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LEARNING OBJECTIVES

Upon completion of this exercise, the participant should be able to

- define the terms “recall” and “withdrawal” as they pertain to blood products.
- recognize the importance of the blood donor interview and the rationale underlying the Food and Drug Administration–mandated donor deferral process.
- explain the differences among types of lookbacks and identify which is more cost-effective.
- describe the importance and roles of various persons and agencies involved in the withdrawal process.
- discuss the lookback process.
- describe the procedure to follow in the event of recall or withdrawal.
HISTORY

A 57-year-old man with severe coronary artery disease underwent a quadruple-graft coronary artery bypass procedure. During the procedure, he received a blood transfusion without complications. Four months later, the transfusion medicine service that issued the transfused blood product was notified by the blood product supplier that the product transfused had been identified in a retrospective analysis as originating from a donor who subsequently admitted to having lived in England from November 1992 through September 1997, and thus was at risk for variant Creutzfeldt-Jakob disease (vCJD). The transfusion medicine service in turn notified the patient’s surgeon. In addition to coronary artery disease, the patient had a medical history of hypertension, dyslipidemia, and prostate cancer, as well as a strong family history of Alzheimer disease. He had quit smoking 3 years before surgery and denied alcohol or illicit drug use.

After informing the patient of the incident and verifying that the patient was in no acute distress, the surgeon referred the patient to a neurologist for consultation. Although the notification process in such instances is deemed “voluntary” by the US Food and Drug Administration (FDA), the patient was informed of his risk for vCJD. The FDA has stipulated that blood obtained from persons living in Western Europe after the appearance of vCJD should not be used for hemotherapy in the United States.1-2 Owing to confidentiality issues, the blood bank could not obtain the clinical status of the person who donated the blood and whether or not the donor had documented vCJD. By conventional terminology this would be categorized as a “risk of a risk” to the recipient.3 However, the blood donation occurred 12 years subsequent to the donor’s last possible exposure to vCJD, implying that no severe neurologic impairment had occurred in this time span. The recipient availed himself of the offer of consultation with the transfusion medicine service. After reassurance that the notification was merely cautionary and that the donor was not a known carrier of vCJD, the recipient was mollified. Based on the neurology consultation, the patient did not exhibit any symptoms, and no laboratory testing was indicated at the time of consultation.

An audit of recalled and withdrawn blood products at the authors’ institution from outside blood suppliers was begun. Blood bank records from 2002 to 2007 were searched for withdrawn and recalled blood products. The authors identified 474 such incidents arising from 6 blood suppliers. Database analysis revealed the most common reason for recall or withdrawal at the authors’ institution during the stipulated time period had been infectious risk associated with the donor unit, whereby documented contamination or deferral due to travel restrictions imparted to transfusion-transmitted disease (TTD) risk (Figure 1). This finding was in line with previous observations in the literature, suggesting that infection risk was one of the most common causes of recall and withdrawal of blood products.3-8 An internal audit showed that risk for hepatitis virus transmission accounted for approximately 50% of the lookbacks for infectious reasons; most involved hepatitis C virus (HCV) infection risk (Figure 2). Other reasons for removing products from circulation include quality control shortcomings, cancer diagnosis in the donor, and misrepresentation of donor history accruing in retrospect. Common modalities in each of these categories are
listed in Table 1 in order of decreasing frequency. Of note, the most common cancer diagnosis not evident at time of donation was melanoma. It should be noted that these are merely illustrative annotations from the authors’ limited records and may not be universally equally representative.

**Figure 1.** Reasons for recalled or withdrawn products. Data collected and analyzed from the archives of the Medical College of Georgia (Augusta, GA) blood bank, recall/withdrawal records, 2002 to 2007.

**Figure 2.** Infectious causes for recall/withdrawal by category of infection. Data collected and analyzed from the archives of the Medical College of Georgia (Augusta, GA) blood bank, recall/withdrawal records, 2002 to 2007. CJD indicates Creutzfeldt-Jakob disease; HBC, donors repeat-reactive for anti-HBV core antigen by enzyme immunoassay; HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T-lymphotropic virus; viral, prodrome symptoms relating to respiratory or gastrointestinal illness.
<table>
<thead>
<tr>
<th>TABLE I. Issues Leading to Withdrawal/Recall.*</th>
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<td>Quality control issues</td>
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<td>Invalidated incubator</td>
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<td>External control not run</td>
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<td>Internal audit</td>
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<td>Discrepancy in collection</td>
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<td>No sterilization of venipuncture area</td>
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<td>Quality control not done</td>
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<td>Less plasma</td>
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<td>Incomplete history</td>
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<td>No sample for West Nile virus nucleic acid testing</td>
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<td>Inaccurate temperature</td>
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<td>Cancer</td>
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<td>Bladder</td>
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<td>Lung</td>
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<td>Breast</td>
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<td>Misrepresentation on donation form</td>
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<td>Had sex for money</td>
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<td>Sexual indiscretions reported by third party</td>
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<td>Contact with needle user</td>
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<td>Partner taking clotting factors</td>
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<td>Contact with HIV risk</td>
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<td>Male-male sexual contact</td>
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<td>Contact with steroid use partner</td>
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<td>Sex partner from Africa</td>
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*Breakdown of cases associated with quality control issues, cancer, and misrepresentation on donor history leading to recall/withdrawal (n=474). Data collected and analyzed from the archives of the Medical College of Georgia, Augusta, GA, blood bank, recall/withdrawal records 2002 to 2007.
TRANSFUSION SAFETY RETROSPECTIVE:
LOOKBACKS, RECALLS, AND MARKET
WITHDRAWALS

A major goal of transfusion medicine practice has been to reduce the risk of
transfusion-transmitted infection to as low a level as possible. The procedure for
screening donors at the donation site is the medical history interview, which contains
questions to protect the recipient from acquiring a transfusion-transmitted infection
and to protect the donor from suffering an adverse reaction after donation.2,9 One
of the consequences of an entirely voluntary unpaid donor population is a low level
of behavioral risk that eludes donor questioning, laboratory testing, or unit exclusion
and callback procedures. Retrospective postdonation interviews of HIV- and HCV-
seropositive donors demonstrated that a high percentage of such donors will admit to a
history of risky sexual behavior or past intravenous drug use that they had denied prior
to donation.10 The data in Figures 1 and 2 illustrate the continuing need to improve
the clarity and comprehension of the screening questions. At the time of blood
donation, donors receive instructions that they may call the blood center sometime
after the donation to report additional pertinent medical history information. Donors
may call back to report the development of an acute illness such as fever, upper
respiratory tract infection, or a gastrointestinal disorder occurring from several hours to
several days postdonation. Donors may also call back to indicate risk factors for HIV
or other infectious diseases that might not have been disclosed at the time of donation.
The FDA’s summary of blood product deviation reports for fiscal year 2009 notes
34,843 reports of postdonation information (combined via telephone callback or at
a subsequent donation) that led to a reassessment of donor eligibility. Postdonation
reports led to 70% of total blood product deviations reported that year.11

The blood transfusion process has been described as a vein-to-vein pipeline, wherein
blood is obtained from a donor, undergoes appropriate testing and manufacturing, is
matched by laboratory testing to an appropriate recipient, and is subsequently infused
into the recipient under medical supervision.9 The emerging process of hemovigilance
has transformed the process to a vein-to-vein-and-back paradigm, whereby any
adverse consequence encountered in the pipeline may be traced back to the donor and
may have bearing on the donor’s medical status. On occasion, an adverse consequence
is identified after the entire pipeline scenario plays out. Thus, there exists a postmarket
surveillance process mandated by the FDA that tracks such events and appropriate
safeguards, and guidelines have been instituted to impart closure to the pipeline.
In this way, the vein-to-vein-and-back concept comprises an effectual multitiered
pipeline with serial circuitry predisposing to extra protection (Figure 3). The case
example illustrates one operative scenario of this pipeline.

Government Regulation of Hemotherapy
The FDA regulates blood products as “biologic products” and thus subjects blood
establishments to quality standards comparable to those expected of pharmaceutical
manufacturers; in this regard blood component regulatory statutes are tantamount to
those regulating drugs. Blood products are subject to considerable biologic variability,
not only in their cellular and chemical constitution but also in the infectious risks of
Figure 3. Navigation along the recall/lookback pipeline. Adapted after the model reported in Heddle NM, Eyles J, Webert KE, et al. A policy informing qualitative study to improve the process of blood product recalls and withdrawals. Transfusion. 2008;48(12):2585-2595. TTD indicates transfusion-transmitted disease.
individual components. As such, blood components are stringently regulated, and ever-increasing vigilance is applied to postdonation infectious disease monitoring.

A consequence of the efficient infectious disease–monitoring pathways instituted by the FDA for blood components is that on occasion, repeat donors become seropositive for restricted infectious diseases, notably HIV and HCV. Therefore, a set of procedures is in place to retrospectively isolate blood products emanating from the incident donor. This process is termed “lookback”—previous donations that are untransfused must be quarantined and subsequently discarded. Patients receiving transfusions derived from suspect donors must be identified and informed of the potential infectious disease risk (Figure 3 and Table II). Previous donations may have occurred during the window period during which the ostensibly infected donor is presumed infectious even though the screen is not yet reactive.

On identifying sentinel TTD risk, the blood collection facility must seek record of the most recent nonreactive unit donated by the index donor and all units donated during the previous 12-month interval.12 When such units are identified, the collecting facility must then notify the transfusing facility. The transfusing facility must then screen its records and identify the fate of units. A recipient of such a unit must then be notified of the theoretical infectious disease risk. The transfusing physician is the optimal envoy to notify, test, and counsel the recipient. In the event the physician is unable or unwilling to act as envoy, the transfusion service should undertake the notification process and should make itself available to counsel and/or test the recipient as needed.2 If the infectious agent is HIV or HCV, notification of relatives or legal representatives is mandatory if the recipient is deceased or has been judged incompetent.2 While lookbacks most commonly address transmission of HIV and HCV,3-4,6-8,13 evidence is accumulating to implement the same lookback strategy for hepatitis B virus (HBV).14 The final run in the pipeline is a report by the transfusion service to the blood collection facility indicating the disposition of the incident. It is incumbent on the collection facility to relate the case history and resolution to the FDA.

**Variant Creutzfeldt-Jakob disease**

Although the lookback for HIV and HCV TTD risk is well established in the transfusion pipeline, considerable concern surrounds the emergence of vCJD. CJD is a severe, invariably fatal neurologic disease that can be acquired either by familial inheritance or by infective transmission via infectious particles called prions. Unlike viruses, prions do not propagate by usual genetic mechanisms, and they are especially difficult to detect and inactivate. Hereditary and sporadic forms have been linked to a unique infectious particle whose distinctive feature is a unique tertiary protein structure owing to specific amino acid changes in an endogenous protein termed prion protein (PrP[Sc]). Issues surrounding the transmission of infectious CJD particles have been discussed in a previous CheckSample exercise.15 The natural history and transfusion medicine issues associated with vCJD have been addressed by the FDA in guidelines for industry.1

The FDA specifically addresses the scenario described in the present discussion, ie, in the context of blood products obtained from geographic risk deferrals as follows:
If you receive postdonation information about a donor with geographic risk factors, you should immediately retrieve and quarantine for subsequent destruction all in-date blood components (including whole blood, blood components intended for transfusion, and source leukocytes), and all in-date cellular blood components intended for manufacturing into injectable products, that are under your control. We also recommend that you follow your SOPs [standard operating procedures] or update your SOPs regarding notifying consignees to immediately retrieve, quarantine, and subsequently destroy (or arrange for the destruction of) the implicated components. Such notification should occur within 1 week of receiving the postdonation information.1

The urgency evident in this directive is due to the devastating manifestations of vCJD. Whereas CJD may appear late in life with mercifully rapid demise, vCJD is a disease that strikes in youth or middle age, with protean symptoms and nominally greater clinicopathologic sequelae marking a relentlessly progressive downhill course. The presumptive zoonotic origin of the disease implies a more perfidious infectious vehicle with ominous potential. As such, prospective donors are meticulously screened to avoid persons with even remote potential to have encountered the transforming bovine spongiform encephalopathy entity in the United Kingdom and western European nations in the 1980s and 1990s.16-17 The close fiscal and cultural relationship of western Europe has patently decimated an otherwise viable US donor pool because of the admitted “risk of a [remote] risk” for transmission of vCJD.3

Specific questions addressing this risk in the donor history questionnaire include questions 29 and 30 in the FDA-approved donor history questionnaire, revised in 200818:

- From 1980 through 1996, did you spend time that adds up to three (3) months or more in the United Kingdom?
- From 1980 through 1996, were you a member of the US military, a civilian military employee, or a dependent of a member of the US military?
- From 1980 to the present, did you spend time that adds up to five (5) years or more in Europe?
- From 1980 to the present, did you receive a blood transfusion in the United Kingdom or France?

Although these regulations are subject to change, current FDA guidelines require donor deferral if he or she spent 6 months on a military base between 1980 and 1990 in northern Europe and between 1980 and 1996 elsewhere in Europe and/or received
any blood transfusion in the United Kingdom or France between 1980 and the present.

According to 2006 American Red Cross data, the number of blood donations collected in the United States in a year totals 16 million, and the tally of persons donating blood in the United States in a year is 9.5 million. In a year, nearly 5 million patients receive a total of 30 million blood components in the United States.19

If a problem with blood product manufacturing or distribution is discovered, the FDA regulates via good manufacturing practices, and delineates the measures to vet the process and prevent consequences to patients if possible. The good manufacturing practices relevant to blood products are categorized as lookbacks, recalls, or market withdrawals, depending on the situation.12

In contrast to the occasional well-publicized pharmaceutical product withdrawal, lookbacks, recalls, or market withdrawals of blood products are fairly common occurrences.2 Due to the hypervigilance mandated by the FDA, these interventions are executed daily with only rare patient harm. However 2 incidents warrant special mention:

1. There may be the occasional withdrawal involving a large number of products, which requires coordination among laboratory collection facilities, transfusion services, and physician offices.
2. The recall of a specific product with assigned risk was portrayed in the case history.

A major concern in both of these cases is that the risk for patients who may have received an implicated product is unclear or unknown.7-8 These situations are challenging for both hospitals and the blood supply pipeline. The current process of recall and/or withdrawal of blood products poses special challenges.

**Lookbacks**

In 2007 the FDA defined “lookback” as a series of actions taken by a blood establishment based on donor test results indicating infection with HIV-1 or HCV. These actions relate to previous donations from the infected donor possibly donated during the window period when HIV-1 or HCV RNA and antibodies were not detectable by screening tests, yet the infectious agent might have been present in the donor’s blood.12 There are 2 types of lookbacks. In a targeted lookback, recipients of blood from donors subsequently found to be positive for a TTD marker are directly notified. In a general lookback, hospital records identify a cohort of transfusion recipients in an at-risk period,7,13 and the FDA recommends that all patients who received blood before the introduction of effective donor screening undergo testing.12 The FDA has concluded that the targeted lookback approach is the most effective alternative to inform recipients of infected blood products when evaluated in terms of ethics and cost-effectiveness criteria.

**Recalls**

In contrast to the individualized approach of a lookback, a recall removes or corrects consumer products that are in violation of laws administered by the FDA (Title 21, Code of Federal Regulations (CFR), section 7.40 (21 CFR 7.40). 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. According to FDA guidelines, recalls may be classified into 3 categories, from the most serious, Class I, to the least serious, Class III (Table II). The FDA stipulates that recalls are “voluntary” by the manufacturer, although an administrative protocol for conducting recalls is mandatory, 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).

Market Withdrawals
Market withdrawals are notices regarding blood components involving postdonation donor information. One of the problems with keeping track of market withdrawals is that these are not published by the FDA, so their magnitude is unknown. A standard operating procedure was adopted by the Center for Biologics Evaluation and Research to deal with withdrawals and recalls situations that would be a public threat. This procedure identifies the agencies to which information must be given. For an end-user of blood products, the standard operating procedure relates specific details about these agencies, including their accessibility at all hours and procedures for notification regarding emergencies, recalls and significant adverse events.

Summary
The FDA provides a system of lookbacks, recalls, and market withdrawals to address postdonation safety issues.

REFERENCES

12. Food and Drug Administration. Current good manufacturing practice for blood and blood components; notification of


