

Key Issues in Hemophilia Treatment¹

Part 1: Products

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Please note that the definitions of words printed in bold type are included in a glossary at the end of the text

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Further information on several of the issues addressed in this document is available from the secretariat. We intend to update this document periodically to include any new information. Should you wish to help us improve this document, please send your comments or suggestions to the WFH secretariat at, The World Federation of Hemophilia, 1310 Greene avenue, Suite 500, Montréal, QC H3Z 2B2, Canada.

Thank you.
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The Facts and Figures series is intended to provide general information on factor replacement products and the administration of hemophilia care. The World Federation of Hemophilia does not engage in the practice of medicine and under no circumstances recommends particular treatment for specific individuals. Statements and opinions expressed here do not necessarily represent the opinions, policies, or recommendations of the World Federation of Hemophilia, its Executive Committee, or its staff.

1 Introduction

Treatment of hemophilia in the world today is only available to about 20% the affected population, and those treated are for the most part in developed countries. This situation is slowly changing as word spreads of the effective treatments available. Public health officials currently engaged in improving hemophilia care in their countries are confronted with special issues requiring that they be knowledgeable about the disease. The present document, prepared by the World Federation of Hemophilia (WFH), is intended to help decision-makers responsible for improving hemophilia care.

Founded in 1963, WFH is a federation of national member organizations representing 88 individual countries. Its mission is to advance services worldwide for people with hemophilia and related disorders.

1.1 Hemophilia

1.1.1 Definitions

Hemophilia is a genetically inherited bleeding disorder. There are two types of hemophilia: **hemophilia A**, or clotting **factor VIII** deficiency, and **hemophilia B**, or clotting **factor IX** deficiency. The degree of deficiency varies from mild to severe. About one third of hemophilia cases occur with no previous family history (**sporadic hemophilia**). It is assumed that these cases are the result of genetic mutation.

Due to the genetic pattern of inheritance, the disorder generally affects males only. About one third of cases occur with no previous family history. Women with a hemophilic gene are called **carriers**. Each daughter of a carrier mother has a 50% chance of being a carrier. Each son has a 50% chance of having hemophilia. Carriers are usually, but not always, symptom-free.

Von Willebrand Disease (vWD) is another more common hereditary bleeding disorders. Patients with vWD have

diminished production of von Willebrand factor or produce von Willebrand factor that does not function normally. This disorder affects both males and females equally, and the symptoms are usually not as severe as those of a person with hemophilia, but do include bleeding from the nose, mouth or intestinal tract.

Von Willebrand disease is probably the most common of the inherited clotting disorders although it is generally the least severe.

1.1.2 Prevalence

The prevalence of hemophilia A in the world population is approximately one in ten thousand males. In its severe form, prevalence is one in sixteen thousand males. There is no known geographical variation in the prevalence of either hemophilia A or hemophilia B. It has been calculated that worldwide there are approximately 350 000 people with severe or moderate hemophilia A. Hemophilia B is five times less common than hemophilia A.

1.1.3 Severity

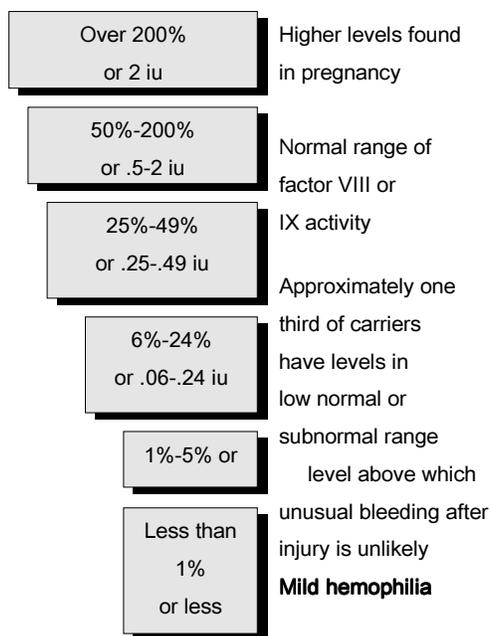
The severity of hemophilia is dependent on the level of clotting activity of factor VIII or factor IX in the blood. A specific quantitative test for activity is not currently available, however, severity is traditionally expressed in terms of percentage of the average normal clotting activity. The average normal activity is defined as 100%. A more recent mode of expression uses numbers of **international units (iu)** of clotting factor per milliliter (ml) of whole blood (see Figure 1, p. 2).

Hemophilia carriers also frequently have factor VIII or IX levels below the normal range. Such women are at risk of clotting problems with menstruation, or when undergoing surgery or dental extractions without appropriate treatment.

The level of clotting factor activity in an individual often determines the clinical severity of hemophilia, although the relationship is not strictly parallel, nor does

an individual experience consistent symptoms. Severely affected individuals bleed spontaneously into their major joints and muscles. Moderately affected individuals usually bleed only after trauma. Cases of hemophilia vary however, and with relative frequency, a person with moderate hemophilia will bleed spontaneously. Persons mildly affected usually bleed only as a result of surgery or major injury.

Figure 1 Range of factor VIII and factor IX activity as a % of normal factor activity in blood and in number of ius per ml of whole blood



Source: Peter Jones. *Living With Haemophilia*. 4th Ed. Oxford UP 1995

1.1.4 Manifestations

Severe hemophilia usually manifests in the first year of life with raised unsightly bruises, at circumcision or when prolonged bleeding suggests something unusual, often from minor lesions in the mouth. Moderate or mild hemophilia often first appears following surgery or dental extraction as prolonged or secondary hemorrhage.

Hemophilic bleeding can occur at any time of the day or night. Without treatment bleeding is prolonged. Untreated bleeding can lead to anemia. Hemophilic bleeding into confined spaces (skull, joints, major muscle

masses) stops only when the pressure of the surrounding tissues equals or exceeds the pressure of escaping blood.

Bleeding into joints or muscles is recurrent. Typically, an individual who is severely affected with hemophilia A bleeds thirty-five times a year. Some individuals, and usually those with hemophilia B, bleed less frequently. Some bleed daily; bleeding frequency is higher in tissues or joints already damaged by uncontrolled hemorrhage.

Acute pain is one of the immediate results of untreated internal bleeding. The best pain control is treatment of the bleeding episode. Repeated bleeding into the same joint eventually results in a breakdown of normal tissues and the development of a chronic, painful and incapacitating arthritis. This type of arthritis is irreversible and functional abnormality or pain may be relieved by major reconstructive surgery.

Untreated hemophilia is a lethal disorder. At the beginning of the century the life expectancy of someone with hemophilia like Prince Alexei (son of czar Nicholas of Russia) was less than fifteen years. Today, with good treatment, Alexei's life expectancy would be ten years less than that of males without hemophilia.

It follows that the basic needs of the individual with severe hemophilia are accurate diagnosis, (which identifies the abnormal level and/or activity of clotting factor), and access to replacement therapy at all times.

1.1.5 Joint Disease

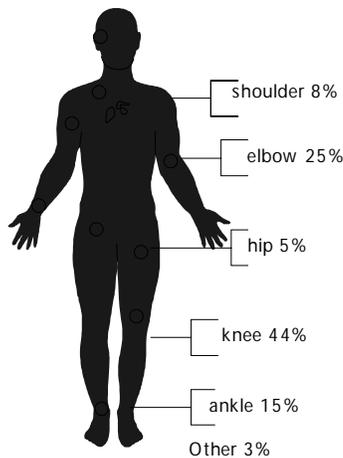
Most joint bleeds are not related to the usual stresses and strains of daily living and are referred to as "spontaneous" bleeding episodes. Once this bleeding has occurred however, the joint will be predisposed to future episodes, and trauma can then be the cause of further bleeding into that joint. Movement of the joint becomes restricted, resulting in joint stiffness and muscle atrophy in the limb.

In severe hemophilia, joint bleeds begin before the age of three. However,

bleeding of a joint may occur throughout that individual's life. Knees, elbows and ankles are the most frequently affected joints while hips and shoulders are occasional sites.

Without treatment people with severe hemophilia eventually need orthopedic surgery.

Figure 2 Incidence of bleeds into specific joints



1.1.6 The Economic Impact of Hemophilia

Hemophilia is eminently treatable, even in its severest form. Untreated, it results in early chronic disability, and too often in premature death. While proper treatment is expensive, inadequate treatment is even more so, for individuals, their families, and the community alike. The lack of prompt, appropriate treatment may lead to the following situations:

- joint damage and the need for orthopedic treatment
- multiple joint damage and loss of normal muscle structure, leading to severely restricted mobility
- permanent use of calipers, crutches, or a wheelchair
- prolonged hospitalization
- the misuse, or possibly even the waste, of expensive therapeutic products
- frequent absences from school, which in turn limit the educational and employment opportunities for individuals with hemophilia

- disruption of family life by the need to seek treatment for children with hemophilia

1.2 Treatment: Summary Description

1.2.1 Basic Treatment

Treatment involves the simple injection of the deficient factor directly into the individual's vein. Treatment can either prevent bleeds or minimize their effects so that the patient remains free of disability and complications.

Bleeding ceases when a sufficient amount of clotting factor reaches the site of injury. Replacement of the deficient clotting factor can be made in anticipation of a bleed, or—as is the most common practice—as soon as possible after the patient is aware that s/he is bleeding. When treatment is given early in a bleeding episode, chances that bleeding will continue are reduced. When treatment is delayed, bleeding continues and spreads, causing more tissue damage; this in turn increases the likelihood of further hemorrhage at a later time. Early therapy therefore results in increased patient capacity and a reduced need for repeat treatments.

Clotting factors are found in the following treatment preparations in order of increasing concentration:

- whole blood
- plasma
- cryoprecipitate
- factor concentrates

The amount of any clotting factor in whole blood or in plasma is insufficient in proportion to volume for adequate therapy for the large majority of bleeding episodes.

In many cases of mild hemophilia A, and most cases of von Willebrand disease, the individual's body is capable of releasing sufficient factor VIII if stimulated by the synthetic hormone **Desmopressin**. This hormone can be given intravenously, by subcutaneous injection or in a highly concentrated preparation, by intranasal spray. Desmopressin does not induce the release of factor IX.

Severe bleeding or surgery require either continuous or intermittent replacement therapy to maintain adequate levels of the relevant clotting factor.

Infection predisposes to further bleeding and early antibiotic treatment is recommended for proven bacterial infections. Such treatment should be given orally or intravenously, and not by intramuscular injection because of the risk of provoking hemorrhage.

Treatment with whole blood or plasma is usually given in hospital. Treatment with blood derivatives or factor concentrates is possible outside the hospital setting, and is called **home therapy**.

1.2.2 Comprehensive Care

The treatment of hemophilia and von Willebrand disease goes well beyond simple injections or treatment with desmopressin. Comprehensive care seeks to address in a coordinated matter the many issues faced by an individual with a bleeding disorder. It therefore addresses everything from diagnosis to musculoskeletal problems, from homecare, mobility and physiotherapy, to the emotional and psychological effects of living with a bleeding disorder for both the individual and his or her family.

Comprehensive care involves a variety of treatments and careful monitoring (bleeding incidents, treatment, inhibitor assays, musculoskeletal and immunological assessments, physiotherapy and exercise assessments, and psychosocial adjustment among other things). By keeping track of the person's overall health, treatments and exercise, and the interrelation of these things one with the other, patients with access to comprehensive care can begin to draw a picture of what practices will most reduce their bleeds and allow them to regain control over their lives. Members of the comprehensive care team work to prevent problems, or to address them at early stages before they affect the health or well being of the individual.

1.2.3 Inhibitors to Factor VIII or Factor IX

Inhibitors are antibodies to factor VIII or factor IX which prevent therapy from being effective. They appear almost exclusively in patients with moderate and severe hemophilia. Inhibitors develop in a minority of patients and it *is* possible to predict a given individual's propensity to develop them if his gene mutation pattern is known. Most inhibitors emerge after relatively few treatments, often early in life. In general, the more treatments a person with a bleeding disorder has had without developing an inhibitor, the less likely he is to get one. The appearance of inhibitors may complicate treatment and make it much more expensive.

1.2.4 Carrier Detection and Prenatal

Diagnosis

Modern techniques, including the application of DNA technology, have opened up options to couples planning families. When there is a family history of hemophilia, it is now possible accurately to identify most females who carry the hemophilia gene. Women who know they are carriers, or might be carriers, may have options for prenatal diagnosis.

In the case of hemophilia A and B it is important to know the girl's factor levels in childhood. The factor VIII or IX clotting activity in a carrier may be low enough to constitute mild hemophilia, and treatment may be necessary.

2 Blood Products:

Collection and Safety

2.1 Blood Products and Factor

Replacement Therapy

Hemophilia results from the absence or reduction of a factor (factor VIII or factor IX) in a person's blood. The treatment of hemophilia requires the replacement of the missing factor with an appropriate product.

Until the recent advent of **recombinant** factor VIII **products**, which are genetically engineered, all treatment was done with **blood-derived products**. (In February 1997, recombinant factor IX was licensed and approved for sale in the U.S.A., but was not yet available commercially.) Today, up to 70% of patients in industrialized countries, and the great majority of patients in developing countries, are treated with blood-derived products.

Blood has three types of cellular components, red cells, white cells and platelets, and a liquid component called **plasma**. Plasma can be used for transfusions or to produce **cryoprecipitate** and plasma derivatives (see Figure 3, p. 6)).

Plasma is also used to make other blood products which are in increasing demand for the treatment of other conditions. The most commonly used are the immunoglobulins and albumin. The process of separating the plasma into its different components is called **fractionation**.

Factor VIII is found in order of increasing concentration in fresh whole blood, **fresh frozen plasma**, freshly separated plasma, dry (**lyophilized**) fresh plasma, cryoprecipitate, blood-derived factor VIII **concentrate**, recombinant factor VIII. The amounts available in fresh whole blood and plasma are insufficient to control major bleeds or to cover surgery.

Factor IX is present (in order of increasing concentration) in fresh whole blood, freshly separated plasma, fresh frozen plasma, dry (lyophilized) fresh plasma, **cryoprecipitate-poor plasma**, blood-derived factor IX concentrates.

2.2 Blood Collection

2.2.1 Individual and Paid Donors

The treatment of hemophilia is highly dependent on blood donations. It is the policy of many national and international bodies,

including the World Health Organization, to recommend that blood and its products be obtained from unremunerated voluntary donors. However, because of the difficulty in obtaining a sufficient quantity of blood through voluntary donations, most of the world's present supply of factor VIII and factor IX concentrates are made by commercial companies, with tested plasma from paid donors. Today, the U.S.A. supplies over 50% of the world's fractionated plasma. Of this amount, 75% comes from **plasmapheresis** of remunerated donors (see section 2.2.3, p. 7).

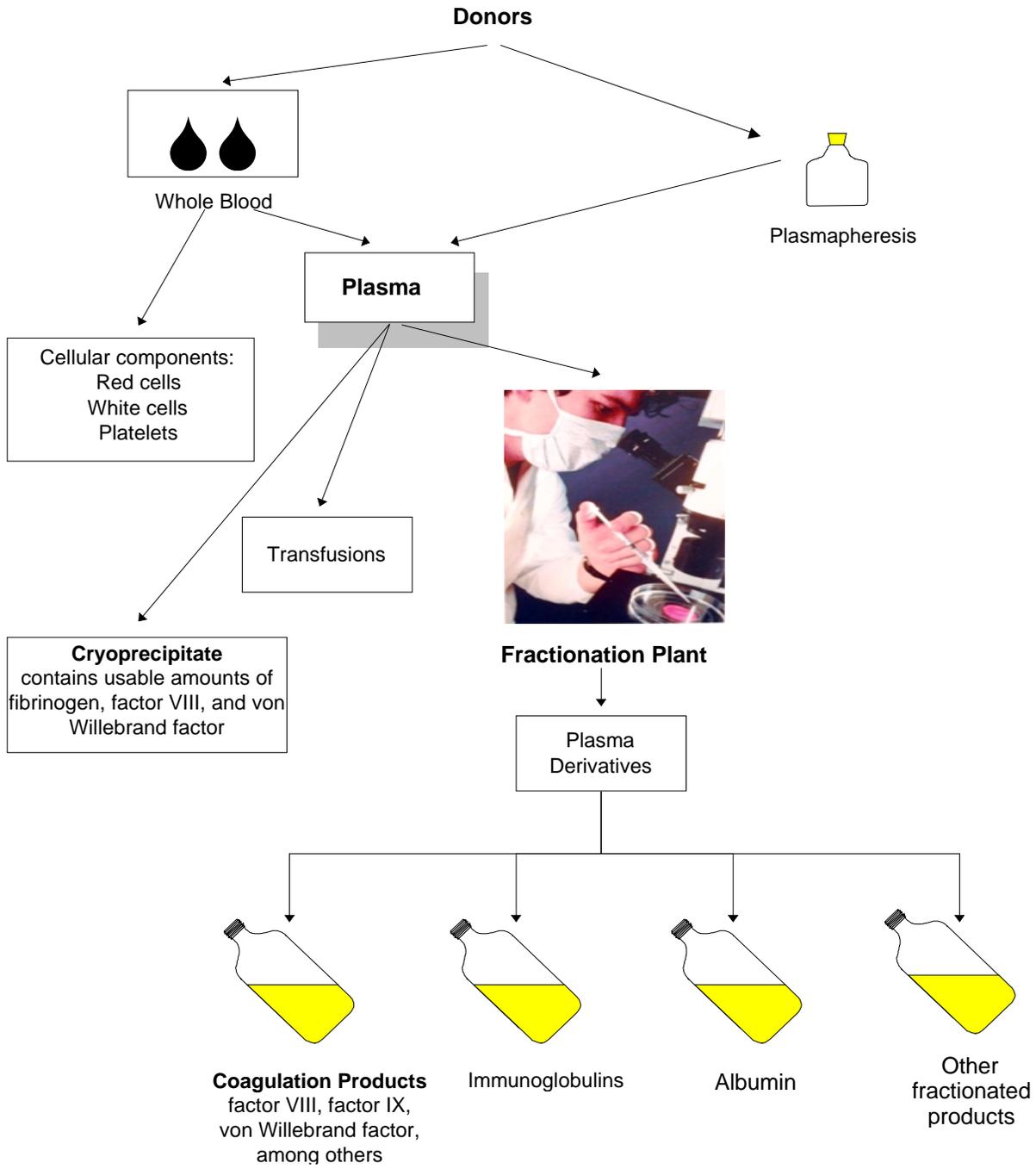
Until viral transmission through blood products was better understood, many paid donors came from populations now known to be at high risk for infectious diseases. Subsequently, both governments and industry have greatly improved standards for blood donor selection and blood testing.

Today, paid donors who are registered in an official programme pose no apparent additional infection risks in comparison to volunteer whole-blood donors in similar programmes which provide for the testing and antiviral treatment of human blood plasma.

An ideal donor, paid or unpaid, should

- be free of communicable disease and free from risk of contracting communicable disease
- agree to be a regular donor
- have a permanent address
- attend a detailed orientation programme to test his or her commitment to the programme
- attend scheduled appointments, a criterion which will eliminate individuals looking for quick money, if paid
- maintain eligibility via repeated screening and testing.

Figure 3 Blood components



2.2.2 Blood Donor Tests

In the U.S.A., the following tests are legal requirements of the Food and Drug Administration (FDA): Syphilis, Hepatitis B antigen and HIV 1 and 2 antibodies. Further to these, the FDA recommends the following tests: Hepatitis B core antibody, Hepatitis C antibody and HTLV-1 antibody. These requirements will change with improvement in technology and knowledge of disease transmission.

2.2.3 Plasmapheresis

Plasmapheresis is a procedure enabling safe collection of plasma from a donor, and which returns his or her red blood cells. The procedure enables a donor to give a larger volume (approximately 600 ml) of high quality plasma than is possible through the donation of whole blood (approximately 200 ml per donation).

2.3 Yearly Volume of Blood Required to Treat Hemophilia A

Table 1 Typical amount of factor VIII required per year to treat an adult with severe hemophilia A in ius

Type of treatment	iu Required
Prophylaxis*	up to 218 000 iu
On demand therapy in industrialized countries	60 000 to 100 000 iu
Moderate level of treatment	40 000 iu
Minimal level of treatment	15 000 to 20 000 iu

* Calculated as follows for a person weighing 70 kg: 20 iu x 70 kg x 3 times x 52 weeks = 218,400.

Table 2 Units of factor VIII required for an example population of 20 000 000 inhabitants, given that half the population is male

Number of cases	10 million x 1/10 000=1000 persons with hemophilia A
Moderate level of treatment	1000 x 40 000 iu per year = 40 million iu of factor VIII

The percentage of donorship in industrialized countries is from 2% to 6% of the total population.

A country with a very well-organized blood donation programme and people who are accustomed to giving blood may be able to produce the plasma that would form the base for the blood products to treat its citizens with hemophilia. Very few countries are self-sufficient in blood collection and can produce all required blood components for its citizens with bleeding disorders. The industrial base needed for concentrate fractionation is complex and the expense greater than it might at first appear. In section three, we will look at the various means available for providing blood products to individuals with hemophilia.

2.4 Safety Issues

2.4.1 Viral Contamination of Blood Products

The presence of Human Immunodeficiency Virus (HIV) in blood products highlighted the vulnerability of the blood supply to infectious agents. When a majority of people with hemophilia in some countries became infected with HIV through the use of virally contaminated plasma concentrates, blood safety became a world issue.

A few years after the HIV epidemic began, Hepatitis C Virus (HCV) was identified. This virus, which has infected approximately 90% of persons with hemophilia, is associated with significant morbidity and mortality. These findings, together with prior knowledge that other infectious agents such as Hepatitis B could be transmitted through blood products, spurred great improvements in the safety of blood products.

Today careful donor selection, individual donation testing and increasingly efficient viral inactivation processes have virtually eliminated transmission risks for most pathogens including HIV and Hepatitis B and C. Additional safeguards include the vaccination of all vulnerable patients against hepatitis A and B. However, the safety of

blood-derived therapeutic products can never be guaranteed absolutely.

2.4.2 Measures Designed to Eliminate Viral Contamination

Combinations of the following measures have been introduced to reduce viral contamination of blood products:

- exclusion of high-risk donors with a possible history of contact with transmittable diseases
- testing of individual blood or plasma donations for known pathogens
- surveillance activities to identify infections in donors or recipients and quarantine periods between collection and distribution, allowing for a further check on donor health
- withdrawal of all material made from batches of source containing donation(s) from individuals subsequently shown to be infected with a transmittable disease
- re-testing once plasma reaches fractionators using relevant methods
- application of new technological procedures for the deactivation of viruses
- modern product purification technology to reduce viral contamination
- attention to the incidence of infection in the population from which donors are chosen. For instance, blood from areas of low prevalence of HIV or Hepatitis C will result in a safer product than blood taken from areas where the prevalence of such factors is higher.

3 Blood Products: Manufacture

3.1 Preparation

The criteria for preparation of therapeutic material include:

- safe donations from healthy blood donors
- individual testing of each donation for known pathogens (especially HBV, HCV, and HIV 1 and 2)

- rapid and skilled processing which conserves the amounts of active clotting factor present and improves final yield
- the use of viral reduction technology to ensure that products are safe from transmittable viral disease

3.2 Plasma

Human plasma is the liquid part of human blood remaining after the removal of red and white blood cells and platelets. It is obtained when whole blood is separated in a device called a **centrifuge**. Plasma can then be used immediately for transfusions, it can be frozen (as fresh frozen plasma, or “FFP”), or it can be fractionated further to obtain a variety of plasma products.

The pooling of plasma from two or more donors is feasible only if the operation is performed under aseptic conditions and the pool is frozen immediately and rapidly to -30°C .

If plasma is not stored frozen at -20°C or lower, clotting factors such as factor VIII will rapidly begin to deteriorate and the yield will be greatly reduced.

3.3 Cryoprecipitate

Cryoprecipitate is prepared by rapidly freezing freshly drawn plasma in a -60°C mechanical refrigerator or an ethanol dry ice bath. It is then thawed slowly at 2° to 4°C and the precipitate is collected by centrifugation.

Cryoprecipitate is rich in factor VIII, von Willebrand factor, and fibrinogen (factor I) and can be used for replacement therapy in patients with hemophilia A (including those with major bleeding or requiring major surgery) or for those with von Willebrand disease. It contains no factor IX and therefore cannot be used for hemophilia B. It is relatively easy to produce with a minimal amount of equipment.

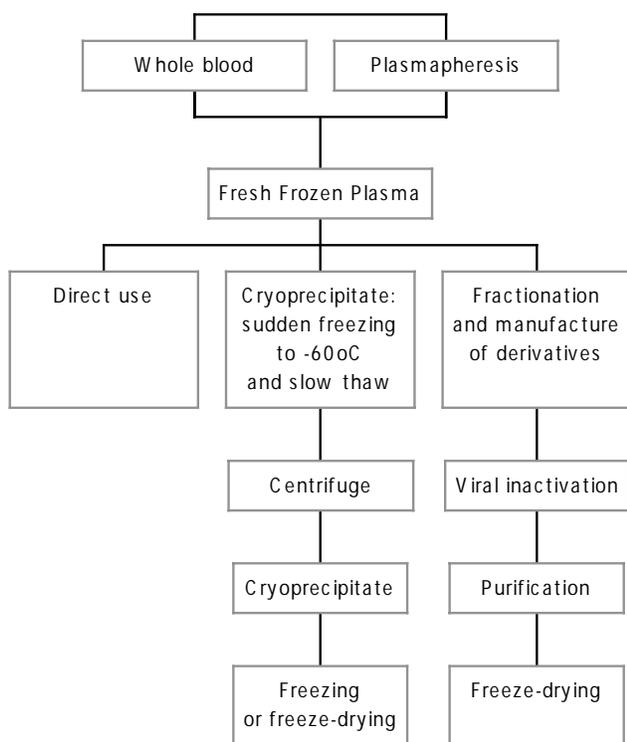
Cryoprecipitate must be stored in a freezer in a frozen solid state at temperatures below -20°C . It has a shelf-life of up to one year when stored at or below -30°C . Such freezers are not always available. Some countries produce lyophilized cryoprecipitate

which can be stored at ambient temperatures and used even for home therapy.

Factor VIII is not as concentrated in cryoprecipitate as it is in factor concentrates by a factor of anything from ten to fifteen. The yield, or proportion of factor VIII is quite unpredictable. If the economic situation of the country does not allow other choices, the production of cryoprecipitate could be the only way to save lives. Other valuable blood products can be made from whole blood in addition to cryoprecipitate.

It is not easy to eradicate viral contaminants from cryoprecipitate and, in the process of doing so, the production cost of cryoprecipitate increases to levels close to the international price of concentrates in some regions of the world. Cost analyses must carefully be carried out.

Figure 4 Key steps in the production of cryoprecipitate and factor concentrates



Note: Purity of the end product depends on what purification technology is used.

3.4 Concentrates

Concentrates are fractionated preparations of individual clotting factors or groups of factors which are freeze-dried. They provide convenient high doses of clotting factor for the rapid treatment of bleeds.

3.4.1 Safety Measures Available During Fractionation

Commercial coagulation concentrates are prepared using pools from thousands of individual plasma donations. The therapeutic safety of each product depends on the prevention, removal and inactivation of any virus present. This can be achieved by ensuring proper donor selection, individual testing of each donation, and a high standard of quality control during fractionation, including special methods for viral removal and inactivation. The methods currently in use include one or more of the following:

Viral Inactivation

- solvent detergent
- Heat treatments
 - wet heat or pasteurization
 - dry heat treatment

Viral Removal

- nanofiltration
- affinity chromatography: separation with monoclonal antibodies

The ultimate safety of any product depends on strict quality control at all stages of collection and manufacture. With the exception of dry heating, all methods of viral exclusion to date are based on steps incorporated into the fractionation process. However none of the methods presently available are guaranteed to render concentrates free of all viral contamination. For example the human parvovirus, which has a protein coat, is known to be resistant. It is also possible that yet unknown rare transmitted agents might enter the blood supply in the future. Therefore, careful monitoring by national agencies is of foremost importance, and manufacturers

must look for ways to further improve the margin of safety.

3.4.2 Purity and Safety

“Purity” refers to the percentage of desired ingredient in a substance, relative to *other* ingredients present. A product containing only factor VIII would be of very high purity, while whole blood is the least pure blood product. Of course, in the process of purifying the product to obtain a higher percentage of *desirable* factor, efforts are also made to remove *undesirable* elements. However the specific effort to remove viral infection is the attempt to improve the “safety” of a product, *not* the purity. **It is important to remember that the word “purity” in a pharmaceutical sense refers to concentration of desired ingredient in a substance and *not* directly to safety concerns.**

In practice, safety must be a high priority in the effort to achieve the purity of blood products. A very high purity factor VIII product is of little use if it is infected with HIV 1, for example. Good manufacturing practices can ensure safety while also improving purity.

Due to the instability of isolated factor VIII, stabilizers must be added to concentrates. These stabilizers themselves reduce the purity of products.

Table 3 Levels of manufacturing purification

Very high purity	Recombinant factor VIII
Very high purity	Blood-derived factor VIII after affinity chromatography
High purity	Blood-derived factor VIII after ion-exchange chromatography
Intermediate to high purity	Blood-derived factor VIII after conventional separation

3.5. Recombinant Factor VIII and Factor IX

The discovery of the molecular structure of both factor VIII and factor IX has led to the development of genetically engineered products, which are prepared using recombinant DNA technology. Because of the instability of isolated factor VIII however, a small amount of human plasma-based albumin is still added to recombinant factor VIII as a stabilizer. However, trials are currently being conducted on new albumin-free recombinant factor VIII.

Two concentrates of recombinant factor VIII (with albumin) and one of recombinant factor IX (without albumin) are presently available in the U.S.A.

4 Blood Products:

Supply and Pricing

When deciding where to procure factor replacement products, the following criteria should be accounted for:

- volume of blood collection relative to the need for blood products at the national level
- ability to enforce strict quality controls for blood collection and manufacture
- ability to build and maintain a high technology plant
- level of reliability of outside suppliers
- availability of financing

Self-sufficiency in the areas of plasma procurement and manufacture of factor replacement products is politically popular. Self-sufficiency policies have been adopted with the objective of reducing or preventing contamination by blood-borne viruses such as HIV. However, it is very important to consider that self-sufficiency is *not* a desirable goal if it means a shortage of products. It is more desirable to treat all persons with hemophilia with a lesser purity product (cryoprecipitate, for example), than to treat some with the highest purity factor, and leave others with nothing at all. Few countries have

been able to achieve self-sufficiency, and there are other options available.

4.1 Manufacture of Cryoprecipitate

Cryoprecipitate is usually made as part of a regular blood collection and banking programme. Otherwise, one refrigerated centrifuge, a cold lab, an industrial grade freezer, and moderate technical know-how is all that is needed to produce cryoprecipitate. Obviously, to produce sufficient quantities for a given population, these basic tools would have to be duplicated. For adequate therapy, a larger volume of cryoprecipitate must be given to the patient to achieve anything like a result similar to that of concentrate therapy. The time involved in storage and thawing and in safe, slow injection make cryoprecipitate a far less convenient and effective treatment than factor concentrates.

4.2 Manufacture of Intermediate Purity

Concentrates

An alternative to cryoprecipitate is the manufacture of intermediate purity concentrate. This is an option when a country has technical know-how and sufficient plasma, particularly if the country in question must avoid imports on principle or for lack of hard currency. However, an initial investment of several million US dollars would be required to establish facilities.

One country that has chosen this option has several such plants in operation. Their production costs per unit come to US.20¢. As the international price of concentrate fluctuates considerably from one country to the other, this option should be compared with the international prices for concentrates prevailing in one's given region.

4.3 Manufacture of High Purity

Concentrates: National

Fractionation Plants

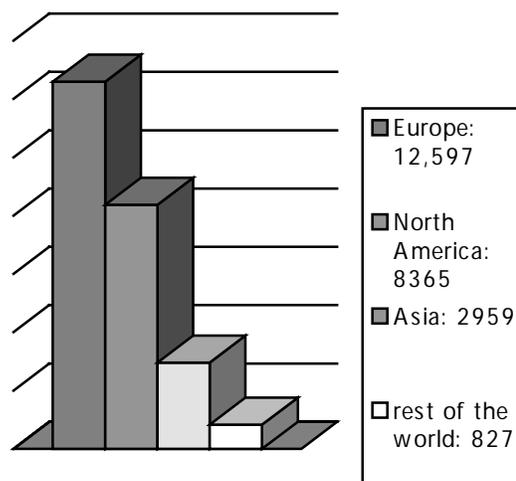
As of 1993, there were ninety-five large-scale fractionation plants in the world. and these

plants were able to process all available plasma. Figure five shows capacity by world region. One third of fractionation plants are owned by non-profit organizations, the others are commercial operations.

The investment required to build a new state-of-the-art plant may be enormous. A plant capable of treating 300 000 liters of plasma would cost close to US \$50 million to build. The costs of maintaining such a plant must also be considered. The Canadian Red Cross is currently building a plasma fractionation facility at an estimated cost of US \$215 million with a yearly plasma capacity of 800 000 liters.

With current technology, the estimated average minimum plasma capacity of a competitive plant active on the international market is 300,000 liters per year. However, this figure greatly depends upon the number of products made, as well as on the local health system environment. The technology required is highly sophisticated.

Figure 5 Worldwide plasma fractionation capacity by region



(in thousands of liters per year)

Source: Survey (1993) by Marketing Research Bureau, Inc.

4.4 Contract Fractionation

“Contract fractionation” is the foreign fractionation of locally collected plasma. There are three types of contract fractionation agreement. In the first, the manufacturer keeps a portion of resultant products which the customer does not need (this might be gammaglobulin, for example). In the second type, plasma is shipped to the fractionation plant and a percentage of the finished product is returned to the country where the plasma was collected. The manufacturer retains the remaining portion of the yield.

For example, if the agreement states that the source country receives 100 iu of factor VIII product per liter of plasma, and the process of fractionation produces 180 iu, the fractionator retains 80 iu to do with as s/he pleases. Such arrangements assume that the manufacturer will sell the product elsewhere. This kind of arrangement existed between a Central American country and an American manufacturer for many years before laws were put in place preventing the export of plasma from that country to the United States.

In the third type of agreement, a fee for plasma fractionation is agreed upon, and all resulting plasma products are returned to the source country. Once returned, they must fulfill all the existing needs of that country.

Experience has shown that the first two types of contract fractionation agreement succeed when both partners have at their disposal a comparable level of technical development; when the plasma collected is acceptable from the technical and safety points of view in both countries and when the will to provide high-quality plasma products is genuine and characterized by integrity.

4.5 International Purchase of Plasma

Derivatives

In order to meet all or some of the needs for blood products in a given country, international purchase of plasma derivatives is an alternative. The choice of supplier should be based on quality of product, safety record, supply reliability, and price.

Table 4 Advantages and disadvantages of supply sources

Supply Source	Advantages	Disadvantages
Cryoprecipitate	<ul style="list-style-type: none"> • Can be prepared with a minimum of technology in blood-banking facility • Other valuable blood products are obtained • Investment is far less than it would be for fractionation facilities (for one centrifuge, freezer, etc., investment is under US \$10 000) • Production of cryoprecipitate produces cryo-poor plasma for the treatment of hemophilia B 	<ul style="list-style-type: none"> • Intermediate purity level • Safety levels are lower than those of concentrates • Yield (in manufacture) is inconsistent; dosage is therefore indeterminable and variable • Inconvenient for home use compared with concentrates • Allergic reactions can occur • Cannot be used for hemophilia B (FFP, cryo-poor plasma, or factor concentrate must be used) • Supply limited by plasma sources
Regional manufacture of intermediate purity factors (conventional separation methods only)	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can accurately be determined • Complete independence for patient • Good control of supply 	<ul style="list-style-type: none"> • Investment required in the millions of US dollars • Intermediate purity levels • Country must be able to retain the highly trained professionals needed • Collection of plasma in country or countries supplied by the plant must be sufficient to make running feasible
Regional fractionation plant for manufacture of higher purity concentrates	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can accurately be determined • Complete independence for patient • Good control of supply • Can be made almost totally safe 	<ul style="list-style-type: none"> • Investment required in the millions of US dollars • Country must be able to retain the highly trained professionals needed • Collection of plasma in country or countries supplied by the plant must be sufficient to make running feasible
Contract Fractionation of Concentrates	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can accurately be determined • Complete independence for patient • Can be made almost totally safe 	<ul style="list-style-type: none"> • Investment required greater than that required for cryoprecipitate • Collection of plasma in country or countries supplied by the contract must be sufficient to supply demands of contract • Contract negotiations are complex

(cont'd)

Table 4 (continued)

Supply Source	Advantages	Disadvantages
International Purchase of Concentrates	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can be accurately determined • Complete independence for patient • Can be made almost totally safe • Accessible for country on demand 	<ul style="list-style-type: none"> • Prices fluctuate • Supply may be unreliable • High cost; drain of hard currencies
International Purchase of Recombinant factor VIII	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can accurately be determined • Complete independence for patient • Can be made almost totally safe 	<ul style="list-style-type: none"> • Long-term effects are unknown • Present supply unreliable • Prices fluctuate • Extremely high cost • Drain of hard currencies • Cannot be used for von Willebrand (FFP, cryo-poor plasma, or blood-derived concentrate must be used)
International Purchase of Recombinant factor IX	<ul style="list-style-type: none"> • Convenient for home use • Yield is consistent and dosage can accurately be determined • Complete independence for patient • Can be made almost totally safe 	<ul style="list-style-type: none"> • Long-term effects are unknown • Present supply unreliable • Prices fluctuate • Extremely high cost • Drain of hard currencies

5 International Marketing Issues

5.1 Price Fluctuations

Currently the price of concentrates fluctuates significantly in relation to many factors, including:

- the distribution system and the number of intermediaries
- custom duties and state regulations controlling blood product imports
- market pricing. The market value of concentrate is established not only in relation to production costs, but to some degree arbitrarily, according to “what the market can bear.”

- the introduction of new products on the market. Recombinant products have increased the total supply of factor VIII worldwide.

5.2 Current Selling Prices

At any time, a key factor in establishing the selling price is the current state of supply. It should also be noted that, as in the case of many products, bulk purchases usually result in lower purchase prices.

Situations can vary tremendously from one country to the other. For example, as of April 1996, in some countries the price per IU ranged from US.20¢ for intermediate purity to \$1 for recombinant, whereas, in

one Asian country, all blood-derived (intermediate, high, very high purity) and recombinant factor VIII, and all factor IX products were selling for about the same price: US.90¢ to \$1 per iu.

5.3 World Production

In 1994, the world production of factor VIII plasma derived concentrates (excluding recombinants) was 1700 million iu. Fifty percent of this quantity was produced in Europe, 25% in the United States. These units represented US \$900 million sales. The world production of factor IX in 1994 was 430 million units, with North America and Europe producing approximately 40% each of this total and Asia a little over 10%. These units represented US \$190 million in sales.

5.4. Current (February 1997) Industry

Trends Affecting Prices

Current data on market penetration of recombinant factor VIII concentrate in its present major markets (U.S.A., Canada, Europe, and Japan) suggest that recombinant products will continue to gain acceptance in the coming years, and may reach over 75% market share overall by 2001, unless unexpected developments occur. The worldwide factor VIII market (plasma derived and recombinant) has increased from 1848 million iu in 1992 to 2130 million in 1995, a 15.7% increase in three years. This trend will likely continue as demand increases worldwide. It is probable that manufacturers will produce increasing volumes of recombinant factor VIII and that new companies will introduce new genetically engineered factor VIII and factor IX concentrates.

Based on the assumption that industrialized countries will use primarily

recombinant factors VIII and IX in the coming decade, several fractionators have already started to offer their blood-derived factor concentrates at more affordable prices in Latin America, Asia, and the Middle East. These companies will probably generate less revenues from sales in these markets than from sales in industrialized countries but they are not likely to abandon the production of plasma-derived coagulation factor even if it is less lucrative.

Demand for plasma-derived products such as the immunoglobulins and albumin is increasing and fractionators will probably continue producing coagulation factors as part of the production process for these products. Albumin-free recombinant will soon be available, and this too will affect trends.

In the coming years, the price of plasma will go up because of additional testing and donor requirements, as well as higher donor rejection rates due to stricter screening measures. For example, an overall increase of 1% to 3% per year may be assumed for the price of plasma in the U.S. over the next five years. The price of plasma will increase more in Europe and Japan than it will in the U.S., because the testing and donor requirements and recruitment costs in these countries are more stringent. There are restrictions on the number of times one donor can donate plasma by plasmapheresis. These restrictions are far more stringent in Europe and in Japan than they are in the U.S.A.

Gene therapy is being investigated, but there is little evidence to date that widespread implementation will be feasible soon. Within the foreseeable future, therefore, the treatment of hemophilia will remain reliant on factor replacement.

Glossary of Terms

The term “**blood-derived**” distinguishes certain products that are derived from human blood and those manufactured by genetic engineering.

carrier In genetics, a term meaning that the gene for a specific characteristic is present in the individual and can be passed on to offspring.

centrifuge An apparatus by means of which particles in suspension in a fluid may be separated out; this is done by whirling the vessel containing the fluid about in a circle; centrifugal force throws the particles to the peripheral part of the rotated vessel.

Concentrates are fractionated, freeze-dried preparations of individual clotting factors or groups of factors. They provide convenient high-dose-to-volume material for the rapid treatment of bleeds. Reconstitution is with sterile water, and administration (as with all blood products) is via a vein.

cryoprecipitate Fraction of human blood prepared from fresh plasma. Cryoprecipitate is rich in factor VIII, von Willebrand factor, and fibrinogen (factor I). It does not contain factor IX.

Cryoprecipitate-poor plasma is plasma remaining after cryoprecipitate is removed from it. Cryo-poor plasma does not contain factor VIII or fibrinogen, but it does contain factor IX.

desmopressin (DDAVP) Synthetic hormone used to treat most cases of von Willebrand disease and mild hemophilia A. It is given intravenously, by subcutaneous injection, or by intranasal spray.

diluent Sterile water or saline used for the reconstitution of lyophilized material.

factor IX One of the blood clotting factors manufactured in the liver. Deficiency or absence of factor IX clotting activity results in hemophilia B.

factor VIII One of the clotting factors manufactured in the liver. Deficiency or absence of factor VIII clotting activity results in hemophilia A.

fractionation Separation and processing of human blood plasma into a range of products for therapeutic use. A fractionation plant is a facility that carries out fractionation. A fractionator is the authority or company owning and administering the plant.

fresh frozen plasma (FFP) Human plasma separated from blood cells and platelets soon after donation and frozen at -30°C. FFP contains all the clotting factors, but at very low concentration to volume. FFP may be freeze-dried (fresh dry plasma) obviating the need for freezer storage.

hemophilia A A condition resulting from factor VIII deficiency, also known as classical hemophilia.

hemophilia B A condition resulting from factor IX deficiency, also known as Christmas disease.

hemophilia carrier see “carrier,” above.

Hemophilia Treatment Centre (HTC) Medical centre providing basic diagnosis and treatment for inherited bleeding disorders. Hemophilia Treatment Centres are usually linked to Hemophilia Comprehensive Care Centres.

Hemophilia Comprehensive Care Centre (HCCC) Medical centre providing a full range of facilities for the diagnosis and management of inherited bleeding disorders.

home therapy Intravenous injection of clotting factor outside the hospital setting.

inhibitors Antibodies that destroy all or part of injected clotting factor.

International Unit (iu) Standard unit measure of volume established through the International System of Units. For the purposes of hemophilia treatment, an iu represents the amount of factor VIII or IX present in one milliliter (ml) of average normal plasma.

lyophilization The creation of a stable preparation of a biological substance (blood plasma, blood clotting factor concentrate, etc.) by rapid freezing and dehydration of the frozen product under high vacuum. The result is an off-white powder cake that can be reconstituted with a diluent.

mild hemophilia Condition resulting from a level of factor VIII or factor IX clotting activity between 6 to 24% of normal activity in the bloodstream.

moderate hemophilia Condition resulting from a level of factor VIII or factor IX clotting activity between 1 to 5 % of normal activity in the bloodstream.

plasma The liquid part of human blood remaining after separation of the cellular elements (red and white blood cells and platelets) from whole blood. It contains many coagulation factors. Plasma is collected for the manufacture of blood derivatives.

plasmapheresis Procedure that allows for the safe collection of plasma from a donor, while at the same time returning the donor's red cells. This method allows a donor to donate a larger volume of plasma per donation (about 600 ml), and to donate more frequently than is possible when donating whole blood (about 200–220 ml of plasma).

Porcine factor VIII Concentrate of factor VIII prepared from pig plasma. Used mainly for the treatment of hemophilia A patients who have inhibitors. Porcine factor VIII must be stored frozen.

prophylaxis Therapeutic method for the treatment of bleeding disorders characterized by a *preventive* intention. Prophylaxis involves the intravenous injection of blood-derived or recombinant product in anticipation of, and in order to prevent bleeding. Primary prophylaxis establishes a regular schedule of preventive treatments with factor replacement regardless of whether injury or bleeding has occurred, while secondary prophylaxis involves preventive treatment prior to particular activities.

recombinant product Concentrate manufactured by genetic (DNA) engineering. Recombinants are not made from a base of human plasma. At the time of printing, most recombinant products

on the market contain a small amount of plasma-derived albumin, added as a stabilizer. Trials are currently being conducted on a wholly recombinant factor VIII product, containing no plasma derivatives whatsoever.

severe hemophilia Condition resulting from a level of factor VIII or factor IX clotting activity of less than 1 % in the bloodstream.

sporadic hemophilia Cases of hemophilia which occur with no previous family history. It is assumed that these cases are the result of genetic mutation.

von Willebrand disease Inherited bleeding disorder resulting from a defective part of the von Willebrand/factor VIII molecule.

