

GAO

Report to the Ranking Minority Member,
Committee on Commerce, House of
Representatives

February 1997

BLOOD SUPPLY

FDA Oversight and Remaining Issues of Safety





United States
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**Program Evaluation and
Methodology Division**

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The Honorable John D. Dingell
Ranking Minority Member
Committee on Commerce
House of Representatives

Dear Mr. Dingell:

You asked us to evaluate the Food and Drug Administration's "layers of safety" that provide the framework for regulating and monitoring the U.S. blood industry. Specifically, you asked us to examine the actual and potential vulnerabilities in the layers of safety that may present a threat to the public health. In this report, we address these potential vulnerabilities in light of changes in the blood industry that have occurred since the mid-1980s, when there was widespread concern about the safety of the nation's blood supply.

You also asked us to examine the disparate estimates of transfusion-associated AIDS and hepatitis cases and asked that we determine the current risks of these viruses in the blood supply. This information, as well as information on other risks known to occur as a result of blood transfusions, is contained in our 1997 report entitled Blood Supply: Transfusion-Associated Risks (GAO/PEMD-97-2).

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 15 days after the date of this letter. We will then send copies of this report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, and others who are interested. If you have any questions or would like additional information, please call me at (202-512-3652). Major contributors to this report are listed in appendix V.

Sincerely,

Kwai-Cheung Chan
Director of Program Evaluation in Physical
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Executive Summary

Purpose

Approximately 4 million patients annually receive life-saving transfusions of blood donated by 14 million donors around the nation. AIDS and the possibility of contracting HIV through blood transfusions have nonetheless focused public attention on the safety of this blood. Representative John D. Dingell, the ranking minority member of the House Committee on Commerce, asked the General Accounting Office (GAO) to identify issues that might threaten the nation's blood supply. Therefore, this report answers the question, What are the elements of the Food and Drug Administration's (FDA's) layers of blood safety and do they ensure that the blood supply is safe?

Background

In testimony on July 28, 1993, before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, the Commissioner of FDA outlined five overlapping "layers of safety" that provided a framework to regulate and monitor the blood industry: (1) donor screening, (2) donor deferral registries, (3) viral testing, (4) quarantining blood until tests and control procedures have established its safety, and (5) monitoring and investigating adverse incidents to ensure that deficiencies are corrected.

Since the mid-1980s, the blood industry, with the assistance of FDA, has instituted standard operating procedures, quality assurance programs, and good manufacturing procedures that have improved donor screening, blood collection, viral testing, and how blood is stored and distributed. These actions have improved the overall safety of the blood supply, as discussed in a companion GAO report, *Blood Supply: Transfusion-Associated Risks (GAO/PEMD-97-2)*, that examined the risks of contracting AIDS and hepatitis from blood as well as other known hazards of blood transfusion, comparing these to other health-related risks.

In this report, GAO examined the five layers to identify areas of potential improvement that would further improve blood safety. GAO reviewed FDA's regulations and guidelines issued between 1989 and the present, interviewed FDA officials and blood industry representatives, visited blood facilities, and attended technical conferences and FDA workshops. GAO also assessed 1990-94 FDA error and accident reports to assess lapses in quality control and collected FDA inspection reports from a nationally representative sample of blood facilities. GAO's analysis of these data is the first and only source of this information on a national level. Finally, GAO queried quality-control directors about the focus and scope of FDA's

inspections and possible changes in FDA's policy to enhance compliance and overall safety.

Results in Brief

The transmission of HIV by transfusion decreased dramatically after HIV testing for donors was introduced in 1985, and more and better tests for other diseases also have reduced the risks from blood transfusions. While the blood supply is very safe, no amount of federal regulation can entirely eliminate blood-transfusion risks because of human error, technological limitations of state-of-the-art tests, and the biological nature of the product itself.

Within the overlapping layers of safety, GAO found areas where FDA can take action that would further improve the safety of the blood supply. For example:

- lack of a uniform donor questionnaire allows variability in donor screening,
- lack of mandatory deferral notification allows some donors who have tested positive for viruses to unwittingly attempt donation again,
- untested units donated for self-use may inadvertently be used for unintended recipients, and
- FDA has been slow to investigate error and accident reports that may warrant a recall.

FDA does not require unlicensed facilities—those that do not engage in the sale, barter, or exchange of blood products across state lines—to report errors and accidents. Because unlicensed facilities constitute more than two thirds of all blood facilities that, together, produce 10 percent of the nation's blood, FDA has not fully monitored the quality of this portion of blood products.

FDA's inspections for both licensed and unlicensed blood facilities appear to be inconsistent in focus, scope, and documentation. In addition, these inspections are often not conducted within time periods set by FDA's own guidelines. Furthermore, FDA does not maintain a central repository for inspection reports and, thus, does not examine national trends. GAO's survey results also indicated confusion within the blood industry regarding the interpretation of FDA policy guidance and regulations.

Principal Findings

The blood industry has made many positive changes in collecting and processing blood in response to FDA initiatives. Facilities have standard operating procedures and good manufacturing practices that detail how to ensure high-quality products. Donor education and screening exclude donors with known risk factors or diseases. Deferral registries of donors whose blood is unsuitable are maintained and consulted. Viral testing with powerful screening tests eliminates most infectious products, and products are quarantined from the general supply until they have been found to meet current requirements.

Nevertheless, some facilities do not use uniform donor questionnaires, do not adequately ensure privacy during donor screening, or do not notify donors who have been permanently deferred. Bacterial contamination of platelets is increasingly recognized but FDA does not require blood facilities' quality-assurance programs to include processes that monitor for bacterial contamination.

Seven tests are routinely used to screen blood, and others are available that reduce the risk of transmitting diseases through blood transfusions. However, FDA does not require additional, confirmatory testing on units that test positive for viral markers except for HIV. FDA requires that blood facilities notify consignees (that is, transfusion services) that receive blood from donors who subsequently test positive for HIV, and these consignees are required to attempt to notify recipients of the units. However, there are no requirements for notifying consignees or recipients of blood that subsequently test positive for other viruses, even though confirmatory tests and treatments are available for some of these viruses and patients who might be notified could take steps to prevent transmission of infection to others.

FDA requires that blood that donors give for their own use proceed through elaborate systems to ensure that it is transfused to the correct patient. However, FDA does not require facilities to test such units for viruses, and some do not. Studies have indicated that untested units can make their way into the blood supply system and can be transfused to unintended recipients.

GAO identified no major safety problems in quarantining blood, but the data indicate that there are problems in inventory management in that many units are unaccounted for or lost before they can be transfused. This is not directly a safety issue but could contribute to instances of blood supply shortages.

Unlicensed facilities are not required to report errors and accidents, and in 1994 they submitted only 1 percent of all error and accident reports, although they collected 10 percent of the U.S. blood supply. Without full reporting of errors and accidents, FDA is unable to monitor the quality control of the entire industry. Further, in a nationally representative sample of establishment inspection reports, GAO found that more than half of all observations of problems by FDA inspectors were issued to unlicensed facilities. The discrepancy between the proportions of problems observed and the voluntarily reported errors and accidents by unlicensed facilities underscores the need for better FDA oversight.

FDA publishes its positions on some important industry issues as guidelines and memoranda, but they are often ambiguous in content and intent, and no public comment is required. Additionally, although inspections are the primary means by which FDA ensures the safety of the blood supply, it does not perform statistical analyses of inspection reports to identify trends in deviations or variability in the implementation of inspection policies. GAO also found problems relating to FDA's ability to discriminate between facilities that are in and out of compliance and to inspect them in a timely manner.

Recommendations

GAO recommends that the Secretary of Health and Human Services (HHS) require blood facilities to

- notify all donors who are permanently deferred that they have been deferred and the medical reasons for their deferral.
- require blood facilities' quality-assurance programs to include processes that monitor for bacterial contamination.
- require viral testing for all self-donated blood units in order to minimize the potential vulnerability of untested autologous units entering the blood supply.
- require confirmatory testing of all repeatedly reactive viral test results for which there is a licensed confirmatory test.
- require that transfused patients be notified when they have been transfused with blood from a donor whose subsequent donations were found to be positive by confirmatory testing. The reasonable time period for tracing back units to recipients varies with each virus, and decisions should be made in consultation with the blood industry.
- require the identification of implicated units that have not been transfused or further manufactured.
- require unlicensed facilities to report all errors and accidents.

Additionally, GAO recommends that the Secretary

- publish in the form of regulations the guidelines that FDA believes are essential to ensure the safety of the nation's blood supply. FDA should clarify its position on the extent to which facilities should adopt its guidelines and memoranda in order to remain in compliance with the agency's regulations.
- correct problems GAO identified in FDA inspection processes—FDA should perform statistical analyses of inspection reports, develop policies for FDA inspectors to list on inspection reports the activities they observe, publish better guidance on the types of activities that warrant reports on deviations and warning letters, and ensure that all blood facilities are inspected in a timely fashion.

Agency Comments

In a written response to a draft of this report, HHS generally concurred with GAO's findings and recommendations regarding donor deferral notification, quality assurance for bacterial contamination, viral marker testing of self-donated units, error and accident reporting by unlicensed facilities, and clarification of FDA guidance to blood establishments.

HHS did not fully concur with GAO's recommendation on requiring confirmatory testing and consignee and recipient notification for diseases other than HIV. HHS concurred that confirmatory testing is important and pointed out that it has recommended such testing for hepatitis B and hepatitis C. However, this procedure is only recommended by FDA; it is not a required activity. HHS disagreed that there should be lookback procedures in place to notify recipients of units from donors who subsequently test positive for viruses other than HIV. However, hepatitis, like HIV, can be transmitted to others; recent studies suggest that there are effective therapies for some patients with hepatitis; and informed patients can curtail certain behaviors (such as consuming alcohol) that could cause more progressive harm after being infected with hepatitis.

HHS also disagreed with GAO's recommendation regarding problems identified in FDA's inspection processes by stating that FDA already reviews and analyzes inspection reports and has several manuals and compliance programs to guide its inspectors. However, GAO found that FDA does not perform statistical analyses of inspection reports that would result in information whereby FDA could determine compliance rates among blood facilities. Also, GAO found differences in the number and kind of

observations of problems across FDA districts as well as inconsistencies in the application of official observations and warning letters.

HHS also provided a number of technical comments, which GAO incorporated into the report as appropriate.

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Abbreviations

AABB	American Association of Blood Banks
ABC	America's Blood Centers
ABRA	American Blood Resources Association
ALT	Alanine aminotransferase
ARC	American Red Cross
BSI	Blood Systems Incorporated
CBER	Center for Biologics and Evaluation Review
CCBC	Council of Community Blood Centers
CDC	Centers for Disease Control and Prevention
CJD	Creutzfeldt-Jakob disease
CMV	Cytomegalovirus
CUE	Confidential unit exclusion
DDR	Donor deferral registry
EAR	Error and accident report
EARS	Error and Accident Reporting System
EIR	Establishment inspection report
FDA	Food and Drug Administration
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HBc	Hepatitis B core
HBsAg	Hepatitis B surface antigen
HCFA	Health Care Financing Administration
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HGV	Hepatitis G virus
HHS	Department of Health and Human Services
HIV	Human immunodeficiency virus
HTLV	Human T-lymphotropic virus
IMIG	Intramuscular immune globulin
IPPIA	International Plasma Products Industry Association
IVIG	Intravenous immune globulin
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
PODS	Program-oriented data system
SOP	Standard operating procedure
UBS	United Blood Services

Introduction

Since the human immunodeficiency virus (HIV) was introduced into the U.S. blood supply in the early 1980s, the benefits of a potentially life-saving transfusion have had to be weighed against the risks posed by the most deadly disease known to be transmitted through blood. The risks posed by HIV have spurred many changes in how blood is collected and processed. Also, the blood industry is concerned about bacterial contamination of the blood supply as well as viral and nonviral agents known to be transmissible through blood such as Chagas' disease, cytomegalovirus (CMV), hepatitis A-G, human T-cell leukemia and lymphoma viruses (HTLV-I and HTLV-II), parvovirus, and syphilis.

In testimony on July 28, 1993, before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, the Commissioner of the Food and Drug Administration (FDA), the agency that has main responsibility for regulating the safety of blood products, described "five layers of safety" that were present throughout the blood industry to help ensure safe blood:

1. screening donors,
2. maintaining donor deferral registries to eliminate unsuitable donors from the rolls,
3. testing blood,
4. quarantining blood until tests and control procedures establish its safety, and
5. monitoring and investigating adverse incidents to ensure that deficiencies are corrected.

Subsequently, Congressman John D. Dingell asked us to examine these layers and FDA's implementation of programs and policies to ensure the safety of the nation's blood products. To do this, we answered the following question: What are the elements of FDA's layers of blood safety and do they ensure that the blood supply is safe?¹

¹Congressman Dingell made this request when he was chairman of the Energy and Commerce Committee of the U.S. House of Representatives. He is now ranking minority member of the renamed House Committee on Commerce. Mr. Dingell asked us at the same time to assess the risk estimates of diseases transmitted through transfusion. We have done this in *Blood Supply: Transfusion-Associated Risks*, GAO/PEMD-97-2 (Washington, D.C.: 1997), noting there that the blood supply is safer than it has ever been and that, in terms of threats to life, receiving a blood transfusion is much safer than many other activities.

Donated Blood and Its Products

About 8 million volunteers donate approximately 14 million units of whole blood each year. This whole blood is rarely transfused into patients. Instead, blood services in the blood industry separate each unit of whole blood into an average of 1.8 specialized components that, in blood-banking terminology, are “products” consisting of various types of blood cells, plasma, and special preparations of plasma. Health care facilities transfuse the resulting 23 million components—4 to 5 units at a time, on average—into as many as 4 million patients to treat specific conditions such as anemia and hemophilia. Donors give an additional 12 million units of plasma each year, for a total of approximately 26 million annual blood donations.

Fewer than 5 percent of the Americans who are eligible to donate blood each year actually do. Most people donate at a blood drive where they work. The average blood donor is a college-educated white male 30 to 50 years old, married, with an above-average income. These statistics are changing, however, as more white women and minority men and women are entering the workforce.

To be eligible to donate blood, a person should be at least 17 years old, weigh at least 110 pounds, be in good physical health, and pass a physical and medical history examination.² Men have about 12 pints of blood in their circulatory system, women about 9. At any one time, donors give about 1 pint of blood each. Interestingly, their bodies replace this fluid in about 24-72 hours, although it may take up to 2 weeks to replace the plasma proteins. It normally takes 6-8 weeks to replenish the lost red blood cells from one unit of whole blood. Thus, those who donate whole blood may do so only once every 8 weeks. Some states limit the number and frequency of donations a person can make in a 12-month period. In apheresis, specific components of the blood are removed and the unremoved portions of the blood are returned to the donor. Because this preserves the donor’s red blood cells, apheresis donors usually can donate once every 48 hours but no more than twice a week. (Apheresis is limited to 20 times a year.)

Red blood cells, commonly used to treat anemia, may be preserved as a liquid for up to 42 days but they may also be frozen for up to 10 years. Plasma can be kept frozen for up to 1 year and may be used to control bleeding. Cryoprecipitate contains clotting factors, useful in controlling bleeding. It is made from fresh frozen plasma and may be kept for 1 year.

²There is no FDA minimum age requirement although some facilities voluntarily implement an age requirement. Donors weighing less than 110 pounds may donate provided that a proportionately smaller volume of blood is drawn.

Platelets are important in controlling bleeding and are used to treat patients with leukemia and other cancers; they should be stored at room temperature for a maximum of 5 days. White blood cells are sometimes used to fight infections but should be transfused as soon as possible after collection and must be transfused within 24 hours of donation.

In addition to separating blood into component products, plasma facilities manufacture “derivative products” by fractionating plasma chemically into concentrated proteins. These include albumin, used to treat shock; immune globulin, used to prevent certain infectious diseases and to treat deficiencies of protein; clotting factor concentrates, used to control bleeding in patients with clotting factor deficiencies; and specific immune globulins, prepared from plasmas collected from donors with antibodies to specific diseases and then used to prevent those diseases in others. Derivatives are commonly made by commercial manufacturers. Depending on the product, they may pool plasma from as many as 60,000 donors for fractionation in order to produce sufficient amounts of the final concentrated material cost-effectively. These therapies processed from plasma also undergo viral and bacterial removal and inactivation procedures that are effective in destroying most of these agents.

The Blood Services Industry

The blood services industry has a volunteer and a commercial sector. Voluntary donors are unpaid and usually donate whole blood. Commercial facilities collect plasma from paid donors for manufacturing various derivatives. Table 1.1 outlines the different types of blood collection services and the amount of blood they collect annually.

Table 1.1: U.S. Blood Collection Facilities and the Blood Units They Collect

Type of facility	Volunteer sector		Commercial sector
	Licensed	Unlicensed	Plasma center ^a
Number of facilities	308	2,274	463
Number of units collected (millions)	12.6	1.4	12

^aAll plasma centers are licensed

The three types of facilities in the volunteer sector are (1) regional and community blood centers, which usually collect and distribute blood and blood components to hospitals within circumscribed geographical areas; (2) hospital blood facilities, which collect and transfuse whole blood and

blood components; and (3) hospitals, which primarily store and transfuse blood but do not collect it.

Regional and community blood centers provide a full range of blood services to a surrounding geographical area. They generally collect, test, and label blood, as well as distribute blood and blood products to hospitals, physicians, and hemophilia care centers. Hospital blood facilities usually provide a smaller range of services, limited to collecting and storing whole blood and its components. Some hospitals conduct their own viral testing, while others send blood and blood products to outside laboratories for viral testing.

The volunteer sector is represented by three organizations: the American Association of Blood Banks (AABB), the American Red Cross (ARC), and America's Blood Centers (ABC), formerly known as the Council of Community Blood Centers (CCBC). ABC member centers collect approximately 45 percent of all blood, ARC collects another 45 percent, and independent facilities collect the remaining 10 percent. The members of the AABB include both ARC and the majority of ABC member centers.

AABB is the professional society of blood facilities and transfusion services and it also includes individual members such as physicians, scientists, nurses, and administrators, among others. ABC is a council of community based blood-collection facilities. ARC is a single corporation consisting of all ARC blood centers. Until 1994, ARC served as an organizational framework for its centers, each operating somewhat independently and self-sufficiently. In an organizational change that began in 1994 and was completed in 1995, ARC centralized and standardized its operations, reducing the number of regions and limiting testing to a few centralized laboratories.

The commercial sector, which is generally called the "source plasma sector" and receives plasma from paid donors, has three main components: (1) collectors, or plasmapheresis centers; (2) fractionators; and (3) brokers. (Brokers do not collect source plasma.) The plasmapheresis centers collect plasma that they either sell to U.S. fractionators (who manufacture derivatives such as albumin from it) or export to fractionators in Europe, Japan, and South America. Some fractionators also operate their own source plasma collection centers.

Plasma brokers purchase and market recovered plasma from whole-blood facilities (that is, the volunteer sector) and sell this directly to

fractionators. Plasma is “recovered” after components have been removed from whole blood or after whole blood has become outdated.

The commercial sector is represented by the American Blood Resources Association (ABRA), a nonprofit trade association that represents the interests of businesses that collect certain biological products (in particular, plasma) for further manufacturing. This sector is also represented by the International Plasma Products Industry Association (IPPIA), which represents all the commercial processors of plasma-based therapies in the United States.

The Five Layers of Safety

The five layers of safety are designed to overlap so that they will prevent the distribution of contaminated blood and blood products. The layers’ overlapping safeguards start where the blood is collected and extend to the manufacturers and distributors of blood products.

Donor Screening

The first layer is designed to prevent the donation of blood by persons who have known risk factors or other conditions such as low blood pressure. High-risk donors, those whose blood may pose a health hazard, are encouraged to exclude themselves. Everyone who seeks to donate blood must answer a series of behavioral and medical questions. If the answers indicate high risk, the prospective donor is deferred. These requirements are completed before the donor is allowed to give blood. If the questions are answered truthfully, they isolate about 90 percent of all persons whose risk of having HIV is too recent for their bodies to have produced sufficient antibodies or antigen to be detected by viral screening tests.

Donor Deferral Registries

The safeguard of this layer is the constant updating of lists, known as “donor deferral registries,” of unsuitable donors and the checking of names of donors with the names in the donor deferral registry to prevent blood being used from donors previously determined to be unsuitable. Individuals who were entered into a deferral registry are those who were found not to meet donor suitability requirements during screening or who have had a positive test for any of the diseases checked at a previous donation. Services that collect blood must check the donor deferral registry for each donor, and if they find a donor listed, they do not distribute that person’s blood. The deferral registry includes the names of donors who have donated in the past 8 weeks and are, thus, ineligible to

donate until this 8-week period has expired. The deferral registry may be checked either before or after blood is donated.

Testing Blood

After a donor's blood has been drawn in a donation, it is tested for an ABO group and Rh type. Additionally, viral testing, the third safety layer, and perhaps the most widely recognized layer, may be the most critical link in protecting the public from the risk of receiving contaminated blood transfusions. Screening tests are performed for hepatitis B surface antigen (HBsAg), hepatitis B core (HBc), hepatitis C (HCV), human immunodeficiency virus (antibody for HIV-1 and HIV-2 and antigen for HIV-1), human T-lymphotropic virus type I (HTLV-I), and syphilis.³

Blood facilities also notify the consignee (the facility that receives the product) if the product is from a donor who may have been in the "window period" at the time of his or her last donation—that is, repeat donors who subsequently test positive for HIV.⁴ Even though the previous donations may have met all test requirements at the time of donation, recipients of blood from such donors may need to be tested to determine whether a disease has been transmitted to them. Additionally, consignees may be notified if they have received blood from donors who subsequent to their donation disclose historical information that would have compromised their eligibility as donors.

Two tests—one for alanine aminotransferase (ALT) and one for hepatitis B core (HBc)—were introduced as "markers" for the major viruses noted above. That is, donors with elevated ALT counts or those found to be positive for HBc have, at times, been found positive for viruses such as HCV and HIV. These two tests were introduced when more specific tests for hepatitis C and HIV had not yet been developed. A positive result on the syphilis test is considered by some to be a surrogate marker for high-risk behavior, since it may be a sign of behavior that increases the risk of infection from HIV. However, more specific tests for hepatitis C have since been developed, and a 1995 National Institutes of Health (NIH) consensus development conference recommended discontinuing the use of ALT as a

³HIV antibody tests detect antibodies that the human body produces as an immune response to HIV, whereas HIV antigen tests detect the actual presence of HIV. HTLV is a retrovirus that can lead to neurologic disease or adult T-cell leukemia and lymphoma. The test for human lymphotropic virus type II (HTLV-II) uses the HTLV-I test; although the HTLV-I test is not specific for HTLV-II, it is the closest test now available for this virus.

⁴The window period is the time from infectivity to the point at which currently licensed test kits can ascertain antibodies or antigens to certain viruses tested for by blood facilities.

surrogate.⁵ AABB also recommended that the ALT test be dropped for donated blood, and FDA has stated that it will not object if it is dropped.

Among the many other infections, viral and nonviral agents that have garnered public attention because of their prevalence in the U.S. blood supply include B-19 parvovirus, Chagas' disease, cytomegalovirus, and hepatitis D-G. For various reasons, however, tests are not routinely conducted for them. Additionally, different components of blood do not harbor all these infectious agents, and much remains to be learned about the location of different viruses in blood components.⁶ Table 1.2 lists the viral and nonviral infectious agents that we discuss in this report.

Table 1:2: Viral and Nonviral Infectious Agents Discussed in This Report

Agent	Disease
Parasite: <i>T. cruzi</i>	Chagas'
Prion, protein (may be a virus)	Creutzfeldt-Jakob
Spirochete: <i>T. pallidum</i>	Syphilis
Virus	Cytomegalovirus
	Hepatitis A-G
	Human immunodeficiency
	Human T-lymphotropic disease

Blood Quarantining

The fourth safety layer that FDA enforces is the quarantine of all donated blood until tests and other controls have established its safety. This means that blood units cannot be used, except in emergencies, until all the requirements of the three preceding layers have been satisfied. At the fourth layer, blood facilities maintain separate storage for untested units of blood and for units that are suitable and units that are unsuitable for use. "Autologous" units are also stored separately from "allogeneic" units. That is, donations a person makes in order to receive his or her own blood—autologous units—are stored separately from donations made allogeneically, by individuals for other people. Autologous donation is often made when a person plans for elective surgery.

⁵This consensus development conference, "Infectious Disease Testing for Blood Transfusions," was held on January 9-11, 1995. The conference also examined the utility of HBc testing and determined that this test should still be used to assist in reducing the risk of HBV and as a surrogate marker for HIV. It was also recommended that syphilis testing continue because it may contribute to the prevention of transfusion-transmitted syphilis.

⁶For example, HIV-1 appears in plasma and platelets, but it is not known whether HIV-1 resides in red cells. Leukocytes do contain HIV and HTLV-I, but HTLV-I is not found in plasma and red cells, and whether or not it is located in platelets is not known.

Monitoring and Investigating Problems

Blood facilities are obligated to monitor and investigate errors and accidents in their procedures, to audit their systems, and to correct deficiencies. Licensed blood facilities—those that may engage in the sale, barter, or exchange of blood products across state lines—must file “error and accident reports” (EARS) with FDA in order to notify it of problems. Unlicensed blood facilities—those that do not ship blood products across state lines—are not required to report EARS to FDA but may do so voluntarily. However, unlicensed blood facilities must follow the same safety procedures as licensed facilities.

All members of the blood industry are also obligated to determine the causes of errors and accidents and to institute changes to make sure such problems do not recur. Finally, this layer includes FDA inspections of blood facilities to monitor compliance with federal requirements.

Federal Oversight and Responsibility

The four federal agencies outlined in table 1.3 have some of the major oversight authority related to blood safety in the United States: FDA, the Centers for Disease Control and Prevention (CDC), the Health Care Financing Administration (HCFA), and NIH’s National Heart, Lung, and Blood Institute (NHLBI). Additionally, the table shows that the Department of Health and Human Services (HHS) has recently organized a national blood safety committee whose director and advisory council help ensure that the government’s response to future bloodborne infectious agents is coordinated.⁷ Although the advisory council was announced in October 1995 and formally approved by HHS in October 1996, HHS has only recently asked for nominations to the council, and council meetings have yet to take place.⁸

⁷This entity was organized as a result of recommendations in an Institute of Medicine report, “HIV and the Blood Supply,” Washington, D.C., July 1995, that examined the federal government’s response to the discovery of HIV and the protection of the blood supply in the early 1980s.

⁸The formation of a blood safety director, blood safety committee, and advisory council on blood safety and availability was announced by the HHS Secretary in testimony before the House Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations, on October 12, 1995.

**Chapter 1
Introduction**

Table 1.3: Federal Organizations Responsible for U.S. Blood Safety

Organization	Responsibility
Centers for Disease Control and Prevention	Collects data on the incidence of infectious diseases (including those affecting hemophiliacs) and on state-reported clinical AIDS cases Provides guidance and recommendation for preventing disease ^a
Food and Drug Administration	Inspects facilities, compiles and summarizes EARs, has regulatory authority, promulgates and distributes memoranda and guidelines, and can recommend product recalls
Health Care Financing Administration	Inspects blood facilities that perform viral testing procedures and blood transfusion services that are reimbursed through Medicare and Medicaid ^b
National Heart, Lung, and Blood Institute	Conducts clinical studies on the effects of blood transfusions in patients with cytomegalovirus and HIV Awards research grants for assessing the risks of transfusion-transmitted diseases, developing virus-screening tests, and assessing new infection agents ^c Funds genetic testing technologies to close the period between donors' giving blood and the subsequent discovery of their infection Sponsors educational conferences and workshops
U.S. Department of Health and Human Services	
Advisory Council on Blood Safety	Examines broad issues of public health and the social implications of blood safety; serves the Blood Safety Committee ^d
Blood Safety Committee	The FDA commissioner and the directors of CDC and NIH report to the Blood Safety Director
Blood Safety Director	Coordinates and oversees Public Health Service blood safety programs

^aAs with FDA's guidance documents, these recommendations are not binding on members of the blood industry.

^bA memorandum of understanding between FDA and HCFA delineates that FDA will inspect manufacturers of blood products, but FDA can also inspect transfusion services that are HCFA's responsibility if there are indications of noncompliance with good manufacturing practices.

^cIncludes the Transfusion Safety Study that tracks the natural history of transfusions associated with HIV and the Retrovirus Epidemiology in Donors Study that has, among other topics, investigated the clinical course of blood donors infected with HTLV-I and HTLV-II.

^dIssues include social choice, informed consent, the allocation of research resources, the availability of blood, and the effect of economic factors on its availability.

The regulations governing oversight of most aspects of blood banking are found in the Code of Federal Regulations (CFR).⁹ FDA also issues memoranda and guidelines as guidance on specific topics to blood facilities. These guidance documents are not binding on the blood facility and, thus, blood facilities may follow the guidance or choose to use appropriate alternative procedures not provided in the guidance.¹⁰

The memoranda topics range widely. Fifty-two that still represent current guidance were issued between August 1982 and August 1994; an additional 22 issued during this period are no longer current. Topics include recommendations for the management of donors who are found to be positive for hepatitis, equivalent methods for compatibility-testing, deferral of blood donors who have received the drug Accutane, and revised recommendations for preventing the transmission of HIV through blood and blood products.

In regard to FDA's responsibility for inspecting blood facilities, a detailed checklist for inspectors was recently abandoned for a more systems-oriented approach in conducting its inspections. Its new "Guide to Inspection of Blood Banks" outlines major areas that an inspection should examine: (1) errors, accidents, and fatalities; (2) facilities, equipment, and personnel; (3) quality assurance; (4) the disposal of infectious waste; (5) whole blood and donor suitability; (6) laboratory operations; (7) uniform blood labeling; (8) compatibility-testing and transfusion reactions; (9) storage and distribution; (10) platelets and pheresis; (11) computerization; (12) red blood cells, plasma, platelets, and cryoprecipitate; (13) records; and (14) operations.

Scope and Methodology

We limited the scope of this report to policies and procedures that became current in 1994. We did not examine problems of the mid-1980s, when HIV was first recognized as a bloodborne disease, or the sequence of changes intended to address HIV. We examined FDA's oversight of licensed and unlicensed blood facilities in the United States, including plasma centers.

The focus of the work is the general policies and procedures in place to help ensure the safety of the blood supply. We did not examine patterns of violations of these policies and procedures by individual blood facilities.

⁹21 C.F.R. parts 210, 211, 606, 607, 610, and 640.

¹⁰FDA's recent "Guideline for Quality Assurance in Blood Establishments" is one example. It is intended to assist blood facilities in developing quality-assurance programs that "are consistent with recognized principles of QA [quality assurance] and current good manufacturing practices . . ."

While many of the recurrent problems in the industry relate to failures to comply with safety requirements, our review considers whether there are proper safeguards in place to identify such occurrences, not which specific blood facilities may have problems in this regard.

We reviewed pertinent documents, interviewed relevant officials, and surveyed and visited blood facilities. The documents we reviewed included FDA statutes, regulations, compliance manuals and compliance program, and memoranda. We supplemented our interviews of various government officials by interviewing other officials of the blood industry as well as interest groups such as AABB, ABC, ARC, and IPPIA. We accompanied FDA officials during an inspection and visited various types of blood facilities. Among the FDA data sources that we analyzed were error and accident reports (EARS) and establishment inspection reports (EIRS), including Form 483 reports of inspection observations. We conducted our review from October 1994 to May 1996 in accordance with generally accepted government auditing standards.

FDA Statutes, Regulations, and Memoranda

We examined FDA's statutes, regulations, and more than 70 memoranda to determine what is required of and recommended to blood facilities to help ensure a safe blood supply. When we reviewed the memoranda, we categorized them by topic, which ranged in scope and specificity from a guideline for deferring donors who have received Accutane to a guideline for the validation of computer systems. We also used these documents to ascertain potential vulnerabilities in the layers of safety.

Interviews

When we interviewed FDA personnel, we asked them about their operations, inspection procedures, and databases. The personnel in the blood facilities additionally gave us important details about FDA's oversight and interactions. The information we gathered from AABB, ABC, ARC, and IPPIA told us about overall blood industry practices and potential safety issues.

Site Visits

We visited seven sites to cover the range of facilities: licensed and unlicensed, ARC and non-ARC, source plasma centers and fractionation companies. At each site, we examined the physical operations of the blood facility and interviewed the staff who were responsible for its daily operations: directors of compliance and quality assurance, medical

directors, vice presidents of research and scientific services, directors of component production and of operations, and executive officers.

Error and Accident Reports

FDA requires licensed blood facilities to report errors and accidents that resulted in an unsuitable unit of blood being made available for distribution. In March 1991, FDA asked unlicensed blood facilities to submit EARS voluntarily. We obtained FDA's annual summary reports of the EARS submitted by licensed and unlicensed facilities for 1990 through 1994, which constitutes data on the universe of EARS in that period.¹¹

FDA's summary EAR data are reported by facility type (licensed, unlicensed, ARC, non-ARC, plasma center, transfusion service) and include the total number of reports received, the type of error or accident (whether in viral testing, labeling, quarantining, or other procedures), the number of events attributable to computer or data entry errors in 1994, and the number of EARS resulting in potential recall of a blood unit. In addition to analyzing these data, we identified changes in rules and regulations that might have affected reporting criteria, analyzed the differences between types of blood facilities, and highlighted the EAR information that shed light on specific blood-banking processes.

In appendix II, we outline these data as FDA compiled them for fiscal year 1994 (in appendix I, we discuss issues relating to viral and nonviral agents). However, we based our report's analysis on the reporting rate per type of blood facility and on the rate of reporting per 100,000 units each type of blood facility collected. We did this because FDA's analysis does not take into account the interdependence of reporting for the different processes by the different facilities used.

Establishment Inspection Reports and Form 483

FDA's annual inspections of blood facilities result in establishment inspection reports that descriptively narrate the activities covered in the inspection and any problems found during the inspection.¹² An inspector who identifies significant infractions that could affect blood safety files a Form 483. We analyzed the most recent EIRS and Form 483s from a nationally representative sample of licensed and unlicensed blood

¹¹In fiscal year 1991, FDA received 3,836 EARS; in 1992, the number was 10,456; the numbers for fiscal years 1993 and 1994 were 8,991 and 11,298.

¹²Beginning in 1995, blood facilities that have complied with FDA requirements for 2 years become eligible for biennial rather than annual inspections. FDA inspectors need to list the activities they observe only if it is a limited inspection. In all other cases, inspectors need only list the compliance program under which the inspection is taking place.

facilities, including plasma centers. We randomly sampled eight FDA inspection districts and, from these districts, a total of 373 EIRS (representing reports from the total of 2,980 U.S. blood facilities).¹³

For the 373 blood facilities in our study, we were able to analyze information on 325: 48 licensed centers, 114 unlicensed centers, 91 transfusion services, and 72 plasma centers.¹⁴ The remaining 48 blood facilities either were plasma brokers, viral testing or reagent manufacturers, testing laboratories, or depot sites or had been inspected for specific purposes that were not part of the annual inspection process.

We analyzed the EIRS in a manner similar to FDA's analysis of EARS. That is, we applied FDA's coding scheme of blood-banking processes to our analysis.¹⁵ By using the same coding scheme, we were able to outline information on EARS and EIRS that highlighted potential safety concerns for specific blood-banking processes.

Survey of Blood Centers

We surveyed all the full-service blood facilities in our sample of inspection reports.¹⁶ This survey gave us additional information on most of the processes we studied in our analysis of EARS and EIRS. One hundred percent of the 45 blood facilities we surveyed responded to our

¹³The districts were Boston, Chicago, Cincinnati, Dallas, Los Angeles, New Orleans, Philadelphia, and Seattle.

¹⁴Licensed facilities may engage in the sale, barter, or exchange of blood products across state lines. They often collect autologous and allogeneic blood. Unlicensed facilities do not ship blood products across state lines but can collect both types of blood. Transfusion services routinely collect only autologous blood. Plasma centers collect source plasma for processing into plasma-based therapies. All of these types of facilities should be registered with FDA.

¹⁵In our analysis of EIRS, we used the same categories of blood-banking processes that are defined in FDA's EARS: (1) donor screening, (2) donor deferral, (3) collection and processing, (4) routine testing, (5) viral testing, (6) post-donation information, (7) product quarantine, (8) labeling, and (9) storage and distribution. FDA used a tenth category, "miscellaneous," that captured errors and accidents related to transfusion-transmitted viruses, recipient reactions, lookback, and emergency release of products. We incorporated these issues into the 9 other categories by their specific topic. We added an eleventh category for our analysis of EIRS, which we called "machines," in order to identify problems related to computer hardware and software issues and quality control of machines (recordkeeping) used in blood-banking. We have not outlined these issues in our report because they were often related to specific topics that we subsumed under FDA's 9 categories noted above.

¹⁶By "full-service facility," we mean one that carries out the full range of activities covered by the five layers of safety: collecting (screening and deferral), testing, processing (quarantine and control), and distributing blood products. Therefore, we excluded, for example, donor-collection centers that send their blood elsewhere for testing.

questionnaire.¹⁷ Appendix III contains the questionnaire used in our survey.

The Strengths and Limitations of Our Study

By examining EIR and Form 483 information with FDA's EAR coding scheme, we were able to present analyses from both data sources for individual blood-banking processes. Furthermore, our sample of blood facilities represents blood facilities in the United States, and our findings can therefore be generalized to the blood-banking industry at large.

However, our analysis of EIRS was predicated on the accuracy of the information contained in them.¹⁸ We did not collect primary data from the blood facilities. Furthermore, our information on EARS was based on FDA's annual summaries and did not involve original data analysis.

The organization of this report reflects the five layers of safety. In chapter 2, we cover issues related to the first two layers, donor screening and deferral, as well as collection processes. In chapter 3, we focus on the third layer, testing; in chapter 4, on the fourth layer, the quarantine of blood and other processes. We discuss the fifth layer, monitoring and investigations, in chapter 5. Finally, in chapter 6, we present a summary of our findings, our conclusions, and our recommendations.

¹⁷Our original sample contained 47 full-service blood facilities, but 2 had closed before we began our survey.

¹⁸Thus, much of our analysis is directed at Form 483 observations because information contained in the EIRs was not a reliable indicator of activities observed by FDA inspectors. See chapter 5 for a discussion on the content of EIRs and the ramifications for our analyses provided in that chapter.

Screening, Deferral, and Collection

Donor screening and deferral are the first two layers of safety. Screening prospective donors by asking them about high-risk behavior and their medical history enables the blood-banking community to exclude unsafe blood. Donor deferral registries, if checked before donation, can help ensure that those who have been deferred do not donate. Collection and processing of blood is another area of blood banking that takes place prior to the testing of blood. Only screening and deferral eliminate blood hazards such as malarial and Chagas' infection, but the redundancy of the three remaining safety layers—testing, quarantining, and monitoring—mitigates many other consequences that would follow without these layers of safety.

We found, however, that (1) questionnaires for screening out high-risk donors are not uniform throughout the blood industry, and accurate responses may be difficult to obtain where respondents are not assured of privacy. Moreover, (2) donating blood before the donor deferral registry (DDR) is checked can cause problems, DDRs can yield false checks where they have not been computerized, and lack of donor deferral notifications may lead to unsuitable donors' continuing to donate blood. Finally, (3) the blood industry's collection processes appear to cause few safety problems but bacterial contamination is a leading cause of blood-transfusion fatalities.

Donor Screening

The blood industry practices several methods for selecting donors of safe blood. One is to exclude particular donor groups; for example, blood is not collected at prisons or mental hospitals where the risk of hepatitis and other diseases is high.¹ Another is to eliminate cash incentives for making whole-blood donations: data show that paid donors have a higher likelihood of being infected with HIV and other diseases than volunteer donors.² Plasma centers still pay donors because a cash incentive is deemed necessary if they are to sit through the 2-hour procedure (whole-blood donations often take less than 1 hour).

¹Patients from mental hospitals can donate at a blood facility, and FDA has recently promulgated guidance on deferring inmates of correctional institutions. New prisoners and those who have been incarcerated for more than 72 consecutive hours during the previous 12 months are deferred for 12 months.

²For example, the California Department of Health Services found that plasma centers, where donors were paid, had a confirmed HIV rate of 0.016 percent (16 per 100,000 units tested) while the rate at blood facilities, where donors were not paid, was 0.002 percent. These were second-quarter 1994 data from 98 percent of all California facilities required to report HIV test results.

Another way of ensuring safe blood donations is to conduct health history interviews designed to defer donors who might transmit infectious disease. Table 2.1 shows the focus of some of the questions blood facilities ask prospective blood donors in order to ascertain risk.

Table 2.1: Donor Screening Questions and Targeted Diseases

Question focus	Targeted disease
Country of birth	AIDS (HIV-2), malaria, Chagas'
Travel history	Malaria
Medical history of a specific disease	AIDS, babesiosis, Chagas', hepatitis, malaria ^a
Medical symptoms compatible with a specific disease	AIDS, bacteremia, viremia
Exposure through transfusion or occupation	AIDS, hepatitis
Medical treatment	Creutzfeldt-Jakob ^b
Sexual contact or drug use of donor or donor's partner	AIDS, HTLV-I and HTLV-II, hepatitis

^aBabesiosis, like Chagas' disease, is caused by a parasite.

^bSome researchers believe that Creutzfeldt-Jakob disease is caused by a prion, a small protein particle. Others suggest it may be caused by a virus. Persons who have been infected can remain asymptomatic for decades but then progress rapidly to dementia and death. Although no scientific evidence supports the notion that it is transmitted through blood products, it has been transmitted through cornea transplants and brain tissue transplants as well as through the administration of the human pituitary-derived growth hormone.

A brief medical examination of all donors is performed, records are maintained, and the donors sign an informed-consent form that outlines the possible consequences of donation deferral.³ The donors medical record and history is intended to determine the time of the last donation; the physical examination is intended to help ensure that the donor is in good health by assessing the temperature, blood pressure, and hemoglobin levels. Donors are also checked to see if there is evidence of respiratory disease or diseases transmissible by blood transfusion and have neither infectious diseases at the site where blood is drawn nor scars that indicate abusive self-injection of drugs.

³See 21 C.F.R. 606.160(b)1. Blood facilities must keep donor records that contain the medical interview and examination record and the informed-consent form. A donor consent form describes to each donor that his or her acceptability will be determined by a medical interview, examination, and laboratory testing. Donors should be informed of all the laboratory tests that are performed on samples of their blood and of the consequences of an unacceptable, or positive, test. These include the possible detection of infectious agents, temporary or permanent deferral, the listing of their names in deferral registries, reporting to the public health agencies, and governmental inspection of the registries and the donors' test records.

Blood facilities impose additional requirements on persons who donate source plasma: acceptable levels of total protein, syphilis-screening every 4 months, and a more detailed annual physical examination that includes urinalysis and may include toxicology screening. This physical examination also includes observations of heart and lung sounds; lymph nodes, mouth, and skin; and abdominal and neurological conditions.

Another screening method is to give prospective donors a chance to exclude themselves. This method may include confidential unit exclusion (CUE) and telephone callback. CUES require donors to place one of two bar code stickers (“transfuse” or “do not transfuse”) on their donation record before they donate. The CUE is intended to help donors who may feel pressured to donate by peers, for example. (A survey published in 1989 found that almost a third of the 304 seropositive donors responded that their colleagues had pressed them to donate.⁴) In a telephone callback, persons who have donated blood call the blood center to report additional information pertinent to their medical history. Often this pertains to post-donation headaches and acute illness, but it may also relate to risky behavior prior to the donation that would have precluded the donation had it been known at the time.

Some fractionation companies have also instituted programs to increase the safety of the blood supply by instituting stringent screening processes for their donors. For example, one plasma company has developed an inventory-hold program in which the company collects all units of plasma that have been screened as safe and usable for production and holds them for 3 months. If during this time one of the company’s donors is found to be reactive to viral screening or surrogate tests, the company has the ability to identify and destroy all plasma units previously obtained from that donor during this 3-month hold period.

This process is used because the company’s data have shown that approximately 96 percent of its plasma collections are followed by at least one additional donation by the same donor. The inventory-hold program thus attempts to identify unsuitable blood during the window period. The company also destroys all plasma from first-time donors who do not return to make a second donation within 3 months. Ninety-five percent of the blood units that test positive for hepatitis B virus (HBV), HCV, or HIV at this company’s facilities are from first-time donors.

⁴Susan Leitman et al., “Clinical Implications of Positive Tests for Antibodies to Human Immunodeficiency Virus Type-I in Asymptomatic Blood Donors,” New England Journal of Medicine, 321 (1989), 917-24.

EAR and EIR Information

Thirteen percent of all error and accident reports submitted to FDA in fiscal year 1994 were for screening errors (see appendix II). These included the facilities' not performing donor deferral screening, their use of incorrect names during a deferral search, and donors' giving a medical history that warranted but did not result in a deferral.⁵ Tables 2.2 and 2.3 provide data from EARS and our analysis of EIRS that highlight the need for continued vigilance in the area of donor screening.

Table 2.2: Screening EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service^b	Plasma center	Total
EAR rate per facility ^c	3.8	0.01	0.53	0.48
EAR rate per 100,000 units collected ^d	9.3	2.1	2.0	5.6

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

⁵Appendix II shows FDA's summary report of the actual number of screening EARs. It also gives the percentage of EARs different types of blood facilities submitted for each blood-banking process we report in chapters 2-4 and the percentage of submissions as they relate to the total number of EARs.

Table 2.3: Screening Problems and Form 483 Observations by Facility Type^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	14 of 38	37%	12 of 83	15%	9 of 36	25%	22 of 52	42%	57 of 209	27%
Facilities receiving Form 483 observations	11 of 38	29	10 of 83	12	7 of 36	19	15 of 52	29	43 of 209	21

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined donor screening during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be noted on a Form 483.

Licensed facilities reported EARS for screening at a rate more than 380 times that of unlicensed facilities and 7 times that of plasma centers. Per 100,000 units collected, the rates of EARS for screening at licensed facilities were 4 and 5 times higher than unlicensed facilities and plasma centers, respectively. However, reporting problems we discuss in chapter 5 make it impossible to draw any conclusions about these rates—that is, neither FDA nor we can say whether the differences stem from licensed facilities’ having more errors and accidents in donor screening or from licensed facilities’ reporting their errors and accidents more readily than unlicensed facilities and plasma centers.⁶

Interestingly, at plasma centers, 15 percent of all EARS were related to donor screening in that screening was not performed but donors were later deferred because of HBsAg or HIV reactivity or a history of hepatitis. Seventy-five percent of screening errors at plasma centers were related to computer malfunctions, suggesting a possible technological reason for these problems.

In our analysis of EIRS, we found that FDA inspectors found many facilities with problems relating to donor screening. In fact, about 40 percent of licensed facilities and plasma centers for which we could determine that

⁶In fiscal year 1994, most of the reports from plasma centers were submitted by one facility (723/856 = 84 percent). The majority of their reports were related to donor screening (206/723 = 28 percent) and donor deferral (514/723 = 71 percent). However, EARS submitted by plasma facilities in fiscal year 1993 resulted in 48 percent of EARS in the areas of donor screening and deferral. Licensed facilities reported EARS in these two areas at a much higher rate than plasma centers.

donor screening was observed by the FDA inspector had problems in this area. Similarly, among facilities for which an EIR indicated an FDA review of this process, 29 percent (11 of 38 licensed facilities; 14 of 52 plasma centers) received Form 483 observations in donor-screening processes. We were unable to draw any firm conclusions or comparisons from these data. Differences in the likelihood of receiving an inspection observation may reflect compliance problems in different facility types or inconsistencies in FDA's inspection criteria for establishing noncompliance among different facility types.⁷ (We discuss this problem further in chapter 5 in relation to FDA's monitoring activities.)

Safety Issues

Two areas of safety that are of concern regarding screening are the lack of a uniform questionnaire and the lack of privacy for donors.

Questionnaire

The types of medical history questions asked and the manner in which they are asked differ from facility to facility and can affect donors' responses and thus, the potential that blood could be drawn from a donor who should have been deferred. Research indicates that asking donors blunt and direct questions about drug abuse and sexual behavior screens out significantly more high-risk donors than less-direct questions; moreover, donors are not offended by explicit questioning.⁸ However, questions must be sensitive to different terminology and the perspectives that respondents may have about high-risk behavior.

For example, the AABB questionnaire asks men about their past sexual activity with other men without asking specific questions about homosexuality. Research has shown that such questioning elicits more accurate responses, since some men might not consider themselves homosexuals although they may have had sex with men.

Other research has found that asking direct oral questions about sexual behavior is associated with a significant increase in HIV deferrals, but the study did not find any evidence of an increase in blood safety as measured by HIV seroprevalence. That is, direct questioning probably resulted in the deferral of at-risk but predominately nonpositive HIV donors.⁹

⁷The same interpretive difficulty holds for all the EIR data we present in chapters 2-4.

⁸Donna J. Mayo, "Screening Potential Blood Donors at Risk for HIV," *Transfusion*, 31 (1991), 466-74.

⁹E. Johnson et al., "The Impact of Direct Oral Questions on Blood Donor Screening for Human Immunodeficiency Virus," *Transfusion*, 34 (1994), 769-74.

California has recently instituted a uniform donor history questionnaire. FDA and AABB have also recommended general guidelines on questions to be asked. However, FDA does not require that a uniform donor questionnaire be followed although ARC uses a uniform questionnaire. It is not known how many blood facilities follow the AABB questionnaire.

Privacy

According to AABB's 1994 accreditation requirements, verbal privacy is mandatory during medical history questioning in order to elicit honest answers. However, when we visited blood facilities, we found that some have not met this requirement. Studies have indicated that from 14 percent to 30 percent of donors feel that screening areas provide inadequate privacy and that 20 percent of donors would have given different answers had they been in a more private situation.¹⁰

Although FDA regulations do not specifically require private interviews, FDA guidance to inspectors states that "interview areas have to offer the donor a degree of privacy so that the donor will be comfortable answering the questions without fear of being overheard."¹¹

Donor Deferral

Blood facilities have several guidelines for deferring donors. Each facility must have a DDR to identify prospective donors who have previously been deferred. Facilities screen prospective donors through physical examinations and medical history questioning, and blood facilities are required to have records available from which unsuitable donors may be identified. FDA prescribes several periods of deferral, defined by the perceived risk of a particular donor's donating unsafe blood. (See table 2.4.)

¹⁰L. S. Doll et al., "Human Immunodeficiency Virus Type 1-infected Blood Donors: Behavioral Characteristics and Reasons for Donation," *Transfusion*, 31 (1991), 704-9, and M. A. Popovsky et al., "Privacy of Donor Screening: Perception vs. Reality," *Transfusion*, 31 supp. (1991), 67S.

¹¹See Food and Drug Administration, *Guide to Inspections of Blood Banks* (Washington, D.C.: September 1994), p. 3. FDA regulations do require that a facility provide space for a private and accurate examination of individuals to determine their suitability as blood donors.

**Chapter 2
Screening, Deferral, and Collection**

Table 2.4: Four FDA-Recommended or FDA-Required Deferral Periods and Some Reasons for Them

Deferral period	Reason
8 weeks	Having made a prior donation of whole blood
1 month	Taking Accutane and Proscar ^a
12 months	Traveling in areas where malaria is endemic ^b
	Coming into close contact with a person who has viral hepatitis
	Paying for sex with drugs or money
	Having sex with
	—anyone who has AIDS or has had a positive test for HIV
	—anyone who has ever taken illegal drugs by injection
	—anyone who has taken clotting-factor concentrates for a bleeding disorder
	—a man who has had sex with another man even once since 1977
	Having received blood or blood products
	Having been tattooed or having had body parts pierced with nonsterile techniques
Permanent	Receiving a positive test for syphilis or treatment for syphilis or gonorrhea
	Coming into contact with blood or body fluids from inoculations through the skin, an open wound, nonintact skin, or mucous membranes
	Being a victim of rape
	Using Tegison ^c
	Having had viral hepatitis after age 11
	Receiving clotting-factor concentrate for a bleeding disorder or human pituitary growth hormone ^d
	Having clinical or laboratory evidence of AIDS or HIV
Being a man who has had sex with another man even once since 1977	
Being an intravenous drug user	
Testing positive for hepatitis B or C, HIV, or HTLV ^e	
Selling sex for money or drugs since 1977	

(Table notes on next page)

Chapter 2 Screening, Deferral, and Collection

^aAccutane, a drug prescribed for the treatment of acne, has been shown to cause developmental malformations in children. When transfused through blood to a pregnant woman, it may increase risks to the developing fetus. Proscar, prescribed for the treatment of enlarged prostate glands, has been shown to cause developmental malformations in male offspring.

^bDeferral is for 3 years if the donor has had malaria and has since been asymptomatic or was an immigrant, refugee, or citizen of an area where malaria is endemic. Donations to be used for preparing plasma, plasma components, or derivatives devoid of intact red blood cells are not recommended for deferral because the malarial parasite is found only in cellular components.

^cTegison is used to treat severe psoriasis but is not to be used during pregnancy because major fetal abnormalities have been reported. Because of this and the possibility that Tegison may remain in the blood for long periods, FDA has recommended permanent deferral of donors who take this drug.

^dPituitary-derived human growth hormone is used in the long-term treatment of children who fail to grow because they secrete normal growth hormones inadequately. Some of its recipients, however, have been reported to have Creutzfeldt-Jakob disease, and animal studies suggest that this disease may be transmitted through blood. FDA has recommended permanent deferral of persons who have received injections of pituitary-derived human growth hormone, although deferral is not necessary for those who have received recombinant human growth hormone, because this product is manufactured with DNA technology.

^eBlood facilities must test prospective donors for hepatitis B (both surface antigen and core), hepatitis C, HIV, and HTLV. Source plasma centers must test for hepatitis B (surface antigen), HCV, and HIV but not hepatitis B (core) or HTLV. FDA has outlined procedures (specific "confirmatory" tests) through which a donor's deferral for hepatitis B and C and HIV (but not HTLV) can be lifted (known as re-entry algorithms). Blood facilities may use these procedures when they can determine that the original positive test results were "false positives," meaning that the donor actually did not have viral infections.

The FDA Guide to Inspections of Blood Banks notes that “records must be maintained to prevent the distribution of subsequent units of blood drawn from unsuitable donors.”¹² Federal regulations also require blood facilities to maintain records of permanent and temporary deferrals and the reasons for them. Source plasma centers must also establish a system to identify donor participation in other plasmapheresis programs in the surrounding area, in order to ensure that individual plasma collections do not exceed recommended volumes.

Some blood facilities, such as ARC, combine their local registries into wider ones.¹³ Data from 1993 show that ARC’s DDR comprised some 300,000 entries. If all ARC DDRs were collated into one file, national and local, its registry would contain approximately 1.6 million entries. Adding non-ARC facilities to this list would raise this number to approximately 3 million entries, representing about 1 percent of the U.S. population.¹⁴ These numbers are one reason why some have suggested that a national DDR would be cumbersome to develop, validate, and maintain.

EAR and EIR Information

Errors and accidents related to such issues as donors being incorrectly identified, deleted, or missing from deferral lists accounted for 8 percent of all EARS in fiscal year 1994 (see appendix II). Tables 2.5 and 2.6 outline EARS reported by different types of blood facilities and data from our analysis of EIRS.

¹²Food and Drug Administration, Guide to Inspections of Blood Banks, p. 2.

¹³ARC collects approximately 45 percent of all blood collected in the United States. California has a statewide DDR. United Blood Services’ (UBS) facilities, which annually collect some 700,000 units of blood, or about 6 percent of the national total, have their own registry that serves communities in 19 states. Source plasma centers have a national DDR that is checked for first-time but not repeat donors.

¹⁴William Sherwood, “Donor Deferral Registries,” in Morris Blajchman (ed.), Transfusion Medicine Reviews, 7:2 (April 1993), 121-28.

**Chapter 2
Screening, Deferral, and Collection**

Table 2.5: Deferral EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	1.26	0.001	1.1	0.30
EAR rate per 100,000 units collected or transfused ^d	3.1	0.2	4.3	3.5

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 2.6: Deferral Problems and Form 483 Observations by Facility Type, 1994^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	15 of 41	37%	8 of 49	16%	0 of 27	0%	23 of 49	47%	46 of 166	28%
Facilities receiving Form 483 observations	10 of 41	24	6 of 49	12	0 of 27	0	20 of 49	41	36 of 166	22

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined donor deferral during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were those problems deemed serious enough to be denoted on a Form 483.

Licensed facilities reported deferral EARs at a rate that was about equal to that of plasma centers but more than 1,000 times that of unlicensed facilities. Their rates per 100,000 units collected were about equal but 15 and 20 times higher, respectively, than the rate for unlicensed facilities. Interestingly, 21 percent of all EARs reported by plasma centers related to missing or incorrectly identified donors on the deferral list who were later

deferred because of HBsAg or HIV reactivity or a history of hepatitis. Combined with the screening data, 36 percent of plasma center EARS were associated with inadequate screening or deferral of donors who were later deferred for HBsAg or HIV reactivity.¹⁵

Our analyses of screening and deferral EIRS and Form 483s proved similar in that the facilities most likely to have had problems found during an FDA inspection and to have received Form 483 observations were licensed facilities and plasma centers. Furthermore, our analysis of EIRS mirrors FDA's information on EAR submissions in that plasma centers seem especially vulnerable to problems in this area.

Safety Issues

Three areas of safety that are of concern regarding donor deferral are the timing of donor deferral registry checks, lack of computerization for these registries, and varied practices for donor deferral notification.

DDR Checks

Blood facilities are not required to query their donor deferral registries before accepting blood from a donor. This is a special problem at mobile sites, from which blood is typically shipped to the main facility where DDR checking occurs after it has been collected. The representatives of blood facilities whom we interviewed cited two reasons for this practice: (1) mobile sites customarily have no computer hookup to the central registry and (2) many computerized registries do not allow blood from a donor who is in the deferral system to be shipped to hospitals, giving the collection facilities confidence that unsuitable blood will not leave the central blood facility.

Such confidence may be misplaced, however, if donors are not "flagged" correctly and unsafe blood passes undetected from the blood facility. Indeed, some blood facilities use portable computers so that their mobile sites can access a main, computerized DDR registry before blood is collected. However, some facilities do not have computerized DDRs or cannot afford the portable systems. Nevertheless, such practices may needlessly subject deferred donors to a blood collection procedure and incur needless costs to the blood facility if viral testing is performed on such units.

¹⁵In fiscal year 1994, most of the reports from plasma centers were submitted by one facility (723/856 = 84 percent). The majority of their reports were related to donor screening (206/723 = 28 percent) and donor deferral (514/723 = 71 percent). However, EARS submitted by plasma facilities in fiscal year 1993 resulted in 48 percent of EARS in the areas of donor screening and deferral. Licensed facilities reported EARS in these two areas at a much higher rate than plasma centers.

Manual DDRs

Regarding the lack of computerization, we found that DDRs are sometimes compilations of alphabetized index cards similar to those of a traditional library card catalog. The potential for error is enhanced in this type of system. In fact, during one of our visits, a blood facility representative found it very difficult to locate a known donor deferral card because the cards had been used but not placed back in alphabetical order. Such problems open up the possibility that a deferred donor's blood would be collected.

Donor Deferral Notification

When donors have been notified that they have been deferred, they are usually told the reasons for the deferral and whether a confirmatory test based on positive viral marker results was performed. However, the information that blood facilities offer differs from one facility to another. Moreover, FDA has recommendations in its memoranda only on notifying donors who test positive for HIV. FDA memoranda on hepatitis B and C do not include language recommending such notification. While many facilities notify deferred donors for ethical and public health reasons, some do not. Those that do not raise the risk that donors of unsuitable blood will unknowingly continue to donate blood or transmit a disease within the community.

Collection and Processing

The normal unit of blood that is drawn is 415 to 495 milliliters in volume (about 1 pint). Units containing a lower volume of red blood cells can be transfused if they are properly prepared with anticoagulant, but other blood components cannot be made from them. Federal regulations require blood facilities to collect this blood in sterile containers and to include it in laboratory testing. Additionally, they are required to prepare a donor's skin where the blood is to be drawn in a way that maximally ensures the container's sterility, and they must identify each unit of blood by its donor.

Every unit of blood and plasma is also to be refrigerated unless the product is to be used as a source of platelets. For source plasma, regulations require that the plasma is to be removed and the cells returned to the donor by sterile and aseptic means.

EAR and EIR Information

The EARS suggest that reported errors and accidents in collection and processing are rare. This would include such issues as bacterial contamination, blood being drawn into outdated bags, and incorrect preparation of components. For fiscal year 1994, blood collection and processing accounted for only 3 percent (362 of 11,292) of EARS submitted

by licensed and unlicensed blood facilities, transfusion services, and plasma centers. (See appendix II.) Tables 2.7 and 2.8 outline EARS reported by different types of blood facilities and data from our analysis of EIRS.

Table 2.7: Collection and Processing EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	1.1	0.004	0.02	0.12
EAR rate per 100,000 units collected or transfused ^d	2.7	0.71	0.07	1.39

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARS. However, these establishments submit their EARS based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARS.

^cWe calculate rate per facility by dividing the total number of EARS by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARS by the total number of units collected.

Table 2.8: Collection and Processing Problems and Form 483 Observations by Facility Type, 1994^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	13 of 38	34%	11 of 95	12%	16 of 45	36%	18 of 51	35%	58 of 229	25%
Facilities receiving Form 483 observations	12 of 38	32	9 of 95	10	11 of 45	24	12 of 51	24	44 of 229	19

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRS and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRS.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined collection and processing during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be noted on a Form 483.

As with screening and deferral data, our analysis of EAR data found that licensed facilities reported collection and processing EARS at much higher

rates than unlicensed facilities. Also, even though collection and processing EARS made up only a small percentage of the total EARS reported to FDA, our analysis of EIRS found that 25 percent of the facilities in our sample for which we could determine that collection and processing were observed by the FDA inspector had problems, while 19 percent had Form 483 observations. Thus, even though few EARS are submitted, FDA inspectors regularly find problems serious enough to warrant a Form 483.¹⁶

Safety Issues

Below we summarize bacterial contamination, the safety issue that we identified in the area of collection processes.

Bacterial Contamination

Bacterial contamination is a serious concern, even though disposable plastic containers and closed systems for blood collection have been used for many years, improving the aseptic preparation of blood and blood components. Data the Canadian Red Cross collected for 1987-91 indicate positive bacterial cultures in approximately 0.4 percent (or 1 in 250) of all units of blood.¹⁷

The incidence of bacterial contamination increases when patients receive platelet transfusions, because these are often concentrated from pools of 5 to 10 different donors and stored at room temperature. In the Canadian data, the risk of transfusing bacterially contaminated units into such patients rose to approximately 2 percent (1 in 50). Some have pointed out that if only 5 percent of those bacterially contaminated units could cause a significant reaction, 1 in 1,000 recipients of pooled platelets would be exposed to septic reactions.¹⁸ Recognizing this problem, blood facilities are increasingly using single-donor platelet preparations in place of pooled platelets because they are thought to offer less risk of contamination. However, there are few data to support a conclusion that the single donor preparations offer a significant reduction in the risk of bacterial contamination.

¹⁶There are, of course, many situations that could warrant a Form 483 observation that may not be required to be reported as an error or accident. Nevertheless, our analysis of EIRS suggests that FDA regularly finds problems in collection and processing procedures.

¹⁷According to FDA, Canadian standards for blood collection and processing differ from U.S. standards. Bacterial contamination is seen as a problem by most experts in the field of blood safety.

¹⁸M. Blajchman and A. Ali, "Bacteria in the Blood Supply: An Overlooked Issue in Transfusion Medicine," in S. J. Nance (ed.), *Blood Safety: Current Challenges* (Bethesda, Md.: American Association of Blood Banks, 1992).

During the past decade, the number of bacterial sepsis episodes (one in which toxins from bacteria are spread) associated with the use of blood components has risen dramatically. The increase mirrors the increase in the use of platelet concentrate transfusions, but reactions to bacterially contaminated red cells have also been reported. Most of the increase in septic episodes stems from the room temperature required for storing platelet concentrates. Twenty to 24 degrees Celsius is ideal for platelet viability and function, but it facilitates bacterial proliferation, as does prolonged storage.¹⁹

With regard to red cells, septic episodes are most likely associated with bacteria that can proliferate at the recommended refrigeration temperature of 4 degrees Celsius. In fact, one risk estimate of infectious complications from blood transfusions points to bacteria as the leading cause of death, compared to viruses, parasites, hemolytic reactions, lung disease, and anaphylaxis.²⁰

Yet another safety concern is that it has been postulated that a small core of skin can enter the needle—and, thus, the blood—at the time of donation. Available data appear to indicate that the vast majority of bacteria isolated from platelet concentrates come from this source.²¹

Data also suggest an increasing number of fatalities associated with bacterial contamination (which is often a result of improper collection and processing of blood products). In 1975, FDA established a registry to compile information on transfusion-associated deaths. From 1976 to 1978, 4 percent of such deaths were attributed to bacterial contamination, a figure that rose to 10 percent in 1986-88.

Corrective Measures

Measures that might eliminate transfusion-associated bacterial sepsis include improving or instituting quality-control programs, extending donor screening, modifying blood collecting and processing techniques, shortening blood-component storage times, testing, and removing or eliminating the bacteria.

¹⁹M. Goldman and M. A. Blajchman, "Blood Product-Associated Bacterial Sepsis," Transfusion Medicine Review, 5 (1991), 73-83.

²⁰R. Dodd, "Adverse Consequences of Blood Transfusion: Quantitative Risk Estimates," in S. T. Nance, Blood Supply: Risks, Perceptions, and Prospects for the Future (Bethesda, Md: American Association of Blood Banks, 1994).

²¹Blajchman and Ali, pp. 220-21.

In an attempt at quality control, some blood facilities (including all ARC facilities) ask screening questions (such as recent dental and medical procedures) to determine whether a prospective donor's blood may be contaminated with bacteria. However, others have pointed out that even a 3-day deferral for such events would lose many potential, healthy donors.

Most organisms introduced into platelet concentrate units show a growth lag of about 1-2 days, followed by rapid proliferation. This suggests that with longer storage times, the frequency of significant levels of bacteria would increase. However, the results of bacteriologic surveys examining this effect of storage time and bacterial contamination are inconsistent.²²

Bacterial testing would help catch contaminated blood units, but traditional culture techniques often require incubation periods of several days and false-positive and false-negative results are often a problem. With this in mind, researchers are developing more rapid and reliable detection techniques. Additionally, recent studies have indicated that bacteria can be filtered from blood by removing white cells.

²²Goldman and Blajchman, pp. 72-83.

Testing

Testing blood is the third layer of safety. Routine testing helps ensure that the right blood type is transfused. Viral testing and inactivation procedures help ensure that transfused units of blood carry no viruses. As we report in Blood Supply: Transfusion-Associated Risks, the risks of viral and nonviral complications from blood transfusions are quite small in relationship to risks from other life activities.¹

In routine testing, both blood facilities and hospital transfusion services make blood-typing errors that can be fatal. We found several problems in viral testing, too (all discussed in this chapter): improvements in testing to close the window period will be increasingly costly with fewer cases of positive units being caught; lack of a requirement to test autologous units for viral markers could lead to the transfusion of infected blood; lack of confirmatory testing of repeatedly reactive blood units could hamper a blood facility's ability to communicate specific information to implicated donors; lack of lookback procedures for viruses other than HIV could mean that recipients of infected units might not be informed, resulting in their failure to seek treatment.

Further, divergent strains of viruses that blood facilities do not test for are rarely found in the United States, although some cases have recently arisen. However, the viral tests currently in use have different levels of sensitivity and, thus, do not catch all blood units that are positive for viral markers. Viral inactivation procedures that are used in plasma fractionation rarely remove nonenveloped viruses (such as hepatitis A and parvovirus). Plasma manufacturers do not always employ inactivation procedures for every plasma product. And emerging viruses that are not being tested for could affect the U.S. blood supply and public health.

Routine Testing

Federal regulations require blood facilities to test each unit of blood they collect to determine the donor's blood type within the ABO system. Discovered in 1900, this system remains the most widely known. Next to it in importance is the Rh system, which designates a person's blood as being either "Rh positive" or "Rh negative." Among the many other blood typing systems, the ABO and Rh groups are the most familiar and the most important in determining which blood can be transfused to which patients.

Type testing is required also for blood from which plasma is recovered but not for source plasma. Additionally, AABB standards stipulate that a donor's

¹U.S. General Accounting Office, Blood Supply: Transfusion-Associated Risks, GAO/PEMD-97-2 (Washington, D.C.: 1997).

previous ABO and Rh record not be used to identify his or her blood type in subsequent donations. This means that when discrepancies arise, typing is to be determined by additional direct testing.

EAR and EIR Information

Tables 3.1 and 3.2 summarize our EAR and EIR information for such ABO blood typing issues as misinterpreted test results, incorrect test procedures, and products being released prior to testing. The EAR data show that routine testing represents 5.7 percent (646 of 11,292) of all EARs reported to FDA (see appendix II).

Table 3.1: Routine Testing EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service^b	Plasma center	Total
EAR rate per facility ^c	1	0.01	0	0.21
EAR rate per 100,000 units collected or transfused ^d	4.8	2.2	0	2.5

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 3.2: Routine Testing Problems and Form 483 Observations by Facility Type, 1994^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	2 of 22	9%	1 of 19	5.3%	6 of 54	11%	0 of 3	0	9 of 98	9%
Facilities receiving Form 483 observations	2 of 22	9	1 of 19	5	3 of 54	6	0 of 3	0	6 of 98	6

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined routine testing during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be denoted on a Form 483.

Licensed facilities reported routine testing EARS at a rate more than 100 times that of unlicensed facilities. (Plasma centers do not conduct routine testing.) But the EAR rate for licensed facilities per 100,000 blood units collected was only 2 times greater than the rate for unlicensed facilities. In our analysis of EIRS, we found that FDA inspectors found occasional problems in routine testing procedures and made few Form 483 observations in this area.

Safety Issues

We describe below the issue of blood typing, a safety concern in the area of routine testing processes.

Blood Typing

Routine testing does not appear to have any inherent weaknesses provided that blood typing is done properly and that correctly typed units are transfused to the intended patient. The frequency of errors is low; however, the consequences of error can be serious.

A study of errors reported in New York State in 1990-91 found 104 erroneous red cell transfusions out of 1,784,641 (0.006 percent), 54 of which were related to ABO incompatibility.² Most of the 50 other errors were related to the transfusion of an incorrect ABO blood type that was

²This is important because transfusing ABO-incompatible blood is a major noninfectious risk. J. Linden, B. Paul, and K. P. Dressler, "A Report of 104 Transfusion Errors in New York State," *Transfusion*, 32 (1992), 601-6.

fortuitously compatible with the recipient's blood type or to the transfusion of ABO-incompatible fresh-frozen plasma.

Fifty-eight percent, or 61, of the 104 erroneous transfusions were solely the result of errors outside the blood facility. The majority were caused by the person administering the transfusion failing to verify the identity of the recipient of the blood unit. Nearly 25 percent, or 25 incidents, were attributable to the blood facility; 17 percent, or 18 incidents, to both the blood bank and hospital service. The authors of the New York study calculated that the incidence rate of ABO-incompatible errors was 0.003 percent, or 1 in every 33,000 transfusions. They also concluded that 3 patients died from acute transfusion reactions, for a death rate of 1 per 600,000 red cell transfusions.

Although the error of transfusing ABO-incompatible units can lead to serious complications for patients, such error occurs most often at the hospital rather than stemming from the misapplication of regulations or procedures at the blood facilities. However, the New York study outlined blood-facility release, clerical, and technical errors that accounted for one fourth of all errors in the study. No data are available that would allow us to assess the magnitude of this problem on a national scale.

Viral Testing

Viral testing has received the most attention in terms of the safety of the nation's blood supply. Many people perceive this to be the "layer" at which most of the unsafe blood can be caught if it has worked its way through screening, deferral, and collection.³ As recently as 1984, blood facilities had to test blood only for HBV antigen and syphilis. Since then, further tests have been protecting the nation's blood supply from infectious diseases. Blood facilities presently conduct seven such tests for viruses: hepatitis B (core antibody), hepatitis B (surface antigen), hepatitis C antibody, HIV-1 and HIV-2 (antibody), HIV-1 (antigen), HTLV-I and HTLV-II, and syphilis.⁴

FDA has licensed a new HIV-1 test to detect the p24 antigen, a protein that is part of the virus itself, rather than merely the virus's antibodies. Because it

³In appendix I, we characterize some viral and nonviral agents that are transmissible in blood and highlight key federal guidance and industry practice as they relate to these agents.

⁴In response to a January 9-11, 1995, NIH consensus development conference, AABB dropped a test to measure alanine aminotransferase (ALT), a surrogate marker for hepatitis. The conference had concluded that ALT testing was not needed as a surrogate marker for non-A, non-B, hepatitis because of the increased sensitivity of HCV tests. FDA has stated that it does not recommend either for or against ALT testing. The CFRs require tests for hepatitis B surface antigen (HBsAg), HIV, and syphilis but not HTLV or HCV. This conference recommended that syphilis testing continue.

detects infections before the HIV antibody tests, it will close the window period from approximately 22-25 days to about 16-19 days. It is projected to prevent up to 25 percent of the window-period cases, or about 5 to 10 cases, of transfusion-transmitted HIV infection per year. FDA recommended that blood facilities begin using this test by June 14, 1996.

FDA's protocols for viral testing stipulate that if the initial test for viruses is reactive, then two duplicate tests should be made to determine whether the blood unit has antibodies to a particular virus. If either duplicate test is also reactive, the blood facilities may perform a more specific, confirmatory test to determine whether the reactivity is false or true.⁵

Deciding whether a donation is or is not positive is affected also by the sensitivity and specificity of the viral tests.⁶ Initial tests are fast and usually automated and screen large numbers of samples. They are extremely sensitive in order to minimize the number of false-negative outcomes. Confirmatory tests are more time-consuming, usually less sensitive than initial tests, but very specific. Table 3.3 outlines the different types of viral test results and the consequent actions.

⁵False-negative blood units are truly positive for a virus that is undetected by the initial test. False-positive units test positive for a virus that proves in a confirmatory test not to be present. Confirmatory tests can also be "indeterminate," meaning that it is not possible to tell for sure whether a virus is or is not present. Some studies have suggested that most indeterminate confirmatory tests are probably negative. However, FDA considers indeterminacy to be a positive reading because of the chance that the blood unit does indeed contain a virus.

⁶"Sensitivity" is the probability of a unit's testing positive if a virus is truly present. As sensitivity increases, the number of persons whose blood contains the virus but who are missed (false negatives) by being incorrectly classified decreases. In other words, sensitivity = true positives / (true positives + false negatives). "Specificity" is the probability of a unit's testing negative if a virus is truly absent. A highly specific test is rarely positive when a virus is not present and therefore results in fewer persons without the virus being incorrectly classified (false positives). In other words, specificity = true negatives / (true negatives + false positives).

Table 3.3: Results From and Actions After Viral Testing

Result	Definition	Action
Initially reactive	Initial test is reactive	Two duplicate tests are performed
Repeatedly reactive	One or both duplicate tests are reactive	A confirmatory test is performed (this test is not always required); the prospective donor is deferred and the collected unit is discarded
Indeterminate	Duplicate tests are repeatedly reactive and confirmatory test is neither positive nor negative	The donor is deferred and the collected unit is discarded
Positive	Duplicate tests are repeatedly reactive and confirmatory test is positive	The donor is deferred and the collected unit is discarded
Negative	Initial test is negative or, if reactive, both duplicate tests are negative	None; the donor is not deferred

Thus, any unit that is repeatedly reactive is considered positive even if a confirmatory test determines that the testing procedure produced a false-positive result. Such results require that the donor be deferred. FDA recommends but does not require that donors who are repeatedly reactive but indeterminate or negative by a confirmatory test should be notified and placed on donor deferral registries.

FDA has also outlined procedures by which donors who have repeatedly tested reactive for HBsAg, HCV, and HIV can be brought back as donors. There are no such procedures for HBe and HTLV because licensed confirmatory tests do not exist for them.

FDA requires all blood facilities to maintain quality-assurance programs and to test their laboratory devices and personnel for proficiency in order to keep testing errors to a minimum. FDA also issues quality-assurance guidance that includes quality-control procedures for standard operating procedures, competency evaluations of personnel training and education, and laboratory proficiency tests. Additionally, laboratories that perform viral testing are inspected by HCFA (through a memorandum of understanding with FDA) and state health departments. Table 3.4 shows key features of viral and nonviral testing.

Table 3.4: Key Features of Viral and Nonviral Testing

Disease	Test	Date licensed or recommended by FDA	Formal requirements	Reentry procedure^a
Chagas'	None licensed		None	None
CJD	None licensed		None	None
CMV	None licensed		None	None
HAV	None licensed		None	None
HBV	Core	Sept. 1991	All units must be tested	For HBsAg
	Surface antigen	1972		
	3rd generation (HBsAg)	Dec. 1987		
HCV	1st generation	Nov. 1990	All units must be tested	Yes
	2nd generation	March 1992		
HIV-1 and HIV-2	1 antibody	March 1985	All units must be tested	Yes
	1/2 antibody	June 1992		
	p24 antigen	March 1996		
HTLV-I	Antibody	Nov. 1988	All units must be tested	None
HTLV-II	None licensed		Tested through HTLV-I tests	None
Parvovirus	None licensed		None	None
Syphilis		Approximately 1960	All units must be tested	Yes

^aProcedures can be followed by blood facilities to allow previously deferred donors to donate again if certain protocols are followed. These protocols are outlined in memoranda to blood facilities relating to specific viruses.

In addition to testing procedures, a series of manufacturing steps remove or inactivate viruses that are in plasma pools from source and recovered plasma donations.⁷ Two main techniques decrease viral ability to infect plasma products: partitioning, or removal of a virus, is the physical separation of the virus or viral particles from the therapeutic component. Inactivation of a virus destroys it so that the remaining viral fragments lack the structure and components needed to infect the blood.⁸

Removal processes include filtration, affinity chromatography, ion exchange chromatography, and polyethylene glycol fractionation. Heating

⁷Cytomegalovirus (CMV) is not present in plasma or plasma products. Nonenveloped viruses such as hepatitis A virus (HAV) and parvovirus are not affected by some inactivation procedures. FDA has not recommended the exclusion of repeatedly reactive HbC plasma because exclusion might decrease the safety of plasma derivatives through the likely reduction of an antibody to HBsAg. Plasma donors are tested for HBsAg, HCV, HIV, and syphilis. Testing of plasma donors for HTLV-I and HTLV-II is not required because of their cell association.

⁸These techniques are not used to remove or inactivate viruses in red cells or platelets because the techniques are usually accompanied by red cell damage.

and solvent detergent treatments are examples of processes that inactivate viruses. Additionally, some processes, such as ethanol fractionation, both remove and inactivate viruses.

In order to be effective, viral removal or inactivation techniques must destroy at least one of the essential elements of viral replication.⁹ These techniques work in different ways to accomplish this task. Photosensitizing techniques use light-activated dyes that are irradiated, causing the dyes to convert to molecules that can destroy DNA or membrane lipoproteins. Heat treatment denatures viral proteins and nucleic acids, rendering them incapable of viral replication. Irradiation processes inhibit viral DNA by inducing breaks and linkages. Solvent detergent techniques destroy the viral envelope in lipid-enveloped viruses.

EAR and EIR Information

Only 2 percent (274 of 11,292) of EARS in 1994 related to viral testing, probably a result of the increasing automation of viral testing procedures. Errors in viral testing included misinterpreting the results, releasing products before testing, and testing incorrectly. Table 3.5 shows that licensed facilities reported viral testing EARS nearly 300 times more than unlicensed facilities and 30 times more than plasma centers. Table 3.6 shows that a large percentage of all types of blood facilities for which we found evidence that viral testing had been observed by an FDA inspector were found to have problems relating to viral testing procedures. Also, 24 percent (9 of 37) of licensed facilities and 50 percent (6 of 12) of unlicensed facilities received Form 483 observations associated with viral testing.

⁹Viral replication requires cell attachment by the virus to a cell receptor, penetration of the cell, replication and translation of viral nucleic acids, and exit from the cell with integrated viral particles.

Table 3.5: Viral Testing EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	0.83	0.003	0.03	0.09
EAR rate per 100,000 units collected or transfused ^d	2.0	0.5	0.1	1.1

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 3.6: Viral Testing Problems and Form 483 Observations by Facility Type^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	10 of 35	29%	7 of 12	58%	4 of 11	37%	3 of 12	25%	24 of 70	34%
Facilities receiving Form 483 observations	9 of 35	26	6 of 12	50	2 of 11	18	2 of 12	17	19 of 70	27

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined viral testing during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be noted on a Form 483.

Safety Issues

Most of the safety issues related to viral testing result in a very remote chance of transfusion-transmitted infections. This is because of the low incidence of infectious disease in the U.S. blood supply and other factors such as transmission rates through blood products.

The Window Period

The window period of undetectability differs from test to test, ranging from 16-19 days for the p24 antigen HIV test to approximately 70 days for the HCV test. Other testing procedures can reduce the window period, but the tests are expensive and are not yet automated. For example, a test that incorporates a technology known as “polymerase chain reaction” may reduce the window period for HIV testing from 16-19 days to approximately 11 days. While the cost of implementing it is roughly \$200 million, it would catch an estimated additional 5-10 HIV transmissions through blood products. Efforts continue to develop more effective tests, but important cost-benefit trade-offs are often part of the discussion as to the merits of such tests.

Autologous Donations

There is no requirement that all autologous blood be tested for viral markers, but recent information on errors involving such blood raises some questions. A 1995 AABB survey of its institutional members found that 1.2 percent of the 1,829 respondents reported giving one or more autologous blood units to an unintended transfusion recipient. Of the 22 who did this, 5 did not test autologous collections for viral markers. Additionally, 3.7 percent of the respondents reported that untested, recovered plasma from autologous donors was shipped for further manufacture; 12.3 percent reported that autologous units had been lost in transit. Lastly, the survey found that approximately half of the respondents did not test for viral markers on autologous collections. This information points to a potential vulnerability of viral testing in allowing the possibility for untested units to be transfused to other recipients. FDA is currently developing a recommendation regarding testing autologous units of blood.

Confirmatory Testing

No FDA guidance requires confirmatory testing of all units that test positive for viral markers, although repeatedly reactive donations are discarded and such donors are permanently deferred. A recent final rule published on September 9, 1996, does require blood facilities to perform more specific tests when a donor who previously donated blood is tested on a

later donation and has repeatedly reactive test results for HIV.¹⁰ However, this requirement is only for HIV.¹¹

Confirmatory tests do not in and of themselves improve the safety of the blood supply. However, without such tests, blood facilities cannot know what specific information they should provide to a donor or whether the donor is infected. This could prove problematic if, for example, a blood facility notified a donor of a repeatedly reactive result but stated that it might be a false-positive finding and counseled the donor that he or she might want to obtain a confirmatory test from a physician. If the donor chose not to do this, public health might suffer.

Lookback Procedures

Lookback procedures have been established by FDA to notify consignees (that is, transfusion services) of blood from donors who subsequently test positive for HIV. These transfusion services are responsible for notifying the physicians of recipients who receive blood from donors. If the physician is unavailable or declines to notify the recipient, the transfusion service is to notify the recipient and inform him or her of the need for HIV testing and counseling. However, these requirements pertain only to repeatedly reactive HIV donations.¹² The result is that patients who are transfused with units that are repeatedly reactive for HBV and HCV may never be told that they may be infected, with potentially adverse consequences for their sexual partners as well as the general public.

Although HCV is the virus most often transfused in blood, lookback procedures for HCV are only now being considered. The reasons given for this are that, first, there was until recently no confirmatory test for HCV, so that false-positive units could not be identified. This is no longer the case since FDA has licensed an HCV confirmatory test.

¹⁰The final rule amended the current good manufacturing practices for blood and blood products by requiring blood facilities to notify consignees who had received blood and blood components at increased risk for transmitting HIV infection. A companion HCFA final rule, "Medicare and Medicaid programs: Hospital Standard for Potentially HIV Infectious Blood and Blood Products," requires all transfusion services subject to HCFA's conditions of Medicare participation for hospitals to notify transfusion recipients who have received blood or blood components from a donor whose subsequent donation test results were positive for antibody to HIV. FDA is requiring transfusion services that do not participate in Medicare, and are therefore not subject to HCFA's final rule, to notify transfusion recipients. Transfusion services are also required to notify the physician of patients who receive units that may be positive for HIV; if the physician refuses to notify the patient, the transfusion service is required to make attempts at notification.

¹¹Not all screening tests have a licensed confirmatory test (for example, HTLV), but such tests are currently available for HCV and HBV, in addition to HIV.

¹²This notification process is to include a minimum of three attempts to notify the recipient and to be completed within a maximum 8 weeks of the receipt of the result of a licensed confirmatory test for HIV. Additionally, the transfusion service is required to document the notification or attempts to notify the recipient's physician or the recipient.

A second argument put forth in the past for not having lookback for HCV was that there was no treatment for persons infected with HCV. Thus, a lookback procedure would not assist a patient in treating conditions resulting from transfusions tainted with HCV-positive blood. However, recent studies of treatment with interferon suggest that it may control HCV and lead to complete or nearly complete recovery in some patients.¹³ Also, some recipients might benefit from being notified so that they might curtail behavior that could cause more progressive harm after being infected with such viruses as HBV and HCV (for example, consumption of alcohol). Furthermore, lookback is recommended for HIV even though no treatment for this virus results in complete recovery.

Third, some point out that the way in which HCV is transmitted is not precisely known. Thus, it would be difficult to tell people how to protect themselves. However, Centers for Disease Control and Prevention (CDC) surveillance data from 1992 note that non-A, non-B, hepatitis (most often HCV) is transmitted through blood transfusions, intravenous drug use, and sexual and household contact.¹⁴ Even though the exact means of transmission have not been defined, it is well understood that certain activities increase the likelihood of acquiring HCV.¹⁵ In a related argument, some have noted that most HCV transmissions are not associated with blood transfusions. This is also true for HIV—most transmissions of HIV are not related to blood or blood products—yet FDA now requires lookback for HIV-implicated blood products.

An internal public health service study, “Public Health Service Options for Identification of Hepatitis C Virus Infection Among Transfusion Recipients,” dated March 28, 1996, pointed out that a decision to conduct lookback should be based on several considerations. One of these was “the cost of case-finding, including diagnosis and treatment, should be reasonably comparable with respect to other medical care and preventive

¹³According to G. Davis et al., “Treatment of Chronic Hepatitis C With Recombinant Interferon Alfa,” *New England Journal of Medicine*, 321 (1989), 1501-6, after 6 months of treatment with interferon, 46 percent of patients had complete or nearly complete recovery with 3 million units of interferon versus 28 percent for those receiving 1 million units and 8 percent in untreated patients. However, relapse of high ALT levels 6 months after the completion of treatment occurred in 47 percent of the patients. This study followed these patients for only 6 months after the treatment ended, and the researchers noted that further follow-up might find a late recurrence in the form of elevated ALT levels. More recent data have shown that approximately 50 percent of patients with chronic HCV respond to alpha-interferon, with 10 to 20 percent achieving long-term response.

¹⁴Centers for Disease Control and Prevention, *Hepatitis Surveillance*, report 55 (Atlanta: June 1994).

¹⁵A recent presentation at the 1996 AABB National Meeting outlined a case of sexual transmission of HCV. See C. Capelli et al., “A Case of Transmission of Hepatitis C Virus Between Sexual Partners,” *Transfusion*, 36 supp. (1996), 51S.

services.” This argument, based on cost considerations, has also been used to argue against lookback for HCV. However, a recent study suggests that the cost-effectiveness of lookback for HCV may be comparable to that of many common public health interventions.¹⁶

As with confirmatory testing, lookback procedures do not increase the safety of the blood supply. However, they do allow the provision of more accurate information to donors and recipients. With such information, a donor who has been identified as having given blood that tests positive and a recipient who receives such blood could alter their behavior to ensure that they did not infect others. Additionally, recipients might be more likely to seek treatment if they knew that they had received blood which was likely to have been infectious.

Divergent Viral Strains

A potential problem for HIV testing is the inability to detect divergent viral strains. Recent CDC work found that 6 of 10 licensed HIV antibody screening tests failed to detect one or more samples of a rare, divergent strain of HIV-1, of which almost all the approximately 100 cases had been identified in West and Central Africa.¹⁷

Additionally, in July 1996 the first documented case of one of these divergent strains (HIV group O) was recognized in the United States.¹⁸ Viral testing of this individual throughout 1995 showed both negative and positive tests for HIV and indeterminate results with confirmatory tests (this individual had emigrated to the United States in 1994). CDC investigators also evaluated five licensed HIV tests using blood samples from this individual in April 1996. At that time, four of the five tests were positive while one test was nonreactive.¹⁹ Current data suggest that, overall, FDA-approved HIV tests now in use detect group O HIV infections approximately 80 percent of the time.²⁰

¹⁶J. P. Aubuchon, J. D. Birkmeier, and M. S. Alter, “Cost-Effectiveness of HCV Lookback,” *Transfusion*, 36 supp. (1996), 51S.

¹⁷C. Schable et al., “Sensitivity of United States HIV Antibody Tests for Detection of HIV I Group O Infections,” *Lancet*, 344 (1994), 1333-34.

¹⁸Almost all the cases of HIV in the United States are from the HIV-M group.

¹⁹Centers for Disease Control and Prevention, “Identification of HIV I Group O Infection-Los Angeles County, California, 1996,” *Morbidity and Mortality Weekly Report*, 45 (1996), 561-65.

²⁰A second documented case of HIV-1 group O infections was identified in the U.S. as part of CDC’s surveillance activities for unusual HIV-1 variants. Both of these individuals have never donated blood or plasma.

The CDC investigators noted that the risk to the U.S. blood supply was remote because most persons infected with this HIV-1 strain are excluded before donating blood by current malaria screening guidelines. Additionally, of the more than 590,788 AIDS and HIV cases reported to CDC through December 1995, 106 have been from persons whose country of origin was in West Africa or Central Africa where group O infections have been reported. CDC has pointed out that divergent strains could infect persons living in the United States and that these often remain undetected by current HIV antibody tests. CDC has also noted that this should be a concern to public health officials and blood facilities. In response, FDA has recommended three additional screening questions relating to birth and travel to several West African countries.

Additionally, FDA has mandated that any new HIV tests being submitted for licensure in the U.S. be capable of detecting this HIV strain. FDA has also directed manufacturers of all currently-licensed tests to modify the test kits to ensure that this strain could be identified in U.S. blood donors.

Test Sensitivity

Most units of infected blood are caught by testing before transfusion.²¹ However, some are not. A recent case of an individual who had AIDS but tested negative on the HIV test illustrates that the tests presently used are not perfect in detecting all donations that have positive viral markers.²² This case, although extremely rare, involved an individual who had a rare immune reaction that interfered with the development of HIV antibodies. Information from CDC indicated that this is one of only a handful of isolated reports of HIV-infected persons who do not produce enough antibodies to be detected. Furthermore, DNA analysis of this individual's blood ruled out an atypical HIV viral strain. This individual was a regular plasma donor and, to date, no HIV infections have been identified among recipients of products from this donor.

HBV is a virus that seems to be at times difficult to detect with available testing procedures. A recent study that examined open-heart-surgery patients who had unexplained posttransfusion hepatitis found that 20 percent of them (4 of 20) had no immunological indications for HBV but were, in fact, HBV positive as determined by polymerase chain reaction

²¹See U.S. General Accounting Office, Blood Supply: Transfusion-Associated Risks, GAO/PEMD-97-2 (Washington, D.C.: 1997).

²²Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report, March 8, 1996.

testing.²³ The results showed that HBV may be transmitted despite rigorous testing of donors for HBc and HBsAg.

The present HCV test can identify most persons infected with the virus, but this test may not capture 10 percent of those who are positive for HCV. This inability stems from the sensitivity of the present HCV test and the potential for a chronic carrier state for HCV that goes undetected by antibody testing. The uniformly high rate of chronic hepatitis after HCV infection suggests HCV may be a major cause of chronic liver disease in the United States.

Recent advances in the sensitivity of the HTLV-I tests to detect HTLV-II have increased the efficacy of this test. The currently licensed HTLV-I tests still do not detect about 3 to 4 percent of HTLV-II positive units.²⁴ The most prevalent strain of HTLV in the United States is HTLV-II, and the results from the Gallo study point out that improvements still need to be made to increase test kit sensitivities for HTLV-II. Until recently, there has been little evidence of a known disease condition associated with the presence of HTLV-II antibodies. However, some recent evidence suggests an association with immunologic impairment with HTLV-II.²⁵

Viral Inactivation

Plasma fractionation companies have introduced several new steps to inactivate viruses but they are not very successful against nonenveloped viruses such as hepatitis A.²⁶ For example, in January 1996, U.S. health officials reported the first documented transmission of HAV through blood-clotting substances.

Furthermore, FDA gives little guidance on the inactivation procedures that manufacturers should use to inactivate specific products from viruses. Thus, a manufacturer may or may not be using inactivation procedures to eliminate viruses from plasma pools. In fact, this problem arose in the fall of 1993 when some intravenous immune globulin (IVIG) products—used to treat patients with lymphocytic leukemia or immune disorders, including AIDS—were implicated in the transmission of HCV to transfused patients.

²³J. Rasenack, "Hepatitis B Virus Infection Without Immunological Markers After Open-Heart Surgery," *Lancet*, 345 (1995), 355-56.

²⁴D. Gallo et al., "Comparison of Four Enzyme Immunoassays for Detection of Human T-Cell Lymphotropic Virus Type II Antibodies," *Journal of Clinical Microbiology*, 34:1 (1996), 213-15.

²⁵E. L. Murphy et al., "Medical Conditions Associated with Human T-Lymphotropic Virus Types I and II (HTLV-I and II) Infection," *Transfusion*, 36 supp. (1996), 43S.

²⁶Most inactivation procedures attack the physical envelope of the virus, negating its ability to replicate. By definition, nonenveloped viruses do not have this envelope and are therefore difficult to kill.

These products were from a fractionation company that did not have an inactivation procedure in its manufacturing process for IVIG, although other manufacturers did.

As of January 1995, 5 of 6 manufacturers had incorporated a viral inactivation step in their IVIG processes. However, this is still a problem because another product, intramuscular immune globulin (IMIG), is not put through an inactivation step by most of the manufacturers.²⁷ As one FDA official noted, “while there has been no transmission of HCV by IMIG, this is a very scary situation.” Some of this problem may have been mitigated when FDA announced that it would test all lots of immunoglobulin products for HCV that had not undergone viral inactivation steps. Nevertheless, this example illustrates disparities among the fractionation companies and how similar products may or may not be undergoing viral removal procedures.

Emerging Viruses

Among a number of emerging viruses that could affect the U.S. blood supply are hepatitis E (HEV) and hepatitis G (HGV). Tests to detect these viruses are not currently available.²⁸ Other emerging viruses, such as ebola, that have gained worldwide attention have not been seen in the U.S. blood supply.

HEV, too, does not appear to be endogenously transmitted in the United States. It should be expected only very rarely in travelers returning from overseas where it is endemic, such as in developing countries where it is transmitted through the oral-fecal or drinking water routes. The major cause for concern with this virus is that, although it mimics HAV in its course of infection, fulminant hepatitis is much more common with HEV than HAV. This is particularly a concern for pregnant women, in whom the overall mortality rate may be as high as 20 percent. Severe complications from infection with HEV may be avoidable in the near future, since recent research has found that an HEV vaccine now going through laboratory studies protects infected persons from developing hepatitis.

The discovery of HGV portends another safety issue in viral testing. This virus is associated with chronic hepatitis and is transmissible through blood transfusions. Preliminary donor studies have indicated that between 1 percent and 2 percent of the U.S. blood donor population is infected with

²⁷FDA has licensed to one manufacturer a viral inactivation procedure for IMIG.

²⁸We do not discuss hepatitis D because it is an incomplete virus that requires the helper function of HBV to replicate. Thus, HDV is acquired as either a co-infection with HBV or a superinfection of chronic HBV.

HGV and that HGV accounts for 0.3 percent of all acute hepatitis in the United States. The risk factors for HGV appear to be similar to those for HCV (hemophiliacs, anemia patients who have multiple transfusions, and intravenous drug users). Additionally, studies show that between 10 and 20 percent of patients with chronic hepatitis that could not be attributed to other causes were infected with the virus.²⁹

Because HGV is a newly discovered virus, there are no tests to detect it. Some have suggested that tests may not be needed because HGV carriers are often infected with other hepatitis viruses. In contrast, the transmission of HGV by transfusion was documented in 3 of 13 open-heart surgery patients at NIH with posttransfusion hepatitis and no evidence of hepatitis A-E. In both cases, an HGV-positive blood donor was identified.

²⁹J. Linnen et al., "Molecular Cloning and Disease Association of Hepatitis G Virus: A Transfusion-Transmissible Agent," *Science*, 271 (1996), 505-8.

Quarantining and Other Processing Steps

The fourth safety layer involves quarantining units of blood. Other procedures discussed in this chapter include gathering postdonation information, labeling, and storage and distribution. Recording postdonation information allows blood facilities to flag units of blood that may be unsuitable for use. Labeling delineates a unit's blood type (ABO and Rh) and product type (such as red cells and platelets) and whether it is for autologous or allogeneic use. Quarantining, the actual safety layer, includes procedures that separate blood that has been tested and found suitable for transfusion from untested blood and from blood that has been tested and found to be unsuitable for transfusion. The storage and distribution processes allow blood facilities to ensure that blood products are stored at proper temperatures and sent to their proper destinations.

More than one third of all EARS submitted to FDA in 1994 were in the area of postdonation information (see appendix II). This could indicate either that the blood safety system is working well or that what relates to postdonation information in FDA's EAR guidance is poorly understood. Additionally, there is a wide disparity between EARS reported by licensed blood facilities and plasma centers with regard to postdonation information. It is unknown why this disparity exists, since these two types of blood facilities collect approximately the same number of units of blood. There are no weaknesses inherent in the labeling and quarantining procedures when they are carried out properly. It should be noted, however, that mislabeling, while not common, can have fatal consequences. We found that only inventory management is a safety issue in storage and distribution.

Postdonation Information

Postdonation information from the donor or someone else—whether a blood facility receives it by telephone or by some other means—alerts the facility as to whether or not the donation should be used. This might include a donor's alert that he or she became ill after donating the blood or other information such as high-risk behavior that would have deferred the donor had it been known earlier. Blood facilities establish and maintain procedures for receiving, evaluating, investigating, and following up possible errors and accidents relating to postdonation information.

FDA recommends that facilities have processes in place to (1) receive and document postdonation information that identifies the information's source, (2) perform medical evaluations that assess and investigate potential risks, (3) make timely investigations of EAR reports to determine whether the quality of blood or blood products has been compromised,

(4) notify those to whom blood is distributed about how to dispose of affected units, and (5) assess the donor's suitability as a future donor.

Blood facilities do not need to submit an EAR if the donor should not have been deferred and if the medical evaluation indicates that the blood product's quality was not compromised. For example, subsequent cold symptoms do not have to be reported. However, FDA may evaluate the situation as a potential recall.

FDA also recommends how blood facilities should handle situations in which donors call and report that their blood should not be used but provide no further information. In such cases, the facilities are to retrieve the blood products donated by those donors.

EAR and EIR Information

Postdonation information represented a large percentage of all EARs submitted to FDA in fiscal year 1994 (3,815 of 11,292, or 34 percent). Postdonation information includes a donor's informing a facility of hepatitis, cold, or influenza symptoms or of sexual partners who have tested positive for HIV. Table 4.1 shows that licensed facilities reported postdonation EARs at a rate more than 3,000 times higher than that of unlicensed facilities and 135 times higher than that of plasma centers. Their rate per 100,000 units collected was 52 times higher than unlicensed facilities and 88 times higher than plasma centers. According to our analysis of EIRs, postdonation information issues resulted in few problems being found by FDA inspectors and rarely resulted in Form 483 observations. In fact, we found that only quarantining and routine testing resulted in fewer Form 483 observations.

**Chapter 4
Quarantining and Other Processing Steps**

Table 4.1: Postdonation EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	12.2	0.004	0.09	1.25
EAR rate per 100,000 units collected or transfused ^d	29.8	0.57	0.34	14.7

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 4.2: Postdonation Problems and Form 483 Observations by Facility Type^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	1 of 28	4%	7 of 74	10%	2 of 40	5%	0 of 30	0	10 of 142	7%
Facilities receiving Form 483 observations	0 of 28	0	5 of 74	7	2 of 40	5	0 of 30	0	7 of 172	4

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined postdonation information during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were those problems deemed serious enough to be denoted on a Form 483.

Safety Issues

Below we provide information on discrepancies between the number of EARS submitted by licensed, unlicensed and plasma facilities, the one safety issue in the area of postdonation information.

EAR Discrepancies

The large number of EARS from licensed blood facilities is a concern. It could indicate that the system is working properly or that FDA should more clearly define what is to be reported. Since postdonation processes in licensed, unlicensed, and plasma facilities are similar, the large discrepancy in their numbers of postdonation EARS is also of concern. The source of the discrepancy might indicate problems in the blood-banking system that require attention. According to one large blood organization, there are no complete guidelines for postdonation EARS, which also may result in over- or underreporting EARS.

Furthermore, EARS associated with postdonation information appear to point to potential problems in donor-screening practices. For example, in fiscal year 1995, 65 percent of all EARS relating to postdonation information stemmed from information obtained at a subsequent donation. It is not known whether blood-facility personnel had erred during the first screening or whether the donors lied or had forgotten about certain activities. Regardless of the reason, the data indicate that information that might have been obtained at earlier screenings was not collected and, therefore, did not lead to warranted deferral. Also, blood industry representatives pointed out that some FDA guidelines do not clearly define the scope of changes requested in a new guidance document. This, they believe, often results in unnecessary reporting of EARS that are not the result of failure to elicit information.

Labeling

Carefully identifying and properly labeling blood units and the tubes they are collected in for testing are essential safety steps. AABB's accreditation manual notes that the "original label and added portions of the label shall be attached firmly to the container and shall be in clear, eye-readable type, which also may be machine readable."¹ Typewritten or computer-generated labels are most often used; handwritten labels are acceptable but only for temporary expedience.²

Each laboratory that processes donor blood must ensure that the unique number it assigns to a donor appears on the donor record, the primary collection bag, all satellite collection bags, and all tubes used for processing. This allows the prompt identification of specific blood units when and if tests reveal abnormal or discrepant results.

¹American Association of Blood Banks, *Accreditation Requirements Manual*, 5th ed. (Bethesda, Md.: 1994), p. 107.

²Labels requiring information that is not standard must be handwritten; for example, labels that require the specific volume of the product such as a frozen plasma unit.

Recently, AABB's Committee on Commonality has been working with the International Society for Blood Transfusion and an FDA liaison member to develop a world standard for labeling blood and blood products with a bar code system that by July 4, 1997, would replace the most widely used bar code system in the United States.

EAR and EIR Information

We found that labeling errors were commonly reported in 1994 (1,503 of 11,292 EARS, or 13 percent), including missing or incorrect labels for ABO and Rh typing, autologous units, and expiration and collection dates. Table 4.3 shows that licensed facilities reported labeling EARS at a rate about 475 times more than that of unlicensed facilities and nearly 300 times more than that of plasma centers. Their rate per 100,000 units collected was 5 times higher than unlicensed facilities and nearly 300 times higher than plasma centers. We found from the EIR information from facilities where we could determine that labeling activities were observed by an FDA inspector that licensed blood facilities had more problems in labeling (based on problems found by FDA inspectors and the percentage of Form 483 observations) than unlicensed ones. (See table 4.4.)

Table 4.3: Labeling EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service^b	Plasma center	Total
EAR rate per facility ^c	4.74	0.01	0.016	0.49
EAR rate per 100,000 units collected or transfused ^d	11.6	2.3	0.04	5.8

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARS. However, these establishments submit their EARS based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARS.

^cWe calculate rate per facility by dividing the total number of EARS by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARS by the total number of units collected.

Table 4.4: Labeling Problems and Form 483 Observations by Facility Type^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	9 of 33	27%	5 of 41	12%	9 of 53	17%	7 of 40	18%	30 of 167	18%
Facilities receiving Form 483 observations	8 of 33	24	5 of 41	12	5 of 53	9	6 of 40	15	24 of 167	14

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined labeling during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be denoted on a Form 483.

Safety Issues

Labeling practices do not appear to have any inherent weaknesses provided labeling is done properly.

Quarantining

The fourth safety layer, quarantining, is very important in preventing the distribution of unsuitable blood. Blood facilities maintain separate storage areas for units that have not yet been tested, units that are to be retested or are repeatedly reactive, and units that are suitable for distribution. Blood intended for autologous use is stored separately from blood for allogeneic use. However, FDA’s guidance states that although products must be stored separately, they do not have to be placed in different refrigerators. In addition to separating products, quarantining is often aided by the use of computer systems to prevent the erroneous release of blood or blood products.

FDA requires that blood facilities promptly (within 72 hours if possible) identify and quarantine units from prior collections dating back 5 years or 12 months prior to the most recent negative screening test, whenever a donor has a repeatedly reactive screening test for antibodies to HIV. For plasma for fractionation, this figure is reduced to 6 months, provided it has not been pooled or further processed. Furthermore, consignees that have been sent such blood products are to be notified so that they can hold them in quarantine. Releasing blood and plasma from quarantine requires

that the donor subsequently tests negative on a confirmatory test for antibodies to HIV-1.³ However, as noted previously these requirements are directed only at units that might be positive for HIV. No such requirements are present for units that might be positive for other viruses.

EAR and EIR Information

EARS submitted in 1994 indicate that quarantining made up 10 percent of EARS submitted to FDA (1,087 of 11,298). This includes the release of products other than those ordered, the release of outdated products, and the failure to quarantine units that are reactive for viral markers. As table 4.5 shows, licensed facilities reported quarantine EARS at a rate more than 300 times that of unlicensed facilities and 85 times that of plasma centers. Their rates per 100,000 units collected were 4.5 and 64 times higher, respectively. In contrast, table 4.6 shows that FDA found very few problems relating to quarantine procedures during inspections, and facilities received the fewest number of Form 483 observations in this area.

Table 4.5: Quarantining EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	3.39	0.01	0.04	0.36
EAR rate per 100,000 units collected or transfused ^d	8.3	1.9	0.13	4.2

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARS. However, these establishments submit their EARS based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARS.

^cWe calculate rate per facility by dividing the total number of EARS by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARS by the total number of units collected.

³Pending availability of a licensed confirmatory test for HIV-2, a second different antibody test for HIV-2 should be used along with a licensed confirmatory test for HIV-1 when the donor's subsequent donation is found to be HIV-2 positive.

Table 4.6: Quarantining Problems and Form 483 Observations by Facility Type

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No	%	No	%
Facilities with problems ^c	1 of 30	3%	2 of 40	3%	2 of 6	2 3%	0 of 30	0	5 of 163	3%
Facilities receiving Form 483 observations	1 of 31	3	2 of 40	5	1 of 6	2 2	0 of 30	0	4 of 163	2

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined quarantining during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas form 483 observations were problems deemed serious enough to be denoted on a Form 483.

Safety Issues

Quarantining practices do not appear to have any inherent weaknesses provided quarantining is done properly.

Storage and Distribution

The storage and distribution of products constitute the last step in blood-banking. Blood facilities should be able to follow every unit of blood (including each component prepared from a unit) through records obtained between screening and final transfusion or destruction. These steps include charting gauges in refrigerators, freezers, and platelet incubation mechanisms and comparing their readings to automated temperature recordings. For example, there are requirements that storage temperatures for source plasma be lower than 20 degrees Celsius. Units exposed to higher temperatures may be issued but must be relabeled as “source plasma, salvaged.”⁴

Furthermore, the AABB technical manual states that when it is necessary to destroy a product, the identification of each of the components destroyed, the reasons for destruction, and the data and methods of destruction must be recorded.⁵

⁴A unit labeled “source plasma, salvaged” has exceeded its expiration date or required storage temperature or has been subject to other problems that prohibit its use in plasma pools. Such units can be used for research, however.

⁵American Association of Blood Banks, Technical Manual, 11th ed., (Bethesda, Md.: 1993), p. 574.

According to AABB's technical manual, blood facilities must, when they ship units, record the name and address of the receiving facility; the date and time of shipment; a list of all donor unit numbers, blood types, and expiration dates; the names of all blood components; the final inspection of whole blood or red blood cell units; periodic tests to determine that the shipping containers have maintained an acceptable range of storage temperatures; and the name of the person filling the order.⁶

According to federal regulations, "Distribution and receipt procedures shall include a system by which distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary."⁷ Essentially, this means the name and address of the facility receiving the blood products, the date and quantity delivered, the lot number of each unit, and the date of expiration or collection.

Several FDA memoranda pertain to the disposition and retrieval of units that have been tested for viral markers from donors who subsequently tested positive or repeatedly test reactive. Other FDA information notes that manufacturers of plasma derivatives are allowed to receive units of source plasma before they receive all written test results (such as viral marker testing) if the collection facility is owned by the manufacturer and has the same license number. Manufacturers that collect source leukocytes can ship them before receiving the written infectious disease test results (because leukocytes have a short shelf life) but they cannot use them except in an emergency.

EAR and EIR Information

EARS submitted to FDA in 1994 were rarely related to storage and distribution issues. Errors and accidents include shipping units to an incorrect facility, losing or failing to receive units, and storing at incorrect temperatures. Less than 5 percent (553 of 11,292) of all EARS submitted were in this area. Only issues related to collection and viral testing had fewer EARS (362 and 274, respectively). Table 4.7 shows that licensed facilities reported storage and distribution EARS at a rate nearly 1,800 times higher than that of unlicensed facilities and nearly 900 times higher than that of plasma centers. Their rates per 100,000 units collected were 31 and nearly 4,400 times higher, respectively. Table 4.8 shows, in contrast to the EAR data noted above, that a large number of facilities for which we could determine that storage and distribution activities were observed by an FDA inspector were found to have storage and distribution problems during FDA

⁶American Association of Blood Banks, Technical Manual, p. 574.

⁷21 C.F.R. 606.165(a).

inspections. This table also illustrates a high percentage of Form 483s related to storage and distribution. In fact, this area received more Form 483 observations than any other layer or process we examined.

Table 4.7: Storage and Distribution EAR Rates by Facility Type, 1994^a

Source	Licensed	Unlicensed or transfusion service ^b	Plasma center	Total
EAR rate per facility ^c	1.79	0.001	0.002	0.18
EAR rate per 100,000 units collected or transfused ^d	4.37	0.14	0.001	2.1

^aThere were 308 licensed blood facilities, 2,274 unlicensed blood facilities and transfusion services, and 463 plasma centers in the United States in 1994.

^bFDA separates error and accident reports by unlicensed blood facilities and transfusion services in its annual summaries of EARs. However, these establishments submit their EARs based on a self-designation as either an unlicensed blood facility or transfusion service and FDA does not check the accuracy of these self-designations. Therefore, we combined this information in our analysis of EARs.

^cWe calculate rate per facility by dividing the total number of EARs by the total number of facilities.

^dWe calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 4.8: Storage and Distribution Problems and Form 483 Observations by Facility Type^a

Source	Licensed		Unlicensed ^b		Transfusion service		Plasma center		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Facilities with problems ^c	21 of 38	55%	12 of 47	26%	30 of 74	41%	17 of 50	34%	80 of 209	38%
Facilities receiving 483 observations	14 of 38	37	8 of 47	17	26 of 74	35	14 of 50	28	62 of 209	30

^aThere were 48 licensed facilities, 114 unlicensed facilities, 91 transfusion services, and 72 plasma centers in our sample (total = 325).

^bIn our analysis of EIRs and Form 483s we separated unlicensed blood facilities and transfusion services based on information contained in the EIRs.

^cThere were 38 licensed facilities, 83 unlicensed facilities, 36 transfusion services, and 52 plasma centers in our sample that contained EIR information that allowed us to determine that FDA had, in fact, examined storage and distribution during its inspection. Problems were those that were characterized by the inspector on the inspection report whereas Form 483 observations were problems deemed serious enough to be denoted on a Form 483.

Safety Issues

One area of safety that is of concern regarding storage and distribution is the issue of inventory management.

Inventory Management

The data indicate that blood facilities either cannot account for or lose a large number of donated units, units that are never transfused. Data from AABB, ABC, ARC, and 3,600 independent hospitals showed that 10.5 percent of the 1989 blood supply (nearly 1.5 million units) was not transfused. Outdated or lost units accounted for 7 percent (994,000 units) of the total number of units collected. Interestingly, 3.5 percent (501,000 units) of the blood that was not used was not accounted for in any way.⁸ Although units that are unaccounted for are not related directly to safety, they highlight the storage and distribution problems at blood facilities.

Our earlier discussion of autologous donations and transfusion to unintended recipients might be relevant here if we could determine that units that were unaccounted for were transfused to the wrong patient. Of course, these data cannot exist because blood facilities cannot account for them. However, a recent AABB survey found that 48 of 491 respondents (9.8 percent) reported that one or more units were associated with inventory management problems, inadvertent crossover (giving a unit of blood to an unintended recipient), improper patient identification, or discrepancies in blood typing. Inadequate processes for inventory control can therefore affect blood safety.

⁸E. Wallace et al., "Collection and Transfusion of Blood and Blood Components in the United States, 1989," *Transfusion*, 33 (1993), 139-44. Recent ARC data indicate that lost units comprised only 0.0028 to 0.0043 percent of produced components in the first half of 1996.

Monitoring and Investigating

In the fifth safety layer, FDA monitors blood facilities for compliance with federal good manufacturing practices and blood-banking regulations by inspecting them. It also requires licensed blood facilities to notify FDA of errors and accidents in the manufacturing of biological products. EARS provide FDA with information on potential problems within a blood facility and give it a means with which to begin product recall procedures.¹

The Food, Drug, and Cosmetic Act and the Public Health Service Act authorize FDA investigators to examine all pertinent parts of a blood facility's operations and report their findings in an EIR; they note objectionable conditions on the Form 483. At the close of an inspection, the investigators present the Form 483 to the head of the facility to ensure that management is aware of their observations.

A licensed facility that refuses to permit such inspections or refuses to permit access to required records can have its license revoked. For unlicensed facilities, refusals can result in judicial action to close a facility.

FDA's annual summaries of EARS suggest that unlicensed blood facilities are underreporting their errors and accidents. (FDA recommends that unlicensed facilities voluntarily report EARS.) We found direct, if unconfirmed, evidence that unlicensed facilities are significantly less likely than licensed ones to submit an EAR even in the most serious cases, when product recalls occur. Also, licensed and unlicensed facilities are not submitting timely EARS and FDA is not timely in confirming that recalls that have been initiated by blood facilities have actually occurred.

We found substantial confusion in the blood industry on the distinction between FDA regulations and guidance in terms of what practices were actually required and what were recommended. Its inspection procedures also have several deficiencies. (1) FDA conducts no statistical analyses of the information contained in EIRS and their corresponding Form 483 observations. (2) While FDA's current list of licensed blood facilities is generally reliable, some of the list's information is inaccurate. (3) FDA fails to inspect some blood facilities within the time periods set by its own guidelines. (4) FDA's present policy on completing EIRS creates problems for determining what blood-banking processes have actually been inspected. (5) There were differences across districts in Form 483 observations given by FDA inspectors. Also, we found inconsistencies in

¹A recall is a blood facility's voluntary removal or correction of a marketed blood product that violates laws administered by FDA. The Public Health Service Act authorizes FDA to require that a manufacturer initiate a recall if there is an imminent hazard to the public health.

what was considered an action that should result in a Form 483 observation or warning letter.

These problems may not directly jeopardize the safety of the blood supply. However, without adequate monitoring of the blood industry, FDA cannot ensure that individual facilities conform to the federal statutes and regulations that are designed to provide safe blood to the nation.

Error and Accident Reports

FDA's regulations require all blood facilities to maintain records of errors, accidents, transfusion reactions, complaints, investigations, and follow-up. Licensed facilities are required to notify FDA of errors and accidents that affect the safety, purity, or potency of blood products, but unlicensed ones are not. They are asked, however, to notify FDA voluntarily.²

FDA's guidance on what constitutes a reportable error or accident includes, among others, the release of blood units (1) that are repeatedly reactive to tests, indicating hepatitis or HIV; (2) in which testing was performed incorrectly or misinterpreted; (3) from donors who are, or should have been, permanently or temporarily deferred; (4) that have not been completely tested or that are incorrectly labeled; and (5) that are contaminated because of an error in manufacturing. A reportable error or accident also includes incorrectly identifying samples used in routine testing, making errors in routine testing that result in the wrong unit's being released for transfusion, and issuing the wrong unit for transfusion. Errors and accidents should always be reported promptly when a product has been made available for distribution.³

EARS are submitted to the Center for Biologics and Evaluation Review (CBER is the FDA center with main responsibility for regulating blood and blood products), and if an EAR clearly does not require further evaluation for a product recall it remains at CBER, where it is entered into the error and accident reporting system (EARS) database. If CBER decides that further evaluation is warranted, it forwards the EAR to the appropriate district office for follow-up as a potential recall situation. The district office determines if the situation does warrant a recall and makes a recommendation to the office of compliance within CBER. This recommendation is evaluated for completeness and to determine if the

²FDA is reviewing a proposed rule that would require unlicensed, registered firms to submit error and accident report.

³EARS are not required when a facility detects an error or accident before a blood product has been made available for distribution.

incident meets the definition of a recall.⁴ If the incident is determined to be a recall, a health hazard assessment is performed and classified as to the severity of the event. A recall is confirmed when CBER notifies the district that a recall should occur. In fiscal year 1994, there were 427 blood recalls involving 8,529 units of blood or plasma, or about 0.003 percent of the approximately 26 million units collected nationally that year.⁵

FDA maintains a database of EARS and compiles annual summaries that total them and categorize them by type of facility and type of error. From October 1991 to September 1994, FDA received more than 30,700 EARS. Postdonation information errors and accidents accounted for by far the greatest number. For example, from October 1992 to September 1994, FDA received 20,289 EARS, of which 7,379 (36 percent) reported postdonation errors and accidents.⁶ Licensed blood facilities account for the vast majority of EARS, reporting 10,283 in fiscal year 1994 while unlicensed facilities reported 146. (In April 1995, there were 739 licensed and 2,241 unlicensed blood facilities in the United States).

Most EARS are not serious problems and do not represent immediate danger. In fact, EARS are an integral part of a system for catching potentially dangerous units of blood before they enter the blood supply. For instance, when postdonation information from a donor alerts a blood facility that a unit of blood should not be transfused, the facility customarily reports this information as an error or accident because of the way in which FDA has defined what is to be reported through EARS. In such cases, the layers of safety are working effectively to protect the blood supply.

Furthermore, few errors and accidents are egregious. For example, only 66 of the more than 10,000 fiscal year 1994 EARS were submitted for HIV-1 and HIV-2 testing that resulted from incorrect testing, misinterpretation, or

⁴FDA may request a firm to initiate a recall when it is determined that a product has been distributed that presents a risk of illness or injury or gross consumer deception, a firm has not initiated a recall of the product, or the agency action is necessary to protect the public health and welfare.

⁵These figures do not include the recall of products used to process blood, such as defective collection bags, nor does it include any lots of intravenous immune globulin manufactured after February 1993—a plasma derivative recalled for potential transmission of hepatitis C.

⁶FDA did not use postdonation information as a category in its fiscal year 1991 summary, so our numbers are based on 1992-94 data. In fiscal year 1991, FDA received 3,834 EARS; in 1992, more than 10,000. The increase stemmed partly from the implementation of the December 5, 1990, memorandum entitled "Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products" that recommended direct questioning about high-risk behavior and the March 20, 1991, memorandum entitled "Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood and Blood Components" regarding the reporting of errors and accidents to FDA. We confined our analysis of EAR data to fiscal year 1994.

product release prior to testing or before testing was completed (0.006 percent). Only 12 EARS reported a failure to quarantine a product that was HIV reactive (0.001 percent). In other words, HIV errors represent approximately 1 out of every 307,692 blood donations.

Safety Issues

The three issues related to errors and accidents that do merit attention are that unlicensed blood facilities appear to underreport them to FDA, many EARS are submitted to FDA long after the problem has occurred, and FDA is not promptly investigating EARS that result in product recalls.

Underreported EARS

Although there are more than three times as many unlicensed blood facilities as licensed ones, the former account for only 1.3 percent of reported EARS (146 of 11,298) whereas the latter (including ARC) account for 91 percent of reported EARS (10,283 of 11,298).⁷ If EARS were related more to the number of units collected than to the number of facilities, we might expect unlicensed facilities to report 10 percent of all EARS because they collect about 10 percent of the nation's blood supply; this is still much higher than their current proportion of EARS. Similarly, plasma facilities collect 12 million units of plasma, which is equal to the total number of whole blood units collected by licensed and unlicensed blood facilities together, yet plasma facilities report less than one tenth of all EARS.

An additional cause for concern is that EARS from unlicensed facilities are just as likely as EARS from licensed ones to result in a potential recall (see table 5.1). Thus, the failure to require unlicensed facilities to report errors and accidents may result in FDA's missing a number of potential product recall problems. Potential product recalls for plasma centers made up 39 percent of all EARS that they submitted in fiscal year 1994.

⁷The remaining 7.8 percent of EARS (rounded) are reported by plasma centers, vaccine manufacturers, and reagent manufacturers. Our interviews with representatives of licensed blood facilities revealed that unlicensed blood facilities may have a competitive edge because they are often not held to the same standards. For example, unlicensed blood facilities do not have to obtain FDA approval for certain changes in their procedures, which, it is alleged, add costs in personnel, salary, and time to licensed facilities that are not borne by unlicensed ones.

Table 5.1: Potential Recalls From Reported EARs, Fiscal Year 1994

Type of facility	Reports received	Potential recalls	Percent recall to reports
Licensed	10,283	512	5%
Unlicensed	146	10	7
Plasma center	856	333	39
Transfusion service	7	0	0

The commissioner of FDA in 1993 noted in testimony before the House Subcommittee on Oversight and Investigations that the issue should be looked at as FDA revises its error and accident reporting procedures.⁸ A May 1995 HHS Inspector General’s report noted that voluntary reporting by unlicensed blood facilities is a major shortcoming in FDA’s notification process and recommended that they be required to submit EARs to FDA.⁹

Unlicensed facilities underreport errors that end in product recalls. In 299 of the 468 recalls in 1994, an EAR was submitted before the district office’s recommendation for recall: 293 from licensed facilities, including plasma centers, and 6 from unlicensed ones.¹⁰ Our statistical analysis of this difference determined that it was highly significant ($t = -8.96$; $p < .0001$). More than 70 percent of licensed facilities submitted an EAR before recall, but only 17 percent of unlicensed facilities did this. Given that EARs are one way of alerting FDA of the need for an immediate recall, we believe that the underreporting by unlicensed facilities is a serious problem.

Untimely EARs

The HHS Inspector General’s report noted that, for a random sample of 163 EARs from October 1992 to April 1993, the time between the date when a blood facility detected an error or accident and the date when it was reported to FDA ranged from less than 1 month to more than 1 year, the average being a little over 4 months. The report also found that about 14 percent of the sampled EARs were submitted within 1 month but that 13 percent were reported 6 months or more after the error was detected.

⁸David Kessler, Commissioner, Food and Drug Administration, “Blood Supply Safety,” Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives, July 28, 1993, p. 50.

⁹FDA officials told us that FDA agreed with the HHS Inspector General’s report and that it is preparing a proposed rule that would require unlicensed blood facilities to submit EARs.

¹⁰Recalls do not always begin with an EAR. In some cases, an FDA inspection uncovers an error or accident that was not reported to FDA and bases a recall recommendation on its severity. Some facilities then submit an EAR even though recall has begun. We did not include these cases in our analysis.

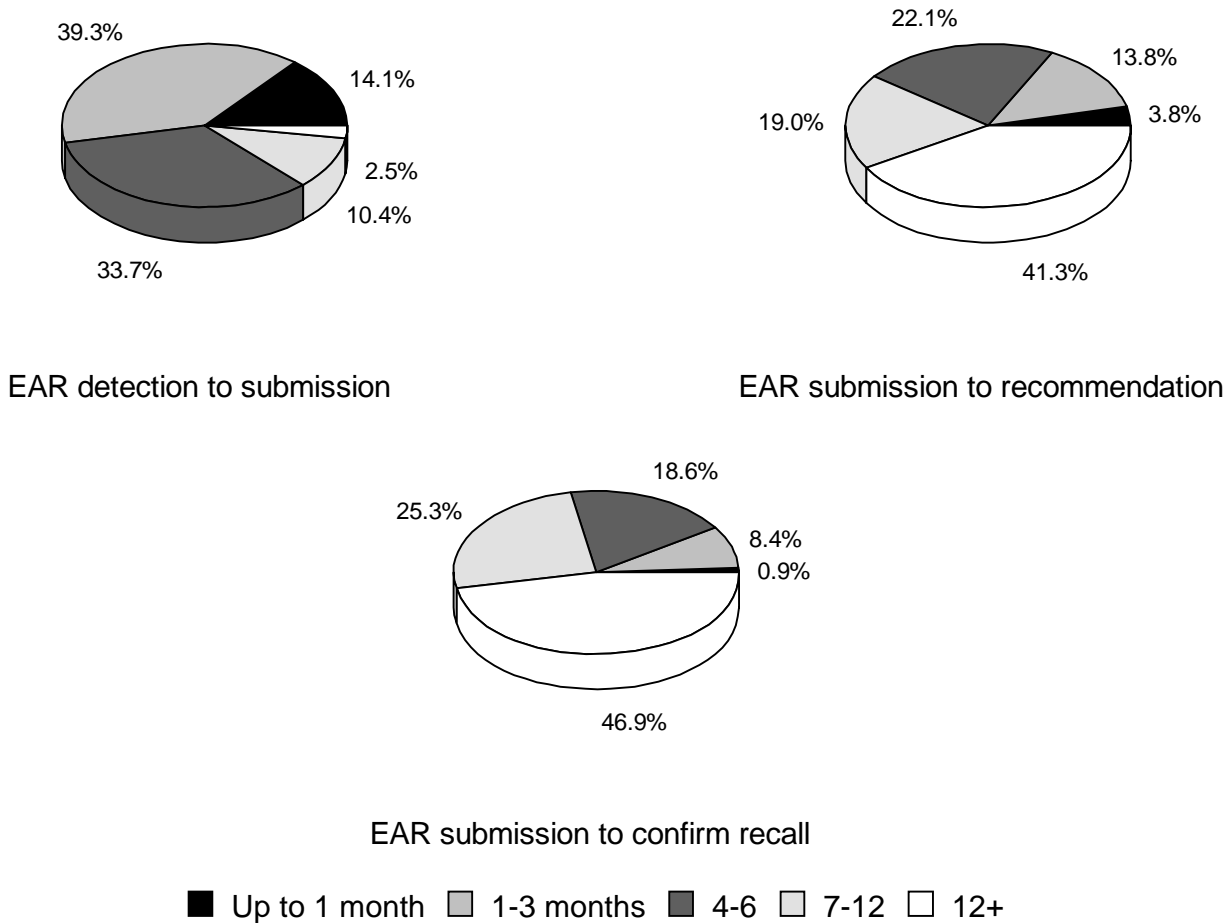
**Untimely FDA Investigation of
EARs**

This untimeliness may hamper FDA's ability to investigate errors and accidents and to monitor blood facility practices.

Once a facility has reported an error or accident to CBER, depending on the severity of the error or accident, the district office evaluates it and may recommend a recall. Our analysis of FDA's recall database outlined in figure 5.1 shows that in 60.3 percent of those cases, 7 months or more elapsed between the time an EAR was submitted and the district recommended a recall to CBER.¹¹ The time for FDA review (the time from a recommendation for a recall and when a recall is confirmed) ranged from none to a year, with a mean of 9 weeks.

¹¹In many cases, a recall has been initiated by a blood facility before an EAR is submitted to FDA. However, the time lag from the submission of an EAR to when FDA completes its evaluation can be lengthy.

Figure 5.1: Time From Error and Accident Detection to EAR to Recall Recommendation to Recall Confirmation



Note: Numbers may not sum to 100 percent because of rounding.

Figure 5.1 also shows that in more than 70 percent of the cases, the total time from EAR submission to when a recall is confirmed and publicly announced is 7 months or more. The total time ranged from a little over a month to 2-1/2 years, with an average of nearly 9-1/2 months. According to FDA, in about 25 percent of cases, a product recall is not initiated by the facility by the time FDA recommends a recall. It is these cases that could

compromise blood product safety given the long time FDA takes to go through its formal recall process.

We also found no significant differences in the time it took for a product recall to go through the process above, based on the severity of the case.¹² That is, more serious cases were not processed faster than less serious ones. Since some of the products that are recalled have been made available for transfusion, it is important that this process be as timely as possible.

FDA's Regulations and Guidance

FDA communicates its requirements through CFR, title 21, and its policies and recommendations through memoranda and letters, compliance manuals and program, compliance policy guides, and a guide for blood facility inspections. The requirements in the Public Health Service Act, Food, Drug, and Cosmetic Act and CFR are the only mandatory requirements.

According to FDA, inspectors do not cite relevant CFR provisions on Form 483s when they find objectionable conditions because numerous regulations may apply to any given situation. However, FDA inspectors are supposed to present their findings to the blood facility immediately after an inspection, including any Form 483 observations. After the inspection, and to ensure that inspectors consider all relevant regulations in an investigation, other FDA officials review EIRS and any Form 483 observations.

Safety Issues

Below we describe the one safety issue we found in regard to FDA's use of regulations and guidance.

Use of Guidelines and Recommendations

We found substantial confusion in the industry on the distinction between FDA regulations and guidance, potentially leading to different interpretations and applications of FDA's requirements and recommendations. Many of our survey respondents were unclear as to which statements had to be followed and which were only FDA recommendations. Twenty-nine of the 45 full-service licensed facilities we surveyed responded to an open-ended question on possible areas for improvement within the blood industry: 10 (or 34 percent) of them answered that FDA's regulations and guidance are ambiguous. They noted

¹²If an incident is determined to be a recall, a health hazard assessment is performed and classified as to the severity of the case.

that recommendations were sometimes used as the basis for Form 483 observations, that the regulations should be updated to incorporate current memoranda, and that the language in the memoranda should be clarified as to whether actions to be taken are required or recommended.

An Institute of Medicine study on blood safety issues has recommended that “when issuing instructions to regulated entities, FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.” Responding to this study, AABB agreed that many recommendations and guidance memoranda are often not clear as to regulatory intent and even when ambiguities have been identified AABB has also stated that they have not been successful in obtaining clarification from FDA.¹³

The issue has practical implications. For instance, although FDA has issued memoranda on procedures for HTLV testing, the regulations do not refer to HTLV testing. Thus, one could view this as only a recommendation and not a requirement. However, not testing for HTLV would probably affect the purity, potency, and safety of blood products, and a facility that failed to test for HTLV could be considered in violation of the statutory legal standards, which explicitly state that blood products are to be tested for purity, potency, and safety, regardless of whether the regulations formally require such specific tests.

Our survey respondents indicated two other areas in which improvements would enhance blood safety: consistent regulation between licensed and unlicensed blood facilities and better regulation of transfusion procedures.

FDA has to its credit historically issued memoranda to give the industry immediate feedback on its position on new issues. This is an important tool for quickly reacting to advances in medical knowledge or technology. However, guidelines and memoranda that have been issued for expediently stating expectations to the blood industry appear to move rarely into the formal regulatory process. For example, FDA has not codified requirements for testing blood for either HCV or HTLV, even though testing for them clearly affects safety and even though FDA has recommended testing since 1988 for HTLV and 1990 for HCV. Only regulations codified in the Code of Federal Regulations benefit from formal public comment, and issuing statements through the CFRs is one of the only ways to clarify FDA’s purpose.

¹³Letter to Assistant Secretary of Health, Department of Health and Human Services, Regarding the Task Force to Review Current Blood Safety Program, Washington, D.C., October 3, 1995.

Blood facilities often adopt FDA recommendations and integrate them into their standard operating procedures (SOPs). Once these recommendations are incorporated into SOPs, the blood facility can receive Form 483 observations for not following its SOPs under good manufacturing practices. This, however, does not overcome the problem of required practices and the issue of public comment opportunities.

Inspections

FDA is required to perform biennial inspections. Facilities that have received warning letters or that have been found deficient in inspections within the past 2 years may be inspected annually until two consecutive inspections pass without significant observations.¹⁴

Inspectors are FDA officers who have “special knowledge of the methods used in the manufacture and control of products.” Their job is to, among other things,

“investigate . . . the methods of propagation, processing, testing, storing, dispensing, recording, or other details of manufacture and distribution of each licensed product, or product for which a license has been requested, including observation of these procedures in actual operation”¹⁵

Suspension or revocation of licenses, injunctions, and prosecutions may ultimately result from a process begun with an inspector’s Form 483 observations of a continuing pattern of deviation. For isolated deviations, FDA acts only when they may jeopardize the safety of donors or products. While FDA views the Form 483 as an observation, the blood industry often sees it as a citation or violation of applicable FDA regulations and guidance.

Currently, FDA uses three levels for classifying inspections; no action indicated (NAI) for insignificant deviations or no identified deviations, voluntary action indicated (VAI) for deviations that are amenable to corrective action by the firm with no compromise to public safety, and official action indicated (OAI) for deviations of a serious nature that require some FDA intervention to ensure that corrections are made. FDA inspectors are directed to list on the EIR the specific areas covered only when a limited or incomplete inspection is done. The inspectors are also

¹⁴Performing yearly inspections of firms previously in violation is FDA’s own requirement. FDA’s inspectors work in 21 district offices in six regions: Pacific, Southwest, Midwest, Northeast, Mid-Atlantic, and Southeast.

¹⁵21 C.F.R. 600.22(d).

instructed to list on the EIR everything they see that is questionable and that could therefore be a violation of the regulations.

Most inspections are conducted in accordance with specific compliance manuals that explicitly state what is to be observed during the inspection. FDA inspectors are also directed to list in the EIR the specific compliance program under which the inspection is performed, and they are not expected to suggest remedies to problems that are found during an inspection, nor are inspectors expected to discuss the regulations that pertain to the problems. By listing the compliance program, FDA officials told us, all directions included in the compliance program were followed unless otherwise stated on the EIR. Further, FDA officials stated that they often have substantial experience with each blood facility, allowing inspections to be tailored to look at areas known to be sources of problems, thus making maximum use of FDA's limited resources.

To examine EIRS, we randomly sampled 8 district offices. Within these, we selected a representative sample of 373 blood facilities, including licensed and unlicensed blood facilities, blood donor centers, plasma fractionators, plasma collection centers, testing laboratories, transfusion services, and viral testing and reagent manufacturers. We looked at their last recorded inspections, separating EIRS into those that should have contained a blood facility inspection checklist and those that did not require one.¹⁶ We also mailed a questionnaire to the 45 full-service blood facilities within our representative sample. (See appendix III.)

Safety Issues

We found several problems in FDA's inspection process in five broad categories: the use of EIR information, the tracking of blood facilities, the timing of inspections, the completeness of inspection reports, and the consistency of inspection reporting.

Use of EIR Information

We were told by FDA that it analyzes EIRS and Form 483s. According to FDA, examples of such analysis were the program-oriented data system (PODS) database; the 1992-93 task force on ARC, which categorized all Form 483s issued to ARC from 1988 to 1992; work performed by FDA that led to injunctions against ARC and BSI; and a study FDA conducted on Form 483

¹⁶Until October 1994, FDA inspectors were required to fill out an inspection checklist that outlined all the areas of blood-banking that an inspector could examine. After October 1994, FDA adopted a "systems approach": the checklist is no longer required and inspectors examine blood-banking processes with a view to establishing that systems adequately address quality-assurance and good manufacturing practices concerns.

observations.¹⁷ Information FDA provided to us on PODs contained no information that would allow FDA to perform systematic analyses of EIRS and Form 483s. PODs contains information on who did the inspection, where the inspection occurred, how long the inspection took, what was covered in the inspection, and the results of the operation. However, what was covered merely identifies products involved in the inspection (for example, food) while the results simply identify whether the firm is operating in or out of compliance.

Furthermore, FDA noted that PODs is in place to provide information on accomplishments by FDA field personnel to justify annual budget requests. It is, therefore, not a system that contains information that would allow for a statistical analysis of blood facility EIRS and Form 483s. Likewise, the 1992-93 task force work is not an analysis of EIRS and Form 483s. It is a listing of Form 483s given to ARC facilities from 1988 to 1992 by category (for example, donor screening, testing, labeling, equipment). No statistical analysis of this list was performed.¹⁸

In sum, without collating, synthesizing, analyzing, and evaluating EIR and Form 483 information, FDA has no means of assessing overall national compliance, assessing trends by type of blood facility, identifying the problems of different types of blood facilities, or evaluating the effect of policy changes on compliance rates.

By performing these types of statistical analyses, FDA could obtain information on different rates of Form 483 observations between district offices, rates of observations by type of activity (for example, donor screening, donor deferral, viral testing), and differing rates between types of facilities. For example, our analysis of Form 483 observations found differences in the number and kind of Form 483 observation given by different FDA districts. Although the reasons for these differences are unclear, such information could provide FDA with important data on inspection findings and FDA procedures for carrying out inspections.

¹⁷See the last section of this chapter, on disparities in inspection reporting, for information pertaining to the study conducted by FDA on Form 483 observations.

¹⁸FDA also summarizes ARC's progress under the terms of a May 12, 1993 consent decree. That is, FDA inspectors give ARC annual reports of Form 483 observations. Similar to the 1992-93 task force work, these reports are listings of Form 483 observations given under topical headings such as management control, quality assurance, and records management. No statistical analyses are performed on these data.

Tracking Blood Facilities

FDA maintains a list of all registered blood facilities with their registration numbers.¹⁹ The vast majority of those that were in our sample were accurately identified. However, we did find problems with FDA's list of registered blood facilities. For example, when we queried FDA about the EIR for a particular blood facility through its registration number, FDA told us erroneously that the registration number in question belonged to a different facility (this was based on its list of registered blood facilities).

We also found a small number of cases in which the last inspection of a blood facility was held more than a decade ago but it was still on the FDA list of active registered blood facilities. In these cases, it appeared that these facilities had closed and were not operating as blood facilities, but the fact that they still had registration numbers and were on FDA's active list highlights inadequacies in FDA's recordkeeping. We also found that FDA could not find 4 EIRs (1 percent of the 373 EIRs in our sample).²⁰ Unfortunately, we cannot know the extent of such monitoring problems or their potential effect on FDA's oversight responsibilities.

Timing of Inspections

Of the 373 blood facilities in our sample, 45 (12 percent) had not been inspected in more than 2 years.²¹ One donor center had not been inspected in more than 3-1/2 years. Since our sample represents all blood facilities in the nation, 348 of the 2,900 registered blood facilities may not have been inspected within the past 2 years.

Completeness of Inspection Reports

We examined each facility in our sample for whether the EIR indicated that a particular function had been examined. For the purpose of our analysis, if it was mentioned at all in the EIR, we considered it to have been examined. If it was not mentioned at any time in the EIR, we considered that one could not determine whether the area had been examined. We excluded functions that inspectors noted were not performed.

For the time period when checklists were required, we found that many blood inspection checklists were not completed. Forty of 224 inspections

¹⁹All blood facilities are registered with FDA and are given a unique registration number. This is distinct from a license number given to facilities that engage in the sale, barter, or exchange of blood products across state lines.

²⁰We were able to analyze data on the tracking and timing of inspections for all 373 blood facilities in our sample. The EIR information below was based on the 325 blood facilities in our sample that were licensed and unlicensed blood facilities, transfusion services, and plasma centers. The 48 other facilities were plasma brokers, viral testing and reagent manufacturers, testing laboratories, and depot sites or had been inspected for specific purposes that were not part of an annual inspection and thus we did not include them in the analyses below.

²¹FDA's response to our query for a list of the blood facilities in our survey was dated August 14, 1995. Thus, 45 facilities had not been inspected since September 1993.

(18 percent) in our sample that should have included an inspection checklist did not have one. We found that the lack of a completed checklist made it very difficult to determine what areas of a blood facility's processes were actually covered during an inspection. Many of the EIRs for which the checklist was missing also lacked narratives from which to obtain the pertinent information. Thus, we often could not determine whether the FDA inspectors based their findings on an observation of certain blood-banking operations or on an examination of written standards of operation.

In many instances, we were unable to determine whether procedures relating to donor screening, deferral, collection, routine testing, viral testing, postdonation information, labeling, quarantining, storage, and "machine" issues were examined at all in individual inspections. In fact, for all the matters in our EIR analysis that FDA could have inspected, we could not find coverage in 33 percent (963 of 2,957).²² Further, we were able to determine in only half of all reviewed reports that inspections covered all activities necessary to ensure compliance. Thus, regardless of FDA's policy on what information should be contained on an EIR, we could not determine what had actually been observed and what practices had been examined only by reviewing SOPs. As table 5.2 indicates, there were many instances in which a given process was not mentioned at all in the EIR.

²²As we noted previously, our EIR sample was based on 325 blood facilities. We categorized blood-banking processes into 11 subjects, or a total of 3,575 potential areas that FDA should have inspected. However, many blood facilities did not perform all the operations we categorized, so that those we could analyze numbered 2,957.

Table 5.2: Percentage of Facilities for Which We Could Determine That Processes Were Checked in Inspection Reports

Process	Blood bank		Plasma center	Transfusion service
	Licensed	Unlicensed		
Screening	83%	77%	74%	64%
Deferral	89	64	70	63
Collection	83	85	73	71
Routine testing	56	50	^a	72
Viral testing	95	67	38	42
Labeling	73	53	56	71
Postdonation information	61	69	43	62
Quarantine	67	53	43	70
Storage	83	63	70	82
Machines	96	79	73	88
Miscellaneous	83	62	58	81

^aDoes not apply.

As noted previously, FDA’s policy is for the inspectors only to list areas on the EIR that were not covered. Thus, when an inspector notes on the EIR the specific compliance program under which the inspection is taking place, this means that all blood-banking practices covered in the compliance program have been examined (unless specifically listed on the EIR). However, we found that this policy is unreliable in ensuring that activities not covered during an inspection are, in fact, listed on the EIR. For example, at a blood facility inspected in 1994, an inspector found that no lookback procedures had been followed in several cases of reported HIV-positive donors identified since 1990.

When we examined the EIR for this facility for the inspection that took place in 1993, we found no mention that lookback procedures were not being followed. This means either that the 1993 inspection examined lookback procedures and did not find the problem that had been evident since 1992 (according to the 1994 inspection) or that the activity was not observed in the 1993 inspection and was not listed on the EIR according to FDA’s own stated policy. In either case, FDA’s policy of not listing all activities covered during an inspection results in the agency’s inability to determine what practices have actually been examined by its inspectors and hampers its ability to perform any meaningful analysis of EIRs and Form 483s. Without knowing what has been inspected, FDA cannot know where a facility is in or out of compliance.

FDA officials told us that they have substantial previous experience with each facility, allowing them to tailor inspections to look at areas known to be sources of problems, thus making maximum use of limited resources. However, because EIRS do not list the activities covered in the previous inspection (and, as noted above, such a policy may not, in fact ensure that some practices are examined even though they were not listed on the EIR), such tailoring of inspections may result in blood-banking practices not being examined for long periods of time at individual facilities. Additionally, even if FDA emphasizes certain areas more than others based on previous “experience,” this could result in missing problems in areas that had previously not been out of compliance. Because of all these problems relating to information contained on the EIRS, we limited our analysis of possible compliance problems to those listed on the Form 483.

We also found that facilities whose EIRS did not have a checklist, whether one was required or not, were significantly less likely to have Form 483 observations than facilities that had checklists.²³ This could mean that checklists promote a more methodical approach to an inspection, resulting in more Form 483 observations, or that formal procedures such as the completion of a checklist focus an inspection on minor details that may or may not be real problems. As we discuss below, this finding may be a result of a lack of clear and concise FDA guidance on what should constitute a Form 483 observation.

In order to focus a current inspection clearly, FDA inspectors are expected to review past EIRS for previously identified problems. Without a checklist or more comprehensive narrative in the EIRS, we often could not obtain such information. Table 5.3 presents the results of a survey question in which we asked facilities to what extent FDA examined standard operating procedures in 12 separate areas.²⁴ In every area except deferral, more than half the respondents indicated that FDA examined standard operating procedures only to a moderate extent or less.

²³ $t_{(372)} = -2.67, p < .01$

²⁴The survey asked respondents to report whether the FDA inspection team examined standard operating procedures and whether the team actually observed or examined firsthand 12 major blood-banking operations: donor screening, donor history and examination, phlebotomy and collection, routine laboratory procedures, viral laboratory procedures, donor deferral, labeling, quarantine and storage, product disposition, postdonation recall and lookback, computer validation, and quality assurance and good manufacturing practices.

**Chapter 5
Monitoring and Investigating**

Table 5.3: The Extent to Which Inspectors Examined Standard Operating Procedures^a

Area	Little or no extent	Some extent	Moderate extent	Great extent	Very great extent	Does not apply
Screening	11%	16%	22%	33%	18%	
Donor history and examination	11	11	22	40	16	
Deferral	7	9	22	29	33	
Collection and phlebotomy	11	11	31	36	11	
Routine laboratory	16	7	40	22	16	
Viral laboratory	11	4	27	27	31	
Labeling	16	13	33	20	18	
Postdonation, recall, and lookback	22	13	24	18	22	
Quarantine and storage	11	13	18	27	31	
Product disposition	7	18	18	29	29	
Quality assurance and good manufacturing practices	18	18	22	29	13	
Computer validation	27	13	13	9	18	20%

^aRow totals may not sum to 100 percent because of rounding.

Similarly, the respondents reported that FDA does not observe or otherwise examine firsthand major activities in the many areas listed in table 5.4. More than 20 percent of our respondents reported that FDA does little or no observation in six different areas.

Table 5.4: The Extent to Which Inspectors Directly Observed Major Activities^a

Area	Little or no extent	Some extent	Moderate extent	Great extent	Very great extent	Does not apply
Screening	13%	20%	20%	22%	24%	
Donor history and examination	9	20	22	27	22	
Deferral	25	30	9	16	21	
Collection and phlebotomy	11	20	18	24	27	
Routine laboratory	20	29	20	16	13	2%
Viral laboratory	11	20	22	20	24	2
Labeling	22	27	18	18	16	
Postdonation, recall, and lookback	32	30	5	14	14	7
Quarantine and storage	18	18	27	13	24	
Product disposition	18	18	23	11	30	
Quality assurance and good manufacturing practices	23	21	25	18	9	5
Computer validation	32	16	5	9	11	27

^aRow totals may not sum to 100 percent because of rounding.

Furthermore, 35 percent of the respondents indicated that FDA evaluated the existence and suitability of only half or fewer of the critical control points their institutions had in place to ensure safety, purity, and potency. Among the facilities in which FDA found a problem, 56 percent reported that FDA did little more than identify that a problem existed. According to FDA, inspectors are not to suggest solutions or discuss the regulations or guidance that pertains to problems found during an inspection. However, contradicting this position is other information provided by FDA in which it has noted that “investigators provide general guidance on applicable documents, policy, regulations, etc. which are the basis for the objectionable condition.”

We also presented respondents with a list of areas that might be examined to assess compliance and asked them to order the list in terms of the emphasis that inspection teams gave to each area during the last inspection. Their ordering shows that inspectors focus on documentation and whether records and files can be traced as well as on adherence and completeness of standard operating procedures. They indicated that quality-control management is not a major focus of inspections. Their ordering of areas was

1. documentation of records and files;

2. adherence to standard operating procedures;
3. traceability of records and files;
4. completeness of standard operating procedures;
5. quality-control management and accountability;
6. employee training;
7. software technology;
8. hardware technology;
9. physical plant and facilities.

About two thirds of the respondents had received a Form 483 or other form of observation or citation. Seventy percent of these indicated that the inspection team was able to articulate the significance of the violations it had identified, but 22 percent indicated that the inspection team was able to do so only to some extent or less. Also, nearly 30 percent of the respondents reported that one or more of the items on their Form 483 were for problems that they had already identified through their own quality-control process and had already corrected before the beginning of the inspection.

To FDA's credit, most respondents thought the FDA inspectors were generally knowledgeable or very knowledgeable about blood-banking terminology, technology, and practices. All respondents to the survey noted that FDA inspectors appeared to follow a systematic approach. Sixty-four percent also noted that most or all critical control points were evaluated.

Just as FDA expects blood facilities to have complete records of their processes and activities between inspections, it is appropriate that FDA have complete information on blood banking operations for every blood facility inspection. Without such information, it is impossible to know if, in fact, blood facilities are in compliance with all federal rules and regulations.

Disparities in Inspection Reporting

Across the 8 FDA districts that we examined, we found disparities in the information on Form 483s and the issuance of warning letters. For

example, more than 27 percent of the Form 483 observations in one district were related to storage issues but only 13 percent in another. Similarly, more than 21 percent of one district's Form 483 observations were related to labeling issues but only about 2 percent in another district. Table 5.5 outlines the variations across districts.

Table 5.5: Percentage District Variation in Form 483 Observations

Area	District 1 (n = 35)	District 2 (n = 38)	Region 3 (n = 40)	District 4 (n = 41)	District 5 (n = 33)	District 6 (n = 46)	District 7 (n = 44)	District 8 (n = 48)
Screening	7.8%	12.8%	18.2%	16.2%	8.7%	10.3%	13.1%	14.6%
Deferral	7.8	14.9	13.6	8.1	13.0	6.9	9.8	17.1
Collection	15.7	14.9	15.9	13.5	13.0	10.3	9.8	19.5
Routine testing	3.9	0	0	2.7	0	0	3.3	2.4
Viral testing	9.8	8.5	2.3	0	8.7	10.3	6.6	4.9
Labeling	5.9	10.6	6.8	5.4	21.7	10.3	8.2	2.4
Postdonation information	2.0	4.3	0	5.4	0	3.5	3.3	2.4
Quarantine	5.9	0	0	0	0	0	1.6	0
Storage	21.6	12.8	15.9	27.0	17.4	20.7	16.4	22.0
Machines	9.8	10.6	22.7	18.9	17.4	24.1	23.0	9.8
Miscellaneous	9.8	10.6	4.6	2.7	0	3.5	4.9	4.9

We found statistically significant differences between districts in blood facilities' receipt of Form 483 observations. For example, blood facilities in district 6 received significantly fewer observations than those in districts 1-3, 7, and 8 (see table 5.6).

Table 5.6: Blood Facilities That Received Form 483 Observations in Districts 1-8

District	Number in EIR analysis	Received observation	
		Number	Percent
1	35	17	48.6%
2	38	16	42.1
3	40	17	42.5
4	41	15	36.6
5	33	11	33.3
6	46	9	19.6
7	44	23	52.3
8	48	22	45.8

We also found disparities in the types of activities that warrant Form 483 observations. Why observations are issued inconsistently is not clear. It could be that different districts have different problems or that different inspectors and supervisors interpret the guidelines differently. FDA officials believe that different districts do, in fact, have different problems. However, they were not able to document for us the information on which they base this claim.

While some activities cited on the Form 483 appeared to be only tangentially related to the safety, purity, or potency of a product, other activities were not cited even though they clearly had the potential to affect safety, purity, or potency. For example, one blood facility was cited because its records did not reflect a machine weld alignment inspection, but another facility was not cited even though the FDA inspector found one donor who had mental retardation and did not understand several donor-screening questions on Chagas' disease, malaria, syphilis, or yellow jaundice (a possible symptom of hepatitis). This donor also told the FDA inspector that she was incapable of filling out the donation record and that the screener at the blood bank filled out all the information for her.

In 1996, FDA conducted a study of Form 483 observations in order to assist in providing clearer guidance in terms of the significance, content, and format of observations.²⁵ The study's conclusions were that the majority of Form 483 observations were valid; however, complete assessments could not be made outside the context of the EIR. The panel that conducted the study determined that the most appropriate manner in which to use these conclusions would be to develop a specific section for writing Form 483s in the blood bank training courses provided to blood bank inspectors. That FDA conducted this study suggests that it is aware of problems in Form 483 consistency and its conclusion about the need for additional training supports this viewpoint.

FDA also issues warning letters inconsistently. For example, one blood facility received a warning letter detailing several instances in which it had no written procedures for several processes such as determining donor suitability and preparing packed red cells. However, another blood facility that did not receive a warning letter knew that some of its blood units had

²⁵The study was conducted by a panel of regional and national biologic expert investigators.

tested positive for syphilis but was shipping them for further manufacture without labeling them positive for syphilis.²⁶

In another case, a blood facility was given 33 Form 483 observations that included problems in transfusion of three HTLV-I positive units of blood to three different patients, transfusion to a patient of an initially reactive HBsAg unit of blood that was not retested in duplicate, failure to file EARS, and “numerous donor deferral deviations, donor reentry deviations, computer entry deviations, lack of internal error and accident investigations, and lack of written SOPs.” However, this facility was not given a warning letter for the lack of written procedures (as well as the many other observations) while the blood facility noted above was given a letter for its lack of written procedures for donor suitability and preparing packed red cells.

Our survey respondents raised several issues that affect the consistency of inspections. Twenty-seven percent reported that they do not know what to expect from one inspection to the next; what one inspector finds acceptable another considers an observable event. And while respondents reported that their current inspection team was generally knowledgeable, 45 percent reported a wide variation in inspectors’ knowledge and training in blood-banking terminology and procedures.

When we asked FDA about its inspector training programs and policies, the agency reported that field investigators undergo a series of formal training courses and receive on-the-job training in all product and program areas. Its investigators are therefore regarded as generalists, particularly those with experience and advanced training. By the time investigators are assigned to conduct inspections, they have mastered basic inspection techniques and have had ample experience. While FDA uses the more experienced investigators for inspections as much as possible, the less experienced investigators do inspect facilities, and the agency has no readily accessible way of determining the frequency with which this occurs.

²⁶This facility had interpreted FDA’s memorandum on donor deferral and product distribution relating to syphilis testing as not requiring such labeling because the memorandum reads “the regulations do not require the labeling of each unit with the screening tests results.” It interpreted this memorandum as stating that source plasma could be used for further manufacture before test results were available because the memorandum reads “source plasma collected before serologic test results are received may be used for further manufacture.” FDA, in contrast, noted that the memorandum was intended to convey that once a plasma-collection facility had become aware of a donor’s positive results for syphilis, all units collected from that donor and held for shipment would have to be labeled as reactive. It appeared that the facility read the memorandum as meaning that as long as the blood was collected before the test results were completed, it did not have to label the products, regardless of the test results.

Such inconsistency in inspection activity has ramifications for FDA's ability to determine whether a blood facility is, in fact, in compliance with FDA rules and regulations. FDA expects blood facilities to have consistent practices that follow blood facility standard operating procedures and FDA guidelines. It is equally appropriate for FDA to make sure that inspections demonstrate consistent enforcement of FDA rules and guidelines as reflected in Form 483 observations and warning letters.

Summary, Recommendations, and Agency Comments and Our Response

We have highlighted many safety issues throughout this report that can be broadly categorized as technology barriers, human error, variations in blood-banking practice, and deficiencies in FDA's inspections and monitoring. Some of the hazards identified in chapters 2-5 are amenable to immediate steps to reduce risk, with some associated costs, while other issues are dependent on further research or actions by the blood industry. FDA can address four major areas: (1) gaps in the layers of safety that could have serious repercussions, (2) error and accident reporting, (3) the agency's regulations, and (4) inspections. Below we first summarize and then make recommendations affecting all four areas.

Summary

We answered the question, What are the elements of FDA's layer of safety and do they ensure that the blood supply is safe? We found 24 issues related to safety in the processes that blood facilities perform, and we summarize them below in tables 6.1 through 6.8. Table 6.1 presents the two issues identified for donor screening processes.

Table 6.1: Safety Issues in Donor Screening Processes

Safety issue	Summary
Uniform donor history	History-taking questionnaires are developed by individual blood facilities. Style and content of history taking may influence the accuracy and completeness of donor's answers. AABB's version is most comprehensive and readily available
Screening privacy	Privacy is required for the medical examination. The amount of privacy for screening donors varies across blood facilities. A lack of privacy during donor screening inhibits forthright communication. FDA recommends privacy for screening and has begun to include this in Form 483 observations

Table 6.2 presents the three issues identified in the area of donor deferral processes.

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Table 6.2: Safety Issues in Donor Deferral Processes

Safety issue	Summary
Timing of donor deferral registry (DDR) checks	Facilities differ on whether deferral status is checked before or after donation. Checking before collecting clearly reduces the likelihood that suspect units enter the system and eliminates unnecessary burden on ineligible donors
Computerizing donor deferral registries	Donor deferral registries vary in form and size from ARC's and ABRA's national, computerized systems to single facility's hard copy filing systems. FDA requires a donor check in some form of registry. Every facility could benefit in efficiency and accuracy with increased use of validated computerized donor deferral systems. Hardware and software costs are cited as a barrier for some facilities. Inexpensive personal computers might serve this purpose better than hard copy systems. Continued verification and validation is important for any system that a blood facility chooses to implement
Donor deferral notification	Donor notification varies by facility practice. FDA recommends the notification of donors deferred for HIV only. Many facilities notify donors who are permanently deferred for other reasons. Some notification does not take place. Not all facilities perform available licensed confirmatory tests to provide adequate information to these donors. Not notifying these donors could create public health problems

Table 6.3 provides a summary of bacterial contamination, the safety issue that we identified in the area of collection processes.

Table 6.3: Safety Issue in Collection Processes

Safety issue	Summary
Bacterial contamination	Bacterially contaminated blood products can cause serious harm. An increase in the use of platelets has added to the number of cases of bacterial sepsis from blood transfusions. Data suggest that this may be the leading cause of fatalities resulting from transfusions. Also, red blood cells are recognized as harboring bacteria under some conditions. Technological limitations for identifying blood products that have been bacterially contaminated make it difficult to test blood and blood products for this problem. However, methods for detecting bacteria immediately prior to transfusions are under development

A summary of the issue of blood typing, a safety concern in the area of routine testing processes, is provided in table 6.4.

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Table 6.4: Safety Issue in Routine Testing Processes

Safety issue	Summary
Blood typing	Human error can lead to incorrect blood typing. The process has no inherent weaknesses if typing is done properly and correctly typed and labeled units are transfused to the intended recipient. Data illustrate that this does not always occur. Although such mistakes appear to be few, the consequences can be fatal

We identified eight safety issues of concern in the area of viral testing processes. These are summarized in table 6.5.

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Table 6.5: Safety Issues in Viral Testing Processes

Safety Issue	Summary
Window period	Increasingly sophisticated tests are closing the window period for viral markers. Gains from additional tests will decrease because of the small window period presently found with current tests. This period will probably never be completely eliminated. Other mechanisms, such as improved donor screening, might eliminate more window period donations than improved viral testing
Autologous testing	Many blood facilities test autologous units for viral markers. Some do not perform these tests. Survey data illustrate that untested units can make their way into the general blood supply system and can be transfused to unintended recipients. This could result in serious patient harm
Confirmatory testing	Facilities vary in confirmatory testing practices. FDA requires confirmatory testing for units repeatedly reactive for HIV. Units repeatedly reactive for other viral markers do not always have confirmatory testing performed. Also, confirmatory tests for some viruses have not been developed by test kit manufacturers or licensed by FDA. Facilities thus cannot adequately inform donors of their disease status, a potential public health problem
Recipient notification and lookback	Facilities vary in their policies for recipient notification and lookback. FDA requires consignee and recipient notification and lookback for units that are from a donor implicated in subsequent donations that are positive for HIV. No requirements exist for other viral markers. Unnotified recipients of units that may be positive for other viruses could represent a public health hazard
Divergent viral strains	Technology barriers hamper the ability of current tests to detect divergent strains of viruses in blood. These are usually rare cases and are not often found in the U.S. blood supply. CDC conducts surveillance to determine the extent of divergent strains of existing viruses in the United States
Viral inactivation	Fractionation companies employ several inactivation and removal techniques to destroy viruses in plasma pools. However, different manufacturers producing similar products may or may not use these techniques
Test sensitivity	Viral testing captures the vast majority of positive units. Some tests are less sensitive than others and some individuals are positive for viral markers but carry low-titre antibody levels that are not caught by current tests
Emerging viruses	Many viruses not present in the U.S. blood supply are not tested by blood facilities. Some newly discovered viruses (such as HGV) may pose a problem, since preliminary data indicate that 1-2% of U.S. blood donors are infected with this virus, which can cause chronic hepatitis. CDC continues to monitor emerging viruses to determine the extent of problems in the United States

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Table 6.6 provides summary information on the one safety issue we identified in the area of postdonation information.

Table 6.6: Safety Issue in Postdonation Information Processes

Safety issue	Summary
Errors and accidents	Information given by a donor after donating that would have excluded that person had it been known at the time of collection accounts for a large number of EARs submitted to FDA. This may indicate that the process is working to ensure a safe blood supply, or it may indicate that the guidance on what is to be included in an EAR that relates to postdonation information is poorly understood. The preponderance of these EARs calls into question the adequacy of screening processes. Also, there is a large discrepancy between EARs submitted by licensed facilities and plasma centers, even though they collect approximately the same number of units

Table 6.7 provides summary information on the single issue we identified in the area of storage and distribution processes.

Table 6.7: Safety Issue in Storage and Distribution Processes

Safety issue	Summary
Inventory management	Data indicate that because of human error, many units are unaccounted for or lost before the unit is to be transfused. Surveys of blood facilities corroborate this problem. Although not directly a safety issue, it results in many donated units not being used

We identified seven safety issues related to FDA's monitoring activities. These are summarized in table 6.8.

Table 6.8: Safety Issues in FDA Monitoring Activities

Safety issue	Summary
EARs	Only licensed facilities are required to submit EARs to FDA. FDA information from annual summaries of EARs suggests that unlicensed facilities are underreporting their EARs (they collect 10% of the blood but submit about 1% of EARs). Plasma centers reported at rates much lower than licensed blood facilities, despite collecting equivalent amounts of blood products. Also, the timeliness of reporting EARs to FDA has been called into question. FDA has also been slow to investigate EARs that may warrant a recall
Use of guidelines and recommendations	FDA guidance to blood facilities is often ambiguous and results in confusion within the blood industry as to what actions are required and what actions are recommended
Use of EIR information	FDA does not perform statistical analyses of information contained in EIRs and corresponding Form 483 observations
Tracking of facilities	FDA's current list of active registered blood facilities contains blood facilities that should not be on the list. Also, information on some blood facilities is inaccurate. The number of these types of cases is small
Timing of inspections	Some blood facilities are not being inspected in the time periods set by FDA's guidelines
Incomplete inspection reports	Many EIRs do not contain pertinent information from which FDA supervisors or subsequent inspectors can determine what blood banking processes have been inspected. Analysis of EIR information could provide FDA with pertinent data on trends in Form 483 observations and other issues that arise during an inspection
Disparities in inspection reporting	Form 483 observations differ between districts and include disparities in what is considered an action that should result in a Form 483 observation or warning letter

In summary, we found that there continue to be issues of safety that FDA, the blood industry, and the research community need to address. As we have indicated in another report, the nation's blood supply is safer than ever before, and the risks associated with blood transfusions are relatively small compared to many other medical procedures and life activities.¹ Yet, some areas can be improved by agency action that would further increase safety.

Recommendations

We have nine recommendations by which HHS could improve the safety of the nation's blood supply. Six concern gaps in the layers of safety, one has to do with error and accident reporting, and two relate to HHS's regulations and FDA inspection processes.

¹See U.S. General Accounting Office, Blood Safety: Transfusion-Associated Risks, GAO/PEMD-97-2 (Washington, D.C.: 1997).

Donor Notification

We recommend that the Secretary of HHS require that blood facilities notify donors who have been permanently deferred. This notification should be based on positive confirmatory results for viral markers (for the viruses that have licensed confirmatory tests) and all other medical reasons that result in permanent deferral (for example, the intake of human pituitary growth hormone). Notification should include the reason for the permanent deferral, possibilities for re-entry as a donor, and counseling or referral to the donor's physician (including, when pertinent, actions to be taken to minimize transmission of viruses to others). We recommend such notification because of the public health consequences of not informing donors.

Collection

We recommend that the Secretary of HHS require blood facilities quality-assurance programs to include processes that monitor for bacterial contamination. Bacteria can enter blood products during collection through a donor's skin contamination or illness. Bacteria can also be introduced during manufacturing, as in the water baths in the making of certain blood components. Both collection and manufacturing processes are within the control of blood facilities and could be modified if quality-control information suggested that products were bacterially contaminated.

Viral Testing

We recommend that the Secretary of HHS require viral testing for all autologous units. Since the practice of viral testing for autologous units varies and since mislabeling and transfusion errors do occur with some frequency, HHS should require that the blood industry minimize this vulnerability in the system by testing all units, whether autologous or allogeneic.

We recommend further that the Secretary of HHS require confirmatory testing of all repeatedly reactive viral test results for which there is a licensed confirmatory test. We recommend this requirement in order that the blood facility be given as much information as possible when it considers whether to conduct lookback and how to counsel donors and recipients who have a positive confirmatory test. However, the information that should be provided if confirmatory tests are negative or indeterminate should be left to the discretion of the blood facilities and the recipients' physicians.

**Recipient Notification and
Lookback**

We recommend that the Secretary of HHS require that transfusion recipients be notified when they have been transfused with blood from a donor whose subsequent donations were found positive in confirmatory testing. Notifying recipients of blood that is negative or indeterminate on a confirmatory test should be left to the discretion of their physicians. This recommendation is intended to reduce the potentially adverse public health consequences of not informing recipients.

We also recommend that the Secretary of HHS require lookback in such situations to find implicated blood units that have not been transfused or further manufactured into blood components or plasma derivatives. The reasonable time period for lookback varies with each virus, and decisions should be made in consultation with the blood industry. Thus, it might be determined that lookback procedures should be implemented beginning at a specific date when a memorandum to blood facilities is made final. We believe that such a recommendation should be a required practice as soon as possible.

**Error and Accident
Reports**

We recommend that the Secretary of HHS require unlicensed blood facilities to report all EARS to the agency. Our information, analysis, and conclusions highlight the need for such a requirement. Such information will provide FDA with additional data from which to direct inspections of particular blood facilities as well as the blood industry as a whole.

Regulations

We recommend that the Secretary of HHS publish in the form of regulations the guidelines that the Secretary believes are essential to ensure the safety of the nation's blood supply and that it clarify its position on the extent to which facilities should adopt the agency's guidelines and memoranda in order to remain in compliance with HHS regulations. The blood industry has consistently identified this ambiguity as a source of confusion and frustration and has raised concerns about the practice of setting standards through inspection observations and warning letters. Policy in the form of guidelines does not have the enforcement power or public input of formal regulations, whereas the use of regulations may increase compliance and decrease the likelihood that guidelines will be misinterpreted or applied inconsistently.

Inspection Processes

Finally, we recommend that the Secretary of HHS correct the problems we have identified in FDA inspection processes. FDA needs to perform

statistical analyses of inspection reports, develop policies to FDA inspectors that would require them to list on the inspection reports what they had observed during an inspection, publish better guidance to inspectors and district offices on the types of activities that warrant observation reports and warning letters, and ensure that all blood facilities are inspected in a timely fashion. We believe that these changes are necessary to improve FDA's ability to discriminate between facilities that comply and those that do not.

Agency Comments and Our Response

In a written response to a draft of this report, the Department of Health and Human Services (HHS) generally concurred with our findings and recommendations. Points of disagreement were primarily related to our findings and recommendations on recipient notification and lookback procedures for viruses other than HIV and FDA's inspection process and knowledge of the compliance status of individual blood facilities and the overall blood industry. HHS also provided a number of technical and editorial comments, which we have incorporated into the report as appropriate.

HHS agreed that notifying donors of their deferral status and the medical reason for deferral could enhance public health. However, HHS pointed out that FDA has historically considered its jurisdiction to apply primarily to product safety, purity, and potency. It agreed to explore regulatory options within its existing authority for requiring notification.

HHS agreed that a reduction in bacterial contamination of blood products is an important safety issue. HHS noted that this issue is not easily resolved because of the limits of technology, and a study is currently under way to estimate the incidence of, and identify risk factors for, bacterial contamination of blood and blood products. We understand the technical limits in identifying bacterial contamination and have recommended that there be a requirement that blood facilities have a quality-assurance program that includes processes to monitor for bacterial contamination.

HHS agreed that testing autologous units for viral markers is an important issue and is working on a recommendation to blood facilities regarding testing of such units. However, we believe that such practices should be required in order to further reduce the risk of transfusion-associated disease transmission.

HHS agreed that units implicated from subsequent donations that are found to be positive for viral markers should be identified and that consignees of such products should be notified. However, HHS requires such action only for HIV-implicated units. We believe consignee notification and identification of blood and blood products should be required for all subsequent donations that are found to be repeatedly reactive for any viral markers currently tested for by blood facilities and for which a positive result on a licensed confirmatory test has occurred. In regard to confirmatory testing, FDA has recommended these tests be performed for HCV and HbsAg. HHS has recently issued a final rule that requires confirmatory testing on units that are repeatedly reactive for HIV. We believe that confirmatory testing should be required for all units that test repeatedly reactive and have a licensed confirmatory test. HHS presently requires notification of recipients of units that are from a donor who subsequently tests repeatedly reactive and is positive by a licensed confirmatory test for HIV. We believe that such procedures should be required for all recipients who received blood or blood products that are from a donor who subsequently tests repeatedly reactive and positive by a licensed confirmatory test.

HHS pointed out several reasons why lookback procedures that include notification of consignees and identification of implicated units, confirmatory testing, and notification of recipients should not be performed for non-HIV viruses. We have outlined in the report reasons that run counter to HHS's arguments. We believe that such lookback procedures should be required for all viruses currently tested for by blood facilities for which there is a licensed confirmatory test in order to further reduce the risk of viral transmission through blood and blood products and to decrease the risk of secondary transmission of these viruses to the public.

HHS agreed that error and accident reporting requirements should be applicable to all blood facilities and is currently working on a proposed rule to require submission of error and accident reports by unlicensed, registered blood facilities.

HHS agreed that clarification of the nature of FDA's guidance documents is an important issue and recognizes the need to have more uniformity in its development and use of guidance documents. To this end, public comments have been solicited on this issue through a notice published in the Federal Register on March 7, 1996 (61 Fed. Reg. 9181). We believe the use of guidance documents is an important tool that FDA can use to react quickly to emerging public health threats and advances in medical

knowledge and technology. We also believe that some recommendations in these guidance documents are important enough that they should be codified in federal regulations. Through this process, such recommendations can also be opened up for public comment for review and possible revision.

HHS disagreed with much of our recommendation that FDA should perform statistical analysis of inspection reports, require FDA inspectors to list on the inspection reports what had been observed during blood facility inspections, provide better guidance on the types of activities that warrant reports on deviations and warning letters, and ensure that all blood facilities are inspected in a timely fashion. HHS pointed out that FDA already reviews and analyzes inspection reports, both for identification of conditions warranting immediate action and for longer-term trends. Furthermore, HHS noted that the compliance program, investigations operations manual, regulatory procedures manual, and other FDA directives to investigators state the information that should be included in EIRS.

Our analysis of EIRS and Form 483 observations was performed to examine compliance rates among a nationally representative sample of blood facilities. After examining the EIRS in our sample, we concluded that compliance rates could not be determined because many of the EIRS had very little information as to what activities had been inspected and observed by the FDA investigator. We were aware that FDA's policy was to allow investigators to list the compliance program under which the blood facility was being inspected. By doing this, FDA assumes that all directions included in the compliance program are followed unless otherwise stated on the EIR. However, as we have pointed out in this report, such a blanket assumption cannot be made, since we found instances in which this policy was not followed by FDA inspectors. We do not believe that it poses a great burden to ask that inspectors write a sentence or two listing the areas they examined, and we found instances in which inspectors made such notations.

As a result of our initial conclusions regarding the robustness of information contained in the EIRS, we performed statistical analyses on Form 483 observations. We found differences in the number and kind of Form 483 observations across FDA districts as well as examples of inconsistent application of Form 483 observations and warning letters. HHS noted that FDA has performed similar analyses and points to the 1992-93 FDA task force on ARC as an example. However, when we reviewed these

analyses, we found them to be simply a compilation of Form 483 observations separated into different categories. No statistical analysis was performed on these data.

Furthermore, FDA conducted a study of form 483 observations made by inspectors. The study's conclusions were that the majority of Form 483 observations were valid, but complete assessments could not be made outside the context of the EIR (of course, with little information in many EIRS, this might be problematic). Those conducting the study determined that the most appropriate manner in which to use these conclusions was to develop a specific section for writing Form 483 observations in the blood banking training courses provided to blood bank inspectors. We believe that conducting this study suggests that FDA was aware of problems in Form 483 consistency, and its conclusion for additional training supports this viewpoint.

We believe that FDA's oversight of the blood industry could benefit from the types of analyses we have recommended. HHS noted that such analysis would be difficult and costly to perform. We disagree with this assessment because we performed analyses on Form 483 observations that provided a wealth of information on the number and kind of observations being handed out by FDA inspectors. Furthermore, such analyses could be similarly performed on EIR information. Of course, this would be worthwhile only if FDA changed its present policy and required its inspectors to specifically note on the EIR the areas of a blood facility that they had inspected. Such a change would provide FDA with needed information on compliance rates between different types of blood facilities, areas of blood banking that might require more or less investigative oversight, possible inconsistent application of FDA guidance by inspectors, and changes in compliance rates as a result of the institution of new recommendations to blood facilities.

Viral and Nonviral Agents Described

In this appendix, we describe viral and nonviral agents that may affect the U.S. blood supply. We provide information on the characteristics of each agent, on how it is transmitted to humans, and on some of the clinical outcomes from infection. We also highlight guidelines and recommendations to illustrate the federal government's role in ensuring that these agents are eliminated from the blood supply.

Viral Agents

Among others, the agents described below are transmissible by blood transfusions and therefore can pose a risk to transfusion recipients: CMV, HAV, HBV, HCV, HIV-1 and HIV-2, HTLV-I and HTLV-II, and parvovirus.¹

Cytomegalovirus

CMV is a DNA virus that belongs to the herpes virus group and becomes latent after primary infection. It is acquired by respiratory or sexual contact or from blood components or organ allografts. It is a cell-associated virus and does not reside in plasma or serum in appreciable amounts. Once a person has been infected with CMV, the host develops a lifelong persistence of CMV antibodies.

CMV is widespread in the general population. While it is asymptomatic in approximately 80 percent of the population—healthy individuals—it is a major cause of morbidity and mortality in immunocompromised individuals, such as newborns, bone marrow or organ transplant patients, AIDS patients, and some oncology patients. People who are at highest risk for CMV infection and disease are those who are seropositive and become infected from reactivation of latent CMV.

There are no regulatory requirements nor does FDA have recommendations pertaining to CMV because it is ubiquitous in the general population and has little effect on immunocompetent individuals. Because between 40 percent and 100 percent of the adult population is infected with CMV (depending on geographic variability), FDA has decided that testing for this virus is not warranted. Recommendations regarding CMV are found in the AABB technical manual, which notes that

“where transfusion-associated CMV disease is a problem, cellular components should be selected or processed to reduce the risk to infant recipients weighing less than 1,200 grams

¹Among the many other viruses transmissible through blood are tropical viruses such as yellow fever, Dengue fever, ebola virus, and malarial infections; others include parasitic infections such as filariasis, toxoplasmosis, babesiosis, and Lyme disease (the latter caused by a spirochete). HDV, HEV, and HGV, discussed in chapter 3, are recently discovered hepatitis viruses that are transmissible through transfusion.

at birth, when either the infant or the mother is CMV antibody negative, or that information is unknown.”²

However, there is some evidence that using CMV-negative blood could actually increase susceptibility to infection in infants whose mothers are seropositive, and some studies do not support the need for specialized components for neonates.

Hepatitis A Virus

HAV is a nonenveloped RNA virus that is very stable and retains its physical integrity and activity at high temperatures.³ It has an incubation period of 2 to 6 weeks and is typically shed in the stool during the final week of incubation, at which time there is transient viremia. It is almost always transmitted through the fecal-oral route or through contaminated water. Transmission through blood products is rare because of the short viremic stage and because no chronic carrier state exists.

Since no viral persistence exists, liver-associated injury is transient. The clinical severity of HAV is directly related to an individual’s age. Jaundice is unusual in children younger than 2 years old, while fulminant hepatitis and death are much more likely in persons older than 50. Approximately 100 deaths are reported each year in the United States.

Approximately 25 cases of transfusion-transmitted HAV had been reported by 1989, representing an overall risk of less than one per million blood units. This is probably because HAV is transmitted through the collection of blood during a short viremic phase during acute infection.

Neither regulations nor memoranda contain information pertaining to HAV because it is rarely transmitted through blood and blood products. However, a recent report noted an outbreak of HAV infection among hemophiliacs who had received pooled plasma products. These products had been inactivated with a solvent-detergent treatment, but this would have had little effect on a nonenveloped virus such as HAV. Some have suggested that the addition of a second virus inactivation procedure (such as heat inactivation) aimed at nonenveloped viruses might eliminate this risk.

²American Association of Blood Banks, AABB Technical Manual, 11th ed. (Bethesda, Md.: 1993), pp. 104-5.

³Viruses are frequently characterized by the presence of an envelope around them. Viruses consist of a nucleic acid core surrounded by a capsid, which protects the nucleic acid from enzymes in a host organism. Capsids, in turn, can be surrounded by an envelope. This envelope is important in the adsorption of the virus into cell surfaces for infectivity.

Hepatitis B Virus

HBV is a small DNA virus. Its replication involves DNA molecules that lead to the formation of RNA intermediate molecules. This, in turn, starts the production of viral DNA by reverse transcription and, eventually, the complete viral genome. HBV's mutation rate is quite high but, because of its small genome, it is often incapable of forming infectious viruses.

The discovery in 1965 of Australia antigen, now known as hepatitis B surface antigen (HBsAg), and its subsequent association with HBV led to the development of sensitive, specific markers of HBV infection. HBsAg can be detected in serum 30 to 60 days after exposure to HBV and persists for varying periods, depending on the severity of the infection. Donor screening for HbsAg began in 1969 and became mandatory in 1972.

HBV is a major cause of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The most serious consequences stem from chronic HBV infection, which occurs in 6 to 10 percent of infected adults, 25 percent of infected children, and 70 to 90 percent of infected infants. In the United States, approximately 300,000 persons are infected with HBV annually. Of these, 50 percent become ill with symptoms of hepatitis, 10,000 require hospitalization, and 350 die of fulminant disease. Furthermore, about 15 to 25 percent of carriers of HBV develop chronic active hepatitis, which often progresses to cirrhosis. An estimated 6,000 persons die each year from HBV-related chronic liver disease. Approximately 80 to 90 percent of patients who receive a component of blood from a donor infected with HBV will acquire the infection.

Several studies have concluded that some persons infected with HBV might transmit it despite being HBsAg negative. A second hepatitis B test was instituted in 1986-87 (anti-HBc) as a surrogate marker for non-A, non-B, hepatitis, but it was also seen as a way of catching some negative HBsAg donations that were, in fact, positive for HBV. However, recent information has shown that HBV may be transmitted despite rigorous testing of donors for HBsAg and HBc antibodies. These cases may be caused by low-titre HBV infections from HBV variants that have mutated.

HBV can be transmitted through percutaneous or permucosal routes, and infective blood or body fluids can be introduced at birth, through sexual contact, or by personal contact. According to CDC, other groups at increased risk include injecting drug users, heterosexual men and women and homosexual men who have multiple partners, infants born to HBV-infected mothers, recipients of certain plasma-derived products

(including hemophiliacs), hemodialysis patients, and health workers who have contact with blood.

A plan that CDC developed in 1989 to eliminate HBV transmission in the United States called for screening all pregnant women for HBsAg and immunizing infants of HBsAg-positive women, integrating HBV vaccines into routine childhood vaccination schedules, and vaccinating high-risk individuals in selected settings. CDC estimated that this would eliminate HBV as a “significant health problem” by 2015. Immunization of infants began in 1993 with the goal of vaccinating 90 percent of them by 1996.

Title 21 CFR section 610.40 stipulates that each donation of blood, plasma, or serum should be tested for the presence of HBsAg, while section 610.41 notes that persons known to have previously tested positive for HBsAg cannot serve as donors of blood, plasma, or serum except for vaccine and laboratory purposes. This also applies to source plasma. FDA’s December 2, 1987, “Recommendations for the Management of Donors and Units That Are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)” outlines several issues pertaining to HBV: all donations should be tested by a third generation test, HBc antibody testing can be used to further evaluate the status of donors, and, following a flow chart for HBV testing, donors who had previously tested positive for HBsAg could be retested for reentry into the donor pool.⁴

As noted previously, FDA recommended the anti-HBc test in 1986-87 as a surrogate marker for non-A, non-B, hepatitis. In 1991, FDA recommended the test’s use to detect products repeatedly reactive for HBV. Additionally, an FDA compliance manual outlined the reentry algorithm for HBsAg, although it did not include a reentry algorithm for anti-HBc because no confirmatory test is available. Source plasma centers must test for HBsAg but do not have to test for anti-HBc because the exclusion of repeatedly reactive HBc plasma from pools processed into derivatives might result in decreased safety of the derivatives as a result of a reduction in antibody to HBsAg.

Hepatitis C Virus

Non-A, non-B, hepatitis was first recognized in 1974. In 1989, HCV was isolated and determined to be the major cause of most transfusion-associated non-A, non-B, hepatitis. Replication of HCV occurs

⁴CDC’s April 19, 1991, Morbidity and Mortality Weekly Report outlines HBV and HCV guidelines for notifying donors and for medical evaluation and counseling.

primarily in the liver; however, the mechanism of cell destruction in acute and chronic infection is largely unknown.

Acute hepatitis C is characterized by mild or asymptomatic infection in most patients with a gradual onset that may include vague abdominal discomfort, nausea, vomiting, malaise, and absence of appetite. Acute HCV infection results in clinically apparent illness in 20 to 30 percent of cases and rarely leads to fulminating fatal disease. Chronic hepatitis develops in an average of 70 percent of infected persons. Even in the absence of biochemical evidence of chronic liver disease, persistent infection develops in at least 85 percent of infected persons.

No effective neutralizing immune response to HCV has been identified. The genetic heterogeneity of HCV and its ability to undergo rapid mutation probably represents the mechanism by which HCV evades host immune surveillance and establishes and maintains persistent infection. Parenteral transmission for HCV includes blood transfusions and recipients of plasma derivatives, hemodialysis and organ transplant recipients, IV drug users, and health care personnel.

HCV is transmitted efficiently by large or repeated percutaneous exposures to blood such as through transfusion of blood or blood products from infectious donors or injection drug use. While overt percutaneous exposures to HCV (for example, accidental needle sticks) have been documented as means of HCV transmission, the role of mucous membrane and inapparent parenteral exposures is not well defined.

With regard to plasma derivatives, hemophiliacs transfused solely with untreated or incompletely inactivated clotting factor concentrates have HCV prevalence of 80 to 90 percent; hemophiliacs who receive appropriately inactivated components or single-donor cryoprecipitate are generally HCV negative. Studies have found that whole-blood recipients who receive a component of HCV-infected blood are 80 to 90 percent likely to acquire the infection.

The natural history of HCV infection is not well understood. An estimated 20 percent of patients ultimately develop cirrhosis, and HCV infection has been associated with hepatocellular carcinoma. Chronic HCV infection may be symptomatic or asymptomatic, and patients with HCV infection commonly have fluctuating levels of aminotransferase. There is no correlation between aminotransferase level and disease severity based on

liver biopsy findings, and up to one third of patients with normal aminotransferase levels have evidence of chronic hepatitis on biopsy.

Population-based studies of patients with chronic liver disease suggest that HCV may be as important as or more important than alcohol as a cause. In one study conducted in Jefferson county, Alabama, 40 percent of identified patients with chronic liver disease had evidence of HCV infection, 25 percent had HCV infection alone, and 14 percent had both HCV infection and a history of excessive alcohol intake. Applying these proportions to the estimated 32,000 deaths each year in the United States from chronic liver disease would find that approximately 8,000 to 10,000 deaths each year may be related to chronic HCV infection.

Title 21 CFR section 640.3(c) states that no person should be allowed to be a source of whole blood who has a history of hepatitis, a history of close contact within 6 months of donation with an individual with viral hepatitis, or a history of having received within 6 months human blood or a derivative of human blood that FDA had advised blood facilities was a possible source of viral hepatitis.⁵ However, there is no specific mention of testing for HCV for whole blood (sections 610.40 and 610.41) or source plasma (section 640.67).

FDA has issued several memoranda regarding HCV since the introduction of testing in 1990. Its April 23, 1992, "Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma, and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen" outlined the major guidance for HCV. It recommended that any repeatedly reactive blood or plasma unit not be used and that a donor reentry protocol could not be followed because of the lack of a more specific licensed test. An August 1993 revision outlined a reentry protocol for donors who were positive for HCV because of the introduction of such a test. However, the recommendation did not recommend any lookback procedures for previously collected products from donors who subsequently tested positive for HCV.

Human Immunodeficiency Virus

HIV-1 and HIV-2 are retroviruses that are unique in their replication cycle: following entry into a host cell, typically by fusion of the virus and host-cell membrane, a reverse transcriptase enzyme copies viral RNA from the virus into complementary DNA. A virus-associated integrase then

⁵This 6-month deferral was changed from a 1-year deferral that had been outlined in an April 23, 1992, FDA memorandum.

mediates the integration of this complementary DNA into random sites in the host's chromosomes. Replication ensues and is followed by a "budding" from the plasma membrane such that the virus can infect other cells and, if shed into body fluids, other organisms.

Although experts now know that the HIV epidemic began to spread in the late 1970s, it was not until 1981 that clusters of Kaposi's sarcoma and pneumocystis pneumonia were recognized in homosexual men in New York and Los Angeles. It was also in late 1982 that AIDS-like illnesses were reported in hemophiliacs and recipients of blood components. Less than a year later, the HIV-1 virus was discovered, and FDA required an anti-HIV-1 test by March 1985.

Several studies have examined factors that affect the transmission rates of HIV. Studies have identified that the rate of progression to AIDS is more rapid for transfusion recipients and for those who receive transfusions from donors who are subsequently diagnosed with AIDS within 2 years of donation. However, subsequent studies have refuted these findings.

Studies have suggested that variables that correlate with the likelihood of HIV transmission include type of blood component and duration of storage. Washed red cells stored more than 21 days had significantly lower transmission rates than other components. Thus, manipulation of blood through the reduction of viable leukocytes or free virus (through leukocyte filtration) in plasma may help reduce infectivity. Furthermore, studies have noted that the age of both the donor and the recipient correlates with the disease's progression rate, older patients showing symptoms of AIDS earlier than younger ones.

According to federal regulations, each donation of blood or blood component is to be tested for antibody to HIV by a test approved by FDA. Additionally, FDA recommends that blood is to be tested for p24 antigen for HIV-1. In dire emergencies, a blood facility can issue blood products before the results of tests for antibody to HIV have been performed. However, such tests must be conducted as soon as possible after the blood products have been issued. These regulations apply also to source plasma.

An April 1992 FDA memorandum entitled "Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products" outlines several steps blood facilities are to take to protect the blood supply from HIV. It recommends education to permit a prospective donor's self-exclusion before giving blood and

criteria for permanent deferral based on risk behavior, reentry algorithms, retrieval and quarantine of prior collections, recalls of HIV positive blood, and “second exclusion opportunities” such as telephone callbacks, or CUES. Additionally, both AABB and FDA have issued a series of questions that donors are to be asked to determine whether they manifest high-risk behavior.⁶

Human T-Cell Leukemia-Lymphoma Virus

HTLV-I is similar to HIV in the manner in which it replicates itself (that is, retroviruses). It has been associated with two main diseases: adult T-cell leukemia (ATL) and tropical spastic paraparesis or HTLV-I-associated myelopathy (TSP/HAM). HTLV-II has been associated with certain neurological diseases similar to TSP/HAM.⁷ It is believed that only about 4 percent of persons who are infected with HTLV-I in childhood develop leukemia-lymphoma, and no cases of ATL have been reported among U.S. transfusion recipients. Estimates vary widely on the rate of infection of HTLV-I with a subsequent diagnosis of TSP/HAM.

In the 1980s, research performed in Japan and the Caribbean, where HTLV was endemic, documented that HTLV could be transmitted through transfusions. As a result, ARC conducted a study in 1986-87 to examine whether HTLV was prevalent in the U.S. blood supply. The study concluded that there would be about 2,800 new HTLV-I infections annually in the United States through blood transfusions. Therefore, U.S. blood facilities began screening for HTLV-I when FDA-licensed test kits became available in November 1988.

Several studies have examined factors affecting HTLV transmission rates. The Transfusion Safety Study found that there was no transmission of HTLV-I or HTLV-II in recipients of seropositive donations from acellular components (such as fresh frozen plasma and cryoprecipitate). This is because of the required cell association of the virus. The study also found that there was no “probable transmission” by components that had been stored more than 14 days.

⁶As noted previously, FDA now requires consignee notification, more specific testing of units repeatedly reactive for HIV, and notification of patients transfused with blood from donors who subsequently test positive for HIV.

⁷A recent study suggests an increased prevalence for a variety of infections in HTLV-II positive donors, which suggests immunologic impairment. See E. L. Murphy et al., “Medical Conditions Associated with Human T-Lymphotropic Virus Types I and II (HTLV-I and -II) Infection,” *Transfusion*, 36 supp. (1996), 43S.

Another study found that 26 percent of recipients of seropositive donations became infected with HTLV (26 out of 95 seropositive donations). This rate compares favorably with rates reported in Japan and the Caribbean that showed cellular component transmission rates at 63 percent and 45 percent, respectively. One possible reason for this difference is that blood in the United States is often stored longer than in Japan and the Caribbean. Estimates vary widely on the rate of infection of HTLV-I and subsequent diagnosis of TSP/HAM (0.068 percent to 2.4 percent).

There are no specific federal regulations on testing for HTLV for either whole-blood collections or source plasma. A November 1988 FDA memorandum entitled "HTLV-I Antibody Testing" outlines several recommendations regarding HTLV: handling of donations that are repeatedly reactive; donor deferral, notification, and counseling; blood product labeling; and education and informed consent. The memorandum also includes background information on HTLV-I and HTLV-II, a summary of recommended actions on repeatedly reactive units, and medical and biological aspects of HTLV-I presented by CDC in its Morbidity and Mortality Weekly Report of December 9, 1988.

Although there are no requirements regarding HTLV, an FDA compliance manual recommends the testing of donations of whole blood and cellular components for HTLV-I. Additionally, firms that have licenses for source leukocytes or red-blood-cell immunization programs must test cells for HTLV-I. However, source plasma centers do not have to test for HTLV because of its cell association. As noted above, there is no reentry algorithm for HTLV because there is no confirmatory test.

Parvovirus

Parvovirus is similar to HAV in that it is a nonenveloped virus. It is a single-stranded DNA virus discovered in 1975 in the serum of normal blood donors; in most surveys, 50 percent of adults show evidence of past infection. The incubation period may vary from 6 to 16 days and illness begins with fever, malaise, and the development of a skin rash on the face, trunk, and extremities. It can also be severely detrimental to fetuses.

In healthy persons, antibodies develop in about 1 week and the infection is cleared fairly rapidly. It is believed that in most healthy persons, the virus does not persist in the circulation but some evidence suggests infected persons remain chronic carriers. Additionally, because it is a nonenveloped virus, hemophiliacs have a 90-percent seropositivity rate.

Solvent-detergent methods of inactivation of plasma products are ineffective, and even heated factor concentrates have a transmission rate of 30 to 60 percent. However, parvovirus is similar to CMV in that it appears to affect only small subsets of the population such as immunocompromised individuals.

Blood facilities do not test for parvovirus because of the ubiquitous nature of the virus in the general donor population; the side effects of infection, which are mild for most individuals; the nonexistence of a licensed test to detect parvovirus; and a short viremic phase that results in only rare transmission of parvovirus through transfusions. As a result, the CFRs contains no requirements nor does FDA have recommendations or guidelines.

Nonviral Agents

Several nonviral agents are transmissible by blood transfusions and therefore can pose a risk to transfusion recipients. Those discussed below are caused by a parasite (Chagas' disease), a prion (Creutzfeld-Jacob disease), and a bacterial spirochete (syphilis).⁸

Chagas' Disease

Trypanosoma cruzi is the causative agent for Chagas' disease. It is a protozoan parasite that upon human infection proceeds to an acute parasitemic phase that lasts a few weeks and a chronic phase that is lifelong. Recent attention to this disease in the United States stems from the growing Hispanic population from Central America and South America, where it is endemic.

Chagas' disease has a 10-to-14-day incubation period after which follow fever and enlargement of the lymph nodes and liver. Approximately 10 percent of persons who are infected show signs of damage to the heart, colon, esophagus, myocardial cells, and cells of these organs. The primary mode of transmission is skin contact with the feces of the reduvid bug. Infections in children can carry a mortality rate of 10 percent in endemic areas, while older persons are more likely to develop a chronic illness with no signs of infection. Two thirds of infected persons have no initial symptoms.

⁸Although no scientific information supports the notion that CJD is transmitted through blood or blood products, it has been transmitted through cornea transplants and brain tissue transplants as well as through the administration of human pituitary-derived growth hormone. There is disagreement in the scientific community as to whether prions are the vehicle by which CJD is transmitted.

It often does not manifest symptoms for 20 years. The classic form of Chagas' disease usually occurs decades after infection. Estimates are that more than 100,000 individuals are infected with *T. cruzi* in the United States. It is also estimated that at least in South America, the transmission rate is between 14 and 49 percent for patients who receive transfusions from donors who are positive for the parasite. Some have estimated that there are probably more than 100 transfusion-associated *T. cruzi* infections each year in the United States. However, the actual incidence is hard to estimate because of the difficulty of diagnosing Chagas' disease and the frequency of asymptomatic infection.

There are no federal regulations pertaining to Chagas' disease and FDA has no requirements because, until recently, *T. cruzi* has rarely been found in the U.S. blood supply. However, the AABB uniform donor questionnaire, which complies with current FDA regulations and recommendations for donor suitability, has a question on whether the donor has ever had Chagas' disease. Additionally, blood facilities in geographic areas with a high proportion of Hispanic immigrants include more detailed questions in their donor history interviews. Prospective donors who do have a history of Chagas' are permanently deferred.

Creutzfeldt-Jakob Disease

There is some disagreement on the cause of CJD, although efforts by some scientists point to a prion, a small protein particle that resists inactivation by procedures that modify nucleic acids. These prion proteins can be found in the brain tissue of patients dying of CJD. The prion is infectious but does not invoke an immune response.⁹ Infection with this agent leads to a degenerative neurologic disease that manifests as progressive dementia with memory loss and poor judgment and intellectual function. The infected person can remain asymptomatic for decades after infection but then progresses rapidly to dementia and death.

Evidence has been found of CJD transmission through human pituitary growth hormone and cornea and brain tissue transplants. In fact, a cluster of cases of CJD, reported to CDC several years ago from patients who had received human pituitary growth hormone, resulted in FDA's recommending that blood facilities defer donors who had received this treatment. Although no cases of transfusion-transmitted CJD have been reported, blood from patients with the disease have infected animals when inoculated directly in the brain. There is no test to detect this disease.

⁹However, findings from a recent study suggest that CJD may not be caused by prions. Instead, the researchers hypothesize that CJD may be caused by a tiny virus or a piece of genetic material.

Although there are no federal regulations pertaining to CJD, FDA promulgated two memoranda outlining precautionary measures after blood facilities acted to protect the nation's blood supply from products that might transmit CJD. This included a November 1994 market withdrawal by ARC and several plasma manufacturers of products that had been manufactured from a donor who was later diagnosed with CJD.

Similar withdrawals had been made four other times between 1983 and 1992, with another in March 1995. As a result, a Special Blood Products Advisory Committee meeting on June 22, 1995, led to recommendations to further develop policies for CJD because of the theoretical risk of its transmission through blood. Despite their recommendation, the committee emphasized that no scientific evidence suggested that CJD was transmitted through blood or blood products. However, CDC is collecting data and pathologic specimens on AIDS and hemophilia patients who have been diagnosed with dementia in order to examine these patients for any evidence of CJD.

The FDA memoranda recommended permanent deferral of donors who had a family history of CJD or who received dura mater transplant grafts.¹⁰ The memoranda also recommended quarantining products and notifying consignees for products from donors who were subsequently diagnosed with CJD, had a family history of CJD, had received human pituitary growth hormone, or had received dura mater transplants. Furthermore, FDA has issued revised guidelines for deferring donors who have a family history of CJD.

Syphilis

Syphilis is caused by the spirochete *Treponema pallidum* as it penetrates small abrasions in epithelium or mucosal membranes. It has an incubation period of 10 to 90 days (usually 21 days), and in its primary stage it is seen as a lesion at the point of entry. The lesion persists for 2 to 6 weeks, which is also the period of infectivity. Tests for syphilis usually become reactive about a week after lesions appear. About 50 percent of persons with syphilis are, however, seronegative during this stage.

The second stage of infection is characterized by fever, malaise, headache, and inflamed lymph nodes. The last stage can take three forms: neurosyphilis, cardiovascular syphilis, or a form that involves skin and bones. Treatment with penicillin in the first, second, or early third stage can result in an absolute noninfectious cure with complete healing of

¹⁰Dura mater is the tough, fibrous, outer membrane covering the brain and spinal cord.

lesions and no development of any of the late manifestations of the disease.

From the 1950s, syphilis was thought to have been brought under control with antibiotics after an intensive national education campaign. In the mid-1980s to early 1990s, there was a geometric rise in the number of cases of syphilis reported to state health departments. Since then, syphilis has declined sharply. One of the main risk factors is drug use, including the exchange of sex for drugs. Transmission through blood is possible but it requires that blood be drawn during the brief period of spirochetemia. The spirochete that causes syphilis rarely survives more than 72 hours at 4 degrees Celsius, so it is usually components stored at room temperature (largely platelet concentrates) or transfused promptly after donation that transmit syphilis.

Most states require reporting of reactive screening results to the department of health, and they rather than blood facilities do most of the confirmatory testing. Whole blood and red blood cells with reactive screening tests and negative confirmatory tests are usually discarded, although FDA has stated that use is acceptable if units are labeled appropriately. Also, source plasma collected before screening-test results have been received has been considered acceptable for further manufacturing. FDA has not recommended product retrieval when repeat donors test positive for syphilis because it does not consider the transmission of syphilis a health risk for plasma derivatives.

The test for syphilis is often negative in the incubation phase of the disease and during much of the first stage. It is also negative during many of the late manifestations, such as cardiovascular symptoms and neurosyphilis. Conversely, most persons whose serum is STS-reactive do not have circulating spirochetes. Thus, syphilis is more likely to be present in the blood during the seronegative phase and absent during the seropositive phase. As a result, the routine STS test does not ensure protection against transfusion-transmitted syphilis.

Federal regulations require that whole blood and plasma are to be tested for syphilis, and FDA has recommended that donors who have been diagnosed with or treated for syphilis in the past 12 months be deferred. Donors with a positive confirmatory test should be deferred 12 months. After 12 months, deferred donors may donate blood if they have a negative screening test. FDA also encourages blood facilities to obtain a letter from a physician documenting evidence of adequate treatment for syphilis.

Errors and Accidents Reported to FDA by Facility Type, Fiscal Year 1994

Process	Licensed		Unlicensed		Transfusion service		Plasma centers		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Donor screening	1,178	10%	30	21%	0	0	244	28%	1,452	13%
Donor deferral	387	3.8	3	2.1	0	0	513	60	903	8
Collection and processing	343	3.3	9	6.2	1	14.3%	8	0.9	361	3
Routine testing	615	6	27	18	4	57	0	0	646	6
Viral testing	255	2.5	7	4.8	0	0	12	1.4	274	2
Postdonation information	3,766	36	8	5.6	0	0	41	4.8	3,815	34
Labeling	1,461	14	32	22	0	0	5	0.6	1,498	13
Product quarantine	1,044	10	25	17	2	29	16	2	1,087	10
Storage and distribution	550	5.3	2	1.4	0	0	1	0.1	553	5
Total	10,283	90.9	146	98.4	7	100.3	856	624	11,292	94

Blood Supply Safety Questionnaire

The U.S. General Accounting Office has been asked by the Congress to evaluate the safety of the nation's blood supply. As part of our evaluation, we are soliciting blood establishments' perspectives on the Food and Drug Administration's (FDA) compliance and inspection programs.

This survey includes questions on the following topics: FDA activities during inspections, areas FDA emphasizes during inspections, and inspections conducted by other agencies or institutions.

Your answers can be reported by checking the appropriate response or by filling in the blanks. The questionnaire should take about 20 minutes to complete. We are asking that you return the questionnaire to us within 10 days, using the enclosed business reply envelope.

If you have any questions, please call Jacqueline D'Alessio or Kurt Kroemer at 202-512-2900. In the event that our business reply envelope is misplaced, our return address is:

U.S. General Accounting Office
Jacqueline D'Alessio
Room 4083
441 G St. N.W.
Washington, D.C. 20548

We ask that the person who completes the survey be the member of your establishment who has the most detailed knowledge about the activities that occurred during the FDA inspection noted below. However, please feel free to confer with other establishment employees as necessary.

Based on our records, FDA completed an inspection of your establishment on _____ for the periods covering _____ to _____.

UNLESS OTHERWISE DIRECTED, PLEASE ANSWER THE FOLLOWING QUESTIONS AS THEY PERTAIN TO THE FDA INSPECTION NOTED ABOVE.

1. Please check that the inspection dates noted above are correct; otherwise please correct in the space below.

2. My position at this establishment is _____ (16)
3. I have been an employee of this establishment for ____ years. (17-18)
4. I have been employed in the blood industry for ____ years. (19-20)

**Appendix III
Blood Supply Safety Questionnaire**

5. To what extent, if at all, did the FDA inspection team EXAMINE STANDARD OPERATING PROCEDURES (SOPs) for major activities in the following areas?

(99) (1) (2) (3) (4) (5)

AREA	NOT APP LIC ABL E	TO LITTLE OR NO EXTENT	TO SOME EXTENT	TO MODERATE EXTENT	TO GREAT EXTENT	TO VERY GREAT EXTENT	
DONOR SCREENING							21
DONOR HISTORY AND EXAM							22
PHLEBOTOMY AND COLLECTION							23
ROUTINE LAB PROCEDURES							24
VIRAL LAB PROCEDURES							25
DONOR DEFERRAL							26
LABELING							27
QUARANTINE and STORAGE							28
PRODUCT DISPOSITION							29
POST-DONATION, RECALL, LOOKBACK							30
COMPUTER VALIDATION							31
QUALITY ASSURANCE AND cGMPs							32

**Appendix III
Blood Supply Safety Questionnaire**

6. To what extent, if at all, did the FDA inspection team ACTUALLY OBSERVE OR OTHERWISE EXAMINE FIRSTHAND major activities in the following areas?

(99) (1) (2) (3) (4) (5)

<i>AREA</i>	NOT APP LIC ABL E	TO LITTLE OR NO EXTENT	TO SOME EXTENT	TO MODERATE EXTENT	TO GREAT EXTENT	TO VERY GREAT EXTENT	
DONOR SCREENING							<i>33</i>
DONOR HISTORY AND EXAM							<i>34</i>
PHLEBOTOMY AND COLLECTION							<i>35</i>
ROUTINE LAB PROCEDURES							<i>36</i>
VIRAL LAB PROCEDURES							<i>37</i>
DONOR DEFERRAL							<i>38</i>
LABELING							<i>39</i>
QUARANTINE and STORAGE							<i>40</i>
PRODUCT DISPOSITION							<i>41</i>
POST-DONATION, RECALL, LOOKBACK							<i>42</i>
COMPUTER VALIDATION							<i>43</i>
QUALITY ASSURANCE AND cGMPs							<i>44</i>

**Appendix III
Blood Supply Safety Questionnaire**

7. **Did the inspection team appear to follow a systematic approach during the inspection?**

(1)	(2)	(3)	
YES	NO	DO NOT KNOW	
			45

8. **Considering together your responses to questions #5, #6, and #7, how thoroughly did your last FDA inspection evaluate the existence and suitability of the critical control points your institution has in place to assure the safety, purity, and potency of your blood products?**

(1)	(2)	(3)	(4)	(5)	
NO CRITICAL CONTROL POINTS THOROUGHLY EVALUATED	MOST CRITICAL CONTROL POINTS <i>NOT</i> THOROUGHLY EVALUATED	APPROXIMATELY HALF OF CRITICAL CONTROL POINTS THOROUGHLY EVALUATED	MOST CRITICAL CONTROL POINTS THOROUGHLY EVALUATED	ALL CRITICAL CONTROL POINTS THOROUGHLY EVALUATED	
					46

**Appendix III
Blood Supply Safety Questionnaire**

9. Consider the following outcomes that might result from an FDA inspection. **BASED ON YOUR LAST FDA INSPECTION, identify the outcome that most closely describes the END RESULT OF YOUR INSPECTION (Check column 1 if no problem was identified; otherwise check one of the columns 2-5.)**

(1)	(2)	(3)	(4)	(5)	
FDA IDENTIFIED NO PROBLEMS	FDA IDENTIFIED SPECIFIC PROBLEMS	FDA DETERMINED EXTENT AND CAUSES OF SPECIFIC PROBLEMS IT IDENTIFIED	FDA SUGGESTED POSSIBLE MECHANISMS TO CORRECT SPECIFIC PROBLEMS IT IDENTIFIED	FDA SUGGESTED POSSIBLE QUALITY CONTROL PROCESSES TO MONITOR AND CORRECT PROBLEMS SIMILAR TO THOSE IT IDENTIFIED	
					47

**Appendix III
Blood Supply Safety Questionnaire**

10. Did you receive a violation report (FDA form 483) or other citation?

(1) (2)

YES	NO	
		48

IF YOU DID NOT RECEIVE A VIOLATION REPORT FROM FDA GO QUESTION 15.

11. To what extent, if at all, was the inspection team able to articulate the significance of these violations?

(1) (2) (3) (4) (5)

TO LITTLE OR NO EXTENT	TO SOME EXTENT	TO MODERATE EXTENT	TO GREAT EXTENT	TO VERY GREAT EXTENT	
					49

12. To what extent, if at all, did the inspection team discuss the regulation and guidance documents that pertained to the violation(s)?

(1) (2) (3) (4) (5)

TO LITTLE OR NO EXTENT	TO SOME EXTENT	TO MODERATE EXTENT	TO GREAT EXTENT	TO VERY GREAT EXTENT	
					50

13. Were relevant regulations and guidance documents listed on the 483?

(1) (2)

YES	NO	
		51

14. Were any items on the 483 problems that your establishment had identified and corrected prior to the inspection?

(1) (2) (3)

YES	NO	DO NOT KNOW	
			52

**Appendix III
Blood Supply Safety Questionnaire**

15. In your opinion, how knowledgeable was the FDA inspection team in the following areas:

	(1)	(2)	(3)	(4)	(5)	(6)	
<i>AREA</i>	NOT AT ALL KNOW- LEDGEABLE	NOT VERY KNOW- LEDGEABLE	SOMEWHAT KNOW- LEDGEABLE	GENERALLY KNOW- LEDGEABLE	VERY KNOW- LEDGEABLE	UNABLE TO JUDGE	
Blood Terminology							53
Blood Products							54
Blood Bank Technology							55
Viral and Routine Testing							56
Content of FDA Regulations and Guidance							57
Implementation Dates of FDA Regulations and Guidance							58
Computer Validation Issues							59
cGMPs and Quality Assurance							60

**Appendix III
Blood Supply Safety Questionnaire**

16. In your opinion, did the inspection team's knowledge and skills levels HINDER, HELP, OR HAVE NO EFFECT on FDA's ability to identify any critical control failures that may have been present during the inspection period?

	(1)	(2)	(3)	(4)	(5)	
<i>AREA</i>	A GREAT HINDRANCE	SOMEWHAT OF A HINDRANCE	NEITHER A HELP NOR A HINDRANCE	SOMEWHAT OF A HELP	A GREAT HELP	
Blood Terminology						<i>61</i>
Blood Products						<i>62</i>
Blood Bank Technology						<i>63</i>
Viral and Routine Testing						<i>64</i>
Content of FDA Regulations and Guidance						<i>65</i>
Implementation Dates of FDA Regulations and Guidance						<i>66</i>
Computer Validation Issues						<i>67</i>
cGMPs and Quality Assurance						<i>68</i>

Comments From the Department of Health and Human Services

Note: GAO comments supplementing those in the report text appear at the end of this appendix.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of Inspector General

Washington, D.C. 20201

OCT 23 1996

Mr. Kwai-Cheung Chan
Director of Program Evaluation
in Physical Systems Area
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Chan:

The Department has carefully reviewed your draft report entitled, "Blood Supply: FDA Oversight and Remaining Issues of Safety." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department also provided extensive technical comments directly to your staff.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely,

Michael Mangano
for June Gibbs Brown
Inspector General

Enclosure

The Office of Inspector General (OIG) is transmitting the Department's response to this draft report in our capacity as the Department's designated focal point and coordinator for General Accounting Office reports. The OIG has not conducted an independent assessment of these comments and therefore expresses no opinion on them.

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Comments From the Department of Health
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**COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE
GENERAL ACCOUNTING OFFICE DRAFT REPORT ENTITLED, BLOOD SUPPLY: FDA
OVERSIGHT AND REMAINING ISSUES OF SAFETY**

The Department of Health and Human Services (HHS) appreciates the opportunity to comment on the draft report, which addresses many issues that are of concern to us. However, several aspects of the report need clarification or significant correction. Among those are the following:

GENERAL COMMENTS

The text of the draft report repeatedly uses the words, "FDA ensures safety ...". This reflects an imprecise understanding regarding the respective roles and responsibilities of the Food and Drug Administration (FDA) and the blood establishments. The FDA issues and enforces regulations which provide a framework for blood establishments to follow to ensure they produce safe and effective blood products. While the FDA serves an essential role, the individual blood establishments ultimately are responsible for the safety of their blood and blood products. The fundamental concept of producer responsibility is basic to FDA's legislative mandate and operations for all FDA-regulated products, not just blood. A more accurate phrase would be "FDA helps ensure..."

Error and Accident Reports

The draft report implies that the district offices are the original recipients of Error and Accident Reports (EAR). This is not correct. The EARs are sent directly to FDA's Center for Biologic Evaluation and Research (CBER) for review. CBER evaluates the EAR and if immediate action is warranted, alerts the district. Those not requiring immediate follow-up are entered into CBER's database for error and accident reports to be used for future reference, trends analyses, and review by district offices prior to inspections.

Recalls Based on EARs

The report links FDA follow-up of EARs with product recall. This is not accurate. Most recalls are actually initiated by the responsible establishment, and most often are completed before FDA learns of them. This is particularly true for recalls that are not safety-based. The draft report also does not accurately state FDA's role with respect to recalls/market withdrawals. The FDA may prompt a firm to initiate a recall, but this is not the usual case. In egregious cases, such as those posing an imminent threat to the public where the blood establishment resists initiating a recall, FDA can initiate product recalls, but has never done so for blood products. Also, to protect the public health, FDA would initiate a health-related recall if a firm with serious problems had gone out of business or for some other reason could not do a recall. This would be a very rare event, however. CBER's role is to determine that a product should be recalled if the establishment has not already done so, and to classify the recall to establish the level of FDA follow-up required to ensure that the public is protected.

See comment 1.

See comment 2.

See comment 3.

See comment 4.

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Establishment Inspection Reports and the Inspection Process

See comment 5.

The discussion of FDA's blood establishment inspection activities and use of the Establishment Inspection Report (EIR) is not accurate. An EIR is an instrument for formally recording, in an established format, the investigator's observations and communicating them to higher-level staff within FDA to determine the regulations/statutes that have been violated, appropriate corrective actions, and to document the violations to support regulatory action should it be required.

See comment 6.

The draft report also states that EIRs are not reviewed, so FDA is unable to determine the overall industry compliance status. This is not correct. The FDA requires that EIRs be routinely reviewed numerous times at multiple levels to determine the compliance status and potential corrective actions as well as to ensure consistency both within and among districts. Furthermore, data from the EIR, including the compliance classification, are entered into the Office of Regional Operations' (ORO) Program Oriented Data System (PODS), which is an historical database used by ORO districts and headquarters to review the compliance history of establishments prior to inspections, schedule inspections, do workload planning, and assess the overall compliance rates of particular segments of the regulated industry, such as food producers or drug manufacturers. The FDA has recognized the limitations of PODS and is in the process of developing a new system with more data fields and analytical capability.

See comment 7.

The EIR usually is written after completion of an inspection. The EIR, including the related Form 483 is then reviewed by a Supervisory Consumer Safety Officer (SCSO) or equivalent in the responsible district's Inspections Branch, who provides the preliminary classification of the current inspection. If the SCSO deems that the inspection does not require official action to correct deficiencies in the establishment's operations, no further review is required. If the SCSO determines that the inspection does require further action, the EIR is reviewed by a district Compliance Officer to ensure that it reflects all significant observations, to determine which regulations apply to the specific situation, and whether the regulations have been violated.

See comment 8.

Currently, FDA is using three levels for classifying inspections; No Action Indicated (NAI) for insignificant deviations or no identified deviations, Voluntary Action Indicated (VAI) for those deviations that are amenable to corrective action by the firm with no compromise of public safety, and Official Action Indicated (OAI) for those deviations of a serious nature that require some FDA intervention to ensure that corrections are made.

The report is not correct in concluding that operations not mentioned in the EIR were not observed by the FDA investigator. To the contrary, FDA investigators are directed to list the specific areas covered ONLY when a limited or incomplete inspection is done. The investigators also are instructed to list in the EIR everything they see that is questionable and therefore, could be a violation of the regulations. The FDA investigators undergo extensive training regarding FDA's requirements for completing EIRs. Further guidance is provided through detailed operations manuals, compliance programs, inspection guidance materials, and vigilant oversight at the FDA district, regional and national levels. Most inspections are conducted in accordance

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with specific compliance programs which explicitly state what is to be observed during the inspection, samples to be collected, and analyses to be done in FDA laboratories. Also, FDA investigators are directed to list in the EIR the specific compliance program under which the inspection is performed. Listing the compliance program under which the establishment was inspected indicates that all directions included in the compliance program were followed unless otherwise stated on the EIR. Further, FDA often has substantial previous experience with each firm, enabling inspections to be tailored to look at areas known to be sources of problems, thus making maximum use of its limited resources. This is not acknowledged in the report.

See comment 9.

The FDA corrective actions, usually called regulatory actions, are also coordinated with all relevant FDA units and are made publicly available once a decision is made that closes the case. Several regulatory actions are available to the agency. For example, the district office is authorized to issue Warning Letters to the deviating firm without headquarters concurrence in some circumstances, while other circumstances require FDA headquarters review and concurrence with the Warning Letter. Finally, issuing a Warning Letter is only the first of many regulatory actions available to FDA. The FDA may seek injunctions to prevent the firm from continuing the deviant practice, suspend or revoke the firm's license, initiate product recalls, seize violative products, impose civil penalties in some instances, and criminally prosecute the firm and its officers. These regulatory actions and the preceding inspections serve as deterrents to violations of the Federal Food, Drug and Cosmetic Act, and coupled with the extensive EIR review, help ensure nationwide consistency, contrary to statements in the draft report.

See comment 10.

Role of FDA Investigators

See comment 11.

The report also is not correct with respect to the role of FDA investigators. The report should make clear that FDA does not expect investigators to tell the managers of an establishment what they can do to correct deviations or to cite the regulations that have been violated. The FDA's experience has been that identified problems may actually violate several regulations which need to be identified by staff trained specifically to do compliance work in conjunction with the investigators and the General Counsel's staff. The investigators' role is to look at manufacturing processes, identify potential problems, and record observations with respect to those observations so the FDA can determine the compliance status of the establishment and the corrective action required. They are expected to discuss the observations with establishment management. The establishment management, however, should not assume that the investigator has identified all the regulations violated. Nor should they assume that any corrective action discussed represents an FDA commitment.

In contrast to the EIR, the Form 483 is an instrument designed to aid in communicating an investigator's observations to the establishment management. From the inspection observations, the investigator lists on the form 483 only those findings that are considered significant. Prior to completing an inspection, the investigator meets with the establishment's senior management to present the Form 483 and to discuss the observations listed on the Form 483, as well as other, less significant observations.

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See comment 12.

Checklists

GAO suggests that inspections made using a checklist result in more Form 483 items than those not using a checklist. The FDA discontinued use of the checklist, however because its use tended to focus attention on completing the checklist rather than on more substantive areas whether or not they were included on the checklist. Moreover, use of a checklist did not guarantee that a deficiency would be found or listed on the Form 483. The checklist was only used as a guide to insure that all areas of a compliance program were covered, and was never intended to supplant the investigator's judgment regarding problems observed or areas needing a closer look. The FDA's experience has been that an inspector's ability to identify deviations is the result of being well-trained and having developed expertise in conducting inspections, not reliance on a checklist. Investigators are expected to report all new or unusual processes they encounter during an inspection, and to assess the impact of such processes on the product. They also are expected to focus on identified problem areas.

It also should be noted that FDA has implemented a systems-based approach to inspections rather than a checklist approach. This enables investigators to spend more time on problem areas and less time on areas where deficiencies have not been found or are not likely to be found. The quantity of Form 483 items is not the point of an inspection, rather, the quality and significance of the inspectional observations are the important considerations.

See comment 13.

FDA's Knowledge of the Compliance Status of Individual Firms and the Overall Industry

We further disagree with the statement that, "...without collating, synthesizing, and evaluating EIR information, FDA has no means of ...determining which practices could best help shape policy guidance ...". To the contrary, FDA has the capability to conduct evaluations that help to shape compliance policy, as discussed in more detail below.

See comment 14.

We generally agree that FDA's ability to conduct program evaluations and trends analyses with respect to blood establishments is somewhat limited. However, this limitation has not prevented FDA from taking regulatory action to protect the public health. The report should acknowledge FDA's recent efforts toward identifying the very significant problems that plagued the American Red Cross (ARC) and the Blood Systems, Inc. (BSI) and led to FDA seeking injunctions, under which they are currently operating. These are good examples of FDA's ability to compile and analyze data even though its data systems are not currently geared toward that end. The information that led to the injunctions also was used to establish a uniform approach to inspections and regulation. It should be noted that a computerized system for analyzing specific findings from inspections and doing trends analyses based on those statistics would be very costly and would require a large investment of time for data entry and validation. The cost of such a system might well be prohibitive. Furthermore, the compliance status of a blood establishment or any other firm must be based on an individual review of the EIR and all circumstances unique to that establishment. Any recommendations for regulatory action must be

See comment 15.

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made on a case by case basis. This approach remains FDA's primary means of protecting the public from unnecessary risks.

See comment 16.

Additionally, each inspection provides the opportunity for investigators to raise policy questions and bring new areas of policy concern to FDA's attention. Questions of policy are handled on a daily basis through contacts between the district, CBER, and Office of Regulatory Affairs (ORA) headquarters staff. Decisions resulting from the policy questions are fed into an on-going process of reviewing regulations and guidances for potential updating. Furthermore, other opportunities to raise policy questions are available, such as monthly conference calls, written guidance, and meetings among CBER, ORA, and FDA's Blood Products Advisory Committee. Finally, FDA schedules liaison meetings with the American Association of Blood Banks (AABB), the Council of Community Blood Centers (CCBC), the American Blood Resource Association (ABRA), and military blood program representatives to acquire their feedback on policy questions as well as provide additional guidance and address areas of mutual concern.

Official Establishment Inventory

See comment 17.

The report also suggests that FDA's Official Establishment Inventory (OEI) is deficient because there are firms included that are no longer active in FDA-related activities. We submit, however, that the OEI, which assigns each establishment regulated by FDA a discrete and permanent identifying number (the establishment registration number for blood establishments) serves both FDA and the public well. When an establishment ceases to come under FDA's jurisdiction for any reason, its file is moved from the active OEI to the auxiliary OEI where it will be available if questions arise or the firm re-enters FDA's jurisdiction. It is essential to keep such a history of a firm and its current status. This is not a deficiency in the system, but a calculated effort to manage information regarding FDA's regulated establishments in a responsible manner.

FDA Training for Investigators

See comment 18.

The report observes that many blood establishment respondents to GAO's questionnaire question the knowledge and ability of FDA investigators with respect to the operations of blood establishments. While FDA investigators are trained in a number of areas and are competent to do inspections of a variety of different types of establishments, FDA has recognized the importance of specialized skills and expertise in each of the product lines under its jurisdiction. To the extent possible, each district has developed a cadre of specialized investigators through continuing education and on-the-job training. While FDA always has recognized the need for continued training, its availability to investigators and other FDA staff is dependent upon resources that must be spread among the many competing agency priorities. Numerous districts have provided in-house training and brought headquarters and field experts to the respective districts to discuss policy, provide guidance, and enhance the technical expertise of investigators. The National FDA Blood Bank Course just completed in Orlando, Florida is an example of continuing efforts to provide training to field personnel. We believe FDA's investigators are

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well-trained, have expertise in their respective areas of responsibility, and are highly professional.

GAO RECOMMENDATION:

1. We recommend that FDA require blood facilities to notify all donors who are permanently deferred that they have been deferred and the medical reason they are deferred.

HHS COMMENT

We agree that notifying donors of their deferral status and the medical reason for deferral could enhance public health. In 1986, FDA and the National Institutes of Health (NIH) jointly sponsored a Consensus Conference which determined that there are ethical concerns about failure to inform donors of HIV test results which led to their deferral and/or will lead to discarding any future blood collections from them. The Department, in a 1991 Public Health Service (PHS) Inter-Agency Guideline, recommended notifying donors of the results of tests for HbsAg, anti-HCV, ALT, and anti-HBc. As it became apparent that not all blood establishments had adopted the consensus guidelines, FDA recommended that blood establishments inform deferred donors of the conditions which led to the deferral (memoranda to all blood establishments, April 23, 1992: Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products). Then in 1993, FDA recommended notification of donors testing repeatedly reactive for HTLV-I. In the 1995 Guideline for Quality Assurance in Blood Establishments, FDA further identified donor notification and counseling as two of the five key elements of donor deferral. As these actions demonstrate, we believe that blood establishments should notify donors of all positive and indeterminant HIV test results. However, FDA historically has considered its jurisdiction to apply primarily to product safety, purity, and potency rather than the practice of medicine, a much broader public health issue. Because this recommendation may involve the broader public health issues, we will explore regulatory options within the Department to determine whether there is existing authority to require notification and how best to bring about industry acceptance of this necessary step.

GAO RECOMMENDATION

2. We recommend that FDA require blood facilities to conduct periodic quality assurance tests for bacterial contamination of blood products.

HHS COMMENT

We agree that a reduction in bacterial contamination of blood products, and especially platelets, is an important safety issue. We also recognize the importance of quality assurance and its implications for Good Manufacturing Practices in manufacturing blood and blood products. The

See comment 19.

See comment 20.

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FDA issued a 1995 Guideline for Quality Assurance to all blood establishments. This issue was discussed by FDA's Blood Products Advisory Committee in 1992 to gain an insight into possible solutions. More recently, this problem was reviewed at a workshop sponsored by the National Heart, Lung, and Blood Institute in September, 1995.

Unfortunately, this issue is not easily resolved because of the limits of technology. Several important parameters such as periodic quality assurance as part of a quality control program for final units, retraining staff in proper phlebotomy techniques, and evaluation of product release procedures must be addressed if progress is to be made toward reducing bacterial contamination of blood. Quality assurance alone, however, will not solve the problems which are inherent in the current technology for product collection and storage.

To further knowledge in this area, the Hospital Infections Program, of the National Center for Infectious Diseases (NCID) and the Centers for Disease Control (CDC), in collaboration with the ARC, the AABB, and the Department of Defense is conducting a pilot study, "Surveillance and Estimation of the Frequency of Bacterial Contamination of Blood Products." All patients receiving blood products through the blood collection agencies associated with these three groups will be followed to identify significant reactions to blood products and the proportion of these that are attributable to bacterial contamination.

This study will estimate the incidence of, and identify risk factors for, bacterial contamination of blood products in the United States and begin to identify methods to screen for and prevent bacterially-contaminated blood products. As part of this study, educational campaigns will be developed and implemented for clinicians and blood bank personnel regarding active surveillance, identification and reporting of episodes of bacterial contamination of blood products.

GAO RECOMMENDATION

3. We recommend that FDA require viral marker testing for all self-donated blood units in order to minimize the potential vulnerability of non-tested autologous units entering the blood supply.

HHS COMMENT

We agree that this is an important issue. In fact, FDA has sought public input on this issue. Currently, FDA recommends that establishments which allow any "crossing over" of autologous units for allogeneic use should screen all autologous collections. The FDA currently is developing a new recommendation regarding testing autologous units of blood. The recommendation will be based on the concept that testing these units will further decrease the potential for transmission of infectious agents if a transfusion occurs to other than the intended recipient. While testing all autologous units will not completely eliminate transfusion-associated risks for disease transmission, this step may serve to further protect the public health.

See comment 21.

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GAO RECOMMENDATION

4. We recommend that FDA require confirmatory testing of all repeatedly reactive viral test results for which there is a licensed confirmatory test, and it should require that transfused patients be notified when they have been transfused with blood from a donor whose subsequent donations were found to be virally positive by confirmatory testing. The FDA should also require the identification of implicated units that have not been transfused or further manufactured.

HHS COMMENT

Because we agree that this recommendation as it applies to HIV and hepatitis is very important for safeguarding the public health, FDA has recommended that confirmatory testing be performed for HIV(1992), HCV(1993) and a neutralization assay for HbsAg (1987). The FDA reiterated the recommendations for additional testing for HIV and HBV and added recommendations for HTLV-I in a July 1996 memorandum regarding quarantine and disposition of units from prior collections from donors with repeatedly reactive tests. This important issue as it concerns other infections for which donors are screened merits further consideration as a broad policy issue and will be discussed at the PHS Advisory Committee on Blood Safety and Availability.

We also agree that consignees should be notified. The FDA, in 1993, issued a proposed rule to amend the Current Good Manufacturing Practices regulations to require that blood centers prepare and follow written procedures for notification of consignees when it is determined that blood, blood components, source plasma and source leukocytes are at increased risk for transmitting HIV. This final rule and the companion Health Care Financing Administration final rule requiring transfusion services and health care professionals to notify recipients were published on September 9, 1996. This important issue merits further consideration as a broad policy issue and was recently referred to the PHS Advisory Committee on Blood Safety and Availability.

We further agree that the identification and retrieval of units collected from donors who later test repeatedly reactive for viral markers is important to protect the public health. Since 1985 FDA has recommended consignee notification and retrieval of products collected from a donor who later tests positive for HIV. The FDA has continually updated and expanded these recommendations. The final rule mentioned above requires quarantine, further testing and consignee notification when a repeat donor seroconverts to HIV. In July 1996, FDA also issued recommendations for quarantine and appropriate disposition of prior collected units from repeat donors with repeatedly reactive tests for HBV, HCV, AND HTLV-I.

Options for retrospective notification of transfusion recipients who may have received blood from donors with HCV infection have been considered by the Blood Safety Committee. The Committee has determined that the best means to identify persons with HCV infection because

See comment 22.

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of prior transfusion would be as part of a comprehensive program of education directed both to health care providers and the general public. The Hepatitis Branch of CDC/NCID has begun to develop and implement such a program.

It should also be noted that among the findings in this report are a variety of issues in which CDC actively is engaged, including its program of domestic and international surveillance for Group O and other divergent strains of HIV-1. CDC and FDA have discussed development of a collaborative plan to expand these activities.

The draft report discusses at length the issue of lookback with respect to notifying both blood donors and recipients when a blood establishment determines that a donor carries certain diseases. Currently, lookback is required for HIV and not other transfusion-transmitted diseases. The issue of lookback for the hepatitis C virus (HCV) and potentially for other transfusion-transmitted infections should be considered in the context that HIV is almost invariably fatal, and is a public health risk in terms of secondary transmission. These factors may suggest that lookback for other agents might not be justified, given the high cost of doing a lookback.

The discussion of treatment for HCV also does not accurately communicate the absence of information concerning effective therapy. It overstates the significance of measurable endpoints such as alanine aminotransferase (ALT). Decreased ALT values cannot be equated with effective treatment or with cure since hepatitis C virus may continue to be present, and the natural history of the disease may include periods of decreased liver (measured by the ALT value). Further, secondary transmission of HCV and other agents from blood recipients is minimal, and is not generally seen as a public health threat.

Finally, it should be noted that targeted testing of all recipients of positive transfusions would include a high proportion of false positive test results because of the high false positive rate of early screening tests; this would result in psychological harm and unnecessary medical expenditures. Furthermore, experience with HIV lookback testing indicates that the number of persons who can be recontacted after 6-12 months is very low. Thus, lookback testing is not cost effective. In contrast, the comprehensive education program is not only likely to be more effective but also provides the opportunity to identify the more than 90 per cent of persons with HCV infection who acquired their infection by a route other than transfusion.

Since the draft report was written, FDA published in the September 9, 1996 Federal Register the final rule, Current Good Manufacturing Practices for Blood and Blood Components: Notification of Consignees Receiving Blood and Blood Components at Increased Risk for Transmitting HIV Infection and the companion final rule issued by the Health Care Financing Administration. These documents require that blood establishments notify consignees that they may have received blood or blood products that are contaminated by HIV. The new requirements will help FDA and blood establishments ensure that recipients of blood products are protected from contaminated products, thus reducing the need for lookback. This should be acknowledged in the final report.

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GAO RECOMMENDATION

5. We recommend that FDA require unlicensed facilities to report all errors and accidents.

HHS COMMENT

The FDA agrees that error and accident reporting requirements should be applicable to all blood establishments. In May, 1995, the Office of Inspector General issued a report which recommended that FDA require unlicensed blood establishments to report errors and accidents. The FDA acknowledged the discrepancy in reporting between licensed and unlicensed blood establishments and agreed to develop regulations to address the problem. A proposed rule to require submission of error and accident reports by unlicensed, registered firms has been drafted and is now being reviewed within FDA. We anticipate publication within the next few months.

GAO RECOMMENDATION

6. We recommend that FDA publish in the form of regulations those guidelines that it believes are essential to ensure the safety of the nation's blood supply. We recommend that FDA clarify its policy on the extent to which facilities should adopt the agency's guidelines and memoranda in order to remain in compliance with FDA regulations.

HHS COMMENT

The FDA agrees that clarification of the nature of its guidance documents is an important issue. The FDA recognizes the need to have more uniformity in its development and use of guidance documents and has solicited public comment on this issue through a notice published in the Federal Register on March 7, 1996, (61 FED. Reg. 9181). The FDA will review the comments received in deciding further steps to take to improve its guidance document procedures. Clarification of the role of FDA guidance documents must be considered in light of how best to communicate with the regulated industry while also protecting the public health and determining appropriate mechanisms for promulgating such guidance. In making decisions regarding how to clarify the status of its guidance documents, FDA also must keep in mind that use of guidance documents allows the FDA quickly to communicate important information to the public while providing the flexibility the government and industry need to adjust promptly to advances in technology and new scientific developments.

GAO RECOMMENDATION

7. We recommend that FDA correct the problems we have identified in its inspection processes: FDA should systematically analyze inspection reports, systematize the information to be contained in them, publish better guidance on the types of activities that warrant reports on deviations and warning letters, and ensure that all blood facilities are inspected in a timely fashion.

See comment 23.

See comment 24.

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See comment 25.

HHS COMMENT

We disagree with much of this recommendation. We believe it is based upon incorrect assumptions which led to erroneous data development and analysis. The FDA already reviews and analyses inspection reports, both for identification of conditions warranting immediate action and for longer term trends. An example of the type of trends analyses that can be done is the review done by the 1992-1993 FDA Task Force on the American Red Cross (ARC) which categorized all FDA Form 483s issued to the ARC from 1988 to 1992.

Furthermore, the compliance program, IOM, Regulatory Procedures Manual (RPM), and other directives to investigators state the information that should be included in EIRs. The FDA has always been concerned with the Form 483s in terms of their significance, content and format. There is guidance on what constitutes a Form 483 observation, which can be found in compliance programs, the IOM, Regulatory Procedures Manual (RPM) and the Warning Letter Reference Guide. Consumer Safety Officers (CSO) receive training on biologic inspections, including the basis for Form 483 citations, through various means: new hires courses, in-house courses, on the job training, national courses, and intra-agency literature, among others. Nevertheless, we will also remind investigators of the format for writing EIRs in ORA's newsletter, *P.A.R. Excellence* and by inclusion of the information in the IOM. Regulation citations are not included on the Form 483 because in many instances, there are several citations that may relate to a specific observation. The FDA 483 is a list of observations by the investigator subject to further scrutiny by other FDA personnel.

While we believe FDA investigators are very familiar with how to write a Form 483, a group of FDA's regional and national biologic expert investigators recently did a study (July 1996) of Form 483s for blood and biologics establishment inspections. The purpose of the study was to provide clearer guidance in terms of the significance, content, and format of observations. The findings of the study will be issued to field staff in the first quarter of FY 97. Meanwhile, interim findings have been discussed in recent biologics training courses. The FDA believes this study will provide even clearer and more specific guidance on writing Form 483s.

Currently, the FDA also is employing innovative training tools, (e.g. videos, teleconferencing, picture computer transmissions, extensive use of the internet, and developing interlinking data bases) to reach CSOs more efficiently.

The GAO draft report further states that FDA is required to inspect blood establishments once a year. Actually, the mandatory time-frame for inspecting blood establishments is one time every two years. For firms that are in compliance, FDA schedules inspections once every 2 years. This allows the agency to focus on firms that exhibit a history of non-compliance. Problems at an establishment generally result in an accelerated follow-up.

The following are GAO's comments on the HHS October 23, 1996, letter.

GAO Comments

1. We recognize the fundamental concept of producer responsibility in FDA's legislative mandate and have changed the wording of the report to reflect that FDA helps ensure blood safety.
2. We understand that EARS are sent directly to CBER. We have clarified the language in the report to convey this point.
3. We understand that most recalls are initiated by the blood facility and have stated so in our report, where we note that "a recall is a blood facility's voluntary removal or correction of a marketed blood product. . . ." (See page 70, footnote 1.) We also note that "recalls do not always begin with an EAR. In some cases, an FDA inspection uncovers an error or accident that was not reported to FDA and bases a recall recommendation on its severity. Some facilities then submit an EAR even though recall has begun" (See page 74, footnote 10.)
4. We understand that this is the case and have clarified the report to note that

"a recall is a blood facility's voluntary removal or correction of a marketed blood product that violates laws administered by FDA. The Public Health Service Act authorizes FDA to require that a manufacturer initiate a recall if there is an imminent hazard to the public health." (See page 70, footnote 1.)

Nevertheless, an FDA official told us that 25 percent of the time FDA must follow up on a recall, meaning that a blood facility had not taken any actions until FDA had recommended to the facility that a product recall was warranted. Additionally, in discussions with a representative of a large blood facility, we learned that facilities often wait for FDA's decision on a product recall before initiating action.
5. See comment 6.
6. Our report does not state that EIRS are not reviewed. However, we do question the ability of FDA to perform an analysis of inspection activities and findings. We understand that EIRS are reviewed, and we stated so in our draft report: "after the inspection and to ensure that inspectors consider all relevant regulations in an investigation, other FDA officials review EIRS and any Form 483 observations." (See page 77.) This

information was obtained from a written FDA response to our inquiry. In that response, FDA noted that to ensure that all relevant regulations are considered, the inspection reports involving Form 483 observations that indicate a potential violation are reviewed by FDA officers. After this review, the findings are sent to the firm in violation for its corrective action.

However, we have added language to the report noting that this characterization by FDA is inaccurate. In fact, representatives within the blood industry have stated that blood facilities do not receive the review performed on the inspector's Form 483 observations by FDA officials except when a warning letter or other regulatory action may arise. Furthermore, comments made by the inspected facility regarding the Form 483 observations are not acknowledged by FDA, nor is any indication given as to the acceptability of any proposed or completed corrective action. Also, blood facilities do not know what classification has been given to their inspection (that is, no action indicated, voluntary action indicated, or official action indicated).

It is only through a Freedom of Information Act request that the blood facility can obtain the actual EIR of its facility. As a result, the blood facility is unaware of the degree to which its practices have not complied with federal regulations and would not know the extent to which corrective actions should be taken. Thus, even if FDA determines the "compliance status and potential corrective actions" during a review of the inspector's Form 483 observations, the blood facility would not receive such information unless the Form 483 observations warranted a warning letter or further regulatory action.

7. We sought information on any analyses that had been performed by FDA on the content of EIRS and Form 483s at a meeting with FDA officials. At this meeting, FDA officials stated that there were no databases that tracked information on EIRS or Form 483s. When we learned of the PODS database, we sought information on it from FDA. The information we received shows that this system does not allow for the systematic analysis of compliance and noncompliance rates at a national level. The data elements contained in this system inform management about the work (operations and resources) performed in the district and regional offices. This includes such information as who performed the operation (employee name and position), where the operation was accomplished (district), what was covered in the operation (products inspected), and the results of specified

operations (classification of the inspection). Thus, it is not a system for tracking Form 483 observations or activities covered during an inspection.

8. Our report states that

“we examined each facility in our sample for whether the EIR indicated that a particular function had been examined. If it was mentioned at all in the EIR, we considered it to have been examined. If it was not mentioned at any time in the EIR, we considered that one could not determine whether the area had been examined.” (See page 82.)

This was done for the purpose of our analysis of compliance rates among a nationally representative sample of blood establishments. We have clarified that this methodology was used for the purpose of the analysis in question.

We were aware that since the use of checklists was discontinued in October 1994, FDA inspectors only needed to list on the EIR the Form 483 observations and the compliance program under which the blood facility was being inspected. As a result of this policy, and after examining the EIRS in our sample, we concluded that compliance rates could not be determined. Because the EIRS often had little information on what operations had been observed by the FDA inspector, we did not believe it was appropriate to analyze the contents of the EIRS.

FDA would have us make the assumption that if an operation was not mentioned, that meant that it was checked and found to be in compliance. We understand that in many instances this would be the case. However, we could not make the assumption as to how often this was the case for several reasons: (1) We were told by FDA inspectors that they focus on certain activities and do not check all practices occurring at a blood facility. FDA’s instructions to its inspectors are that, unless it is a limited inspection, inspectors should list on the EIRS the areas that they did not inspect that are outlined in the compliance program under which the inspection is taking place. Yet, very few EIRS noted areas that were not covered during an inspection. (2) We were told by FDA officials that an inspector cannot check everything on any one inspection yet, again, few EIRS delineated what was not covered.

(3) Individual EIRS illustrate to us that FDA’s stated policy is not being followed. For example, a blood facility inspected in 1994 resulted in a Form 483 observation that no lookback procedures had been followed at the firm in 1992-94. However, when we examined the EIR for this facility

for the inspection that took place in 1993, there was no mention in the EIR that lookback procedures were not being followed. This means that either the 1993 inspection examined lookback procedures and did not find any problem that had been evident since 1992 (according to the 1994 inspection) or the activity was not observed in the 1993 inspection and was not listed on the EIR.

(4) We were told by FDA that it often tailors its inspections because it has substantial previous experience with each blood facility, enabling an inspector to examine areas known to be sources of problems. However, when we examined the EIRS, we could not determine which inspections were “tailored” and which inspections examined all areas of a blood facility’s practices. In short, we know that there are instances in which the inspector failed to note areas that were not examined. We were not able to determine the percentage of cases this occurred in.

Because of FDA’s policy, it would be impossible for an FDA supervisor, outside auditor, or blood bank facility to determine what activities had been observed and what areas the blood facility had and had not complied with by simply reviewing the EIR. We believe that there is no analytical basis from which one could determine that the inspector is following the compliance program by simply listing the program under which the inspection is being conducted. Therefore, we found that a meaningful analysis of compliance rates among blood facilities based on EIRS could not be performed. Thus, we reported only Form 483 observation rates in chapters 2-4 because this was the only meaningful information that one could analyze from the EIRS.

FDA officials also stated that the reason FDA does not have a policy requiring inspectors to list all the practices at a blood facility and whether they observed them or not was that such a practice was found to add significant time and cost with no value added. However, our analysis of Form 483 observations shows, in fact, that a statistically significant difference does occur when a checklist is used. This is not to suggest that a “checklist” approach is necessarily a better method than a “systems approach” to inspecting blood facilities. However, we do not believe that listing what had been observed during an inspection on the EIR would be a major burden to FDA or individual inspectors. In fact, in several examples, inspectors did note on the EIR what areas had been observed.

9. We understand that this is the case and say so in our report: “suspensions or revocation of licenses, injunctions, and prosecutions may

ultimately result from a process begun with an inspector's Form 483 observations of a continuing pattern of deviation." (See page 79.)

10. We have several pieces of information that illustrate that there is inconsistency in inspection activity. (1) We found a statistically significant difference between the number of Form 483 observations when inspectors did and when they did not use a checklist to inspect a blood facility. (2) We found a statistically significant difference between the kind and number of Form 483 observations between the eight FDA districts examined in our analysis of Form 483s.

(3) In our survey of blood facilities, we found that 27 percent of the respondents did not know what to expect from one inspection to the next, and 45 percent noted a wide variation in inspectors' knowledge and training in blood banking terminology and procedures. (4) During a recent forum at an AABB national meeting, FDA officials were asked to comment on a Form 483 observation received by an audience member's facility. The FDA officials stated that the observation in question should not have been a Form 483 observation and that that was why FDA inspectors were now being sent to auditing training. (5) Eighteen percent of all inspections in our sample that were supposed to have a checklist did not have one. (6) We found instances of the inconsistent application of Form 483 observations and warning letters, which we have outlined in the report. From these points, we conclude that there is not nationwide consistency in the EIR process, contrary to FDA's comments.

11. We have added language to note that it is FDA's policy that inspectors are not expected to suggest remedies to problems that are found during an inspection nor are inspectors expected to discuss the regulations that pertain to the problems. Statements in our draft report were based on FDA's written response to our inquiry regarding requirements that FDA might have on delineating specific guidance to its inspectors. In its response, FDA noted that "investigators provide general guidance (to the facility) on applicable documents, policy, regulations, etc. which are the basis for the objectionable condition." Thus, there appears to be some confusion within FDA as to the policy for its inspectors when it comes to discussing Form 483 observations with a blood facility.

12. The report does not take a position on whether a checklist approach is a more useful method than a systems approach for inspecting blood facilities. We do note that there is a statistically significant difference in the number of Form 483 observations for the inspections that use a

checklist. As we note on page 85, we could not determine why this difference occurred. In regard to FDA's limiting inspections to areas where problems are likely to be found, we believe FDA has not performed the statistical analyses that would be necessary to determine these areas. Also, one would need to examine all areas intermittently in order to determine those that are not likely to require extensive inspection oversight.

13. We are unaware of any nationwide analysis performed on the content of EIRS, Form 483 observations, compliance and noncompliance rates of blood facilities, or disparities in inspection activities between inspectors. We have added language acknowledging FDA's injunctions against ARC and Blood Systems Incorporated (BSI). However, our discussion with ARC representatives indicates that the uniformity mentioned above was only transient and that present inspections have reverted back to a situation in which ARC finds large disparities between inspection practices at its facilities. FDA has pointed to work performed by a 1992-93 task force that categorized all Form 483 observations issued to ARC in 1988-92 as an example of its ability to conduct evaluations that help shape compliance policy. However, when we examined this work, we found that it was merely a list of Form 483 observations broken down by categories. No analysis had been performed on this information that could assist FDA in determining compliance rates among ARC facilities or trends in the types of problems found.

FDA issued to ARC annual reports in 1994, 1995, and 1996 on its progress under the terms of the May 12, 1993, consent decree. These annual reports list the Form 483 observations given to ARC facilities in the preceding year and categorized these observations by topical headings covered in the consent decree. This work demonstrates that FDA has the ability to perform analyses on Form 483 observations. However, this has only been done for ARC facilities and is still merely a listing of the number of Form 483 observations by category.

14. We do not believe that a database that included a nationally representative sample of blood facilities that contained information on the type of facility, registration number, areas observed and not observed by the inspector, date of inspection, areas where inspection observations were found, and classification of the inspection (that is, NAI, VAI, or OAI) would be costly or overly burdensome. In fact, we established such a database for our analysis of EIR content and Form 483 observational differences.

15. We agree. However, a national analysis of the types of problems that are being found by FDA inspectors would provide valuable information to FDA on the activities in blood banking that might need more or less attention and oversight. An analysis of such problems might also provide information on areas where FDA has made recommendations that might require further clarification in terms of FDA's regulatory intent. Lastly, such analyses would also provide information as to the application of FDA inspection procedures across different districts.

16. We believe that addressing policy questions with investigators and industry representatives is a worthwhile practice and FDA should continue such contacts. However, the evidence presented in this report regarding inconsistencies in the application of FDA's policies and guidance illustrates that such activities are not preventing such problems.

17. We stated in our draft report that "FDA maintains a list of all registered blood facilities with their registration numbers. The vast majority of those that were in our sample were accurately identified." (See page 82.) However, when we queried FDA for the latest EIR for a representative sample of blood facilities, we were forwarded some for which no inspections had occurred for several years. Our query to FDA was based on establishments that were denoted as being active. Those that were denoted as being "out of business/no blood processing" were not part of our query. Thus, our findings regarding long periods between inspections was based on the active list of blood facilities. Furthermore, we found cases in which an inspector visited a facility only to find that there was no business in operation. It is clear that the districts charged with inspecting such establishments were not aware that the facilities were not open. This could mean that a blood facility did not notify FDA of its intentions to close or that this information was not conveyed to the district and appropriately noted on the active list of blood facilities. In either case, these examples were still listed as "active" on FDA's list of registered blood establishments.

18. The report does not state that inspectors are not knowledgeable or are not highly professional. We do note in the report that, in fact, all the survey respondents felt that the FDA inspectors appeared to follow a systematic approach during the inspection. (See page 88.) Also, our report states that the survey respondents found inspectors to be generally knowledgeable. (See page 88.) However, these same respondents noted that there was a wide variation in the inspector's knowledge and training in blood-banking terminology and procedures. This may be a result of who inspects blood facilities. There are 321 field investigators who conduct inspections of

blood facilities. Of these, 22 (7 percent) are dedicated to inspecting blood facilities. This may be one reason for the survey respondents' noting inconsistencies between the level of knowledge of blood inspectors. The survey respondents also noted inconsistencies in how inspections are conducted. Additionally, as noted in comment 10 above, there are several pieces of information that call the consistency of the actual inspections into question.

19. Notifying donors of positive and indeterminant test results is not the same as requiring the notification of donors that they have been permanently deferred. Criteria that require that a donor be permanently deferred (such as positive test results for viral markers, being an intravenous drug user, or receiving human pituitary growth hormone) should be in place to protect the safety, purity, and potency of blood products by notifying such donors that they cannot donate in the future. FDA's recommendation to permanently defer donors for positive HIV test results is in place not only to protect the safety, purity, and potency of blood products but also to protect the public health from transmissible diseases. Other viruses, such as HBV, have relatively high rates of transmissibility and should be considered by FDA in a similar fashion as HIV in terms of protecting the public health from secondary infection.

20. We are aware of the technological limitations of identifying blood products that have been bacterially contaminated before transfusion. We are also aware that bacterial contamination is one of the leading causes of adverse outcomes in blood transfusions.¹ We have modified our recommendation to take note of these technological limitations. As a result, we recommend that FDA require a blood facility's quality assurance program to include processes that monitor for bacterial contamination. This would permit the inclusion of multiple procedures to recognize and manage transfusion-associated sepsis and septic complications. Further, we believe that the study that is under way to estimate the incidence of, and identify risk factors for, bacterial contamination of blood products is a good first step in addressing this problem. Results from this study should be used to assist FDA and the blood industry in identifying ways to overcome problems relating to the bacterial contamination of blood products.

21. We have added language to the report indicating that work is under way within FDA to examine this issue and that a recommendation from FDA

¹See U.S. General Accounting Office, Blood Supply: Transfusion-Associated Risks, GAO/PEMD-97-2 (Washington, D.C.: 1997).

is currently being developed. However, we are recommending that testing of autologous units be required (not recommended). Again, we believe that this should be required to assist in protecting the safety, purity, and potency of blood and blood products.

22. We recommend that blood facilities be required to perform confirmatory testing on all repeatedly reactive test results for which there is a licensed confirmatory test (this would currently include HBV, HCV, and HIV). We recommend this because we became aware that some facilities do not always perform confirmatory testing on repeatedly reactive tests for which there are confirmatory tests available. Thus, we believe this should be a required, and not just a recommended, practice. This should be done to enhance the safety of blood products as well as to notify donors of their deferral status (see recommendation 1) and to have as complete information as possible for retrospective notification of recipients. We also believe that consignee notification should be required for units that have been shipped for further manufacture so that such units can be pulled from inventory if they have not been transfused. This should also be done to assist in tracing recipients of the implicated units that have been transfused.

We have added language to the report noting that FDA has issued a final rule that requires consignee notification for blood products potentially contaminated for HIV. We note, however, that this final rule pertains only to HIV.

We also recommend that there be a required lookback for patients who have been transfused with units that are from donors who subsequently test repeatedly reactive and confirmatory positive for viral markers. Several reasons have been presented in public forums regarding the pros and cons of lookback. FDA's comments to our report point out four such issues that argue against lookback. First, the present policy regarding lookback for HIV is in place because it is almost always fatal and there is a public health risk from secondary transmission. Thus, lookback might not be justified for other viruses, given the high cost of doing a lookback. However, as noted above, other viruses are also known to have high secondary transmission rates (such as HBV). Furthermore, a recent study presented at the 1996 AABB annual meeting suggests that, given certain assumptions regarding the blood supply, lookback for HCV could be as cost-effective as other common health-related interventions.²

²J.P. Auchon, J.D. Birkmeyer, and M.J. Alter, "Cost Effectiveness of HCV Lookback," *Transfusion*, 35 Supp. (1996), 51S.

Second, FDA points out that treatment for HCV is often not effective. However, some studies suggest that long-term recovery may, in fact, occur with alpha interferon therapy for those diagnosed with HCV (especially those diagnosed at the early stages of infection).³ Additionally, FDA has recently approved an interferon therapy to treat chronic HCV in adult patients. In clinical trials for this product, it was found that 23 percent of the patients had a complete response at the end of their treatment. Also, some recipients might benefit from being notified so that they might curtail behavior (such as consuming alcohol) that could cause more progressive harm after being infected with such viruses as HBV and HCV.

Third, FDA has argued that considerations for implementing a program to identify HCV-infected persons should be based on certain principles, one of which is that effective treatment and acceptable guidelines or criteria should be available to determine which patients should be treated. However, other viruses such as HIV do not have an effective treatment, yet FDA now requires lookback for this virus.

Fourth, FDA notes that secondary transmission of HCV and other agents from blood products is minimal and is not generally seen as a public health threat. However, the transmission of HIV through blood products also rarely occurs, yet FDA now requires lookback for HIV. Thus, the mere fact that transmission of a given virus rarely occurs as a result of transfusions has not precluded FDA from requiring lookback. Also, secondary transmission does occur with HCV and other viruses.⁴

Fifth and finally, FDA notes that targeted testing of all recipients of positive transfusions would include a high proportion of false positive test results because of the high false positive rate of early screening tests. Experience with HIV lookback indicates that the number of persons who can be recontacted after 6 to 12 months is very low. Thus, lookback testing is not cost effective. Our report does not outline how FDA might handle specific lookback procedures for non-HIV viruses. We do note, however, that “the reasonable time period for lookback varies with each virus, and decisions should be made in consultation with the blood industry.” (See page 100.) Thus, it might be determined that lookback procedures should be implemented beginning at a specific date when a memorandum to blood

³G. Davis et al., “Treatment of Chronic Hepatitis C With Recombinant Interferon Alpha,” *New England Journal of Medicine*, 321 (1989), 1501-6.

⁴A recent presentation at the 1996 AABB national meeting outlined a case of sexual transmission of HCV. See C. Capelli, “A Case of Transmission of Hepatitis C Virus Between Sexual Partners”, *Transfusion*, 36 Supp. (1996) 51S.

establishments is finalized (we do recommend that such a recommendation be required in the future). FDA should also note that our recommendation relates only to units that are repeatedly reactive and confirmatory positive.

23. We have added language to the report to indicate that a proposed rule change is now under review.

24. We are aware of the need for guidance documents and state so explicitly in the report where we noted that “FDA has to its credit historically issued memoranda to give the industry immediate feedback on its position on new issues. This is an important tool for quickly reacting to advances in medical knowledge or technology.” (See page 78.) However, as the information in the report suggests, there is, in fact, substantial confusion within the blood industry on the different uses and practical implications of regulations, memoranda, and guidance documents. Furthermore, some activities within blood banking should be required and not simply recommended. For this reason, we have recommended that FDA publish such activities in the form of regulations in order to more thoroughly ensure blood product safety.

25. FDA’s reply to this recommendation has several points. First, FDA noted that it already reviews and analyzes inspection reports, both for identification of conditions warranting immediate action and for longer term trends. Our use of the words “systematically analyze” in our recommendation was meant to convey the notion that FDA should perform statistical analyses on the contents of EIRS, activities that have and have not been observed, compliance and noncompliance rates, and Form 483 observations. We know that FDA does not presently perform these types of analyses.

Second, FDA’s comment notes that an example of trends analyses performed by FDA is the 1992-93 FDA Task Force on ARC that categorized all Form 483s issued to ARC in 1988-92. At an interview with FDA officials to discuss databases that were present within FDA, we asked whether any databases existed that tracked information from Form 483s. We were told at that meeting that there were no databases that had such information. Regardless of this, we do not view the task force work as the kind of nationally representative analysis described above. The analysis performed by the task force was merely a list of all Form 483 observations given to ARC in 1988-92, separated into different categories. No further

analysis was performed on this information that could inform FDA of trends in inspection findings or compliance rates.

Third, the FDA reply outlines several manuals and other directives that are available to FDA investigators that include what is to be contained in an EIR and Form 483. Our data suggest that FDA investigators do not always follow such information. One example of this is our analysis of the checklists completed by FDA investigators prior to fiscal year 1995. We found that 18 percent of the EIRS did not contain a checklist when they should have. Thus, policy directives to complete a checklist did not always result in the checklists being completed by the investigators. Also, at the 1996 AABB national meeting, FDA officials were asked to comment on a Form 483 observation received by an audience member's facility. The FDA officials stated that the observation in question should not have been a Form 483 observation and that was why FDA inspectors were being sent back for more training. Furthermore, in our analysis of Form 483 observations, we found a statistically significant difference between the kind and number of Form 483 observations between FDA districts.

Information contained in some EIRS that we reviewed had such little information that it would have been impossible for FDA reviewers, outside auditors, or future investigators to determine what had and had not been observed during the inspection. Therefore, we believe that FDA cannot determine compliance and noncompliance rates among the blood facilities that it inspects. We are aware that FDA has a policy that allows inspectors to only list on the EIR the Form 483 observations and the compliance program under which the inspection is taking place. However, in comment 8 above, we illustrated that this does not always occur.

Our survey respondents noted that in many cases FDA inspectors do not always observe several practices that take place at the blood facilities. Because FDA inspectors do not always write down on the EIR what was not inspected, FDA would be unable to determine in which areas a blood facility was in or out of compliance. Thus, the presence of manuals and directives to inspectors does not guarantee correct implementation contained in these guidance documents or consistency in what is to be considered an objectionable event.

Fourth, FDA's comment mentions that regulation citations are not included on the Form 483 because in many instances there are several regulations that may relate to a specific observation. We are aware of this and have added language to the report on this topic. It was also noted that while FDA

believes FDA investigators are very familiar with how to write a Form 483, a group of FDA's regional and national biologic expert investigators performed a study in July 1996 that was to assist in providing clearer guidance in terms of the significance, contents, and format of observations. When we asked FDA for the results of this study, we were provided some information. The conclusions of the study were that the majority of Form 483 observations were valid but that complete assessments could not be made outside the context of the EIR. The panel determined that the most appropriate manner in which to use the general conclusions drawn would be to develop a specific module for writing Form 483s in the blood-banking training courses provided to blood bank inspectors.⁵

That FDA conducted this study suggests that the agency is aware of problems in Form 483 consistency, and the conclusion on additional training supports this viewpoint. Additionally, our analysis of regional differences in the kind and number of Form 483 observations indicates that additional training is warranted. Furthermore, FDA's admission at the recent AABB national meeting regarding further training of inspectors on what should be included on a Form 483 would appear to be a good first step in resolving these problems.

Fifth, FDA's reply described how the agency has changed its inspection frequency so that blood establishments that are in compliance may be inspected once every 2 years. We actually noted this in several places in our draft report, most conspicuously on page 24, footnote 12. Thus, we were aware that FDA is now using this less frequent inspection time and we used this in our analysis of whether the inspections were occurring within the required time periods. (See pages 79 and 82, footnote 21.)

⁵We did find problems in the way in which this study was conducted, although the conclusions drawn from the study support our findings on inconsistent inspection activity as it relates to Form 483 observations. Problems with this study included (1) a nonrepresentative sample of Form 483s, (2) reviews of the Form 483s by two investigators without determining interrater reliability, and (3) no formal coding scheme for classifying the Form 483s.

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