in the hospital, there would not be a possibility of either treatment for HIV or risk of exposure to family, friends, etc. Thus, the Red Cross recommends that FDA grant an exemption from notification if the patient died while still in the hospital after the transfusion.

VII. Outdated Products

The proposal does not establish specific requirements for outdated products nor are outdated products specifically mentioned. The Red Cross assumes that FDA expects Lookback notifications to be sent to consignees for outdated products similarly to in-date products. However, we request that FDA clarify the actions required for outdated products in the final regulation.

Additionally, we request that FDA apply a different time frame for notification of outdated products from that of in-date products. Specifically, instead of a 45-day time frame, we request a 90-day timeframe for the outdated products. This will allow blood establishments to retrieve records that may be stored off site and in varying forms or which may require additional search and review efforts less likely to be encountered for in-date products.

VIII. Review of Historical Records and Identification of Donors Tested Using a Single Antigen Screening Test [6]

In § 610.48(d), the proposal defines the cases where review of historical testing records and identification of donors tested using a single antigen screening test will be necessary. Blood establishments must identify records and identify previously distributed blood and blood components with a potential transfusion risk. ARC believes that FDA also intended to establish how the signal-to-cutoff (S/CO) ratio would aid in determining record review and product quarantining actions. (§ 610.48(d)(3) and (4)). However, the proposal, as written, makes no differentiation in the actions that blood establishments must take, even when the S/CO is calculated and meets FDA's cutoff levels.

The Red Cross recommends that FDA revise this section. The Red Cross believes that product quarantine should not be necessary or if the results of the follow-up testing defined later in the rule indicate that Lookback and notification are not necessary. Additionally, neither record review nor product quarantine should be necessary if the S/CO ratio calculations indicate there is no transfusion risk. Thus, the Red Cross recommends eliminating § 610.48(d)(3).

Several factors indicate that this change does not pose an additional health risk. The purpose of the S/CO calculation is to aid in determining the risk, and therefore, if the calculated value is below the level set by FDA, i.e., 2.5, there should be no additional need for review of donor records to identify in-date products or require quarantine.

[6]The Red Cross has additional detailed comments on Attachment 2 regarding the specific test results proposed.

In addition, the single antigen test was used by blood establishments at least eight years (1992) ago, and potentially much longer by the time the rule is finalized. Few, if any, in-date products will be available for transfusion so that safety concerns are minimized.

IX. Add Unlicensed Tests to the Decision Criteria

In several sections, the proposal discusses the use of additional testing to indicate that quarantine is not necessary. For example, § 610.48(g)(2)(ii) allows an exclusion if the **licensed** 2.0 RIBA or 3.0 RIBA is negative on the original sample or on a follow-up sample or if the 3.0 EIA screening test is negative. The Red Cross agrees with these decision criteria. However, we request that FDA clarify that their application will be evaluated, and compliance based on these criteria will only be required for testing performed after the rule is finalized. For decisions made previously under existing regulations and guidances and prior to finalizing this proposal, blood establishments should be expected to use the existing criteria only.

Moreover, the proposal is silent on whether and how blood establishments may use the results of unlicensed tests for making quarantine, Lookback and notification decisions. Some unlicensed tests were performed under Investigational New Drug (IND) research, others as part of in-house testing services provided by the test kit manufacturers prior to licensure.

The June 1999 Draft HCV Lookback Guidance proposed to allow blood establishments the use test results of "RIBA 3.0 assays used under an Investigational New Drug (IND) or provided as an in-house service by the test kit manufacturer." The Red Cross believes that FDA had taken a step forward in supporting additional research in improving blood testing by making such a proposal. The Red Cross believes that these tests should be acknowledged in the final regulation and incorporated into the decision criteria along with the other tests. Although they were unlicensed, they were being investigated because the experimental evidence prior to IND testing indicated strong potential to improve the sensitivity or specificity of the existing test.

Thus, their use in making quarantine, Lookback, and notification decisions is appropriate. The Red Cross also believes this is an opportunity for FDA to encourage continued research on new and improved safety measures and avoid inadvertently penalized those who chose to do so.

ARC also suggests that FDA build into the final rule a mechanism for recognizing and using new generations of viral tests for future Lookback decisions. This will simultaneously encourage use of new technologies, and provide for more appropriate notifications in the future.

ARC proposes use of a statement such as the following:

> If another HCV or HIV test protocol is performed under either IND or as an in-house service, the Lookback shall extend back the maximum time frame under this rule until

licensure of the new test protocol. Upon licensure, the Lookback shall extend as stated in agency guidance or consistent with manufacturer's instructions for that test.

ARC recognizes that unlicensed tests, although most likely an improvement over an existing test, have still not had final FDA review and licensure approval. Thus, it is appropriate to use the same decision criteria for the unlicensed tests as that of the licensed tests.

X. Reconsider Specifications for Lookback Based on Outside Test Results

The requirement to conduct Lookback activities when the blood establishment "has been made aware of other test results indicating evidence of...infection..." when the testing was performed by a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory (§ 610.46 (a) and § 610.48 (a)) is a concern. The Red Cross urges FDA to reconsider and to revise the final rule to eliminate this requirement. While FDA's intentions are understood, the type of information, the source(s), and the reliability of the information indicating a potential risk are not specified in the proposal. For example, there is no clear indication of what constitutes being "made aware" or what is considered "evidence."

Current blood establishment safety practices, while not specifically outlined in the proposal, will appropriately address the circumstances that appear to be FDA's concern, i.e., when additional information is made available, but the test is not performed by the blood establishment. Specifically, if a donor or other informant, calls the Red Cross and indicates that the donor just received a positive test result, the Red Cross would immediately attempt to evaluate the validity of the report and quarantine the donation and conduct Lookback actions, if appropriate.

Moreover, determining whether a test result was obtained from a CLIA laboratory is problematic for blood establishments. The Red Cross is unaware of any existing list of laboratories certified by CLIA. Since such information is not available, blood establishments would need to determine where the testing was performed and then determine an individual laboratory's CLIA certification status.

ARC believes that the current practice described above is the appropriate action, indeed, it is a more conservative action, and therefore, that no safety hazard would result from eliminating the requirement. Thus, we urge FDA to remove this requirement.

In closing, ARC appreciates the opportunity to submit these comments. If there are any questions on this letter, or if you wish to discuss these concerns in greater detail, please contact Anita Ducca, Director, Regulatory Relations, 703-312-5601 or Linda Chambers, MD, 703-312-5610.

Section of Proposed Regulation	Requirement	ARC Comment
	HIV LOOKBACK	
610.46(a)	This Section states: "For blood and blood components collected from that donor..."	It appears that the word "indate" was inadvertently omitted from this phrase. ARC requests the insertion of "indate" so that this phrase will read: "For in-date blood and blood components collected from that donor..." This change will make the HIV Section consistent with the HCV Section. Additionally, the action to quarantine is not necessary nor appropriate for outdated products.
610.46(a)	For HIV LB, the proposal states that blood establishments must take appropriate action "when the blood establishment has been made aware of other test results"	See comments in Attachment 1, Section X . The Red Cross recommends deleting this requirement.
610.46(a)	This Section states "whenever records are available"	The Red Cross recommends using records that date back ten years, and going back further if they are "computerized electronic". See comments in Attachment 1, Section I.
610.46(a)	The regulation calls for quarantine "within 3 calendar days of the date on which the donor tested repeatedly reactive"	The Red Cross agrees with the standardization of the time period with that currently required for HCV. However, the quarantine requirements would appropriately apply to "in-date" products only. Red Cross suggests the proposal be modified to include the term "in-date". Alternatively, if FDA does not change this Section to refer to "in-date" products only, Red Cross requests a separate requirement for "outdated" products to require quarantine within 3 *working* days of the date on which the donor tested repeat reactive. (Attachment 1, Section IV)

610.46(a)(2)	The rule indicates that "Consignees notified in accordance with paragraph (a)(1)(ii) of this Section shall quarantine all such prior collections of blood and blood components held at that establishment..."	ARC recommends simplifying this Section for the consignees by indicating that they should quarantine upon notification by the blood establishment. If the final rule includes ARC recommendation in Attachment 1, Section III, the burden of determining when quarantining and other Lookback actions need to take place is the responsibility of the blood establishment.
610.46(b)	This Section requires blood establishments to notify consignees of additional test results within 45 calendar days.	ARC agrees with harmonizing this requirement for HIV with that currently required for HCV. However, ARC recommends that FDA allow an exemption if the product has been returned or destroyed. Since transfusion did not take place, no risk exists and no additional notification is needed.
610.46(c)	The proposal grants an exception from quarantine if the "blood or blood component was collected more than 12 months prior to the most recent negative screening test when tested for HIV in accordance with 610.40(a)"	The proposed testing regulations only specify the virus to be tested for, there is no mention of the methodology, e.g. the proposal does not provide for antibody testing vs. methods that detect virus at an earlier date in the donor's seroconversion sequence. ARC requests that FDA include exceptions from quarantine provisions for these alternative methods. Specifically, ARC recommends that the rule allow the exception to quarantine if the blood or blood components were collected more than 3 months prior to the most recent repeat reactive HIV-1 p24 antigen test or from the most recent reactive HIV Nucleic Acid Test. (Attachment 1, Sections I, II, III, and IX)
610.46(e)	The proposal contains specific requirements if the unit will be made available for in vitro use. The unit "shall be appropriately relabeled" including adding the word "Biohazard" and "collected from a donor who subsequently tested positive for anti-HIV. An increased	ARC recognizes the reasons for adding a cautionary statement to the blood bag once a positive test result is obtained. In practice, however, there are practical concerns. The label "Biohazardous" will warn those who may handle the blood bag to use universal precautions to safeguard against potential blood exposure. Those safeguards will not change regardless of the type of biohazard the donation may represent, so the extra cautionary labeling

	risk for transmission of human immunodeficiency is present."	will not induce any additional safety precautions. Also, many different circumstances requiring labeling modifications could occur, beyond those that might be discovered while conducting the Lookback. We point this out to because we believe it is important to request that the labeling requirements remain flexible so that when the product is issued we may communicate the risk without having different labels for each individual circumstance. We urge FDA to change this requirement. Our preference is to limit the relabeling solely to the word "Biohazardous." This will help reduce the amount of handling the unit is subject to while labeling it, and therefore the potential exposure risks for those performing the labeling tasks. If wording is still required on the unit itself, provide maximum flexibility to the blood establishments to indicate the positive marker only. This will aid blood establishments to simplify labeling for this regulation or other FDA guidances currently in place.
610.47(c)	This Section includes notification specifications when the transfusion recipient is deceased.	As noted in Attachment 1, Section VI ARC recommends an exception if the recipient died after the transfusion during the same admission. Risk of exposure is extremely small, and is likely non-existent.

Section of Proposed Regulation	Requirement	ARC Comment
HCV LOOKBACK		
610.48(a)	The proposal states that quarantine should occur if the blood was collected "at any time prior to the repeatedly reactive test, whenever records are available..."	As noted in Attachment 2, Section I, ARC recommends a language revision to clarify the time frame for record review. Additionally, define the term "available" to mean "computerized electronic".
610.48(a)(1)(ii)	Quarantine "within 3 calendar days..."	Since quarantine of in-dated products is required in 610.48(a)(1)(i), and quarantine includes gaining control of products that have already been distributed, ARC recommends revision to require notification to consignees within 3 calendar days of the date we identify the product(s) associated with the repeat reactive test.
610.48(a)(2)	The proposal indicates that consignees must quarantine once notified, but refers consignees to exceptions described in paragraph 610.48(g)(1).	As noted in Attachment 1, Section III ARC believes it would be more efficient to place all such exceptions in the Section of the CFR referring to blood establishments. This change will reduce unnecessary notifications for blood facilities, and will simplify the Lookback for the consignees who would no longer need to make determinations about quarantine, just do so when notified.
610.48(b)	"in the case of a repeatedly reactive screening test...blood establishments *shall* perform further testing..." *(emphasis added)*	ARC recommends that the Lookback and consignee notification be conducted only if the 3.0 RIBA test is positive.
610.48(b)	The blood establishments "shall notify the consignee(s) of the results ... within 45-calendar days..."	ARC recommends that FDA allow an additional time frame for notification of outdated components. In such instances, we request 90 days. (Attachment 1, Section VII)
610.48(c)	"based on available required records...dating back indefinitely for computerized electronic records and	ARC recommends that the retrospective Lookback be based on a review that extends back indefinitely for computerized records where donation and shipping information is available or back to January 1,

	to January 1, 1988 for other readily retrievable records"	1988 whichever is longer. (Attachment 1, Section I)

610.48(c)(2)	Second instance: (review of historical test records/multiantigen screening test) if 2.0 or 3.0 EIA is RR, RIBA indeterminate	ARC does not believe it is necessary to quarantine when the 3.0 RIBA (supplemental) is indeterminate since there is no Lookback requirement. In addition, since the July 19, 1996 memorandum for component retrieval, retrieval has gone back 5 years or more (to 1991). (See also Attachment 1, Section IV)
610.48(c)(4)	Fourth instance: if the 2.0 EIA is RR, no RIBA and no NR 3.0 EIA on this or later sample	ARC requests that these criteria be amended to also apply when there is no record of a negative 2.0 RIBA or a negative or indeterminate 3.0 RIBA.
610.48(d) 1.0 Retro. HCVLB	The proposal outlines requirements for review of "historical testing records" (single antigen screening test) including those "dating back indefinitely for computerized electronic records and to January 1, 1988," for other readily retrievable records.	ARC recommends modifying the language describing the record review to clarify the review extends indefinitely for computerized records or back to January 1, 1988 whichever is longer. (Attachment 1, Section I)
610.48(d)(1)	First instance: 1.0 RR & 2.0/3.0 EIA RR on this or a later sample	ARC requests modification of the first instance to include a clarification that also applies "when there is no RIBA test result" available.
610.48(d)(2)	Second instance: 1.0 EIA RR and ind. or pos. on 2.0 or 3.0 RIBA on this or a later sample	ARC recommends clarification that blood and components with 3.0 RIBA indeterminate test results do not need to be quarantined. (Also, Attachment 1, Section IV).
610.48(d)(3)	Third instance: 1.0 EIA RR, no RIBA or 2.0/3/0 EIA and < 2.5 S/CO	ARC requests modification to clarify that quarantine is not required if there are no negative results. Specifically, this Section should be eliminated since the calculation of the S/CO ratio < 2.5 indicates that the risk value meets the cutoff point.

610.48(d)(4)	Fourth instance: if 1.0 EIA RR S/CO ≥ 2.5 or no S/CO for all 3 EIAs, and no RIBA or 2.0/3.0 EIA results on this or later sample.	The Red Cross urges modifying the text to indicate that use of the S/CO ratio for decision making to allow for cases where only two EIA tests (instead of 3 as described in the proposal) have been performed. That is, (1) if the S/CO is ≥ 2.5 based on 2 or more EIA tests and (2) if only two tests were performed and one is < 2.5 and the other is ≥ 2.5, or S/COs cannot be calculated.
610.48(e)(2)	Notify consignee within 3 calendar days of identifying 2.0/3.0 RR result	Since quarantine of in-dated products is required in 610.48(e)(1), and quarantine includes gaining control of products that have already been distributed, ARC recommends revision to require notification to consignees within 3 calendar days of the date we identify the product(s) associated with the repeat reactive test.
610.48(e)(3)	"Consignees notified in accordance with paragraph (e)(2) shall quarantine prior collections…"	Simplify to indicate consignees shall quarantine components only upon notification. (Attachment 1, Section III).
610.48(f)(1)	Quarantine by consignees.	Simplify to indicate consignees shall quarantine components only upon notification. (Attachment 1, Section III).
610.48(g)(1)(i)	Exemption from quarantine: No quar. of components >12 months prior to most recent negative EIA when tested in accordance with 610.40(a)	The proposed testing regulations only specify the virus to be tested for, there is no mention of the methodology. The proposed Lookback regulation does not provide for antibody testing vs. methods that detect virus at an earlier date in the donor's seroconversion sequence. ARC requests that FDA include exceptions from quarantine provisions for these alternative methods including limiting the retrieval period when Nucleic Acid Testing is performed. (Attachment 1, Section IX)
610.48(g)(1)(ii)	Appropriate RIBA is completed in 3 calendar days and is negative	• The Red Cross agrees but also requests exceptions described in Attachment 1, Section VI • The Red Cross emphasizes that the final rule should specifically exclude products that have already been pooled for further processing [under the proposed rule's current structure, the exclusion for pooled products would create new Sections 610.48(g)(1)(iii) *Prior collections subject to quarantine under paragraph (a)*; 610.48(g)(2)(iii) *Prior collections subject to quarantine under paragraph (e)(1)*; and 610.48(g)(3) *Prior*

		collections subject to paragraph (f)(1)]
610.48(g)(2) **2.0/3.0** **RHCVLB**	Prior collections subject to quarantine under (e)(1)	The Red Cross believes it would be appropriate to allow the use of unlicensed tests under an IND or in-house testing service to reach decisions under this Section [610.48(g)(2) and (3)] (Attachment 1, Section IX)
610.48(g)(2)(ii) (A)	No quar. if 2.0 EIA RR, negative 2.0 or 3.0 RIBA or NR 3.0 EIA on this or later sample	ARC recommends that FDA allow the testing carried out prior to the final rule to be used to evaluate the required actions. In addition, ARC believes it would be appropriate to allow the use of unlicensed tests under an IND or in-house testing services. (Attachment I, Sections V and IX)
610.48(g)(2)(ii) (B)	No quar. if 3.0 EIA RR, negative 3.0 RIBA on this or later sample	ARC also recommends that there is no need to quarantine if the 3.0 RIBA test results are indeterminate i.e. a decision was made under earlier guidances. (Attachment 1, Section IV)
610.48(g)(3)(iii) (A)	Prior collections subject to quarantine under (f)(1) and exclusions. No quarantine if 1.0 RR, 2.0 EIA RR on this or later sample and 2.0 or 3.0 RIBA is negative on this or a later sample.	ARC believes it would be appropriate to allow the use of unlicensed tests under an IND or in-house testing service to reach decisions under this Section [610.48(g)(2) and (3)] (Attachment 1, Section IX)
610.48(g)(3)(iii) (B)	No quar. if 1.0 RR, 3.0 EIA RR on this or later sample & 3.0 RIBA negative on this or later sample [(d)(1)]	ARC also recommends that there is no need to quarantine if the 3.0 RIBA test results are indeterminate i.e. a decision was made under earlier guidances. (Attachment 1, Section IV)
610.48(h)(1) and (2)	Further testing following review of historical testing records and options for further testing	The Red Cross recommends allowing blood establishments to apply testing results performed prior to final rule. In addition, ARC believes it would be appropriate to allow the use of unlicensed testes under an IND or in-house testing services. (Attachment I, Sections V and IX)
610.48(h)(3)(i)	Notify consignees within 45 days of completing additional testing, except for those exempt from quarantine.	ARC believes we should only be required to notify consignees within 45 days if we attempted to retrieve an indate product and it was transfused. No notification should be required if the product was returned or if the consignee destroyed it. Notification for outdated

		products should occur within one year of the final rule and only if the test results indicate consignees must take action to notify the recipients.
610.48(h)(3)(ii)	Within one year of final rule notify consignees of donors from (c)(1) through (c)(5)	This Section creates an undo burden on consignees, who would receive test results that they are not required to take action on. ARC recommends moving specific test results requirements from 610.49(a) to this Section (Attachment 1, Section III). ARC also recommends requiring notification only for outdated components from donors, after all retesting to complete and the final results are: • 2.0 RIBA positive - (c)(1) • 3.0 RIBA positive - (c)(1) • 2.0 RIBA indeterminate - part of (c)(2) • 3.0 EIA Repeat Reactive, 2.0 RIBA negative - (c)(3) • 2.0 EIA Repeat Reactive, no supplemental available - (c)(4) • 3.0 EIA RR, no supplemental available (c)(5)
610.48(i)(1)(i)	Further testing following review of historical records and consignee notification: If 1.0 EIA RR S/COs ≥ 2.5, may perform licensed RIBA on this or later sample [(d)(4)]	ARC recommends revising this Section as follows: • Specify that blood establishments will not be subject to new requirements in the regulation after it has been finalized if they have been using FDA guidances to conduct Lookback up until finalization, i.e. allow them to use all test results obtained prior to the final rule, including unlicensed tests, and avoid requiring retesting after the regulation is finalized. • Provide an option to use EIA and RIBA results from available unlicensed testing performed under an IND or In-house testing service. • Permit blood establishments to use the EIA 3.0 test and if the results are repeat reactive, allow further follow-up testing by the RIBA 3.0. (Note, this is permitted in §610.48 (i)(2)(ii)) • See also Attachment 1, Section V and IX.
610.48(i)(2)	"Blood establishments that have performed the review of records and identified collections in accordance	ARC recommends revising this Section to permit further testing of prior collections in accordance with paragraph (d) (3) as well as (d) (1) and (d) (2).

	with paragraphs (d) (1) or (d) (2) of this Section..."	
610.48(i)(2)(i)	Options for further testing: if 1.0 EIA is RR and 2.0 or 3.0 EIA is RR, may perform licensed appropriate RIBA on this or later sample [(d)(1)]	ARC recommends the following modifications: • Allowing the use of unlicensed test results (Attachment 1, Section IX). • Permitting the use of 3.0 EIA testing on a follow-up/fresh sample. If the test results are repeat reactive, allow testing under 3.0 RIBA on a fresh sample. ARC believes this is consistent with FDA policies to allow the most recent test methods to be used in decision making.
610.48(i)(2)(iii)	Options for further testing: If 1.0 RR S/COs < 2.5, no RIBA and no 2.0/3.0 EIA, may perform licensed 2.0/3.0 EIA or licensed 2.0/3.0 RIBA [(d)(3)]	The Red Cross recommends elimination of this Section if FDA agrees to eliminate requirements to review records and quarantine under 610.48(d)(3). If FDA does not agree to eliminate 610.48(d)(3) ARC recommends revising this Section as follows: • ARC agrees with this Section as long it applies only to the purpose of determining if an in-date product in quarantine may be released. • Allow blood establishments to use all test results obtained prior to the final rule, including unlicensed tests, and does not require retesting after the regulation is finalized. • Provide an option to use EIA and RIBA results from available unlicensed testing performed under an IND or in-house testing service. • Permit blood establishments to use the 3.0 EIA test and if the results are repeat reactive, allow further follow-up testing by the 3.0 RIBA. (Note, this is allowed in 610.48 (i)(2)(ii)) • See also Attachment 1, Sections V and IX.
610.48(i)(3)(i)	Notify consignees within 45 days of completing additional testing, except those exempt from quar.	The Red Cross recommends that this notification be performed only if the consignee has been previously notified of indate components. Consignees will not be able to transfuse outdated components regardless of the test results.

610.48(i)(3)(ii)	Within 1 year of final rule notify consignees of donors from (d)(1) through (d)(4)	ARC requests revision of this Section. Specifically it should not be necessary to notify consignees if they are not required to take action. (Attachment 1, Section III). This notification should be limited to outdated components from donors, after all retesting, with the following final results: • 2.0 RIBA positive • 3.0 RIBA positive • 2.0 RIBA indeterminate • 2.0 EIA RR, no supplemental • 3.0 EIA RR, no supplemental • EIA Repeat Reactive, 2 or more EIAs with S/COs $\geq$ 2.5 or only • 1.0 EIA Repeat Reactive and only 2 EIAs with one S/CO < 2.5 and one $\geq$ 2.51.0 EIA RR S/CO $\geq$ 2.5 or no S/CO for all 3 EIAs, & no RIBA or 2.0/3.0 EIA results on this or later sample
610.48(j)(2)(i)(A)	Release from quarantine under (e)(1): if (c)(4) and if further testing was performed under (h)(1)(i)(A) and if the 2.0 RIBA test was negative	610.48(h)(1)(A) allows EIA testing. However, 610.48(j)(2)(i)(A) only references negative RIBA test results. Therefore, ARC recommends including with the appropriate negative RIBA either a negative 2.0 EIA or negative 3.0 EIA or appropriate negative RIBA for the EIA performed. If after retesting, the final 3.0 EIA test result is negative, or RIBA 2.0 is negative, the final 2.0 EIA is nonreactive, or 3.0 RIBA is negative, allow components to be released. ARC also recommends allowing blood establishments to use unlicensed RIBA test results conducted before the final rule. (Attachment 1, Section IX)

610.49(a)	Transfusion Services	The Red Cross recommends simplifying the regulations by including only the prospective Lookback in the final regulation. (Attachment 1, Section V) Alternatively, simplify this Section by placing the exemptions allowed by Transfusion Services under the Section of the regulation pertaining to blood establishments, so that the transfusion services will not need to make the interpretations of the test results as part of their notification decisions. (Attachment 1, Section III)
610.49(a)(6)(iii)	The result of the licensed supplemental test or multiantigen screening test is positive.	ARC recommends revision to clarify that notification is not required for 3.0 RIBA test results if they are indeterminate i.e. a decision was made under an earlier guidance. (Attachment 1, Section IX)
610.49(a)(9)	RIBA or EIA is positive	ARC recommends that the regulation be amended to clarify the triggering results are RIBA tests (when positive) or where the multiantigen EIA is repeat reactive and there are no RIBA test results available.

American Red Cross

National Headquarters
Washington, DC 20006

August 23, 1999

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

RE: 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) [64 Fed. Reg. 33309 (1999) (Docket No. 98D-1878) June 22, 1999]

Dear Docket Officer:

This letter is to provide public comments on behalf of the American Red Cross (Red Cross) concerning the Food and Drug Administration's (FDA or Agency) Draft Guidance for Industry published on June 22, 1999 (the Guidance). The Guidance provides recommendations for blood collection facilities and their consignees for following Lookback procedures for donors who test positive for the Hepatitis C virus (HCV).

Red Cross, through its 37 Blood Services regions, supplies almost half of the nation's blood component transfusion needs. Red Cross has initiated efforts to comply with the previous HCV Guidances published on March 20, 1998, and September 23, 1998. The June 22 Draft Guidance, that is intended to eventually replace the current Guidance dated September 23, 1998, contemplates a number of changes that have a potentially far-reaching impact on blood facilities and their hospital customers. Therefore, we appreciate the opportunity to share additional views with FDA relevant to the Agency's policies.

As a member of the American Association of Blood Banks Interorganizational Task Force on HCV (the Committee), Red Cross first wishes to note that we fully agree with the comments submitted by the Committee on this guidance. However, given the direct and very large impact of the contemplated revisions, Red Cross wishes to express our views individually, as well.

FDA's Guidance was intended to clarify the Agency's expectations with regard to autologous donors, retesting of donors, and to add new policies to include HCV 1.0 positive donors. The Guidance contains a mechanism for identifying donors with anti-HCV 1.0 EIA repeat reactive test results who may represent a risk of infection for transfusion recipients. We believe this mechanism, known as the "signal to cutoff ratio," is a reasonable process for determining which donors to include in 1.0 HCV Lookback.

However, the Guidance also, unexpectedly, extended the record review portion of Lookback beyond the original timeframe for review of donations from donors who subsequently tested positive from 10 years to an indefinite period. In effect, this policy would require both the reopening and extension of 2.0/3.0 Lookback under the Agency's earlier guidances as well as the initiation of 1.0 Lookback for a large number of donors extending back indefinitely.

Red Cross' concerns are discussed below, chief of which is that the public health benefits of expanding Lookback in this manner are, at best, doubtful. Additionally, there is substantial room for open-ended interpretation of the guidance's expectations for "readily retrievable" records. Given the differences in storage media and other conditions, there is little support for the Agency's expectation that extension will produce records that are useable as well as retrievable. Finally, the extension may actually do more harm than good. Recipients of blood products, such as hemophiliacs and transfusion recipients may be led to believe that, if no notification during this targeted Lookback is received, they are not at risk, when, in actuality, they may not receive such a notification due to either lack of manufacturing records, lack of transfusion service records, or lack of ability to trace recipients.

Indefinite Lookback

By setting up a requirement for an "indefinite" Lookback, the draft Guidance has defined a set of requirements that is far more sweeping that originally envisioned. Specifically:

Section III.1.A., Quarantine of Prior Collections from Donors Who Subsequently Test Repeatedly Reactive for anti-HCV, states:

> "Blood establishments should identify prior collections extending back *indefinitely* to the extent that electronic or other readily retrievable records exist." [emphasis added]

Section III.2.A., Review of Records and Quarantine of Prior Collections, states:

> "The record search should extend back *indefinitely* to the extent that electronic or other readily retrievable records exist." [emphasis added], and,

Section III.2.B., Notification of Consignees and Transfusion Recipients, states:

> "For previously distributed blood or blood components collected from the same donor dating back *indefinitely* (that is, prior to January 1, 1988), blood establishments should begin notification of consignees as soon as feasible. This notification of consignees should be completed by September 30, 2000," [emphasis added] and

Section III.3.A., Review of Records and Quarantine of Prior Collections, states:

> "The record search should extend back *indefinitely* to the extent that electronic or other readily retrievable records exist." [emphasis added]

The Canadian Red Cross and its successors have been performing indefinite Lookback for their positive HCV donors for approximately five years. They have found a diminishing rate of return in their ability to find and contact recipients that directly correlates with the length of time for which the donation dates extend back. It has been estimated that the current Lookback, which extends back to donations collected in 1988, will reach only 1% of patients that received blood before 1990. Clearly, the further back in time the Lookback is extended, the smaller the rate of return will become.

The "Model of Success Rate for HCV Lookback" (Attachment I) provides a prediction for the rate of success of contacting at-risk transfusion recipients who then present for testing and the success rate of contacting recipients who do not already know that they are anti-HCV positive. The model uses data from a survey of Red Cross' 37 regions and their consignees, but it does not correct for either the retrievability or the usefulness of the records. The consignee response rate to the survey was 62% (2076/3370). The model shows that the likelihood of a HCV positive donor being traced to a recipient who then presents for testing (contact success rate) is only 2% ten years after the transfusion. It also shows that the likelihood of tracing a HCV positive donor to a recipient who learns for the first time of their HCV infection (medical success rate) is 1% ten years after the transfusion.[1]

There are no hard and fast numbers established for success rates to be used when setting Lookback timeframes. However, once the interval between a donation and the Lookback initiative is greater than 8-10 years, the exercise is highly unlikely to achieve the medical objective. Investigations should be limited to donations within the 10 years

[1] See Attachment II for a review of the consignee responses received by one Red Cross region.

prior to the time of the investigation, regardless of when the donors were originally found to be HCV positive.[2]

Red Cross strongly believes that the targeted Lookback should not be extended indefinitely, that it should go back an identified, limited time period. Thus, Red Cross recommends that: (1) for prospective Lookback, a rolling 10 years be the required time frame for all new Lookback cases, and (2) for retrospective Lookback, the indefinite requirement be deleted and that all Lookback go back no further than January 1, 1988.

Records

Red Cross thinks it still must comment on the term "readily retrievable" as there are many possible definitions. This term will give rise to a wide variation of interpretation not only among the various blood collectors but also between these establishments and the FDA. Further, without clear and consistent parameters on how to define "readily retrievable," FDA investigators may interpret the guidance differently among themselves. This potential disparity permits no clear prediction or expectations for blood establishments undergoing inspections.

Along with the diminishing rate of return as the length of the Lookback is extended, there is a concurrent incremental decrease in the uniformity and condition of the records resulting in a diminishing value to the review, even if the records exist. For example, as collection facilities deal with older storage media, the logistics, training and quality control assessments associated with the review of those records become more significant. Thus, older records for each donation require more blood bank staff time to research the donation, component, and shipping records.

Moreover, when dealing with older records, there is little assurance of a direct link, such as direct coding, between the component production record and other records that trace components to the final shipping location so that the consignee and, eventually, the recipient can be identified. For example, while older order and distribution records may be on microfilm or microfiche, they are ordered by date of issue. To determine if a component was shipped for transfusion, a search of the records during the entire dating period of the component will be required (i.e., up to 45 days for a Red Blood Cell or 12 months for a Fresh Frozen Plasma).

Red Cross believes that only records that can be located and linked together within 10 working days from the beginning of the search should be considered "readily retrievable." But this interpretation may not be universally acceptable to either other blood establishments or to FDA investigators.

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[2] The implication from the model is that Lookback for HCV 1.0 on a donation in 1990, investigated in 1999, should encompass 1989 and 1990 donations only.

The term "readily retrievable" also does not address whether the records themselves are reasonably legible. Over time, microfiche can fade, ink becomes smeared, and handwriting that is not clear to begin with can become unreadable from exposure to heat, or other normal environmental conditions. Thus, older documents may be "retrievable" but may not be usable.

HCV 1.0 Signal to Cut Off Calculation

Section III.3.B.2.(i) states that signal to cut off (S/CO) calculations should be done on three anti-HCV EIA test results and that the Lookback decision be made based on whether two of the three calculations are less than or equal to/greater than 2.5.

This section should also permit S/CO calculations even when only two EIA test results are available. If the S/CO values agree, a Lookback decision can be made, but if one value is <2.5 and the other value is ≥ 2.5, then either further testing using a stored or new sample should be performed prior to making a Lookback decision or Lookback should be required.

Completion Period

Red Cross is further concerned by the requirement that all of the additional retrospective Lookback notifications must be completed by September 30, 2000. The proposed new requirements to include both EIA 1.0 positive donors as well as the indefinite extension of the record review for 2.0/3.0 positive donors cannot be completed within six months after the March 23, 2000, deadline for the current Lookback requirements. This expectation is even more unrealistic given the greater difficulty of reviewing significantly older records as described previously. Red Cross supports the Committee's recommendation that with or without an indefinite Lookback, the Lookback for 1.0 positive donors should begin by May 1, 2000, and the Lookback be completed by May 1, 2001.

Public Health Campaign

Red Cross strongly believes that a public health education effort aimed at specific high risk groups in combination with the current targeted Lookback requirements (including the EIA 1.0 Lookback requirements) is a much more effective mechanism to reach those at-risk of HCV infection. A targeted Lookback may actually be detrimental to the overall public health, because recipients may be falsely convinced that, if they are at-risk, they will receive a notification. In reality, they may not. Given the diminishing rate of return from notifications and the constraints on record review, there can be no assurance that a targeted Lookback will reach all at-risk transfusion recipients. Moreover, those at far greater risk, such as IV drug users, will receive no notification.

The public health notifications for physicians and health care providers already initiated by the Centers for Disease Control are a good start. Additional public notifications and similar communications will have an equal or greater chance of reaching those at risk of contracting HCV than the extended Lookback will have.

A complete public education program should reach most of the remaining recipients who received transfusions before the current January 1, 1988 cutoff. Such education programs could target audiences most likely to have received a transfusion, such as hemophiliacs and women who have delivered through Caesarian sections. It would also better meet the real public need of identification and treatment of HCV positive persons by providing the basic information to a much larger group of at risk individuals.

In sum, Red Cross urges FDA to revise the Lookback to retain the 10 year Lookback timeframe. This requirement is extensive and is consistent with all available evidence that those recipients most at risk are most likely to receive a notification. Additional notifications should be carried out through alternative public health education mechanisms and other means. Longer term, alternative mechanisms for notification are more likely to reach those at risk of HCV exposure than an indefinite Lookback can realistically accomplish.

Again, Red Cross appreciates the opportunity to submit its views on the Guidance to the FDA. If there are any questions on this letter, or if you wish to meet to discuss these concerns in greater detail, please contact Anita Ducca, Director, Regulatory Relations, at 703-312-5601.

Sincerely,

Anita T. Ducca for

Glenn M. Mattei, Esq.
Senior Director, Quality Assurance and
Regulatory Affairs
Biomedical Services
American Red Cross

Attachments

cc: Paul Mied, Ph.D.

MODEL OF SUCCESS RATE FOR HCV LOOKBACK
Estimates from published studies and 3/99 Red Cross survey

Years

current retrospective lookback possible intervals
current prospective lookback possible intervals
proposed lookback possible intervals

# years between donation/transfusion and lookback investigation (1)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
% donor programs with records linking donor to donations (2,3)	100	100	100	100	100	100	100	100	100	100	97	94	91	88	85	82	78	75	72	68
% donor programs with records linking donation to components (2,3)	100	100	100	100	100	100	100	100	100	100	95	90	85	80	75	70	65	60	55	51
% donor programs with records linking component to consignee (2,3)	100	100	100	100	100	100	100	100	100	95	90	85	80	75	70	65	60	55	50	46
% transfusion programs with records linking component to final disposition (3,4)	99.6	99.4	99.1	98.4	97.8	91.9	88.1	83.7	80	75	67.1	51.1	46.5	42	36.6	31.5	28.6	25.4	22.7	18.1
% components transfused (5)	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
% living recipients (6)	50	44	38	32	26	20	17	12	10	9	8	7	6	5	5	5	5	5	5	5
% recipient hospital records with valid addresses(7)	100	92	84	76	70	60	50	50	40	40	40	30	30	30	25	25	25	20	20	20
% recipients contacted who present for testing(8)	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
♦ Contact Success Rate (9)	**32%**	**26%**	**20%**	**15%**	**11%**	**7%**	**5%**	**3%**	**2%**	**2%**	**1%**	**1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**
% test positive, recipients who didn't already know (10)	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45
♦ Medical Success Rate (11)	**14%**	**12%**	**9%**	**7%**	**5%**	**3%**	**2%**	**1%**	**1%**	**1%**	**1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**	**<1%**

(1) lookback year to donation year, ie for index donations in 1991 subjected to retrospective lookback in 1999, the interval begins at 8 years and goes up from there
(2) extrapolated from ARC 3/99 survey
(3) frequency of records available; no correction for whether they are organized, in one location, physically accessible, successfully located, etc.
(4) directly from ARC 3/99 survey; no correction for whether they are organized, in one location, physically accessible, successfully located, etc.
(5) Canadian experience reported in Transfusion 1999; 39: 194-200; East coast ARC region experience with 200 responses on 397 notifications had 23/200 components not transfused is 88%
(6) findings from CJD Lookback Study, confirmed by Canadian experience
(7) extrapolation from Canadian experience report, which had 30% lost to followup at a median of 5 years transfusion-to-lookback interval
(8) Canadian experience reported 100% response; Pittsburgh experience per Dr. Triulzi is that about half respond. Used an intermediate number.
(9) likelihood of being able to trace from HCV positive donor to a living recipient who gets tested
(10) Canadian experience was 61% positive of which 53% already knew. Assume US patients half as likely to have already been tested (assume 26% already know)
(11) likelihood of tracing from an HCV positive donor to a recipient who learns for the first time that he/she is infected with HCV.

REVIEW OF CONSIGNEE RESPONSES TO HCV LOOKBACK FROM ONE RED CROSS REGION

This east coast region collects about 160,000 donations per year. To date, the region has sent 397 Lookback notifications and has received 200 responses. A review of the consignee responses is provided below. The recipient contact success rate for this region is better than the model in Attachment I: 4.5% vs. 1%. However, even with a better contact rate, the medical success rate is worse than the model: 0% vs. 1%.

	# of Responses	Years post transfusion
Deceased recipients	132 (65%)	N/A
Recipients lost to follow up	5 (3%)	7, 9, 10
Discarded components	23 (12%)	N/A
Transfusion service reported recipient not notified or unknown	29 (15%)	N/A
Newly tested recipients (nonreactive)	9 (5%)	6, 8, 9, 10, 11
Recipients (positive, previously known)	2 (1%)	*
Total Responses Received	200	N/A

* One of these donors was tested for HCV in 1998, and the other was tested twice, once in 1991 and a second time in 1994.