
2. **Overview**

Contents

| | <i>Page</i> |
|---|-------------|
| Part 1: History of Federal Interest | 33 |
| Part 2: Blood and Blood products | 36 |
| Part3: The Blood Donor | 38 |
| Risk for Donors | 39 |
| Part4: Federal Activities | 41 |
| Introduction | 41 |
| Payment for Blood Products and Services | 42 |
| National Institutes of Health | 43 |
| Food and Drug Administration | 45 |

LIST OF TABLES

| <i>Table No.</i> | <i>Page</i> |
|---|-------------|
| 2. Ten Policies and Six Critical Issues in Support of National Blood Policy Goals | 35 |
| 3. Blood Components and Plasma Derivatives in Therapeutic Use. | 37 |
| 4. FDA Statutory Authority to Regulate Blood Products and Blood Banking Technologies | 45 |
| 5. Blood Products Recalls, June 1975 to November 1983 | 46 |
| 6. Significant Deviations Leading to Plasma Center Suspensions, Oct.1, 1979 to Aug.31, 1981 | 46 |
| 7. Types of Numbers of Blood Processing Errors, 1981-82 | 47 |
| 8. New Blood Products and Procedures Approved by FDA in the Past Two Years (approx. 1982-83) | 47 |
| 9. Blood Products and Related Technologies in the Approval Process as of Early 1984 | 48 |

PART 1: HISTORY OF FEDERAL INTEREST

Federal interest in assuring an adequate and safe blood supply has a long history. President Truman called blood a “critical national resource vital to the country’s well-being and security.” The Federal Government regulates blood banking (as do State governments), monitors the safety and efficacy of blood products, and promotes research on blood diseases and resources.

In the **1960s**, scientists recognized the correlation between high rates of posttransfusion hepatitis and blood obtained from paid donors. Cardiac surgery and other advances in medical care increased the use of whole blood for transfusion, and with this increased use came increased concern for the safety of blood transfusions. Separation of whole blood into components and the use of platelets and plasma derivatives became increasingly widespread. One result of this heightened interest in blood was the establishment of a National Blood Resources Program at the National Heart and Lung Institute in 1967. In 1972, the program was reconstituted as the Division of Blood Diseases and Resources in the expanded National Heart, Lung, and Blood Institute (NHLBI), where it still operates.

In the early 1970s, there was a surge of public interest that prompted Federal policymakers in both the executive and legislative branches to review the Nation’s blood program. This round of debate was sparked largely by the publication of *The Gift Relationship* by Professor Richard Titmuss, a British scholar and student of social welfare policy. Professor Titmuss excoriated the commercial market for whole blood in the United States on both safety and ethical grounds. His book received much attention in the news media and inspired a television documentary which highlighted the hepatitis problem and featured pint after pint of blood being poured down the drain to dramatize the wastage problem.

During this time period, over 40 bills designed to regulate blood resources were introduced in the 92d Congress, including H.R. 11828, introduced by Representative Victor V. Veysey, which proposed that a National Blood Bank Program be located in the Department of Health, Education, and Welfare (DHEW, the predecessor to the current Department of Health and Human Services, or DHHS) (485). Simultaneously, the increasing input of private sector health organizations prompted the executive branch to take a stand on the blood issue.

President Nixon’s annual health message to the Congress in March 1972 described blood as a “unique national resource,” and he subsequently charged a DHEW task force with the assignment of developing a safe, fast, and efficient nationwide blood collection and distribution system.

In May 1972, monitoring of blood resources was transferred from the National Institutes of Health (NIH) to the Food and Drug Administration (FDA). Since that time, FDA’s Bureau of Biologics (currently renamed the Office of Biologics Research and Review) has been the principal regulator (States also play a regulatory role) of blood collection, processing, testing, and marketing. As a result of this change, all blood banking in the country, not just interstate blood trade, came under direct Federal regulation.

Following extended examination and debate, including the DHEW Task Force Report which found that: 1) the supply of blood was sometimes inadequate, 2) the quality of blood was uneven and reliance on commercial blood was contributing to a high rate of hepatitis, 3) gross inefficiencies existed, and 4) the cost of blood therapy was a burden to many people, a National Blood Policy (NBP) was enunciated by the Federal Government in 1973. There were four goals underlying the National Blood Policy (180):

1. **Supply.** A supply of blood and blood products adequate to meet all of the treatment and diagnostic needs of the population of this country.
2. **Quality.** Attainment of the highest standard of blood transfusion therapy through full application of currently available scientific knowledge, as well as through advancement of the scientific base.
3. **Accessibility.** Access to the national supply of blood and blood products by everyone in need, regardless of economic status.
4. **Efficiency.** Efficient collection, processing, storage, and utilization of the national supply of blood and blood products.

The National Blood Policy was broken down into 10 specific policies, along with six issues which were to be examined critically. Prominent among the policies were adoption of an all-voluntary blood collection system, coordination of charges and costs for blood services, and regionalization of blood collection and distribution. Critical examinations of the nonreplacement fee, the plasmapheresis industry, and standards of care for hemophiliacs and other special groups were also recommended (table 2).

A number of Federal and private sector initiatives were undertaken in order to begin implementing the National Blood Policy. In 1974, DHEW accepted the private sector plan to establish an American Blood Commission (ABC), which was to implement "the lion's share" of the National Blood Policy (180). The National Heart, Lung, and Blood Institute provided partial funding for ABC activities until recently, when the existing contract expired (ABC may still apply to NIH for funding of specific projects, but on a competitive basis). ABC now depends on membership fees and donations, and it has been experiencing difficulty in retaining some of its organizational members.

There were no direct government actions to ban the sale of whole blood and plasma, although steps were taken to regulate the safety of plasma products and discourage the use of commercial whole blood. FDA became increasingly involved in regulating the plasma industry, building on its initial involvement which had begun during the

late 1960s (506). In 1973, FDA's Bureau of Biologics published additional standards for source plasma and required all plasmapheresis operating facilities to file an application for licensure of both their establishments and products; a formal compliance program began in mid-1977. FDA oversight over the plasmapheresis industry was relaxed somewhat in 1977, when responsibility for annual inspections was transferred from the Bureau of Biologics to FDA field investigators and supervisors (506).

No Federal efforts were made to ban commercial plasma collections. Regulators realized that the demand for plasma supplies could not be met by the existing voluntary sector. Since the collection of whole blood and preparation of blood components were largely in the province of the voluntary sector, an FDA rule was implemented in 1977 to identify the source of whole blood and its components (red cells, platelets, single-donor plasma, cryoprecipitate). This action was taken on the basis that available data indicated a greater risk of transmission of hepatitis with the use of blood and blood components from paid donors. Under this regulation (21 CFR sec. 606.120(b)(2)), whole blood and its components are labeled as collected from a "paid donor" or "volunteer donor." The regulations state that a paid donor is a person who receives monetary payment for a blood donation, while a volunteer donor is a person who does not receive such payment. Other benefits that are not readily converted to cash, such as time off from work and cancellation of nonreplacement fees, are not considered as monetary payment. These labeling requirements do not apply to source plasma or plasma derivatives, since plasma derivatives produced from plasma obtained from paid or volunteer donors are considered to be equally at risk for transmission of infectious agents.

Steps were also taken to assure that hemophiliacs were afforded access to care. The Public Health Service Act of 1975 (Public Law 94-63): 1) established Federal funding for comprehensive hemophilia diagnostic and treatment centers, and 2) authorized funds for projects to develop and expand blood derivative operations in the event the Secretary of DHEW found that there was an

Table 2.—Ten Policies and Six Critical Issues in Support of National Blood Policy Goals**Ten policies:**

1. Efforts toward an all-volunteer system for blood and blood components were encouraged, fostered, and supported.
2. The establishment of a system for the collection and analysis of all relevant information concerning plasmapheresis, plasma fractionation, and the flow of plasma and plasma products within the United States and other countries was to be encouraged, fostered, and supported. This information was believed necessary to determine the sufficiency of domestic sources of plasma fractions; develop future positions on the relationships between plasmapheresis and plasma fractionation and whole blood banking; and develop a degree of interdependence between the United States and other countries with respect to plasma and plasma products.
3. Continuing data and information collection and processing systems to describe all elements and functions in the blood banking sphere on a continuing basis. The purpose of this policy was to acquire fundamental information on the nature and transmission of diseases by blood and blood products and the occurrence of transfusion mishaps, as well as to design and create changes which would enhance the effectiveness of the blood banking system.
4. Resource sharing and areawide cooperation in the collection, processing, distribution, and utilization of blood.
5. Ample donations were to be assured through encouraging: a) improved accounting and reporting systems to identify the relationship between costs and charges; and b) public and health professional education.
6. Educational and other programs to assure appropriate use.

7. Adherence to the highest attainable standards for blood products, including plasma derivatives, through use of or extension of Federal regulatory authorities were to be employed.
8. Research, including systems analysis and other management approaches to extend shelf life, and to identify and control diseases transmittable by blood.
9. Insurance benefits for the service aspects of blood components and both the acquisition and service aspects of plasma derivatives. The acquisition costs of plasma derivatives were to be covered in recognition that commercial acquisition may still be necessary.
10. The Secretary of Health, Education, and Welfare was to be responsible for implementing this policy.

Six critical issues to be examined:

1. The adequacy of any proposed implementation action in meeting the extraordinary demands for blood that may arise in national and regional emergencies.
2. The appropriateness of the replacement fee in an all-voluntary system.
3. Systems approaches to the integration of various functions and segments of the blood banking industry.
4. Regionalization of blood services management.
5. Appropriate inducements and authorities, whether existing or to be sought, necessary to exclude commercial acquisition of whole blood or blood components.
6. Special problems of accessibility for hemophiliacs and others with continuing or extraordinary needs for blood or blood products.

^aA seventh issue was stated as "other issues relevant to the four principal goals."
SOURCE: *Federal Register*, Mar 8, 1974.

insufficient supply of blood derivatives available to meet the treatment needs of hemophiliacs. A contractor's report to DHEW (554) projected that sources of supplies of antihemophilic factor and prothrombin complex were adequate to meet hemophiliacs' needs through and beyond the authorization period, so the treatment centers were established but projects to develop and expand blood derivative operations were not funded.

The nonreplacement fee became an issue when the American Red Cross, in order to make its practices conform to its philosophy of community responsibility, withdrew from the AABB National Clearinghouse system, which used blood credits and nonreplacement fees. The lack of cooperation between the three major blood supply organizations (American Red Cross, American Association of Blood Banks [AABB], and the

Council of Community Blood Centers [CCBC]) led to concerns over the possibility of blood shortages in some regions, and to the introduction of two bills in Congress (S. 1610, introduced by Senator Schweiker in 1979; and S. 140, introduced by Senator Hatch in 1981). The Schweiker and Hatch bills would have eliminated the nonreplacement fee and provided donors with a discount on the charge for blood when they were patients.

The nonreplacement fee was also the focus of concern that Medicare was overpaying for blood (546). Medicare guidelines require that patients pay a three-unit blood deductible by either replacing or paying for the first three units of blood transfused. A General Accounting Office (GAO) investigation found that billing and replacement practices of blood banks and hospitals had caused substantial Medicare overpayments for blood and

blood products, that blood banks had prevented the use of blood replacement credits to reduce blood fees whenever Medicare would pay the fees, and that hospitals charged nonreplacement fees to Medicare patients for blood supplied by community blood banks that charged only processing fees.

In addition to improved monitoring practices, one of GAO's recommendations was that the Health Care Financing Administration (HCFA) undertake a study of the relationship between the costs and charges for blood. Such a study has not been conducted by HCFA. (In addition to a blood replacement fee, there are fees for blood processing, typing and crosshatching, and for transfusion services, which are charged whether or not a blood replacement fee is imposed. In 1980, for

example, average total charges for transfusing a unit of red cells was \$88.17, including an average replacement fee, when charged, of \$27.98 (576).)

Other Federal interests in the issues surrounding blood services delivery have come in the form of support for a variety of basic and applied research, principally from the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute (556). Most recently, the same division has begun efforts to improve the appropriate use of blood products (e.g., the "Transfusion Medicine Academic Awards"). Current activities of the Federal Government with respect to blood services, policy and technology are set forth in part 4 of this chapter.

PART 2: BLOOD AND BLOOD PRODUCTS

Blood is a mixture of specialized cells suspended in plasma, which itself is a complex liquid containing proteins, nutrients, salts, and hormones. Blood has many functions, including transport of oxygen and nutrients to body tissues, removal of carbon dioxide and other wastes, and transfer of hormonal messages between organs. It also plays a major role in the body's defenses, inhibiting invasion and spread of organisms by transporting antibodies and infection-fighting cells to the sites of infection. Albumin, the principal protein found in plasma, helps maintain blood volume by maintaining an osmotic gradient (oncotic pressure) between the vascular system and surrounding tissue, and serves as the carrier molecule for fatty acids and other small molecules (467). A complex clotting system to prevent blood loss involves both cellular (i. e., platelets) and protein elements of blood.

In blood banking terminology, "components" refers to products separated from whole blood and consist of the various types of blood cells, plasma, and special preparations of plasma. Components are usually separated from single whole blood donations, using a sterile system of plastic bags attached to the collection bag.

"Derivatives" refers to products derived from the chemical fractionation of plasma to concentrate selected blood proteins. Plasma from many donors is pooled prior to chemical fractionation in order to yield sufficient amounts of the final concentrated material for cost-effective production.

Blood components and plasma derivatives and their general indications for use in medical therapy are listed in table 3.

Hazards associated with therapeutic use derive primarily from immunologic incompatibility between donor and recipient and from transmissible diseases. Incorrectly typed and crosshatched blood or mislabeled blood can lead to reactions ranging from transient fever and chills to death. More subtle incompatibilities that may not be uncovered in routine typing and crosshatching may lead to sensitization of the recipient and hypersensitivity reactions from subsequent transfusions.

Infections of various types can occur through collection of blood from donors whose blood contains the infectious agent or from contaminants introduced in the collection, processing, or transfusing procedures. Syphilis was one of the first bacterial diseases known to be transmitted through

Table 3.—Blood Components and Plasma Derivatives in Therapeutic Use**Components and their therapeutic use:***Whole blood:* Replacement of large volume blood loss.*Packed red cells:* Anemia; provision of oxygen-carrying capacity.*Leukocyte-poor red cells:* As for packed red cells; used in patients with reactions to leukocytes.*Frozen red cells:* As for packed red cells; used in patients with more severe reactions to leukocytes; provision of rare red cells.*Platelets:* Platelet deficiency; platelet function abnormalities.*Fresh-frozen plasma:* Multiple coagulation factor deficiencies (indications under review).*Single-donor plasma:* Uncommon use.*Cryoprecipitate:* Provision of Factor VIII, von Willebrand's factor, fibronectin, fibrinogen.

Leukocytes; Bacterial infections in immunocompromised patients (rarely used).

Derivative:*Albumin:* Plasma volume expansion.*Immune serum globulin:* Infection prevention (immunodeficiency states, travelers).*Hyperimmune gamma globulin (e.g., Varicella Zoster immune globulin, Hepatitis B immune globulin):* Prevention of specific infections.*Factor VIII (antihemophilic factor):* Factor VIII replacement in hemophilia A.*Factor IX Complex:* Factor IX replacement in hemophilia B.*Anti-inhibitor Coagulant Complex:* Hemophilia A patients with high levels of Factor VIII inhibitor.

SOURCE: J. Pindyck, S. Gaynor, R. Hirsch, et al., "Prevention of Infection Transmission by Transfusable Blood, Blood Components or Plasma Derivatives." 1984.

blood, but in general, bacterial contamination is not a problem in modern blood banking. Protozoal diseases such as malaria and sleeping sickness can also be transmitted through blood, but most of these diseases are not endemic to the United States, and a history of travel to endemic areas or exposure to the disease that is uncovered during the medical screening of blood donors has effectively kept these diseases out of the blood supply.

Viruses are the major class of infectious agents that are transmitted through blood. Of these, hepatitis B and non-A, non-B hepatitis are the most prevalent. Surveys of blood donors show a frequency of hepatitis B of 5 to 7 percent. In the 1970s, development of increasingly more sensitive laboratory tests for the detection of hepatitis B that are now applied to every blood donation resulted in a dramatic reduction of posttransfusion hepatitis B cases. However, a new form of hepatitis (non-A, non-B) appeared, which, although

no agent(s) has been isolated, is presumed to be a virus. * Currently, 5 to 18 percent of Americans who receive five or more units of transfused blood develop non-A, non-B hepatitis (271b). About 90 percent of all post-transfusion cases of hepatitis are non-A, non-B, and about 10 percent are due to hepatitis B (558).

Other viruses are relatively common in the general population and normally are of no consequence in transfusions. One exception is cytomegalovirus, which can cause infections in premature infants and immunosuppressed recipients, such as kidney or bone marrow transplant recipients. Other viruses are fairly common but not known to lead to transfusion-related disease (e.g., Epstein-Barr virus, the agent for infectious mononucleosis), while other, recently discovered rare viruses could be theoretically transmitted through transfusions. AIDS, which is now accepted as being transmittable through blood, is now considered to be of viral etiology (i.e., the retrovirus-HTLV-111) (256).

All blood components and some plasma derivatives are capable of transmitting viral infections. Components are stored either at room temperature (platelets), in cold storage (whole blood, red cells), or frozen (red cells, plasma), and none of these processes inactivate viruses. Of the plasma derivatives, only albumin (and a related product, plasma protein fraction) and immune serum globulin (ISG) appear to be free of active viruses. Albumin is heated for 10 hours at 60° C in the presence of stabilizers to help maintain the structure of albumin, and this pasteurization inactivates viruses. Inactivation of viruses in immune serum globulin appears to be due to two factors: 1) the cold ethanol fractionation method appears to precipitate ISG in a fraction separate from the fraction containing viruses (61); and 2) ISG contains many antibodies against many viruses, which may diminish or destroy their infectivity (217).

Until recently, virus inactivation for the plasma-derived clotting factors had not been available be-

*A retrovirus has now been implicated as the cause of non-A, non-B hepatitis (493).

cause heat treatment caused loss of function. Heat-treated clotting Factor VIII, however, has recently been licensed by the FDA. It is not known how much Factor VIII activity is lost in the heat treatment process, and, since a balance has to be maintained between loss of function and inactivating viruses, the conditions under which these products are heated may not inactivate all viruses. (Current research suggests that the presumed AIDS agent, HTLV-III, is inactivated by this process.)

PART 3: THE BLOOD DONOR

Approximately 8 million people, representing about 3.5 percent of the population or about 10 percent of those eligible to give, donate blood in a year. There are no nationwide sources of data which profile blood donors. Nevertheless, many individual blood banks and donor recruitment centers have conducted studies to find out who constitutes their pool of donors, by characteristics such as age, sex, race, socioeconomic and occupational status, as well as by geographical location (e.g., urban, suburban, and rural). From these studies has emerged a picture of the "typical" blood donor: a white, middle-class male family member who gives at his place of work. The prevalence of male donors is a worldwide phenomenon, and it has been estimated that between 60 and 70 percent of all those donating blood in the United States are male (291).

Mobile blood collections have traditionally taken place in corporate and institutional settings, where relatively well-educated, middle-class white males are most likely to be found. This picture may be changing. Women have entered the work force in increasing numbers and hence are more likely to be subject to recruitment and to have convenient opportunities to donate.

Members of minority groups, and blacks in particular, may be harder to motivate (450), with speculation that it may be due to mistrust of the health care system in general, or existence of a sociocultural gulf between donation officials and potential minority donors. Blood bankers have attempted to overcome some of these hurdles by special recruitment tactics. These efforts include

Other methods of inactivating viruses include heating the derivative in the dry state (529), using detergents and organic solvents instead of heat (447), or neutralizing viruses by the addition of antibodies, a method which requires the use of specific antibodies against each type of virus to be inactivated (100). The Netherlands Red Cross is reportedly producing derivatives containing specific antibodies against hepatitis B virus (373).

involving leaders and spokespersons for minority groups in recruitment efforts and reaching out to cohesive minority fraternal, social and civic groups. Churches, which have long been a mainstay of recruitment drives, are particularly fertile grounds for such efforts.

Lower socioeconomic status may also compromise the willingness to give, in view of the finding that altruism is almost always at the top of the list of reasons for donating. Donors invoke altruistic reasons even when participating for the purpose of blood credits/replacements or being paid (49,71,409). Even scholars who have questioned the depth and the validity of altruism as a motivating force have concluded that, because it is a socially accepted motivation and one most often verbalized, it should continue to form the basis for appeals for donors (417,433).

There are certain physical limitations that are applied to potential donors. In general, any healthy person who weighs more than 110 pounds and is between the ages of 17 and 66 can be a blood donor. The upper age limits are imposed by blood collection agencies and are subject to some exceptions, while the lower age limits are imposed by State law. Blood donors who weigh less than 110 pounds are rejected because the standard amount of whole blood collected (450 ml) amounts to too great a percentage of their blood volume, a loss which could result in a serious hypotensive episode. Pregnant women are excluded from donating, as is anyone who has undergone major surgery in the preceding 6 months.

Many States have made statutory exceptions to the age of majority (usually 18) by allowing 17 year olds to donate. This allows entry into high school, which is not only a convenient donation site, but also inculcates youngsters with an understanding of the need for blood donors. The cut-off for those aged 66 or older has attracted some criticism. Critics argue that a more rational end point would be based not on age alone, but rather on health status, weight, and donation history. By these measures, many older people can give blood safely into their later 60s and 70s.

Physical limitations aside, most donations appear to be influenced by motivational and situational circumstances. Both donors and nondonors are aware of the need for blood, and personal experiences with the need for blood is distributed widely throughout the population (35). But many who claim they intend to donate do not actually follow through, and the “slippage” between those who say they will donate and those who actually do so maybe as high as 60 to 65 percent (192). This general acknowledgment of the need for blood and its contrast with those who actually donate have led to criticisms of generalized appeals through the mass media to donate blood. Much of the efforts of recruitment officials has involved generalized announcements of the continued need for blood donors. These most commonly take the form of television or radio public service announcements, often showing celebrities in the act of giving blood or recipients whose lives have been saved through transfusions. Such advertising campaigns, geared toward raising awareness of the need for blood, are ineffective in helping to overcome fears of donating, and suggestions have been made that advertising dollars may be better spent in allaying such fears.

More frequent and convenient donation opportunities, rather than knowledge of the need for blood, are correlated with increased donation rates (35). Observing others donating increases the chances that a person will also donate. Social and peer pressure can be an important force in donor motivation, especially regarding first-time donors, who often report to the donor site accompanied by friends (132,133). And the existence of an identifiable patient in need heightens awareness and the feeling of an obligation to give, even

when the specific patient in need is identified anonymously (e.g., “a young mother with children”) (489).

Most of the research on blood donors has focused on the motivations and characteristics of donors, not on factors involving the donation setting and the recruitment process. Research has most often been undertaken in one location, where a single donation ideology has motivated recruiters. There have been few comparisons of urban v. rural donors, fixed v. mobile sites, or cross-cultural studies. Factors such as the length of time it takes to donate and the donor’s perception of how he or she was treated by the staff and peers may be better predictors of donor commitment than attitudes toward moral obligations, etc.

Little attention has been devoted to determining what forces convert a first-time donor into a committed, repeat donor. Recruitment professionals play a key role in garnering first-time donors and in converting them into repeat donors. The personal convictions of the individual recruiter are important factors in motivating donors, and donor recruiters are often active donors themselves (236). Many large blood collection centers have donor recruiters as full-time staff members to organize local media efforts, to encourage and coordinate corporate and institutional drives, and to direct appeals to particular individuals, such as former donors. The conversion of first-time donors into repeat donors is a particularly important aspect, as the retention of past donors may be considerably more efficient than recruiting new donors (382).

Risks for Donors

The risks of whole blood donation are minor and rarely result in serious complications. For virtually all blood donors the loss of 450 ml of blood (up to 13 percent of total volume) is experienced with no untoward effects. Potential risks include local injuries such as bruises or reactions to antiseptics and dressings. The phlebotomy (needle stick) can result in **arterial** puncture **or air embolism**. Infections also occur on occasion, but they are usually infrequent and localized (577). The low level of risk to blood donors is evidenced not only by the medical literature and statistics kept by

blood donation centers, but also by the dearth of activity in the courts. In contrast to the number of lawsuits brought on behalf of recipients of contaminated blood products, there have been very few court cases involving injuries to donors.

Vasovagal syncope (a transient reaction marked by pallor, nausea, slow heartbeat, and a rapid fall in arterial blood pressure which sometimes results in fainting) is a risk for a small percentage of donors. Although it is impossible to predict with certainty which donors are at risk, certain factors, such as age, weight, a history of fainting and inexperience in donating, may be predisposing.

Along with loss of blood volume from donating, other factors can influence the amount of blood circulating to the brain. Vasovagal activity tends to pool blood in the skeletal muscles and gravity tends to pool blood in the distal veins; this is exacerbated if sitting erect. Eating and drinking pools blood in the stomach and intestines. Vasovagal reactions can, on occasion, include a blocked airway or cardiac arrhythmia. Blood donor centers are advised to keep resuscitation equipment on hand. Donors are observed for impending signs of fainting and are usually accompanied to a lounge for a brief period following donation. Obviously, part of the danger in fainting is from resulting bruises, lacerations, or other injuries. Yet, fainting following blood donation is uncommon; an acceptable level of such incidents is 0.3 percent, according to the Red Cross (44).

Plasmapheresis donors undergo some of the same risks as whole blood donors—for example, those associated with phlebotomy (e.g., arterial puncture or air embolism). Unlike conventional blood donation, plasmapheresis involves the removal of whole blood, separation by centrifuge into its constituent parts and reinfusion of cellular components into the donor. Thus, the plasmapheresis procedure entails the additional risk of reinfusion of cells from another donor, which could occasion a hemolytic reaction; Federal regulations specifically require that this risk be disclosed as part of the informed consent process (21 CFR pt. 640.61).

Labeling requirements have been adopted by plasmapheresis centers to decrease the likelihood

of such an occurrence, and some centers use portable centrifuges by the donor's chair, which further reduces the chance of a mixup. New technologies being developed to speed up the plasmapheresis process and make it more efficient would remove this risk, as these generally involve membrane or centrifugal separation of blood components in a self-contained system to which the donor is attached continuously.

The greatest controversy regarding risk to plasmapheresis donors has involved limitations on the volume and frequency of donation. The average adult male of 175 lbs has a plasma volume of 3,000 ml. Under Federal regulations donors in the United States can give 1,000 ml of plasma per 48-hour period up to twice a week. (Donors weighing more than 175 lbs can give 1,200 ml per donation (21 CFR 640.65 (4-6).) The regulations allow plasmapheresis donors to give up to 50 or 60 liters of plasma each year; this contrasts markedly with limits set by other industrialized nations—generally 10 to 25 liters annually. Regulations require that plasmapheresis donors undergo a serum protein electrophoresis and a measurement of immunoglobulin every 4 months to determine whether they are in normal range.

The effects of plasmapheresis on short- and long-term levels of plasma proteins and other blood components have been vigorously contested. Often the scientific debate has been overshadowed by social, ethical, and political questions concerning commercial plasmapheresis, especially in developing countries. The relative frequency with which U.S. regulations allow plasmapheresis has been decried, especially by European critics (347,348). One critic of U.S. policies regarding commercial plasmapheresis has stated that, "It defies comprehension that the necessary quantities of plasma are not procured by the simple expedient of increasing the number of donors sufficiently to minimize the individual risk" (346).

A group of experts convened by the World Health Organization (WHO) and the League of Red Cross Societies concluded that "no consistent clinical abnormalities have been detected during periods of up to 6 years in donors who have undergone adequately controlled plasmapheresis"

(593). They concluded that plasmapheresis is generally safe when limited to 15 liters per year, and called for retrospective and prospective studies because of “possible effects on lipid transports and deposition, decreased resistance to infections through frequent removal of immunoglobulins and even changes in immune responses toward oncogenic viruses cannot be ruled out Disorders might arise out of too frequent plasmapheresis, active immunization and frequent restimulation” (595).

A number of studies have concluded that even frequent plasmapheresis appears safe for both short- and long-term donors who are otherwise healthy and of good nutritional status (150,475). Other studies of plasmapheresis donors over 3 to 4 years have shown small, but statistically insignificant decreases in albumin levels (206,244). In the first 4 to 6 months there is a statistically significant rise in the concentration of α and β globulins and a decrease in the concentration of the immune globulins IgG, IgA and IgM. After a few more months of continued plasmapheresis IgG and IgA concentrations return to normal, while IgM levels continue to be slightly depressed but still within normal limits (206).

Many, including representatives of the plasmapheresis industry, have urged that further studies be conducted “because there are questions about frequency and all the answers are not in” (327).

The studies done to date have been criticized for looking only at donors who are least likely to be at risk, excluding those in poor nutritional status and those who may have stopped donating for health-related reasons (429). Studies have also been difficult to design because of variables such as regularity of donation, volume donated at each session and total cumulative volume (206). Although it is agreed that plasmapheresis can exacerbate problems associated with poor nutritional status and alcoholism, there is still some controversy over whether such individuals continue to form any portion of the donor pool, in spite of the Federal regulations and screening processes at work since the mid-1970s. Because of this uncertainty, it has also been suggested that this screening process should include tests of nutritional status (161).

Other suggestions for long-term studies include assessments of the long-term risks to hyperimmunized donors who supply high-titer antibodies after being immunized with tetanus toxoid or herpes zoster. One group of specially immunized donors produces Rh immune globulin, a product which has saved many lives by dramatically reducing the incidence of erythroblastosis fetalis (hemolytic disease of the newborn). Experts have questioned whether this process is safe for donors over the long term (408a).

PART 4: FEDERAL ACTIVITIES

Introduction

The Federal agencies with primary responsibilities in the blood resources area are the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). NIH supports research and development activities, and FDA is responsible for regulating the efficacy and safety of blood products and the technologies associated with them. Other agencies such as the Centers for Disease Control (CDC) may be involved in specific issues at any given time, such as in AIDS research, where some of CDC's investigations involve blood-transmitted AIDS.

The Medicare program for the elderly (and disabled) also makes the Federal Government a major purchaser of blood products. Escalating costs since Medicare's inception in the mid-1960s have led to a search for methods to restrain cost increases, and in 1983 Congress passed the Social Security Amendments of 1983 (Public Law 98-21), which is based on prospectively paying for inpatient hospital care by diagnosis-related groupings (DRGs), instead of payment on a cost-incurred basis. The Health Care Financing Administration (HCFA), the Federal agency responsible for operating Medicare, began to phase out the cost-based hospital reimbursement system in Oc-

tober 1983, and the DRG system's phase-in is to be completed by October 1986.

The activities of these three Federal agencies, HCFA, NIH, and FDA, are briefly described in the following sections. Payment for hemophiliac care is also briefly described in the first section.

Payment for Blood Products and Services

Health Care Financing Administration

The Medicare program consists of two parts: Part A, the hospital insurance program, and Part B, a supplementary medical insurance plan. Part A is available without charge to those who are eligible, while Part B is optional and requires payment of a monthly premium (about \$15/month in mid-1984). Enrollees must choose not to participate in Part B, since premiums are deducted automatically from Social Security checks. In 1982, 99 percent of the elderly and 92 percent of the disabled enrolled in Part A were also enrolled in Part B (544).

The Medicare law has been amended through the years, and various limits have been placed on both hospitals' and physicians' charges; beneficiaries' cost-sharing has also been modified. However, the situation is roughly as follows.

Medicare will pay for the first 90 days of hospitalization, minus a deductible (\$356 in 1984). After 60 days, a daily copayment (\$89 in 1984) is assessed until the 90th day of care. After the 90th day, a lifetime reserve of 60 days can be drawn upon, but a larger copayment is required (\$178 per day in 1984). A copayment of \$45 per day is also required for the 21st through the 100th day in a skilled nursing facility.

Under Part B, there is an annual deductible (\$75 in 1984) and a coinsurance of 20 percent for the remainder of approved charges (certain limits were placed on the actual level of reimbursement to physicians, although payment is still related to what they charge). Physicians can also accept the level of payment that Medicare will approve on a bill-by-bill basis. If they agree, Medicare will pay them 80 percent of approved charges directly (the patient's coinsurance is 20 percent, which is

paid directly by the patient to the physician), but they cannot charge their Medicare patients for the difference between what they charged and what Medicare has determined is the actual level of reimbursement. If they do not agree to accept Medicare's payment as payment in full, Medicare pays the 80 percent to the patient, and the physician has to collect the full amount from the patient—the 80 percent from Medicare, the 20 percent coinsurance which is the patient's responsibility, and the difference between what the physician charged and the amount Medicare determined would be paid.

Part A insurance pays for blood transfusions, drugs, and biological when furnished as part of services provided in hospitals or skilled nursing facilities. Part B pays for blood transfusions and drugs and biological that cannot be self-administered when provided by physicians or by outpatient hospital services. Part B payments are subject to the deductible and coinsurance payments described earlier.

For both Part A and Part B, the patient is responsible for any nonreplacement fee charged for the first three units of whole blood or packed red cells (the fee applies only to these two blood products). After the first three units, Part A will pay the nonreplacement fee in addition to the processing and transfusion charges, and Part B will do the same subject to the annual deductible and 20 percent coinsurance (568).

Under the diagnosis-related grouping system of prospective payment for Part A, which began to be phased in during October 1983 and which is to be completed by October 1986, 470 diagnosis-related payment categories have been constructed. Hospitals will therefore be paid a single price regardless of how much it costs to provide that care, including the costs of collecting/processing or purchasing blood products. Hospital outpatient services and physicians' services are still based on a charge-based system, and there is no similar limit on the amount of reimbursement that can be made as was legislated for hospital and skilled nursing home care. (Recent and proposed changes in Medicare are discussed in detail in the OTA report on "Medical Technology and Costs of the Medicare Program," July 1984.)

Payment for Hemophilia Care

In 1975, Public Law 94-63 authorized funding for two activities to aid hemophiliacs: comprehensive hemophilia diagnostic and treatment centers, and development and expansion of blood separation centers. Both types of centers were to be administered by public and nonprofit private entities. Funding for blood separation centers was predicated on finding that there was an insufficient supply of coagulation products to meet the needs of hemophiliacs, but it was determined that supplies would be sufficient through 1980 (554). As a consequence, only funds for treatment centers were actually appropriated.

The law required that funds establishing comprehensive hemophilia centers were to be granted in geographic areas with the greatest need for services. However, it also required that programs be established linking geographically designated centers with other, more remote providers of services. Under the law, hemophilia care centers were to provide programs for training of professional and paraprofessional personnel in hemophilia research, diagnosis, and treatment; programs for diagnosis and treatment of hemophiliacs being treated on an outpatient basis; programs of social and vocational counseling for hemophiliacs; and individualized written comprehensive care programs for each individual treated by or associated with the center. Funds for the direct care of patients were never provided. Only \$3 million to \$4 million were authorized for the establishment of the comprehensive centers for the first 2 years. In 1982, \$2.6 million was appropriated (401).

Since 1975, from 22 (504) to 24 (6) major comprehensive care centers, plus many satellites, have been funded, serving about half of the Nation's estimated 15,000 hemophiliacs (6). The centers are funded through the Department of Health and Human Services' Bureau of Community Health Services/Office of Maternal and Child Health.

Unlike the End-Stage Renal Disease Program under Medicare, which recognizes patients with end-stage renal disease as being totally disabled and thus eligible for Medicare coverage for dialysis and transplants, hemophiliacs can receive Medicare coverage only on a case-by-case determination. Self-administered coagulation proteins

are also not covered by Medicare. Therefore, in addition to providing for the distribution of coagulation products and establishing a multidisciplinary hemophilia care team, hemophilia care centers have engaged in efforts to establish funding for individual hemophiliacs (504). A variety of State and third-party sources have been used (see, e.g., 400), as, for example, to provide home care coverage (478).

National Institutes of Health

The institute with primary responsibility for blood resources is the National Heart, Lung, and Blood Institute (NHLBI) and its Division of Blood Diseases and Resources (DBDR). In 1948, the National Heart Institute was established under the National Heart Act. In 1969, it was redesignated the National Heart and Lung Institute, when pulmonary diseases were added to its responsibilities. NHLBI was organized in 1976, when its research responsibilities were to include "the use of blood and blood products and the management of blood resources."

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423), however, has most influenced NHLBI. The 1972 legislation established separate funding and renewal periods for the Institute, as had been established for the National Cancer Institute in the previous year. In contrast, other institutes at NIH fall under the general research authority of the Public Health Service Act, which places no specific disease category allocations or time limits on their authorization. The 1972 Act specified the following responsibilities:

- research into the epidemiology, etiology, and prevention of heart, blood vessel, lung, and blood diseases, including the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences;
- research in basic biological processes and mechanisms of the heart, blood vessel, lung, and blood;
- development and evaluation of techniques, drugs, and devices used in diagnosis and treatment of these diseases;
- programs to develop technological devices to assist, replace, or monitor vital organs;

- programs for field studies and large-scale testing, evaluation, and demonstration of approaches to these diseases;
- research in blood diseases and the use of blood resources;
- education and training of scientists, clinicians, and educators in these fields;
- public and professional education in these diseases;
- programs for research of these diseases in children; and
- programs for research, development, demonstration, and evaluation in emergency medical services.

The 1972 legislation also required that: 1) an Interagency Technical Committee (IATC) be established to coordinate Federal health programs and activities in these diseases; 2) no less than 15 percent of appropriated funds be used for programs in lung diseases, and 15 percent in programs for blood diseases and blood resources; and 3) annual reports be issued summarizing that year's accomplishments and plans for the next 5 years from the director of the institute and from NHLBI's National Advisory Council.

The Director of NHLBI chairs the Interagency Technical Committee, which includes representatives from all Federal departments and agencies whose programs involve research in diseases of the heart, blood vessels, lung and blood, and in transfusion medicine. Three reports have been issued, on 1977, 1979 and 1981 activities. The functional arms of the IATC are its working groups, such as those on smoking and blood resources; these meet separately. In 1979, NHLBI provided over \$71 million for programs directly related to blood diseases and resources, while other NIH agencies provided nearly \$43 million, and other Federal agencies, outside NIH, nearly \$21 million (557).

Research program interrelationships between NHLBI and other Federal agencies are the result of activities in similar areas but for different missions. For example, the Department of the Army's 1983 research budget on hemoglobin solutions was approximately equal to NHLBI's (403). The Army is interested in its military applications as a battlefield and other emergency situation resus-

citation fluid, and the NHLBI is more interested in its civilian applications and its use in selected circumstances in addition to its use as an emergency resuscitation fluid.

Another example is in research on AIDS. CDC, FDA, and NIH have all been involved in investigations into the cause and treatment of the disease. CDC is conducting various epidemiologic and laboratory studies on AIDS. At FDA, studies of antiviral agents such as interferon and mediators of immunological function such as interleukin-2 were modified to permit interaction with AIDS clinical protocols and to determine in vitro efficacy in correcting immunologic defects. At NIH, work is primarily concentrated in three Institutes—the National Institute for Allergy and Infectious Diseases (NIAID), the National Cancer Institute (NCI), and NHLBI—with AIDS patients also being treated at the NIH Clinical Center (508a). Officials of the various agencies also regularly attend meetings convened by the other agencies; for example, the AIDS Working Group, consisting of non-Federal researchers, which advises NHLBI's Division of Blood Diseases and Resources, has observers/participants from FDA and CDC in attendance.

The Division of Blood Diseases and Resources has four program areas: 1) bleeding and clotting disorders, 2) red blood cell disorders, 3) sickle cell disease, and 4) blood resources.

In 1982, NHLBI conducted a 10-year review of its activities since passage of the landmark 1972 legislation and identified activities that should be undertaken over the next 5-year period (556). Research needs and opportunities were identified in the areas of: 1) blood bank management, 2) cellular elements, 3) plasma and plasma derivatives, 4) safety, 5) apheresis, 6) immunology, 7) blood substitutes, 8) clinical trials, and 9) education. An early 1984 "snapshot" view of the projects which DBDR was supporting in these areas, categorized by the study group's recommendations, is summarized in appendix A. In addition to the laboratory, clinical, and management studies which were being supported, Transfusion Medicine Academic Awards were instituted in 1983 for the integration of educational programs in transfusion medicine into the medical school curriculum, and

a study was to be funded in June 1984 to determine future blood data collection, analysis, and reporting activities.

Food and Drug Administration

The Food and Drug Administration's authority to regulate blood products and blood banking technologies derives from several statutory acts (table 4). (The regulations interpreting these statutes are contained in the Code of Federal Regulations, ch. 21, pts. 600 et seq.) Regulation is organized in FDA's Center for Drugs and Biologics, with blood products and blood banking technologies under the purview of the Office of Biologics Research and Review. Within the Office of Biologics, the Division of Blood and Blood Products is responsible for all new blood establishment and blood product license applications and amendments, and for approval to market blood products and related technologies, such as products used in typing and compatibility testing and in preserving and storing blood products. The division has five branches: 1) blood products, 2) immunohematology, 3) plasma derivatives, 4) coagulation products, and 5) hepatitis testing (162).

Scientific activities related to the Division of Blood and Blood Products are based at NIH, along with the Office of Biologics Research and Review's other scientific divisions. The Scientific

Director of the Center for Drugs and Biologics integrates the scientific and research activities of these divisions with those of the NIH and serves as a member of the NIH's Scientific Directors' Committee.

In 1978, FDA and HCFA signed a Memorandum of Understanding which was approved by the Secretary of the Department of Health and Human Services and published in the *Federal Register* on March 30, 1980 (45 FR 19316). The memorandum provided for HCFA to assume sole responsibility for inspecting all registered blood establishments that did not perform routine collection, processing and transmission of blood and blood products. These facilities were already being inspected by HCFA (including facilities inspected and accredited by the Joint Commission on Accreditation of Hospitals (JCAH) and American Osteopathic Association (AOA) as well as those inspected by the Medicare State survey agencies) for approval to participate in the Medicare program.

As a result of the agreement and its extension, there are approximately 5,000 facilities which are no longer subject to dual inspections (252). HCFA uses the good manufacturing practice regulations and the compliance guidelines and checklists prepared by FDA. FDA inspects blood collection and source plasma establishments biannually, as does HCFA for the establishments for which it has

Table 4.—FDA Statutory Authority to Regulate Blood Products and Blood Banking Technologies

| Statutory authority | Group affected | Mechanisms of control |
|--|---|---|
| Public Health Service Act and Food, Drug, and Cosmetic Act—1902 and amendments | Blood banks engaged in interstate commerce. | Licensure of establishment, and individual products. Inspection. Labeling review. Amendments to original license applications for nonstandard or new technologies and new blood products. |
| Public Health Service Act—1902 | Manufacturers of biological reagents for blood bank use. | Licensure of establishment and products. Lot release control. Labeling review. |
| Food, Drug, and Cosmetic Act—1938 | Developers of new anticoagulants, collection or storage systems or new blood products. | Investigational New Drug Application. |
| Medical Device Amendments of the Food, Drug, and Cosmetic Act—1976 | Manufacturers of other reagent solutions, supplies and equipment used in blood banking. | Registration. Inspection. Premarket notification or approval. Labeling review. |

SOURCES: J. M. Solomon, "Legislation and Regulations in Blood Banking," *Federal Legislation and the Clinical Laboratory*, Morris Schaeffer (ed.) (Boston, MA: G.K. Hall Medical Publishers, 1981); and U.S. Department of Health and Human Services, Public Health Service, Food and Drug Administration, *Working Relationships Agreement Among the Bureaus of Medical Devices, Radiological Health and Biologics*, April 1982.

assumed responsibility. Manufacturers of plasma derivatives and diagnostic reagents used in blood banking are inspected annually by FDA (252).

In regard to medical devices, the Division of Blood and Blood Products performs some of the review functions for blood-related devices for the Office of Medical Devices of the National Center for Devices and Radiological Health. Medical devices are regulated through a three-tiered regulatory structure, with only Class III devices needing to undergo full premarket approval similar to that used in the process of evaluating drugs. Other devices are essentially regulated by manufacturing controls and inspections, and manufacturers need only to notify FDA of their intent to market these devices and to conform to the good manufacturing practices regulations.

The Division of Blood and Blood Products in the Office of Drugs and Biologics, through the interoffice agreement, reviews the notice of intent to market new device products; applications for clinical investigations of Class III devices to gather the information needed to support a premarket approval application; and the application itself for premarket approval of Class III devices that are used in blood banking (162). (The medical devices industry, including its regulation by FDA under the Medical Device Amendments of 1976, is the subject of another OTA report, "Federal Policies and the Medical Devices Industry," published in October 1984.)

Product recalls are voluntary actions and may be taken as a result of FDA findings during inspections, reports from consumers, or new scientific data indicating risks. Although voluntary, a formal procedure is invoked. After FDA is notified, the potential hazard is classified as a market withdrawal (hazard unknown) or Class I, II, or III recall in decreasing severity, and FDA monitors the product recall. FDA may invoke its seizure powers if the health hazard is definable and voluntary recall is not made.

Table 5 summarizes individual recalls between June 1975 and November 1983. Recall actions have been classified since November 1978, and of the 61 recalls since that time, only two (involving whole blood and albumin) have been listed as Class I, considered to be an immediate, serious to deadly hazard. (Reasons for each recall were not tabulated until 1983.)

**Table 5.—Blood Product Recalls,^a
June 1975 to November 1983**

| Product | Number |
|---|--------|
| Diagnostic reagents: | |
| Reagent red cells | 31 |
| Typing antisera | 23 |
| Hepatitis test kits | 6 |
| Plasma derivatives: | |
| Normal human albumin | 12 |
| Purified protein fraction | 2 |
| Immunoglobulin | 8 |
| Factor IX Complex. | 2 |
| Source plasma. | 11 |
| Recovered plasma. | 6 |
| Whole blood and components | 21 |
| Blood containers and preservative solutions | 6 |

^aThe number of recalls is not indicative of the relative quality of these products. A single unit of red cells would be listed as a recall, while a lot of albumin might represent 20,000 donors, and 10,000 or more units of albumin.

SOURCE: D. Donohue, personal communication, 1984.

Between 1974 and 1984, there were 175 voluntary suspensions and revocations. Fourteen involved establishments providing whole blood and/or components; the rest affected source plasma centers. Most suspensions are temporary, and establishments are reinstated after corrections are verified by reinspection. Deviations in whole blood collections were for hepatitis testing and recordkeeping, particularly in component preparation. Table 6 summarizes the types of actions that led to suspensions of 13 plasma centers in fiscal years 1980-81.

Table 6.—Significant Deviations Leading to Plasma Center Suspensions, Oct. 1, 1979 to Aug. 31, 1981

| Deviations ^a | Number of occurrences |
|---|-----------------------|
| Over bleeding (10% or more), | 1 ^b |
| Donor suitability inadequately determined | 4 |
| Four-month test requirements not met | 3 |
| Aseptic technique not used in collection, separation, and/or reinfusion | 3 |
| Records incomplete | 3 |
| Personnel inadequately trained and/or informed | 3 |
| Unsuitable donors drawn | 2 |
| Units shipped before receipt of written HBsAG test results | 2 |
| Hazards of plasmapheresis not explained | 2 |
| Donors drawn after loss of red cells | 1 |
| Number of locations suspended. | 13 |

^aMore than one deviation may have been incurred by a plasma center.

^bAt least five locations also had inaccurate recordings of whole blood weights.

SOURCE: D. Donohue, personal communication, 1984.