SYNOPSIS

The American Blood Resources Association, whose members manufacture a variety of coagulation concentrates, is sensitive to the human trauma that the hemophilia community is suffering as a result of the fact that people with hemophilia were unknowingly exposed to the human immunodeficiency virus (HIV).

In the six years since evidence first started accumulating that freshly linked coagulation concentrates to the transmission of the human Immunodeficiency Virus (HIV), significant advances have been achieved in finding ways to prevent further spread of the disease.

New technologies are now being employed to provide the worldwide hemophilia community with effective clotting factors consistent with the current state of the art. However, these new technologies have had a profound economic effect on the fractionation industry and in the marketplace. While it is difficult and awkward to discuss the impact of AIDS in sheer economic terms, such a discussion is necessary to avoid misunderstandings and establish a framework for solving problems that may occur in the future.

To reduce the risk of AIDS transmission, the industry has employed viral inactivation and purification methods that have significantly reduced yields of coagulation concentrates from the available supply of plasma. The economic results include:

- increased research and development costs;
- increased production costs;
- reduced supply; and
- increased consumer costs.

In addition, other factors are affecting the cost and availability of coagulation concentrates, for example:

- a decline in world demand for albumin has had the effect of increasing production costs for coagulation concentrates;
- the American Red Cross has temporarily removed its plasma derivatives and coagulation concentrates from the market because of quality control problems;
- donor recruitment has become more difficult and costly; and
- new testing requirements being considered may further increase costs and reduce the supply of plasma.

The fractionation industry is acutely aware of the changes in supply, demand, and cost that have resulted from the AIDS epidemic. The market for coagulation concentrates is in transition and the hemophilia community is shouldering medical, social, and economic burdens that no one could have predicted in the early 1980s.

The fractionation industry is committed to working with the hemophilia community and its treasurers to:

- avoid supply disruptions;
- encourage conservation of available supplies;
- maintain and appropriately allocate inventories of coagulation concentrates to meet emergency needs; and
- conduct research and development programs aimed at increasing yields and creating new technologies to provide a safe, effective, and sufficient supply of coagulation concentrates.

The industry believes that nothing could be more important during this difficult transition period than maintaining the cooperative relationship it has enjoyed with the hemophilia community, the organizations that represent the community's interests, and the physicians who treat people with hemophilia. Such a close and direct relationship is essential to meeting the challenges that the industry and the community face today and in the future.
COAGULATION CONCENTRATES
A 1988 Status Report
October 15, 1988

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EXECUTIVE SUMMARY

The American Blood Resources Association (ABRA), whose members manufacture antihemophilic factor VIII (AHF), factor IX and other clotting factors, is sensitive to the human tragedy that the hemophilia community is suffering as a result of the fact that people with hemophilia were unknowingly exposed to the acquired immune deficiency syndrome (AIDS) virus, and recognizes that the medical, social and economic costs of the AIDS tragedy will be felt for years to come.

The purpose of this paper is to address the difficult and complex issues that have surfaced as a result of the AIDS crisis in the hemophilia community in a responsible and understandable fashion. Specifically, this document explores:

1. The fractionation industry's efforts to develop technology to reduce or inactivate viruses that may be present in the plasma-derived products.
2. The industry's response to the discovery that the human immunodeficiency virus (HIV) could be transmitted through clotting factor concentrates.
3. The impact of new clotting factor production technology on the supply and cost of coagulation concentrates.
4. Ongoing research and development activities aimed at viral reduction, viral inactivation and purification of coagulation concentrates.
5. Other market, regulatory and legal issues and events that are influencing the supply and cost of plasma and plasma derivatives.
6. Economic and market forces that affect the fractionation industry's ability to produce coagulation concentrates and other plasma derivatives.
7. Actions necessary to assure a sufficient supply of clotting factor for the worldwide hemophilia community.

The companies that manufacture coagulation concentrates remain committed to providing the worldwide hemophilia community with a sufficient supply of safe, effective clotting factors consistent with the current state of the art.

The industry believes that the cooperative relationship it has historically enjoyed with the hemophilia community, the organizations that aggressively represent the community's interests, and the physicians who treat people with hemophilia must continue. Such a close and direct relationship is essential to the best interests of the community and this industry during the difficult transition period now before us.

1. HISTORY OF THE FRACTIONATION INDUSTRY

1.1 Overview

On a January day in 1982, Dr. Bruce Evatt of the Centers for Disease Control (CDC) received a telephone call that signaled the beginning of a public health crisis in the hemophilia community. That crisis would ultimately produce human tragedy and complex social and economic repercussions for years to come. Dr. Evatt's telephone conversation about an aging hemophiliac who a succumbed to Pneumocystis carinii pneumonia would later be noted in medical history as the first clue that the disease now known as acquired immune deficiency syndrome (AIDS) could be associated with people with hemophilia.

More than six years have passed since evidence first started accumulating that finally linked coagulation concentrates to the transmission of the human immunodeficiency virus (HIV). Progress has been made toward understanding the disease and developing potentially effective weapons for treating the symptoms of people who have been infected with HIV. However, perhaps the most significant advances to date in responding to the AIDS crisis in the hemophilia community have been achieved in finding ways to prevent further spread of the disease.

The long-standing and uniquely cooperative relationship among people with hemophilia, their physicians and the manufacturers of coagulation concentrates has once again proven absolutely critical during a time when the health and well being of thousands of people are at risk.

—ABRA
The fact that new and innovative fractionation technology, combined with the National Hemophilia Foundation's AIDS prevention education program, now makes the spread of AIDS preventable in the hemophilia community, is testament to the cooperative efforts of the past and to the continuing need for a viable partnership in the future: a partnership dedicated to providing a safe, effective, and sufficient supply of coagulation concentrates to the people who require them.

It is in keeping with this spirit that the American Blood Resources Association shares, in this paper, the views of its members on important issues currently of concern to people with hemophilia.

The progress made over the past six years toward developing source plasma screening programs and ionization technology to reduce markedly the risk of AIDS from coagulation concentrates has not occurred without significant economic and social side effects. It may be difficult to discuss supply, demand, and cost issues in the midst of the human suffering attendant to the AIDS epidemic. However, these issues must be addressed in a responsible and understandable fashion to ensure that all segments of the hemophilia community fully understand the dynamics of this transition period, when new technology is evolving and old technology is being retired.

The members of the American Blood Resources Association are aware that there are critics of the fractionation industry who deserve a response to their concerns. The industry acknowledges an obligation to present factual evidence to explain the changes taking place in the marketplace. That is the objective of this paper.

1.2 The Evolution of Fractionation Technology

Appreciating the dynamics of the plasma fractionation industry of the 1980s requires a basic understanding of its past.

Fractionation technology evolved from another time of international crisis. The battlefields of World War II served as a catalyst for the development of dried plasma, an effective front line alternative to whole blood, which was urgently needed to treat shock and blood loss in the wounded.

Dried plasma, however, had its drawbacks. Chief among those recognized at the time were the risk of exposure to hepatitis B virus and the time required to reconstitute the plasma in a form usable in the field.

Dr. Edwin J. Cohn of the Harvard University Medical School is credited with providing the Armed Forces with an effective alternative to dried plasma that could be carried into battle in ready-for-use liquid form. Dr. Cohn pioneered the methodology to produce a concentrated solution of the plasma protein albumin, the most efficient agent for maintaining the fluid volume of blood in battlefield casualties.

The U.S. government encouraged the commercial production of albumin for the war effort. Seven laboratories were asked to produce albumin on a broad scale using Dr. Cohn's fractionation process. By the end of 1942, the first fractionation plant was producing and delivering the much-needed albumin to the Armed Services.

At war's end, the emerging plasma fractionation industry sought new uses for plasma derivatives. Gamma globulin, a plasma protein containing antibodies for diseases such as measles, infectious hepatitis, and polio, was manufactured and supplied to the health care system. Specific gamma globulins were isolated for pertussis, tetanus, and mumps. The industry's early commitment to research and development produced a virtual revolution in the prevention and treatment of life-threatening diseases.

The post-war period also brought with it the introduction of plasmapheresis to the American market. Plasmapheresis is a procedure that allows for the safe collection of plasma from a donor, while at the same time returning the donor's red cells. The process was increasingly employed in the U.S. in the late 1960s. Plasmapheresis, which has now been automated in many collection centers, is the foundation for obtaining the large volumes of plasma needed to meet demand for coagulation concentrates and other plasma derivatives.

WORLDWIDE SUPPLY

Today, the U.S. supplies 60 percent of the world's fractionated plasma. Of this amount, 75 percent, results from the plasmapheresis of compensated donors. Were it not for the rapid advance of plasmapheresis technology in the U.S., the ability of the fractionation industry to supply the world with coagulation concentrates would be significantly diminished—if in fact it could exist at all.
Research focusing on the development of coagulation factors for the therapeutic treatment of people with hemophilia began in the early 1950s. The researchers had their work cut out for them: an antihemophilic factor proved to be very difficult to separate completely from other plasma proteins.

The first factor VIII concentrates used to treat people with hemophilia were produced in the 1950s from animal sources. However, these animal products produced allergic reactions after limited treatment and were of very limited use.

A technique for producing a human factor VIII was first reported from Sweden in the mid-1950s. The process, however, could not produce sufficient quantities of AHF for use by a hemophilia community the size of that in the U.S., and its production costs were extremely high.

A major breakthrough occurred in 1965 when researchers discovered cryoprecipitate, a human plasma residue rich in coagulation factors. Cryoprecipitate could be refrozen and stored for up to a year and could be easily produced in blood banks and hospitals. Cryoprecipitate was relatively safe, inexpensive and effective. For people with hemophilia, the discovery of cryoprecipitate marked an end to ineffective and risky high-volume blood transfusions and signaled the beginning of in-home care.

While the discovery of cryoprecipitate was heralded as a medical milestone, people with hemophilia hoped for the day when a stable, easily stored coagulation concentrate would be available for their use.

University researchers, working closely with the fractionation industry, continued to achieve positive laboratory results in producing high-potency clotting factor concentrates. By the end of 1966, four methods had been developed for providing concentrates in a clinical setting. On April 26, 1968, the Wall Street Journal published a front-page story announcing that a factor VIII concentrate thirty times as potent as plasma would soon be marketed commercially.

As a result of coordinated research between scientists from industry and academia, factor IX complex also became available to the hemophilia community. Other clotting factors have since been isolated for use in treating different disorders, and research efforts are continuing.

Although the technology for producing coagulation concentrate had reached a stage that allowed the manufacture of clotting factors for the marketplace, fractionation industry researchers continued to work aggressively through the 1970s to produce yields of clotting factor sufficient to supply the hemophilia community with the safest, most effective concentrates.

By the mid-1970s, the vast majority of people with hemophilia were being treated with clotting factor concentrates. Clinical management of people with hemophilia was revolutionized during this time: government-aided hemophilia centers were created that emphasized comprehensive care and training for patients and their families in the home use of coagulation factors.

By 1980, the fractionation industry was meeting the needs of the American hemophilia community with millions of units of clotting factor VIII stable, concentrate form that was easy to administer, store and transport. An industry that had not existed prior to World War II was playing a significant role in enabling people with hemophilia to lead more productive, independent lives.

In 1985, no one in the hemophilia community or the fractionation industry could have predicted the magnitude of the challenges that would soon threaten to reverse the progress made toward extending the life expectancy of people with clotting disorders. A detailed discussion of the challenges posed by AIDS is offered in a subsequent chapter of this paper.

1.3 The Business of Plasma Fractionation

Today’s plasma fractionation industry is the product of market forces that have shaped every aspect of the industry’s growth and development.

From the beginning, technology and labor costs attendant to the fractionation process have made entry into the business very expensive. And while start-up costs are high, research and development expenditures, an absolute necessity in the fractionation industry, are even more significant. Countless millions of dollars were invested in the research and development of coagulation concentrate technology before the first vial of concentrate entered the marketplace.

While the industry has always required a significant up-front investment, companies that have the resources to enter the market discover quickly that the fractionation industry is one of the most competitive industries in America.

The competitive nature of the major companies that manufacture coagulation concentrates has been one of the driving forces stimulating the continuing research and development of safe and effective coagula-
tion concentrates for use by the hemophilia community. It has also translated into highly competitive pricing strategies that have benefited the consumer.

The combination of low pricing and high research and development costs has resulted in lower profit margins which make the industry vulnerable to volatile changes in the marketplace.

The fractionation industry is regulated by the Food and Drug Administration (FDA), which is responsible for regulating the collection, processing, testing, licensing, and marketing of blood and blood derivatives.

Adding to the high cost/margin aspects of the industry are the necessary and stringent, albeit costly, government regulations that control the operation of plasma fractionation facilities and govern the pre-market testing and licensing of plasma derivatives.

Perhaps the single most important feature of the business climate in which the industry operates is its unique relationship with the hemophilia community, the health care professionals that serve that community, the state and national organizations that serve as advocates for people with hemophilia and the government agencies that regulate the manufacture of coagulation concentrates.

The benefits of this open and cooperative relationship between the industry and the hemophilia community have been highlighted previously in this paper. However, it is worth noting that the exchange of ideas, constructive criticism, and information between all segments of the community has fostered positive market pressures that can be credited for the industry's ongoing commitment to the development and manufacture of "state-of-the-art" coagulation concentrates.

1.4 A Commitment to Safety

Coagulation concentrates are prepared using large donor pools from thousands of individual plasma donations. Someone with severe hemophilia may require 50 or more treatments each year, and may be exposed to literally hundreds of thousands of donors in the process. Before AIDS, hepatitis B and non-A, non-B hepatitis were the major infectious agents of concern to the hemophilia community and the fractionation industry.

For decades, the fractionation industry aggressively sought ways to reduce or inactivate attendant viruses and enhance the purity and effectiveness of coagulation concentrates. For example, in 1968, following the discovery of a detectable agent of hepatitis B known as a surface antigen, significant progress was made in the development of testing procedures that allowed fractionators to identify and exclude plasma units that tested positive for the agent.

By the early 1970s, every unit of plasma destined for fractionation was tested for the presence of hepatitis B virus. As a result, the incidence of viral hepatitis among people with hemophilia was reduced significantly.

Cases of viral hepatitis that continued to surface proved to be a different virus known as the non-A, non-B variety. However, despite years of research, scientists were unable to develop a direct means of testing for the presence of this virus. Recent reports indicate that a specific test for non-A, non-B virus is in development.

The industry's ongoing commitment to quality has also produced significant advances in the mechanics of converting plasma into increasingly effective, safe coagulation concentrates. Manufacturing operations have been continuously upgraded to ensure exclusion of microbiological and other contaminants from the production environment. State-of-the-art quality control tests for sterility and biological safety are a fundamental aspect of the fractionation process.

Moreover, a variety of techniques have also been developed and utilized by the industry to minimize the potential for viral transmission. Heat, chemical and affinity chromatography are among the processes that are now being employed to remove or inactivate viruses potentially present in the plasma used to produce coagulation concentrates.

When considered in combination with donor screening and plasma testing programs initiated by the industry, the processes used in the manufacture of coagulation concentrates have clearly led to improved safety.

2. RESPONDING TO AIDS

2.1 The Initial Response to AIDS

In July 1982, the CDC reported the first three suspected cases of AIDS among people with hemophilia. The causes of the disease and underlying immune suppression were unknown at the time. The relationship between these cases and other cases among identified high risk groups was initially unclear.
Virtually no reported progress was made during 1982 in identifying the cause of AIDS. Tragically, as would be confirmed years later, a majority of the people with hemophilia who would become afflicted with the AIDS virus had already been infected.

Of the 15,000-20,000 people with hemophilia in the U.S., 773 have developed AIDS, according to a report issued by the CDC on October 3, 1988. It has been estimated that about one-half of the population of people with hemophilia has been exposed to human immunodeficiency virus (HIV); the rate of exposure is about 75 percent among people with severe hemophilia.

The unknown and previously undetectable presence of HIV in some donors of blood and plasma represented a medical tragedy for the hemophilia community and posed a sudden, major technological challenge to the fractionation industry.

The fractionation industry immediately accelerated research efforts already under way to develop techniques for inactivating hepatitis viruses, with the hope that they might prove effective against a yet-to-be-identified AIDS virus. Collaborative research with universities and government agencies was undertaken, and effective inactivating technologies for hepatitis viruses were rapidly developing technology to mass-produce a blood test that would identify potential HIV carriers.

Scientists from industry, the CDC and the academic community conducted research that increasingly demonstrated the effectiveness of the new heat treatment technologies for inactivating the AIDS virus.

By the spring of 1983, when the FDA licensed tests designed to detect HIV antibodies, it became possible to test plasma donors for the presence of HIV. The industry quickly and voluntarily initiated testing of all donors some two years before testing became mandatory.

2.2 The Current State of Fractionation Technology

The cumulative effect of steps taken by the fractionation industry, the National Hemophilia Foundation and the federal government resulted in a significant reduction in the incidence of new HIV infections among people with hemophilia.

The positive results, produced by the screening of donors for HIV antibodies in combination with effective heat treatment technology, led to a consensus in mid-1985 within the fractionation industry, in conjunction with the FDA, to cease voluntarily the distribution of non-heat treated coagulation concentrates.

Today there are several different manufacturing processes available to reduce and inactivate viruses in coagulation concentrates, and multiple variations exist within each category.
MANUFACTURING PROCESSES—

Physicians now have a wide variety of safe, effective clotting factors available to treat people with hemophilia:

- **Dry Heating**—involves heating dry concentrates in their final container at high temperatures for prolonged periods to inactivate HIV.
- **Pasteurization**—inactivates the AIDS virus by heating concentrates before they are freeze-dried. Previous research had shown that pasteurization of albumin eliminates viral risk; thus, the process was successfully applied to coagulation factor concentrates.
- **Suspension Heating**—involves heating concentrate in an organic solvent to accomplish viral inactivation.
- **Vapor Heating**—involves heating dry concentrate under controlled conditions of humidity and pressure to achieve viral inactivation.
- **Solvent-Detergent Treatment**—involves the treatment of AHF concentrate with antiviral agents.
- **Monoclonal Antibody Purification**—utilizes the principle of immunofinity chromatography as a means of viral reduction.

While all of these processes offer many benefits to the hemophilia community, it is important to acknowledge that they have their limitations:

- Coagulation concentrates are currently produced from human plasma sources.
- The changes in production processes resulting from new technology have significantly reduced the yield of coagulation factors from the donor pool.
- These processes add costs to the manufacturing process.

The ultimate objective of these viral reduction and inactivation processes is to offer the hemophilia community safe, high quality coagulation factors. When taken in combination with improved donor screening and plasma testing programs, the processes currently being used by the fractionation industry have produced coagulation concentrates that pose far less risk of viral transmission.

However, the fractionation industry recognizes that processes that inactivate viruses such as HIV do not necessarily render clotting factor concentrates free from all possible side effects. For example, it has been known for some time that people with hemophilia may have immune system abnormalities regardless of whether they have been exposed to the AIDS virus.

Coagulation concentrates contain materials known as antigens. It is not known how these antigens affect the immune system; however, some medical researchers have suggested that elimination of these materials from coagulation concentrate could produce beneficial results. Clinical studies will be necessary to prove these theories.

ABRA members have initiated research and development programs to identify new technologies aimed at producing concentrates of the highest possible purity.

### 2.3 Research and Development

Even though the threat of AIDS transmission from coagulation concentrates appears to have been virtually eliminated, the fractionation industry is continuing to invest millions of dollars and considerable human resources in the development of new technology. In doing so, the industry is affirming its long-term commitment to the coagulation concentrate market and, more importantly, to marketing safe and effective concentrates for use by the hemophilia community.

Research is now under way to identify and develop new ways to utilize immunofinity chromatography for purifying human plasma derivatives.

In addition, in 1984 two groups of researchers announced that they had succeeded in utilizing genetic engineering techniques to create a synthetic, non-plasma-based factor VIII. A number of other groups have since announced research efforts to develop a recombinant DNA (DNA) factor VIII concentrate.

A genetically engineered clotting factor could have the advantage of being free of viruses and unwanted proteins traditionally associated with concentrates derived from donor blood.
It is difficult to predict when a genetically engineered factor VIII will be offered commercially. Clinical trials are under way. However, there are a number of issues that must be confronted before an rDNA clotting factor becomes readily available:

- Factor VIII is a very fragile protein that has proven to be difficult to reproduce in volume.
- Researchers will have to determine whether immune reactions will result from the use of genetically engineered factor VIII.
- The overall safety and effectiveness of the rDNA factor VIII will have to be quantified and subjected to the licensed/protocol of the FDA.
- The price of new rDNA factor VIII may be higher than plasma-based concentrates, because of the huge costs associated with its research and development and the construction of completely new and specialized production facilities.

The challenge of the future for people with hemophilia, their physicians and the fractionation industry will be to efficiently utilize available concentrates, technologies and screening procedures to safely meet the needs of the hemophilia community, while assuring a sufficient supply of coagulation concentrates at the lowest possible cost.

3. THE ECONOMICS OF FRACTIONATION

3.1 Cost/Price Effects of New Technology

The market for coagulation concentrate is subject to economic forces that affect the manufacture and marketing of commercial products. Supply, demand, competition, manufacturing and research costs, pricing and product mix are all interrelated. Together, they produce economic results that are often unpredictable and occasionally difficult to manage—at least in the short term.

While it is both difficult and awkward to discuss the impact of AIDS on the hemophilia community and the fractionation industry in such economic terms, such a discussion must take place to avoid misunderstanding and establish a framework for solving problems that may occur in the future.

The new fractionation technology that developed rapidly in response to the AIDS crisis has had a profound economic effect on the industry and the market. In the past the fractionation industry focused on methods that would allow for an increased yield of safe coagulation concentrates. However, to reduce the risk of AIDS transmission, the industry began to employ viral inactivation and purification methods that have significantly reduced yields.

Table 1 highlights the impact these new manufacturing methods have had on the yield of Factor VIII from a liter of plasma.

<p>| TABLE 1 |</p>
<table>
<thead>
<tr>
<th>Technology</th>
<th>Approximate Yield (U/Liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Heat Treated</td>
<td>250 (plus)</td>
</tr>
<tr>
<td>Dry-Heat Treated</td>
<td>175 (plus)</td>
</tr>
<tr>
<td>Solvent/Detergent Treated</td>
<td>150 (plus)</td>
</tr>
<tr>
<td>Monoclonal Purified Factor VIII</td>
<td>100 (plus)</td>
</tr>
<tr>
<td>Pasteurized/Wet/Vapor</td>
<td>100 (plus)</td>
</tr>
</tbody>
</table>

*Industriewide estimates, yields achieved by individual manufacturer will vary.
† Removed from market.

As Table 1 shows, there is a significant difference in factor VIII yields from current manufacturing methods employed by the industry compared to the relatively high yield of 250 (plus) international units of factor per liter (IU/L) of plasma for unheated factor VIII.

The reduced yield attendant to the new, safer technologies has resulted in absolute production cost increases for the fractionation industry. The purity of the concentrate is linked to the cost to produce it.

Assume, just for the purposes of this discussion, that a manufacturer is able to produce 200 items from a fixed supply of raw material that costs $100 to purchase. In addition to the raw material, the manufacturer must also spend $50 in labor and equipment costs to produce the 200 items. Thus, the production cost for each item amounts to 75 cents.

But what happens if the manufacturer must begin to use new production methods that reduce the number of items that can be produced from the same amount of raw material and labor? If raw material and labor costs remain the same, and production output is cut to 100 items, the cost for producing each item increases to $1.50.
This example illustrates what has occurred in the production of clotting factors as new technology has been utilized to achieve viral inactivation and purification. Production costs have increased markedly, and are necessarily reflected in the cost of coagulation concentrates to consumers.

In addition, an array of costs must be accounted for are the research and development expenditures made by individual companies to develop the much needed viral inactivation and purification technologies available today.

In a free market environment, companies that are unable to recoup research and development costs through appropriate pricing structures will eventually terminate new development programs. The results are predictable. Companies become uncompetitive, if they survive at all. And consumers are denied the benefits of the new technologies and production efficiencies that are the products of research and development programs.

3.2 Supply Challenges

In addition to the cost issues just discussed, it must be recognized that the supply of coagulation concentrates available to the market has also been reduced as a direct result of lower production yields. The fractionation industry also acknowledges that marketing solutions linked to the quest for safety, as well as the rapid transition from old to new technology, have also affected available supplies.

The supply of coagulation concentrates to the hemophilia community is influenced by other key issues that merit consideration.

The absolute requirement that only safe and effective clotting factors be allowed to enter the marketplace will influence the volume of coagulation concentrates available in the future, as it has in the past. The fractionation companies are committed to marketing safe and effective clotting factors. They face demanding moral, legal and regulatory challenges should they fail to meet that commitment.

The availability and cost of plasma and other materials used in the manufacture of coagulation concentrates also play a role in determining the volume of supply to the marketplace. While the availability of plasma earmarked for fractionation has steadily increased over the past decades because of the advent of plasmapheresis, commercial donor programs and new automation technology, recent events have disrupted supplies of plasma and coagulation concentrates.

Specifically, the American Red Cross has experienced quality control problems in its blood and plasma collection system. While the Red Cross is working closely with the FDA to remedy those problems, the fact remains that the supply of plasma derivatives, and especially AHF concentrates, has been significantly disrupted.

Before it removed its plasma derivatives from the market, the American Red Cross supplied approximately 20-25 percent of the factor VIII concentrate used by people with hemophilia in the U.S. The fractionation industry has done all that it can to respond to this serious supply problem, and the industry will continue its efforts until the problem is corrected.

Other problems also affect the supply and cost of plasma and plasma derivatives. For example, concern about AIDS has influenced donor recruitment programs despite public education campaigns aimed at eliminating the misconception that AIDS can be transmitted to a person who donates plasma. Moreover, the relative prosperity that our society has enjoyed in the recent past has also made donor recruitment more difficult and costly.
EFFECT OF TESTING ON SUPPLY—

Compounding the current plasma supply situation is the question of expanding testing requirements in the future. These new tests, which are the subject of considerable debate, will reduce the supply of plasma available for fractionation and increase costs.

It is estimated that new donor screening tests may result in a loss of approximately 160,000 liters of plasma and 28 million units of AHF in the first year. Cost estimates directly associated with the tests are in the range of $20-$25 million annually.

If AHF is the only marketable derivative from the final liters of plasma because the demand for albumin has not been met, and if the production yields for AHF are down to 100 units per liter, which sell for $0.50 per unit, the revenues produced from a liter of plasma would amount to $50.

Consider the cost side of this equation. If a manufacturer pays roughly $50 for a liter of plasma, plus an approximate AHF production cost of $20 per liter, as well as research, development and marketing costs, then that manufacturer would suffer a net loss of more than $30 on every liter of plasma processed purely for the production of AHF, unless there is an adjustment in price.

Yet another issue that has surfaced as a result of concern over the availability of factor VIII in the U.S. market centers on the exportation of plasma and plasma derivatives to people with hemophilia in other regions of the world. There are approximately 225,000 people with hemophilia worldwide. Some 15,000-20,000 reside in the U.S.

As illustrated previously, the U.S. generates over 60 percent of the world’s fractionated plasma. Of this amount, more than 75 percent comes from the plasmapheresis of compensated donors. It is reasonable to ask why, in a time of short supply, the U.S. fractionation industry should continue to export its concentrates overseas.

The fractionation industry has always viewed the hemophilia community as an international community in need of safe, effective clotting factors regardless of political or geographical considerations. The industry’s production and marketing structure is geared to an international marketplace, and depends on a global market to remain viable and efficient.

The dominance of the U.S. industry in the world plasma derivatives market has produced many benefits not only for the individual companies that have pursued export market opportunities, but also for individuals with hemophilia who reside in the U.S.

Americans with hemophilia pay less for coagulation concentrates than their counterparts in other countries, in large measure because the concentrates are produced in the U.S., and because by importing these concentrates and the technology they represent, foreign buyers have helped underwrite research and development programs essential to the production of safe, effective clotting factors at the lowest possible cost.

Any action or event that influences the supply or cost of plasma destined for fractionation will ultimately influence the supply and cost of coagulation concentrate to the hemophilia community. The industry will work to prevent plasma supply disruptions by expanding the recruitment of donors and by adopting new automation technology that can increase the volume of plasma collected for fractionation.

However, persons unfamiliar with the economics of the fractionation industry might reach the conclusion that all the industry needs to do is increase its demand for plasma to accommodate reduced AHF yields. The issue is far more complex.

Until very recently, the plasma industry was driven by world demand for albumin, with factor VIII an underlying component of the production process. This demand-supply relationship created an over supply of factor VIII, which lowered prevailing prices in the U.S. market. However, both the demand and price of albumin has declined, while factor VIII yields have fallen. It is now apparent that factor VIII has replaced albumin as the primary demand stimulant for the plasma industry.

This market shift translates into increased production costs for clotting factor manufacturers. A simplified analysis of the economics of this manufacturing process illustrates the point. The numbers used below to demonstrate this are arbitrary and do not reflect actual current costs.
Moreover, Americans have been the beneficiaries of innovations that would not have been forthcoming without the economic underpinning of a worldwide market for these coagulation concentrates.

As the industry and the hemophilia community work cooperatively to resolve the complex issues that have surfaced as a result of the AIDS epidemic, it must be acknowledged and understood that the industry does depend on foreign markets to support its economic infrastructure and to help pay for continuing research. To abandon those markets under the current circumstances would result in untold human tragedy.

It would be naive to think that the entire U.S. fractionation industry could withdraw from the international market and, at some point in the future, successfully re-enter that market without considerable opposition. Foreign governments and competitors would most certainly retaliate against such an ill-advised and callous decision.

It is also naive to assume that the U.S. industry has a monopoly on science and technology. An action to cut off U.S.-made coagulation concentrates and technology from foreign markets could result in Americans being denied access to products and technology developed overseas. In short, no one would benefit.

Cutting off the supply of clotting factors to people with hemophilia who happen to live in areas of the world that are not self-sufficient in the manufacture of coagulation concentrates is an unthinkable option.

3.3 Demand Challenges

The fractionation industry is acutely aware of the changes in supply, demand and cost that have resulted from the AIDS epidemic. The market for coagulation concentrates is in transition and the hemophilia community is shouldering medical, social and economic burdens that no one could have predicted in the early 1980's.

During this transition period from old to new technologies, nothing could be more important than close cooperation among the fractionation industry, the hemophilia community and its health care providers to assure that the finite supply of coagulation concentrate resources is effectively and efficiently utilized.

Appropriate utilization of available concentrates is far more complicated today than it was eight years ago when essentially only one basic process existed for preparing factor VIII concentrate. Now, several different technologies have been developed in response to the AIDS crisis. Each has its own set of benefits which must be closely matched to the needs of individuals with hemophilia.

The fractionation industry assumes responsibility for providing the hemophilia community and its care providers with scientifically derived information about the benefits of specific technologies. The industry also recognizes that physicians are fully responsible for gauging the needs of their patients and for matching the correct coagulation concentrate specifically to those needs.

In addition to the absolute necessity for a needs-based distribution of the AHF concentrate mix, the fractionation industry supports efforts by the National Hemophilia Foundation and individual physicians to encourage conservation of available coagulation concentrates.

Reasonable conservation measures that do not threaten the health and well-being of people with hemophilia will go a long way toward assuring that a sufficient supply of factor VIII concentrate is available to the community.

The supply of coagulation concentrates maintained in the inventory is also influenced by the market forces present in this transition period. The fractionation in-
Industry is working to maintain inventories required to meet emergency needs.

The industry must rely on physicians treating people with hemophilia to determine when medical circumstances merit emergency access to existing concentrate inventories. The industry recognizes that the burden of determining when a medical emergency exists properly belongs to the treating physician and cannot be assumed by industry personnel.

4. OTHER KEY ECONOMIC ISSUES

4.1 Liability Insurance

Because of the inherent legal and financial risks currently associated with the manufacture of clotting factor concentrate, the fractionation industry can no longer obtain AIDS liability insurance. The industry has assumed considerable financial risk in continuing to manufacture coagulation concentrates.

It must be acknowledged that the absence of liability insurance does play a role in research, development and marketing decisions made by individual companies.

The industry is proud of its relationship with the hemophilia community and its record of achievement in developing and marketing safe and effective concentrates. At the same time, it must also make prudent decisions that protect the rights of shareholders and investors whose trust must be honored.

Until other mechanisms are found to provide companies with reasonable insurance protection from DS-related liability claims, this issue must be an element of industry decision-making.

4.2 Litigation

Lawsuits have resulted from the tragic, yet at the time unknown, exposure of people with hemophilia to the AIDS virus. To be sure, people have the absolute right to seek remedies in our legal system, and the fractionation industry is not immune to litigation.

However, the industry continues to argue that sound public policy precludes the imposition of so-called strict liability on the manufacturers of plasma derivatives and that to do otherwise would put the continued availability of coagulation concentrates at stake.

At present, virtually all states have statutes or court decisions that preclude the imposition of strict liability or implied warranty claims against blood derivative producers. In fact, nearly all states have enacted laws that specifically limit the liability of manufacturers of blood and plasma derivatives to proof of negligence.

The fractionation industry remains hopeful that the courts will continue to recognize that coagulation concentrates are not like manufactured consumer or industrial items. Coagulation concentrates fit into a class of items that, given the present state of technology and testing limitations, are quite incapable of being made 100 percent safe for their intended use, but provide an important and essential service to society.

The simple fact is that if the cost of coagulation products reflected the financial risk the fractionation industry would incur under strict liability, these clotting factors would be unquestionably unaffordable to the vast majority of the people with hemophilia who currently benefit from their availability.

—ABRA
WHAT IS ABRA?
The American Blood Resources Association was established in 1972 to represent the interest of companies involved in the collection, manufacture, or distribution of blood or plasma for further manufacture. The Association has evolved and now represents over 60 corporations worldwide. The corporations who support ABRA operate over 10 percent of the commercial U.S. plasma collection programs and include a majority of the commercial plasma fractionation companies worldwide. These organizations provide over 50 percent of the worldwide plasma requirements.

The programs and activities are directed by an active, volunteer Board of Directors currently consisting of 15 business and medical leaders from the blood and plasma and biopharmaceuticals industries.

ABRA MEMBERSHIP
Any association invites any firm interested in preserving and supporting the viability of the plasmaapheresis industry to consider membership in ABRA. There are two classes of membership:

- *General Membership*—Any firm or entity which is engaged in the business of collecting, manufacturing, processing, or distributing blood and/or blood derivatives. Only General Members in good standing shall be eligible to vote at Membership meetings.
- *Associate Membership*—Any firm or entity which is engaged in the business of providing products or services to companies which are eligible to be General Members, or which is a tax exempt and so engaged as a business which would otherwise entitle it to be a General Member.

Benefits of ABRA Membership

- Associate with professionals
- Access to legislative aid
- Industry contacts
- Industry representation
- Industry education programs
- Public/Demperor education programs
- Advertising/promotional materials
- Committee involvement
- Discounts on ABRA meetings/publications

COMMITTEES

Committee members are employees of ABRA member firms. These individuals are actively involved in committees whose area contributes to the betterment of the industry and the benefit of the general public. Active committees include:

- ABRA/DPAA Liaison
- Industry Affairs
- Legislation
- Laboratory Directors
- Medical Directors
- Media Relations
- Operational Directors
- Public Affairs
- Plasmaapheresis Establishment

ASSOCIATION OBJECTIVES

To foster and promote the interest of those individuals, partnerships, firms, associations, and corporations who are engaged in or connected with human blood products and related activities.

- To promote and encourage research in the development of blood and its products, and to better utilize this vital resource for the betterment of mankind.
- To encourage better understanding of the proper terminology by the general public.
- To adopt a code of uniform standard of conduct and to disseminate a standard code of operation for purposes of accreditation.
- To establish and maintain a representative and centralized agency to consider and act on matters affecting the activities of its members.
- To cooperatively strive to establish a more harmonious understanding and relationship among the members of this association and those in other industries and institutions related to and services the proprietary blood industry.
- To foster reasonable and just regulations by city, state, or other governmental agencies and authorized to supervise the proprietary blood industry and to mutually resolve any problems affecting the individual and general well-being in the industry.
- To cooperate for the improvement of all conditions related to such activities and to encourage the correction of abuses relative thereto.
- To exercise all, and every power for which a non-profit membership corporation organized under the laws of the State of Tennessee may be authorized to exercise.
- To inaugurate beneficial projects on behalf of the proprietary blood industry where such projects shall contribute to the best interests of the blood industry and the American public.

ABRA MEETINGS

Plasma Forum

Each year, ABRA hosts an international medical-technical scientific conference providing an opportunity for public debate on a variety of topics of interest and concern to the plasmaapheresis industry. The three-day conference is held in June of each year and is open to anyone interested in attending.

Business Forum

This ABRA membership and business meeting is held preceding the American Association of Blood Banks' annual convention. The Business Forum is limited to ABRA members only and includes discussion of business and economic concerns to the plasmaapheresis industry and presentations on the state of the Association. Election of directors is held during this annual meeting.

Plasmaapheresis Center Managers Development Program

This program is designed to help plasma center managers improve their abilities to effectively manage plasmaapheresis centers. The program includes presentations by industry representatives with expertise in regulatory compliance, personnel training, and general center management, as well as presentation by FDA national and regional field personnel on inspections and inspectional policies. The program is offered in March and September of each year and travels between the East and West Coasts.

Regional Managers Forum

Established in 1987, this ABRA program is designed for operational directors/managers of multi-center locations to participate in a workshop to consider the operational implications of current controversial issues affecting plasma center operations. This two-day workshop is held once a year during the summer months and attendance is available exclusively by invitation to ABRA members.

For additional information on the plasma and plasma products industry or specific ABRA meeting dates and locations, contact the ABRA National Office, P.O. Box 3346, Annapolis, MD 21403, (301)263-6396.

ABRA PUBLICATIONS

PLASMAapheresis

The content of the magazine focuses on the business, operational, regulatory, and scientific needs of the commercial blood and plasma collection. The ABRA Newsletter is included in the magazine and is restricted to more timely briefings on current news and announcements. PLASMAapheresis is distributed bi-monthly per year:

January, February, March, April, May, June, July/August, September, October, and November. Contact the Association's National Office for current subscription and advertising rates.
American Blood Resources Association

Code of Ethics

It is the hope, promise and the duty of the members of the
American Blood Resources Association to:

- INSURE an adequate and safe supply of blood and blood derivatives for
medical, pharmaceutical and scientific use.
- MAINTAIN the highest professional standards in their facilities and personnel.
- UTILIZE modern tested collection methods to insure maximum donor safety.
- INFORM the public of the need for and uses of blood and blood derivatives.
- ENCOURAGE the public to participate in blood derivative programs.
- FOSTER research and development in all areas of blood and blood derivative utilization and collection.
- COOPERATE with all levels of government initiating programs affecting blood and blood derivative collection, utilization and safety.
- PROMOTE and maintain cordial and unselfish relationships with members of their own profession and other professions for the exchange of information concerning the utilization and preparation of blood and its products to the
advantages of mankind.
- RECOGNIZE that the ultimate purpose of the membership is service to the
patient.