

# Managing Recalls and Withdrawals of Blood Components

Glenn Ramsey

Donor centers are issuing a growing number of recalls and market withdrawals to hospital transfusion services about blood components. More than 1 in 2,000 units were recalled in the late 1990s in the United States. The most common reason for these notices from donor centers is postdonation donor information. Most of these units had been transfused, and many present a "risk of a risk" (ie, a problem might have been present that might have affected the recipient). A few regulations and standards address recalls in general terms, but transfusion services generally have wide discretion in the management of specific common recall problems. The Food and Drug Administration (FDA) is now including posttransfusion evaluations in its guidelines for

emerging infectious threats to the blood supply. We suggest that hospital transfusion services should have standard operating procedures for managing recalls and that the hospital transfusion committee and the quality management program should provide local input or oversight. Using the FDA's categories of donor center biological product deviations, we provide recommendations to consider for when to notify the recipient's physician, after postdonation information is received about a previously transfused blood component. More study of this important everyday issue in transfusion medicine is highly desirable.

© 2004 Elsevier Inc. All rights reserved.

**B**LOOD COMPONENTS are regulated as drugs. However, because they are derived directly from humans, they will always be subject to biological variation. Their unit-by-unit production, testing, storage, distribution, and record keeping are also more complex than other medications, leading to further opportunities for deviations from the expected. The US Food and Drug Administration's (FDA) current good manufacturing practices extend to after manufacturing so that, if problems are found with the finished drug, measures must be taken to correct the product or prevent consequences to patients if possible.

Over the past 10 to 15 years, the stricter application of these principles to blood components has led to a growing number of recalls and withdrawals by blood suppliers, as well as a concomitant increase in the numbers of notices sent to transfusion services about blood products they have received. Furthermore, because platelets and red blood cells have a short shelf life and because hospitals do not keep a large reserve of blood components in storage, most of these notices about nonconforming blood products are often received after the units had been transfused. In retrospect, many of these recalled units presented a "risk of a risk" (ie, that

the problem might have affected the patient if it had actually been present but whether it was truly present is often unknown).

The lookback requirements for tracing units from donors later found to have human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections have been formalized by the FDA in rules and guidances.<sup>1,2</sup> (A revised rule for HIV and HCV lookbacks was proposed in 2000 but not finalized as of this writing.<sup>3</sup>) HCV and HIV lookbacks have been discussed elsewhere<sup>4,5</sup> and will not be covered in depth here.

In contrast to HIV and HCV lookbacks, other types of notices about blood products have few specific formal rules or guidelines as to how they should be handled by the transfusion service. The purpose of this review is to discuss the management of recalls and withdrawals of blood components.

## RECALLS, MARKET WITHDRAWALS, AND BIOLOGICAL PRODUCT DEVIATIONS

"Recall is an effective method of removing or correcting consumer products that are in violation of laws administered by the Food and Drug Administration" (Title 21, Code of Federal Regulations (CFR), section 7.40 (21 CFR 7.40)). The FDA classifies recalls into 3 categories, from the most serious, Class I, to the least serious, Class III (Table 1). All recalls under FDA jurisdiction are published on line in the weekly FDA Enforcement Report.<sup>6</sup> There is a lag time of weeks to months from the recall to publication, and the Enforcement Report does not say when the original problem

---

*From the Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL.*

*Address reprint requests to Glenn Ramsey, MD, Northwestern University, Feinberg 7-301, 251 E. Huron St., Chicago, IL 60611. E-mail: g-ramsey@northwestern.edu*

*© 2004 Elsevier Inc. All rights reserved.*

*0887-7963/04/1801-0004\$30.00/0*

*doi:10.1016/j.tmr.2003.10.005*

**Table 1. FDA Definitions of Recalls and Market Withdrawals, 21 CFR 7.3**

Recall:	Removal or correction of a marketed product that the FDA considers to be in violation of the law it administers and against which the agency would initiate legal action, eg, seizure.
Recall classification for use of, or exposure to, a violative product:	
Class I:	Reasonable probability [of] serious adverse health consequences or death.
Class II:	May cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.
Class III:	Not likely to cause adverse health consequences.
Market withdrawal:	Removal or correction of a distributed product which involves a minor violation that would not be subject to legal action by the FDA or which involves no violation, eg, normal stock rotation practices, routine equipment adjustments and repairs.

occurred. The FDA says recalls are “voluntary” by the manufacturer, although conducting recalls is required, and the FDA has the power to initiate recalls if the manufacturer does not act as required.

Recalls can include public warnings in serious situations (21 CFR 7.42). In 1 blood component recall involving improper donor testing in a large centralized laboratory, several blood centers who had used that laboratory made community media announcements and advertisements notifying transfusion recipients to seek testing if desired.<sup>7</sup>

Market withdrawals are also defined in Table 1. The FDA has stated that withdrawals because of problems beyond the control of the manufacturer may be classified as withdrawals. For example, the US nationwide removal of Tylenol (McNeil-PPC, Ft Washington, PA) from stores because of fatal cyanide tampering in Chicago in 1982 was classified as a market withdrawal not a recall.<sup>8</sup> Most notices about blood components involving postdonation donor information are now categorized as market withdrawals. Market withdrawals are not published by the FDA so their magnitude is unknown.

Ramsey and Sherman<sup>9</sup> analyzed recalls of blood components published by the FDA from 1990 through 1997. During this 8-year period, recalls were announced for nearly a quarter-million blood components, comprising about 1 in 700 units available to hospitals. Seventy-six percent were in Class III recalls, 24% were of Class II, and only 12 units were designated in Class I (because of viral or bacterial infection). Three fourths of the recalled units involved incorrect or incomplete testing for syphilis or viral infection. The next largest categories were for donors with reactive or previously reactive infectious disease tests, which involved 10% of recalled units. Nearly 90% of recalled units were included in a small number (22) of large recalls of over 1,000 units each.

By 1998, the final year examined, published blood component recalls had shifted away from incorrect or incomplete infectious-disease testing (down to 20% of units) and toward donors with previously reactive infectious-disease tests (51% of units).<sup>10</sup> Also in contrast to 1990-1997, two thirds of the recalled units were included in a growing number of smaller recalls of under 1,000

**Table 2. FDA Publications Addressing Notices From Blood Collection Facilities to Consignees**

Type of Publication	Topic	Date of Release	Reference
Rule	HIV lookback	Sep 9, 1996	1
Rule, proposed	HCV lookback	Nov 16, 2000	3
Guidance	HTLV	Aug 15, 1997	15
Guidance	HCV lookback	Oct 21, 1998	2
Guidance	Anthrax	Oct 17, 2001	24
Guidance	CJD	Jan 9, 2002	16
Guidance, draft	Xenotransplantation	Feb 1, 2002	23
Guidance	Smallpox vaccination	Dec 30, 2002	20
Guidance	SARS	Apr 17, 2003	21
Guidance	West Nile virus	May 1, 2003	19
Guidance, draft	Syphilis	Jun 25, 2003	22
Blood Memo	Donor HBV, HTLV	Jul 19, 1996	14

NOTE. The FDA web site [www.fda.gov/cber](http://www.fda.gov/cber) lists rules, guidances, and blood memos separately; in reverse chronological order of release.

units each. About 10,000 blood components were recalled in the 1998 Enforcement Reports. When compared with the total annual blood components distributed in the United States, the risk of a unit being recalled after issue was about 1 in 2,000.

Another gauge of the types of problems found with blood components comes from the recent requirement for reporting biological product deviations (BPDs) to the FDA. By definition, BPDs involve products that had been issued but that were later found to have safety, potency, or labeling problems. BPDs should include all problems that lead to recalls or market withdrawals. The FDA has summarized the first full fiscal year (FY 2002) of BPDs reported from licensed blood facilities.<sup>11</sup> Their statistics are presented as the number of reports, not the number of units involved, so the overall frequency of blood components involved is unknown. One BPD for incorrect testing could involve many units, whereas BPDs for donor suitability are often reported on a unit-by-unit basis. However, the categories and numbers of BPDs offer a useful FDA-defined framework for categorizing problems found in blood components currently.

Nearly 22,000 BPDs were reported from licensed facilities (excluding plasma centers) in FY 2002. (Reports which actually did not need to be reported were excluded.) Seventy-six percent were for postdonation information concerning donor high-risk behavior and history. The most common categories here, in order, were travel to malaria and Creutzfeldt-Jacob risk areas, cancer, tattoos, disease or surgery, deferring medications, and intravenous drug use.

The next largest type of BPD, in 10% of cases, was for quality control and distribution problems, such as clotted or hemolyzed units or segments, inappropriate product release (eg, unacceptable quality control, outdated), incorrect temperature, and failure to quarantine after another problem was found.

The rest of the donor-center BPDs were in donor screening (6.0%), labeling (4.3%), routine testing (1.2%), component preparation (1.2%), collection (0.7%), miscellaneous (0.6%), donor deferral (0.2%), and viral testing (0.2%). The most common items within each of these areas were as follows: donor screening, deferring history, but not deferred; labeling, incorrect autologous donor tag; routine testing, incorrect Rh typing; component

preparation, incorrect temperature; collection, bacterial contamination; miscellaneous, HCV lookback deviation; donor deferral, previous deferral for history; and infectious disease testing, incorrect syphilis testing. Incorrect infectious disease testing, previously the most common category of recalled units in the 1990s, was the least common category of BPDs in FY 2002. This may reflect the current widespread use of large, dedicated centralized testing laboratories for donors.

#### REGULATORY REQUIREMENTS AND GUIDANCES

The FDA has detailed regulations and support documents for the conduct of recalls by the manufacturer. 21 CFR 7.3 defines recalls, and 21 CFR 7.40-7.59 describe the manufacturer's obligations and the FDA's processes for monitoring and assessing recalls. Two publications by the FDA's Office of Regulatory Affairs provide details for their inspectors about how to inspect recall operations: the Investigation Operations Manual, Chapter 8, and the Regulatory Procedures Manual, Chapter 7.<sup>12,13</sup> These 2 publications are on line at [www.fda.gov/ora](http://www.fda.gov/ora). The FDA may conduct effectiveness checks, which are follow-up surveys of consignees such as transfusion services, to verify that recalls are carried out appropriately by the manufacturer.

In contrast, the FDA provides much less general information about the response to recalls. One line in the CFR is addressed to consignees: "Responsibility of recipient. Consignees that receive a recall communication should immediately carry out the instructions set forth by the recalling firm and, where necessary, extend the recall to its consignees in accordance with . . . this section (21 CFR 7.49 [d])." Therefore, if the hospital transfusion service has shipped the recalled component, or part of it, to another facility, it should conduct a recall to the second facility. For example, some hospital transfusion services send source plasma to a manufacturer so the source plasma buyer should be notified if the original unit is recalled. If the transfusion service is notified about an unsuitable product, but then issues it inadvertently, then a BPD report would be required.

HIV and HCV lookbacks have been referred to previously (Table 2).<sup>1-5</sup> Donors with reactive tests for hepatitis B virus (HBV) and human T-cell lymphotropic viruses (HTLV) I and II were ad-

dressed by the FDA in a 1996 recommendation<sup>14</sup> (now listed under Blood Memos) and a 1997 guidance for HTLV.<sup>15</sup> The FDA recommended withdrawing in-dated components from donors with HBV and HTLV markers but stated that they were not recommending consignee notification for the purpose of recipient notification. In our own practice, we perform lookback on units from donors with confirmed hepatitis B surface antigen (HBsAg) or anti-HTLV (see Management of Specific Problems), but this is not required by the FDA.

Recent FDA guidances about emerging infection issues have included provisions about post-transfusion actions. In the January 2002 guidance<sup>16</sup> on Creutzfeldt-Jakob disease (CJD), the FDA stated that notifications about donors deferred for travel, bovine insulin, United Kingdom transfusion, or a single family member with CJD were intended only for product removal, and not for notification of recipients. For other more direct donor connections to CJD, including actual donor CJD subsequent to transfusion, "consignee notification could enable the consignee to inform the physician . . . so that recipient tracing and medically appropriate notification and counseling may be performed at the discretion of health care providers."

There is an ongoing study by the US Centers for Disease Control and Prevention (CDC) and the National Blood Data Resource Center to investigate transfusion recipients of blood from subsequently diagnosed CJD patients.<sup>17</sup> In this approved study, the recipients are not notified, but national deaths are monitored to see whether any of the recipients die of CJD. As of August 2002, 331 transfusion recipients with 1,325 person years of follow-up had been studied. A similar study is being conducted in Great Britain for recipients of blood from donors with later variant CJD (vCJD).<sup>18</sup> No secondary cases of CJD or vCJD have been reported to date. If a notice were received in the United States about a blood component from a donor with later CJD, the CDC or the National Blood Data Resource Center should be contacted.

In the May 2003 West Nile virus (WNV) guidance,<sup>19</sup> if a donor has a medical diagnosis of WNV, then other units from -14 days before to +28 days after the onset of illness should be traced for consideration of notifying the recipients' physicians. If the donor is the suspected likely source of another

WNV transfusion case, then other units from that donor collected from -28 days to +28 days from the infectious donation should also be traced and the recipients' physicians notified. "However, in cases when a donor is potentially associated with a case of transmission of WNV, but the epidemiological investigation has not established the specific donor as a likely source of transmission of WNV, we are not recommending notification of the transfusion service." This is slightly misworded because units from recent donors associated with a transfused WNV patient should be sought for precautionary quarantine and retrieval from the transfusion service, but the implication is that the recipients' physicians need not be notified if the donor is not the likely source. WNV nucleic acid testing (NAT) began in the US and Canada in the summer of 2003. When a donor tests reactive by WNV NAT, the FDA has not specified at this writing whether to use a 14-day lookback period (as per donor WNV illness) or a 28-day period (as per donor transmission of WNV) for recent donations.

The December 2002 guidance on smallpox vaccination and blood donation<sup>20</sup> addressed postvaccination blood collections. If a donor should have been ineligible, but his/her units already have been transfused, then "we recommend that medical directors consider the need for prompt record tracing and, as appropriate, notification of the treating physicians or notification of prior recipients of the affected blood and blood components previously collected from that donor."

The April 2003 FDA guidance<sup>21</sup> on severe acute respiratory syndrome (SARS) gave recommendations for lookback investigation. If a blood product has been transfused from a donor who should have been ineligible at the time of donation, then "we recommend that the establishments consider notifying the treating physician of those recipients about the post donation information, including whether the donor developed suspected SARS." Donors are deferred for 28 days after recovering from suspected SARS or for 14 days after exposure to a person with SARS or travel to SARS-risk areas. However, the guidance states that if the donor is symptom free for more than 14 days after exposure, then product retrieval and quarantine (and thus presumably notification of the treating physician) are not necessary.

In the June 2003 draft guidance on donor syph-

ilis testing,<sup>22</sup> lookback, quarantine, and consignee notification are not recommended for previous units from donors with later syphilis or a confirmed syphilis test.

The recent FDA draft guidance on xenotransplantation<sup>23</sup> and on anthrax<sup>24</sup> call for withdrawal of blood components inadvertently collected from donors with these unusual exposures. The anthrax guidance has recommendations on when to notify the recipient's physician after transfusion of a suspect unit.

#### ACCREDITATION REQUIREMENTS

In the 22nd edition of the Standards of the American Association of Blood Banks (AABB), effective November 2003, chapter 7 is on deviations, nonconformances, and complications.<sup>25</sup> Standard 7.0 requires policies, processes, procedures and defined responsibility for detecting, investigating, and reviewing deviations. Standard 7.1 and its subsections call for nonconforming products to be evaluated, traced, segregated if still present, and prevented from unintended use. Blood banks and transfusion services must have processes for identification, quarantine, retrieval, and recall. Nonconforming products that already have been released must be evaluated for quality, and when quality may have been affected, the nonconformance shall be reported to the customer. (The "customer" is defined elsewhere as the receiver of a product or service, either another organization or another department within the same organization. In this context of nonconforming products, the "customer" does not refer to the patient who received the product.) Records of product nonconformances and actions about them must be maintained for 5 years (reference standards 6.2A and 6.2C).

The transfusion medicine checklist of the Laboratory Accreditation Program of the College of American Pathologists (December 2002 edition)<sup>26</sup> has 2 questions touching on some aspects of recalls and notifications. TRM.42120 asks if there is a procedure to identify and quarantine all previous components from donors who now test repeatedly reactive in viral marker screening tests. TRM.42170 asks for a "procedure consistent with [Medicare] and FDA regulations/guidelines for notification and counseling of recipients who have been transfused with a potentially infectious blood component." The commentary for this question

refers to federal requirements for notifying recipients about subsequent confirmed positive infections in their donors. The main intent of the question is to require HIV and HCV lookback. However, the mention of guidelines in the question may be construed to include other recent FDA guidelines as discussed earlier.

Some hospitals collect blood products, and some blood collection centers have transfusion services. The previously mentioned regulations and standards apply to those facilities as well (ie, notices should be transmitted from the collection arm to the transfusion arm of the same establishment when necessary).

#### GENERAL RECOMMENDATIONS

Within the extant regulations and standards summarized previously, the transfusion service has broad latitude on how to manage recalls and notifications from blood suppliers, other than HIV and HCV lookback. The remainder of this article offers recommendations based on our experience. However, these are only recommendations, and others may choose to use different approaches. Given the paucity of literature about this important everyday area of activity in transfusion medicine, we hope the following will be helpful in providing a framework for others to organize their programs as suited for their hospitals. Future study, analysis, and discourse on the management and outcomes of recalls and notifications will be very helpful. In particular, the yield of problem investigations and the medical benefit of these notices for transfusion recipients deserve more examination.

At a minimum, we would suggest that recall management processes include the following key elements:

1. Have a standard operating procedure. However one chooses to manage recalls and notifications, and in however much detail desired, a procedure is a prerequisite for instructing staff in these key elements.
2. Act immediately to quarantine and discard, or return, blood components as instructed by the supplier. Time is of the essence when a notice is received. Immediate action should be taken to quarantine the unit and prevent release. Is a recalled unit of plasma being thawed in the waterbath? In case a large number of units is involved, the transfusion service staff should have round-the-clock ac-

cess to facsimile or secure electronic mail to facilitate transfer of information and prevent transcription errors from verbal messages. For laboratories with blood bank computer systems, both computer and physical quarantine must be done, although computer quarantine may be done first to expedite prompt blockage of issue. As noted previously, if a unit is erroneously released after a notice is received to quarantine it, then a biological product deviation report must be sent to the FDA.

3. Review and determine the medical implications of units already transfused. This is further discussed later.
4. Keep records of all notices and actions as required (eg, 5 years in AABB standards).<sup>25</sup> Telephone instructions should be logged and obeyed, but also documented pending written follow-up. Record systems should include the capability to track investigations in progress. Transfusion services may want to consider means to search recall records by unit number or patient or the ability to tag the unit or patient laboratory record that a recall has occurred. Large hospitals may find a confidential database useful.

Transfusion services may wish to review their general strategies for oversight, management, and record keeping with the hospital's risk management and/or legal counsel. Although most of these problems occur before the hospital receives the units, there could be potential medicolegal implications for the hospital and the physician. For example, it may be advisable to consider these investigations as a subcategory of the hospital's overall incident management program for quality improvement or at least to bring serious problems to this forum.

The transfusion committee or its local equivalent may wish to provide general oversight for the recall management process. There are several advantages to performing recall investigations under the aegis of the transfusion committee. This educates key physicians in the range of problems found with blood components after transfusion. It provides the medical staff's representatives a forum to review and approve the general and specific features of the procedure. The transfusion committee also provides a logical venue to bring all or

selected recalls into the hospital quality improvement program.

Some other resources of expertise in the hospital may be helpful in certain problems. The infection control office can provide advice on transfusions, which may have posed a serious infection risk in hindsight. Potentially, this consultation could include immediate measures such as baseline patient infectious disease testing (eg, a donor calls back to report recent previously unsuspected exposure to HIV) or antimicrobial therapy (eg, a platelet culture becomes positive after the product was already transfused). For perplexing conundrums in post-transfusion problems, the hospital ethics committee might provide a useful forum for discussion. The hospital public relations office should be informed when a problem could be of concern to the news media and the public, such as a large recall of blood products in the community.

#### MANAGEMENT OF SPECIFIC PROBLEMS

Many transfusion recipients have died of their underlying illness by the time a notice arrives about one of their blood components. In an HIV lookback, their next of kin must be notified. However, for other problems, no further investigation is needed.

Table 3 gives suggestions for whether to inform a recipient's physician about a problem transfusion. The list of problems is adapted from the FDA's categories of donor-center BPDs, with some additions. Our general approach is that if a blood component might have posed a tangible infectious or other risk, then the patient's physician should evaluate whether the patient may have been affected. On the other hand, if the problem with the product did not pose a tangible risk to the patient, then the transfusion service physician, with the oversight of the transfusion committee if desired, can exercise informed medical judgment to not notify the recipient's physician.

Blood suppliers should provide adequate information for the transfusion service to evaluate the problem and counsel the physician if needed. Without violating the donor's confidentiality, the transfusion service may seek further information from the blood supplier if the first notice is insufficient for a decision.

Many physicians are not familiar with the details of when and why blood donors should be deferred. When the patient's physician is informed about a

**Table 3. Suggested Approaches for Follow-up of Blood Components Discovered After Transfusion to Have Been in Nonconformance (Biological Product Deviations)**

Type of Deviation	Notify Patient's Physician?
<b>Postdonation information</b>	
At donation of unit in question, donor should have been deferred for:	
Malaria-risk travel	Yes, if RBCs, granulocytes, or platelets
vCJD-risk travel, bovine insulin, one CJD relative, or United Kingdom transfusion	No (FDA guidance <sup>16</sup> )
Other vCJD risks	No (see post-donation CJD below)
Tattoo or ear/body piercing	Yes, if sterility uncertain*
Cancer	No
Disease/surgery	Assess details for medical impact
Intravenous drug use	Yes*
Antibiotics or other medications	Yes, if teratogenic medication and pregnant recipient. If possible bacterial contamination, did a transfusion reaction occur?
Smallpox vaccination	See FDA guidance <sup>20</sup>
Previously transmitting transfusion-related infection	Yes*
Seeking testing or asking for blood to be discarded	Yes*
Risk factors for HIV or hepatitis exposure	Yes*
Severe acute respiratory syndrome (SARS), or exposure	Yes, unless donor was well for >14 days after exposure (FDA guidance <sup>21</sup> )
After unit in question, donor later developed:	
HIV infection	Yes* (HIV lookback <sup>1,3</sup> )
Clinical hepatitis, or confirmed anti-HCV, HCV RNA, or HBsAg	Yes* (lookback if HCV <sup>2,3</sup> ) (Note: FDA does not require HBV lookback <sup>14</sup> )
Confirmed anti-HTLV-I or II	Yes*, if cellular product (although transmission unlikely after 10 days of refrigeration) (Note: FDA does not require HTLV lookback <sup>14,15</sup> )
Confirmed syphilis antibody	No (FDA draft guidance <sup>22</sup> )
West Nile virus illness or positive WNV NAT	Yes, if within dates of FDA guidance <sup>19</sup>
SARS	Yes, if within 14 days after donation <sup>21</sup>
CJD	Contact National Blood Data Resource Center <sup>17</sup> (see text)
Indeterminate anti-HIV, anti-HCV, or anti-HTLV	No
Reactive screening test, but negative supplemental testing	No
Reactive anti-HBc or elevated ALT	No (Anti-HBc, FDA memorandum <sup>14</sup> )
<b>Donor screening and deferral</b>	
Vital signs unacceptable or not documented	Did recipient have septic transfusion reaction?
Hematocrit unacceptable	No
Screening incomplete (history, arm check, donor signature)	No
Incorrect re-entry after reactive screening test	Assess details of timing and results of testing
<b>Quality control and distribution</b>	
Clotted or hemolyzed unit or segment	Did recipient have transfusion reaction?
Outdated product	Did recipient have transfusion reaction?
Shipped or stored at incorrect temperature	Did recipient have transfusion reaction?
Unacceptable RBC, platelet, or clotting factor content	No
Not irradiated, leukoreduced, or CMV-safe as ordered	Yes, if patient did not receive required product
<b>Labeling</b>	
Recipient ID incorrect (including autologous)	Did wrong patient receive unit?
Expiration extended erroneously	If unit was given after true expiration, did recipient have transfusion reaction?
ABO, Rh, or RBC antigen label incorrect	Did recipient have transfusion reaction or receive Rh-incompatible RBC-containing product?
Irradiation, leukoreduction, or CMV status incorrect	Yes, if recipient did not receive required need
Donor number incorrect	No, but fix patient and lab record with correct unit number
Product type incorrect	Assess medical impact
Anticoagulant incorrect	No
<b>Testing (of the unit in question)</b>	
Incorrect infectious disease testing	Yes*
Reactive infectious disease testing	Yes, unless supplemental testing is negative
Confirmed bacterial detection in product or co-component	Yes
Reactive indirect bacterial screen (e.g., pH, glucose), not confirmed	No
Incorrect ABO, Rh, or RBC antigen testing	Did recipient have transfusion reaction or receive Rh-incompatible RBC-containing product?
Incorrect RBC antibody testing	No
<b>Component preparation</b>	
Incorrect irradiation or leukoreduction	Yes, if recipient did not receive required need
Sterility compromised	Did patient have transfusion reaction or infection?
Incorrect temperature	Did patient have transfusion reaction?
Additive solution not added, or added incorrectly	Was unit actually outdated when given?
<b>Collection</b>	
Sterility compromised	Did patient have transfusion reaction or infection?
Outdated collection bag	Did patient have transfusion reaction or infection?
Phlebotomy time or volume incorrect	No

\*Unless donor later tested negative for marker(s) in question, after the appropriate seroconversion period (Table 4 and text). HIV or HCV nucleic acid tests (NAT) have short seroconversion windows, but postdonation NATs have not been incorporated yet into FDA rules and guidances on HIV or HCV lookbacks.<sup>1-3</sup>

problem with a nonconforming blood component, some background information is often useful. For recurring notices such as malaria-area travel, a form letter may be convenient. For most routine notices, we have not required follow-up information from the physician. However, for sensitive issues, the transfusion service physician may offer assistance in patient counseling if desired.

When there is concern about the possibility of infection risk from the donor, testing of the donor and/or patient may be indicated. When a donor is deferred for a risk factor before donation, no testing is done at that time. From the collection facility's standpoint, this may discourage test seeking by ineligible donors. Unfortunately for the transfusion services, which have previously received blood components from that donor, the current infection status of the donor is thus left unknown.

If the donor has been tested since the donation in question, the last date of testing should be included in the notification or be sought by the transfusion service. In serious donor risks, such as known HIV exposure, the transfusion service may ask the collection facility to seek donor testing if feasible.

Seroconversion window information is helpful for counseling and donor testing after exposure or for recipients after transfusion. If the donor has tested negative after the seroconversion period of the test in question has elapsed, then donor infection at the time of the donation can be ruled out. Table 4 shows seroconversion window periods for viral tests required in blood donors. The CDC recommendation for HIV antibody testing after needlestick exposure is 6 months,<sup>29</sup> that is more conservative than the table figures. In the 1996 HIV lookback rule and the 2000 proposed look-

back rule for HIV and HCV,<sup>1,3</sup> the FDA required 12 months before a negative antibody test to rule out the need for lookback in prior donations. NAT for HIV and HCV has much shorter window periods than antibody testing. The CDC recommends 4 to 6 weeks of follow-up testing for HCV RNA after needlestick exposure.<sup>29</sup> NAT has not yet been factored into FDA lookback rules and guidances.

REDUCING RECALLS AND WITHDRAWALS

Blood centers have greatly reduced infectious disease testing errors and problems that predominated in recalls of the early and mid-1990s. Today's challenge is the donor who does not reveal a deferring risk factor or condition. An anonymous survey of blood donors for risk behaviors revealed that 1.9% had a deferrable risk at the time of their donation (1.7% after testing and confidential unit exclusion).<sup>30</sup> Efforts have been made to reshape screening questions to improve their comprehension by donors.<sup>31</sup> Computer-assisted interviews may offer donors a more comfortable way to reveal risk factors.<sup>32</sup>

Because many current donor risk factors are based on international travel, another area for consideration is making information more widely accessible for travelers and their physicians about when not to donate blood. For example, the CDC's key international travel health publication, the "Yellow Book," does not tell physicians and travelers about when to avoid blood donation, and for how long.<sup>33</sup> Likewise, when blood donor deferrals began for SARS-area travel, this was not included in CDC information pages for travelers.<sup>34</sup> More publicity about the consequences of travel on blood donation might reduce recall rates for geographic donor risks.

CONCLUSIONS

In today's regulatory climate, hospital transfusion services receive numerous recalls and market withdrawals from their blood suppliers. Hospitals should have procedures for managing the quarantine, medical evaluation, and records of these recalls. The transfusion committee may provide oversight for local preferences about when to inform the recipient's physician. More study of the medical importance of recalls for transfused patients is needed.

Because the predominant reason for notices

**Table 4. Seroconversion (Window) Periods for Donor Viral Tests After Infection**

Test	Mean (days)	Range (days)
Anti-HIV	22	6-38
HIV NAT	NA	7-12
Anti-HTLV	51	36-72
Anti-HCV	70	54-192
HCV NAT	NA	10-29
HBsAg	56	37-87

NOTE. See text for CDC and FDA recommendations for testing in occupational exposure and HIV and HCV lookback. Abbreviation: NA, not available.

Data from Schreiber et al<sup>27</sup> and Interorganizational Task Force on Nucleic Acid Testing (NAT) of Blood Donors.<sup>28</sup>

about blood products is postdonation information about the donor, this is an important area for quality improvement by blood suppliers. New mea-

asures to improve donor understanding and communication about deferring information could help reduce blood component recalls and withdrawals.

## REFERENCES

1. Current good manufacturing practices for blood and blood components: notification of consignees receiving blood and blood components at increased risk for transmitting HIV infection; final rule. Rockville, MD, Food and Drug Administration, September 9, 1996
2. 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. Rockville, MD, Food and Drug Administration, October 21, 1998
3. 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"); proposed rule. Rockville, MD, Food and Drug Administration, November 16, 2000
4. Goldman M, Juodvalkis S, Gill P, et al: Hepatitis C lookback. *Transfusion Med Rev* 12:84-93, 1998
5. Busch MP, Young MJ, Samson SM, et al: Risk of human immunodeficiency virus (HIV) transmission by blood products before the implementation of HIV antibody screening. *Transfusion* 31:4-11, 1991
6. FDA Enforcement Report. Rockville, MD, Food and Drug Administration (weekly). Available at: <http://www.fda.gov> (internet). Accessed April 18, 2003
7. Steinhauer J: Blood center ads, meant to be calming, prove alarming. *New York Times*, October 21, 1998, p B3
8. Nordenberg T: Recalls: FDA, industry cooperate to protect consumers. *FDA Consumer Magazine* 29(8), October 1995
9. Ramsey G, Sherman LA: Blood component recalls in the United States. *Transfusion* 39:473-478, 1999
10. Ramsey G, Sherman LA: Blood component recalls in the United States, 1998. *Transfusion* 40:253-254, 2000 (letter)
11. Biological product deviation reports-FY02 annual summary. Rockville, MD, Food and Drug Administration, April 23, 2003, Available at: [www.fda.gov/cber/biodev/bpdrfy02.htm](http://www.fda.gov/cber/biodev/bpdrfy02.htm). Accessed April 24, 2003
12. Recall activities, in *Investigations Operation Manual* 2002. Rockville, MD, Food and Drug Administration, 2002, pp 352-358, Available at: [www.fda.gov/ora/inspect\\_ref/iom](http://www.fda.gov/ora/inspect_ref/iom). Accessed April 18, 2003
13. Recall and emergency procedures, in *Regulatory Procedures Manual*. Rockville, MD, Food and Drug Administration, 2001, chapter 7. Available at: [www.fda.gov/ora/compliance\\_ref/rpm\\_new2/default.htm](http://www.fda.gov/ora/compliance_ref/rpm_new2/default.htm). Accessed April 18, 2003
14. 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). Rockville, MD, Food and Drug Administration, July 19, 1996
15. Guidance for industry: Donor screening for antibodies to HTLV-II. Rockville, MD, Food and Drug Administration, August 15, 1997
16. Guidance for industry: revised preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood products. Rockville, MD, Food and Drug Administration, January 9, 2002
17. Creutzfeldt-Jakob disease investigational lookback study—updated 08/26/02. Bethesda, MD, National Blood Data Resource Center. Available at: [www.nbdrc.org/research/cjd.htm](http://www.nbdrc.org/research/cjd.htm). Accessed April 17, 2003
18. Hewitt P, Llewelyn C, Will R: Follow up of donations from patients with vCJD. *Vox Sang* 83:1, 2002 (Suppl 2, abstr)
19. Guidance for industry: Revised recommendations for the assessment of donor suitability and blood and blood product safety in cases of known or suspected West Nile virus infection. Rockville, MD, Food and Drug Administration, May 1, 2003
20. Guidance for industry: Recommendations for deferral of donors and quarantine and retrieval of blood and blood products in recent recipients of smallpox vaccine (vaccinia virus) and certain contacts of smallpox vaccine recipients. Rockville, MD, Food and Drug Administration, December 30, 2002
21. Guidance for industry: Recommendations for the assessment of donor suitability and blood product safety in cases of suspected severe acute respiratory syndrome (SARS) or exposure to SARS. Rockville, MD, Food and Drug Administration, April 17, 2003
22. Draft guidance for industry: Revised recommendations for donor and product management based on screening tests for syphilis. Rockville, MD, Food and Drug Administration, June 25, 2003
23. Draft guidance for industry: precautionary measures to reduce the possible risk of transmission of zoonoses by blood and blood products from xenotransplantation product recipients and their intimate contacts. Rockville, MD, Food and Drug Administration, February 1, 2002
24. Guidance for industry: recommendations for assessment of donor suitability and blood and blood product safety in cases of possible exposure to anthrax. Rockville, MD, Food and Drug Administration, October 17, 2001
25. Fridey JL: *Standards for Blood Banks and Transfusion Services* (ed 22) Bethesda, MD, American Association of Blood Banks, 2003
26. Transfusion medicine checklist, in *Laboratory Accreditation Program*. Northfield, IL, College of American Pathologists, December 2002. Available at: [www.cap.org/html/checklist\\_html/TransfusionMedicine\\_1202.html](http://www.cap.org/html/checklist_html/TransfusionMedicine_1202.html). Accessed April 18, 2003
27. Schreiber GB, Busch MP, Kleinman SH, et al: The risk of transfusion-transmitted viral infections. *N Engl J Med* 334: 1685-1690, 1996
28. Report of the interorganizational task force on nucleic acid amplification testing of blood donors: Nucleic acid amplification testing of blood donors for transfusion-transmitted infectious diseases. *Transfusion* 40:143-159, 2000

29. Centers for Disease Control and Prevention. Updated US Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for post-exposure prophylaxis. *MMWR* 50(No. RR-11):21-27, 2001

30. Williams AE, Thomson RA, Schreiber GB, et al: Estimates of infectious disease risk factors in US blood donors. *JAMA* 277:967-972, 1997

31. Orton SL, Virvos VJ, Williams AE: Validation of selected donor-screening questions: structure, content, and comprehension. *Transfusion* 40:1407-1413, 2000

32. Sanchez AM, Schreiber GB, Glynn SA, et al: Blood-

donor perceptions of health history screening with a computer-assisted self-administered interview. *Transfusion* 43:165-172, 2003

33. Health Information for International Travel. Atlanta, Centers for Disease Control and Prevention. Available at: [www.cdc.gov/travel/yb/index.htm](http://www.cdc.gov/travel/yb/index.htm). Accessed April 22, 2003

34. Interim guidelines about severe acute respiratory syndrome (SARS) for persons traveling to SARS-affected areas. Atlanta, Centers for Disease Control and Prevention, April 22, 2003. Available at: [www.cdc.gov/ncidod/sars/travel\\_advice.htm](http://www.cdc.gov/ncidod/sars/travel_advice.htm). Accessed April 22, 2003