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FYI - FDA will issue when reg goes to the Register

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NEW PRECAUTIONARY MEASURES TO REDUCE THE THEORETICAL RISK OF NEW VARIANT CJD FROM BLOOD PRODUCTS

FDA today issued guidance to blood establishments to reduce the theoretical risk of new variant Creutzfeldt-Jakob Disease (nvCJD) to recipients of blood products. This guidance, a precautionary measure, asks blood centers to exclude potential donors who have spent six or more cumulative months in the U.K. between Jan 1, 1980, and December 31, 1996 from donating blood.

NvCJD, a fatal degenerative disease found almost exclusively in the United Kingdom (U.K.), has been linked to an outbreak of bovine spongiform encephalopathy (BSE) there.

No evidence exists that the disease has been transmitted by blood transfusion, but current studies cannot exclude this possibility.

The risk of nvCJD from BSE exposure is unknown. However, if the number of cases of nvCJD in the U.K. remains low for the next several years, then scientists estimate

-More-

that the overall risk of nvCJD to people exposed to BSE will be small. No cases of BSE or nvCJD have been identified in the U.S.

Also included in this deferral are donors who have received bovine insulin or other injectable products made from cattle in BSE endemic countries, although there are no reports of nvCJD transmission by such products.

The U.K. is defined as England, Scotland, Wales, Northern Ireland, the Isle of Man and the Channel Islands.

Previous guidance recommended that potential donors with risk factors or a diagnosis of classical forms of CJD should be permanently deferred and that any blood products or plasma derivatives from these donors should be immediately retrieved, quarantined, and destroyed. However, under the revised guidance, withdrawal of plasma derivatives is no longer recommended in these cases. (The guidance remains the same for blood components not manufactured into plasma derivatives.) The reason is that laboratory and large epidemiologic studies suggest that the risk of classical CJD from plasma derivatives is extremely low. In addition, shortages of plasma derivatives have caused serious disruptions in patient care.

Although there are no reports of transmission of classical forms of CJD from blood or blood products, nvCJD differs both in its symptoms and biology. In addition, less

-More-

is known about nvCJD and whether it is transmissible through blood or blood products, although laboratory and epidemiologic studies are underway to evaluate this risk. Therefore, until more is known about the risk of nvCJD, withdrawal of all blood components and plasma derivatives made from donations from people later diagnosed with nvCJD is recommended.

The guidance can be obtained on FDA's website at www.fda.gov ~~(get exact location from Joanne Binkley.)~~

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Blood Supply: FDA Oversight and Remaining Issues of Safety (Chapter Report, 02/25/97, GAO/PEMD-97-1).

Pursuant to a congressional request, GAO evaluated the Food and Drug Administration's (FDA) "layers of safety" that provide the framework for regulating and monitoring the U.S. blood industry, focusing on the actual and potential vulnerabilities in the layers of safety that may present a threat to the public health.

GAO found that: (1) the transmission of human immunodeficiency virus (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 the risks from blood transfusions; (2) 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; (3) within the overlapping layers of safety, GAO found areas where FDA can take action that would further improve the safety of the blood supply: (a) the lack of a uniform donor questionnaire allows variability in donor screening; (b) the lack of mandatory deferral notification allows some donors who have tested positive for viruses to unwittingly attempt donation again; (c) untested units donated for self-use may inadvertently be used for unintended recipients; and (d) FDA has been slow to investigate error and accident reports that may warrant a recall; (4) 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; (5) 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; (6) FDA's inspections for both licensed and unlicensed blood facilities appear to be inconsistent in focus, scope, and documentation; (7) in addition, these inspections are often not conducted within time periods set by FDA's own guidelines; (8) FDA does not maintain a central repository for inspection reports and, thus, does not examine national trends; and (9) GAO's survey results also indicated confusion within the blood industry regarding the interpretation for FDA policy guidance and regulations.

---------- Indexing Terms ----------

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TITLE:	Blood Supply: FDA Oversight and Remaining Issues of Safety
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SUBJECT:	Acquired immunodeficiency syndrome
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	Inspection
	Testing
	Reporting requirements
	Product safety
	Medical supplies
	Quality control
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	FDA Program Oriented Data System
	FDA Error and Accident Reporting System

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** This file contains an ASCII representation of the text of a **
** GAO report. Delineations within the text indicating chapter **
** titles, headings, and bullets are preserved. Major **
** divisions and subdivisions of the text, such as Chapters, **

Cover
========== COVER

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

February 1997

BLOOD SUPPLY - FDA OVERSIGHT AND REMAINING ISSUES OF SAFETY

GAO/PEMD-97-1

Blood Supply: Oversight and Safety Issues

(973418)

Abbreviations
========== ABBREV

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

Letter
========== LETTER

B-271101

February 25, 1997

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
Systems Areas

EXECUTIVE SUMMARY
========== Chapter 0

PURPOSE
---------- Chapter 0:1

Approximately 4 million patients annually receive life-saving transfusions of blood donated by 8 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
---------- Chapter 0:2

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
---------- Chapter 0:3

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

---------- Chapter 0:6

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 procedures in place to notify recipients of units from donors who subsequently test positive for viruses other than HIV ("lookback"). 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.

INTRODUCTION

========== Chapter 1

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

\1 Congressman 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

---------- Chapter 1:1

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. 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.

\2 There 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.

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

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

\a All 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

---------- Chapter 1:3

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

---------- Chapter 1:3.1

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

---------- Chapter 1:3.2

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

---------- Chapter 1:3.3

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

\3 HIV 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.

\4 The 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.

\5 This 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.

\6 For 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.

BLOOD QUARANTINING

Chapter 1:3.4

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.

MONITORING AND INVESTIGATING PROBLEMS

---------- Chapter 1:3.5

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

---------- Chapter 1:4

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

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	Conducts clinical studies on the effects of blood

Blood Institute	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

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\a As with FDA's guidance documents, these recommendations are not binding on members of the blood industry.

\b A 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.

\c Includes 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.

\d Issues 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.

\7 This 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.

\8 The 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.

\9 21 C.F.R. parts 210, 211, 606, 607, 610, and 640.

\10 FDA'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 . . . ."

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. 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

---------- Chapter 1:5.1

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

---------- Chapter 1:5.2

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

---------- Chapter 1:5.3

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

---------- Chapter 1:5.4

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.

\11 In 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.

ESTABLISHMENT INSPECTION REPORTS AND FORM 483

---------- Chapter 1:5.5

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 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.

\12 Beginning 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.

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

\14 Licensed 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.

\15 In 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.

SURVEY OF BLOOD CENTERS

---------- Chapter 1:5.6

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

\16 By "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.

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

THE STRENGTHS AND LIMITATIONS OF OUR STUDY

---------- Chapter 1:6

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.

\18 Thus, 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

========== Chapter 2

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

---------- Chapter 2:1

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).

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

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\a Babesiosis, like Chagas' disease, is caused by a parasite.

\b Some 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.

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.

\1 Patients 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.

\2 For 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.

\3 See 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.

\4 Susan 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

---------- Chapter 2:1.1

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 2.3

Screening Problems and Form 483 Observations by Facility Type\a

	Licensed		Unlicensed\\ b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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 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.)

\5 Appendix 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.

\6 In 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.

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

SAFETY ISSUES

---------- Chapter 2:1.2

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

---------- Chapter 2:1.2.1

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

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.

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

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

PRIVACY

---------- Chapter 2:1.2.2

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

\10 L. 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.

\11 See 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.

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.)

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
	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
Permanent	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

\a Accutane, 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.

\b Deferral 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.

\c Tegison 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.

\d Pituitary-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.

\e Blood 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.

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

\13 ARC 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.

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

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.

Table 2.5

Deferral EAR Rates by Facility Type, 1994\a

	Unlicensed\ or transfusion	Plasma

Source	Licensed	service\b	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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\\ b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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.

\15 In 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.

SAFETY ISSUES

---------- Chapter 2:2.2

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

---------- Chapter 2:2.2.1

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.

MANUAL DDRS

---------- Chapter 2:2.2.2

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

---------- Chapter 2:2.2.3

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

---------- Chapter 2:3

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

---------- Chapter 2:3.1

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\\ b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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

\16 There 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.

SAFETY ISSUES

---------- Chapter 2:3.2

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

BACTERIAL CONTAMINATION

---------- Chapter 2:3.2.1

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.

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.

\17 According 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.

\18 M. 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).

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

\20 R. 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).

\21 Blajchman and Ali, pp. 220-21.

CORRECTIVE MEASURES

---------- Chapter 2:3.3

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.

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.

\22 Goldman and Blajchman, pp. 72-83.

TESTING

Chapter 3

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.

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

ROUTINE TESTING

Chapter 3:1

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 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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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

---------- Chapter 3:1.2

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

BLOOD TYPING

---------- Chapter 3:1.2.1

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 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 them 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.

\2 This 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.

VIRAL TESTING

---------- Chapter 3:2

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 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.

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 HBc 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

\a Procedures 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 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.

\3 In 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.

\4 In 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.

\5 False-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).

\7 Cytomegalovirus (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.

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

\9 Viral 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.

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.

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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

---------- Chapter 3:2.2

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

---------- Chapter 3:2.2.1

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

---------- Chapter 3:2.2.2

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

---------- Chapter 3:2.2.3

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.

\10 The 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.

\11 Not 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.

LOOKBACK PROCEDURES

---------- Chapter 3:2.2.4

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.

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 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.

\12 This 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.

\13 According 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.

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

\15 A 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.

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

DIVERGENT VIRAL STRAINS

---------- Chapter 3:2.2.5

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

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.

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

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

\19 Centers 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.

\20 A 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.

TEST SENSITIVITY

---------- Chapter 3:2.2.6

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 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 to 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

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

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

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

\24 D. 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.

\25 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.

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. 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.

\26 Most 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.

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

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 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.

\28 We 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.

\29 J. 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

========== Chapter 4

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

---------- Chapter 4:1

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.

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

Unlicensed\\ Transfusion Plasma

Source	Licensed No.	%	b No.	%	service No.	%	center No	%	Total 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

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

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

\c There 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

---------- Chapter 4:1.2

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

---------- Chapter 4:1.2.1

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

---------- Chapter 4:2

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.

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.

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

\2 Labels 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.

EAR AND EIR INFORMATION

---------- Chapter 4:2.1

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

	Unlicensed

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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

---------- Chapter 4:2.2

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

QUARANTINING

---------- Chapter 4:3

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.

\3 Pending 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.

EAR AND EIR INFORMATION

---------- Chapter 4:3.1

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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We calculate rate per 100,000 units collected by dividing the total number of EARs by the total number of units collected.

Table 4.6

Quarantining Problems and Form 483 Observations by Facility Type

	Licensed		Unlicensed\\ b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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
---------- Chapter 4:3.2

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

STORAGE AND DISTRIBUTION
---------- Chapter 4:4

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

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.

\4 A 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.

\5 American Association of Blood Banks, Technical Manual, 11th ed.,

(Bethesda, Md.: 1993), p. 574.

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

\7 21 C.F.R. 606.165(a).

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 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

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

\b FDA 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.

\c We calculate rate per facility by dividing the total number of EARs by the total number of facilities.

\d We 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

	Licensed		Unlicensed\\ b		Transfusion service		Plasma center		Total	
Source	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

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

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

\c There 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

Chapter 4:4.2

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

INVENTORY MANAGEMENT

Chapter 4:4.2.1

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.

\8 E. 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

========== Chapter 5

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 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.

\1 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.

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 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.