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When we look at the future of haemophilia therapy globally, we are not talking of a situation where there would be a need only for biotech products. There is and will continue to be a global need for both recombinant *and* plasma-derived products. Recombinant products have increased their market share in many countries over the last five years, but there is a continuing need for plasma-derived concentrates in the future. In addition, transgenic production and gene therapy offer intriguing possibilities for the future.

Increased Use of Recombinant Products

In 1994, 2.1 billion units of factor VIII and 430 million units of factor IX were used worldwide [1]. Of the total units of factor VIII used, only 400 million units were recombinant factor VIII, the remainder was plasma derived. At the time, there was no recombinant factor IX available. Since 1994, global use of factor concentrates has increased by at least 30 per cent. Use of recombinant factor VIII has increased dramatically in many countries, and recombinant factor IX has become available. If we look at the market share of recombinant factor VIII, we see that recombinant is used primarily in developed countries with well-resourced economies. Recombinant factor VIII now has 100 per cent of the Canadian market and 50 to 65 per cent of the U.S. market. It has 30 to 50 per cent of the market in Western Europe, and the trend is continuing. In the last year, Ireland switched to using recombinant products exclusively, and in the United Kingdom recombinant factor VIII is being used for all people with haemophilia under the age of 16.

Between 1992 and 1995 the amount of factor VIII concentrates used globally increased by 15.7 per cent. There has been a similar, if not greater, increase between 1995 and 1998. There are several reasons for the increase in use of recombinant products in developed countries. They include safety perception, safety, cost levelling, clinical consensus, and prophylaxis.

1. Safety Perception

In the early 1990s, even before recombinant was widely available, there was a perception in the haemophilia community that recombinant products were inherently safer because they were not primarily human based. At an interactive symposium at the 1994 WFH congress in Mexico, 90 per cent of people with haemophilia surveyed believed that recombinant products were inherently safer [2]. This was at a time when the vast majority of them did not have access to recombinant products. It is hardly surprising, therefore, that recombinant products have increased their market share to such an extent in the intervening years.

The reason for this perception is not difficult to understand: the haemophilia community has been devastated by the side effects of plasma-derived therapy in the past. In most countries where people with haemophilia had access to plasma-derived concentrates in the 1970s and 1980s, HIV and hepatitis ravished the haemophilia community. The beneficial effects of factor concentrates resulted in an increase in the average life expectancy for people with haemophilia, and by 1980, average life expectancy was 60 years. However, by 1994 it had fallen to 40 years, almost entirely as a result of AIDS [3].

HIV infection occurred in up to 70 per cent of people with severe factor VIII deficiency in many countries and in 30 to 40 per cent of the haemophilia population as a whole. The majority of people with haemophilia were also infected with hepatitis B and/or hepatitis C. In the European Community, 60 per cent of people with haemophilia were infected with hepatitis B and 70 per cent with hepatitis C [3]. AIDS is the main cause of death among people with haemophilia in developed countries (although the situation is now improving, thanks to combination therapy). The second leading cause of death is liver disease and it will likely overtake AIDS as the leading cause of death among people with haemophilia in the coming years. This horrendous experience has taught the haemophilia community to insist that safety be the primary concern when choosing treatment for people with haemophilia.

There are also several current concerns with relation to safety. These include Creutzfelt-Jakob disease (CJD), New Variant Creutzfelt-Jakob disease (nvCJD), non-enveloped viruses, and the development of inhibitors. While there has been concern with regard to both plasma-derived and recombinant products in relation to CJD and nvCJD, there is no doubt that the continuing transmission of non-lipid-enveloped viruses by plasma-derived products is a major concern. Transmission does not occur with recombinant products. While non-enveloped viruses such as parvovirus B19 and hepatitis A do not have the traumatic clinical consequences of HIV and hepatitis C, there is concern that the next non-enveloped virus may have devastating effects for people with haemophilia.

In relation to inhibitor formation, there was a reluctance to use recombinant products in the mid-1990s because of fears that the incidence of inhibitor formation from these products would be much higher. It now appears that the incidence of inhibitor formation from recombinant factor VIII is similar to that which occurs with high purity plasma-derived factor VIII concentrates. The easing of this particular concern is also a factor in the increased use of recombinant products.

2. Safety Record

No viral transmissions and no transmission of non-enveloped viruses have been linked to recombinant factor concentrates to date. The product is effective and the risk of inhibitor formation appears to be similar to that of high purity plasma-derived products. Concern over the use of human albumin to stabilise products has led to the development of a second generation of recombinant products that do not contain human albumin.

3. Cost Levelling

In addition to the perceived risk of inhibitor formation, cost was a major constraint to the use of recombinant products at first. Recombinant products were initially much more expensive than plasma-derived concentrates. While they are still more expensive, there has been a reduction in the differential between the price of recombinant and plasma-derived products. In a survey of 25 European countries carried out in 1997, the average cost of recombinant factor VIII was US$0.87 per unit [4]. The average cost of plasma-derived factor VIII concentrate was US$0.68 per unit. This meant that recombinant factor VIII was on average 27 per cent more expensive than its plasma-derived equivalent.

There is enormous variation in the prices paid for both recombinant and plasma-derived products. In Europe, the price of recombinant products varies from US$0.65 to US$0.96 per unit; the price for plasma-derived concentrate varies from US$0.25 to US$0.83 per unit [4]. Many factors affect the price of the concentrates in different countries, including what the market will bear, local and national negotiation, the role of pharmacies and intermediaries, and duties and taxes.

When looking at the cost of using plasma-derived or recombinant products, another factor one must take into account is the hidden cost in using unsafe products. In the past, the use of unsafe plasma-derived products has led to additional costs for treatment and compensation for HIV and hepatitis C in the haemophilia community. For example, Ireland has a total population of 380 people with haemophilia of whom 220 were infected with hepatitis C and 103 with HIV [5]. Additional costs for treatment and compensation

over the period 1988-2000 will be approximately US$80 million, or US$6.6 million per annum. Using recombinant instead of plasma-derived products costs an additional US$2 million per year. While the cost of providing concentrate has increased, the enormous hidden costs of using unsafe products will be avoided.

4. Clinical Consensus
Recombinant factor VIII has been recommended as the first choice for replacement therapy for people with haemophilia by the Medical and Scientific Advisory Council of the National Hemophilia Foundation in the U.S.A. [6], by the Medical and Scientific Advisory Council of the Canadian Hemophilia Society, and by the United Kingdom Haemophilia Centre Directors Organisation [7].

5. Prophylaxis
One of the reasons for the increase in use of concentrate is the recognition of the value of prophylaxis, especially for children. As far back as 1994, there was consensus that prophylaxis should be considered as optimum therapy for children with severe haemophilia A and B. While the doses and regimes vary, there has been a steady increase in the use of prophylactic therapy.

Factors Restricting Use of Recombinant Products

There are also some disadvantages to recombinant products.

1. Cost
Recombinant products are more expensive than plasma-derived products. This has limited their use in many countries and prohibited their use in others. In addition, the duties and taxes charged on recombinant products can differ from those on plasma-derived products (e.g., in the European Community, value-added tax is charged on recombinant products but not on plasma-derived products). Reimbursement mechanisms can also cause problems in relation to the differential between plasma-derived and recombinant products.

2. Supply
Over the last two years the demand for recombinant products has exceeded the supply in many countries. There is a need for increased production of recombinant concentrates.

3. Threat to Plasma-collecting Capability
If a country switches to using recombinant concentrates exclusively, there is a danger that the existing national plasma-collecting capability will degenerate.

4. Safety
There are uncertainties regarding the threat posed by nvCJD and the potential presence of mammalian viruses in the culture medium for recombinant products.

Continuing Need for Production of Plasma-derived Concentrates

While there has been a trend over the last four years towards increased use of recombinant concentrates, there is still a need for good quality plasma-derived concentrates. It must not be forgotten that plasma-derived concentrates are effective and prevent or control bleeding in people with haemophilia. The major reasons for the continued need for the production and use of these products are safety, cost, supply and demand, and continuity of supply.

1. Safety
Plasma-derived concentrates produced nowadays are safer than ever before. Lessons have been learned from the tragedies of the past and steps have been taken to improve the safety of plasma-derived concentrates, at all stages of the collection and manufacturing processes. In plasma collection, there has been movement towards using repeat donors and quarantining plasma for defined periods of time. Specific measures such as the quality plasma programme in the U.S.A. and the E.U. directive on donor selection [8] have contributed to improved safety. In terms of testing donors, Genomic Amplification Techniques (GAT) testing has been introduced and its use will be increased in the coming years. GAT testing of plasma pools is currently available, and testing of

individual donations, which will also increase the safety profile of individual donor products, will be available in the near future. The beneficial effects of GAT testing can be seen in the reduction in the risk of window-period donations for hepatitis C and HIV [9].

Table 1

Effect of GAT Testing on Window Period

Virus	Current Window Period (Days)	Window Period with GAT (Days)
HCV	82	23
HIV	22	11
HBV	59	34

It is estimated that GAT testing for hepatitis C and HIV will eliminate more than 90 per cent of the residual risk of hepatitis C infection and more than 80 per cent of the residual risk of HIV infection. In addition, improvements have been made to viral inactivation techniques, such as nanofiltration.

While there is increasing confidence in the safety of plasma concentrates in general, there are still several concerns. There is concern over the continued transmission of non-enveloped viruses. There is concern regarding CJD and, more particularly, nvCJD, which led to the withdrawal of British plasma in 1998. There is certainly concern with regard to the risk of infection from the use of cryoprecipitate. In many countries cryoprecipitate is the standard therapy for haemophilia. In some of these countries, donors are not screened for HIV or hepatitis C, so there is a significant risk of infection. Even in countries where cryoprecipitate is produced from screened donors, there is a residual risk of infection, which varies with the prevalence of donors in the window period. One study carried out as part of a WFH project demonstrated that the risk of HIV infection from cryoprecipitate in the U.S.A. was 1 in 360,000 bags [10]. In Venezuela, because of the higher prevalence of donors in the window period, the risk was 1 in 12,000 bags. The lifetime risk of developing HIV infection for a person with severe haemophilia using cryoprecipitate is 3 per cent in the U.S.A. and 40 per cent in Venezuela. In both countries, donors are screened for HIV antibody. Clearly, switching to a virally inactivated concentrate would be a major benefit in countries where cryoprecipitate is still a major therapeutic option.

2. Costs

Seventy-five per cent of people with haemophilia worldwide have no access to treatment. The global population is approximately 5.5 billion. If the incidence of severe haemophilia is 1 in 16,000, it follows that there are about 340,000 people with haemophilia. The WFH estimates that 85, 000 of those have access to treatment and 255, 000 have no access to treatment with concentrates. If treatment were provided at a level of 30, 000 units per year (minimal on-demand therapy) then, based on the average cost of recombinant and plasma-derived concentrates in Europe, treatment with recombinant would cost US$26,000 per person per year and treatment with plasma-derived concentrate would cost US$20,000 per person per year. Even if plasma-derived concentrates were made available at a relatively low price of US$0.30 per unit, the cost would be US$9,000 per person per year, which is still unrealistic in many countries where the per capita health spending is very low. (For example, India spends approximately US$10 per person per year on health care.)

The percentage of gross domestic product (GDP) spent on health care in developing countries is often similar to the proportion spent in developed countries. However, in developing countries, the absolute amount of money available is much lower. In Ireland, 7.9 per cent of GDP is spent on health care. People with haemophilia in Ireland are treated with recombinant products and prophylactic therapy is available to all children with haemophilia. Nicaragua also spends 7.9 per cent of its GDP on health care. However, people with haemophilia have no access to concentrates, either recombinant or plasma derived, because the total amount of expenditure on health care per person is significantly lower than in Ireland.

In many developing countries it is difficult to envisage how modern haemophilia treatment could become available without a major shift in government commitment. The cost of providing a minimum level of treatment globally for people with haemophilia who are not currently treated is approximately US$2.3 billion annually. (This is roughly equivalent to the cost of two stealth bombers.)

In countries where per capita health spending is low, plasma-derived concentrate is expensive, but the cost of recombinant concentrates is prohibitive. In countries where the per capita health spending is reasonable but the per capita usage of concentrate is low, it would be possible to increase the use of plasma-derived concentrate to allow a reasonable level of treatment for each person with haemophilia as opposed to introducing recombinant concentrates which are more expensive per unit. In countries where there is no modern treatment for haemophilia care, the options are:

- do not treat;
- upgrade the transfusion service to provide basic products;
- purchase concentrate at best available price; or
- contract the fractionation of plasma abroad, providing the transfusion service has been upgraded.

In countries where there is inadequate treatment, the most realistic option for increased resources would be to increase per capita usage to at least provide a realistic level of on-demand home therapy. In this type of situation, the price per unit is crucial. Even within the European Community per capita usage varies enormously from 0.5 units per capita in Greece to 5.7 units per capita in Sweden [4].

In 1996, 4.8 billion US dollars was spent on concentrates worldwide:

- 31 per cent in the U.S.A.;
- 37 per cent in Europe;
- 27 per cent in Asia (mainly Japan and Korea); and
- 5 per cent in the rest of the world.

In countries where there is inadequate treatment or no treatment (mostly found in the “rest of the world” category), it is totally unrealistic to consider the use of recombinant products as a first step. A gradual improvement in the products available and a gradual increase in per capita usage of products are more realistic goals. Therefore, the major market for recombinant products is and will continue to be the 85,000 people with haemophilia who are currently receiving treatment. Countries with adequate treatment will continue to use plasma-derived products at different levels, but the major market for plasma-derived products in the future may well be the 255,000 people with haemophilia who currently receive no modern treatment.

3. Supply and Demand

It is unrealistic to talk about the need for plasma-derived or recombinant products exclusively when there has been a market shortage of both products over the last two years. Ten out of 25 European countries surveyed in 1997 had experienced supply problems [4]. The U.S.A. has also experienced major supply problems [11]. In 1997-98 it experienced shortages of the following products:

- Recombinate, Bioclate (Baxter); Kogenate (Bayer)
- FEIBA, Autoplex T (Nabi), Hyate C (Speywood)
- Koate HP (Bayer), Alphante (Alpha)
- Humate P (Centeon)
- Monoclate P (Centeon)
- Mononine (Centeon), Alphaine SD (Alpha)
- Konyne 80 (Bayer)

There were several reasons for the supply problems.

a. insufficient production. There was clearly insufficient production of recombinant factor VIII. Plasma fractionation plants were also underused. In 1995, 25 million litres of plasma, which could potentially have produced 4.5 billion units of factor VIII,

produced approximately 2 billion units of factor VIII [1].

b. increased demand.

c. temporary plant closures. Many fractionation plants were closed temporarily due to inspections, regulatory requirements, and changing manufacturing processes.

d. withdrawals. In the U.S.A., products were withdrawn if a plasma donor died of CJD or had a significant risk factor for it. This led to the withdrawal of a significant proportion of concentrates, both plasma derived and recombinant, over the last two years.

e. inefficient fractionation. In some instances, collected plasma was fractionated to manufacture only albumin and immune globulins, instead of fractionating factor VIII and factor IX as well.

f. continuity of supply. There was a lack of continuity of supply in many countries. After switching to recombinant products some countries allowed national collection facilities to wither. Factor VIII and factor IX, which could have been produced from plasma collected, were not fractionated. A lot of potential product was wasted at a time when there was a global shortage. There is also an argument for keeping a national plasma collection system functioning fully, even in the event of a switch to recombinant products. Continuing this capacity will ensure them of a guaranteed backup supply of factor VIII and factor IX concentrates in the event of a shortage. In addition, excess factor VIII and factor IX could be used globally.

Improving Treatment for Haemophilia Globally

Several steps are necessary to increase the availability of treatment for haemophilia on a global basis. The capacity for production of recombinant factor concentrates must be increased and the cost per unit of recombinant product needs to be lowered. Plasma fractionation plants should operate at full capacity to increase the available supply of plasma-derived concentrates. Countries that are currently collecting good quality plasma could look at the option of contract fractionation to yield albumin, immune globulin, factor VIII, factor IX, and other necessary products. This should also apply to countries that are using only recombinant products. They may not require the factor VIII or factor IX themselves, but it could be made available, by agreement, on the global market. In many countries where there is currently inadequate or no treatment, the availability of treatment depends on plasma-derived products being available at a lower price per unit. This process could be assisted by the provision of factor VIII and factor IX from plasma collected in countries that are using recombinant products. In this situation, albumin and immune globulin would cover the price of plasma, and the factor VIII and factor IX could possibly be made available at a lower price.

In developing countries, there are several options. One is to upgrade the transfusion service to improve the quality and quantity of plasma and plasma-derived products. This option is one for which government commitment might be forthcoming. It would not lead to an immediate improvement in treatment available for people with haemophilia, and purchasing plasma-derived concentrates at the best available price per unit should be considered. Additional resources for haemophilia care could then be used to increase the per capita usage with the aim of getting to a point where on-demand home therapy is available. If the transfusion service is upgraded to a point where a sufficient quantity of plasma of acceptable quality is being produced, the country could look at the possibility of contract fractionation of its plasma abroad.

In terms of improving treatment in developed countries, increased resources in any country should first be targeted at ensuring adequate per capita usage of concentrate to allow at least adequate on-demand home therapy. The next improvement could be providing prophylactic therapy for children, and then examining the possibility of increasing the amount of

recombinant products being used within the country.

Transgenic Production and Gene Therapy Offer Intriguing Possibilities for the Future

1. Transgenic Production of Concentrates

The production of concentrates using transgenic technology is an intriguing possibility. These products are not yet available, and we do not know when and if they will be available in sufficient quantities to make a measurable impact on the global situation for people with haemophilia. In theory, these products have several advantages. They should be free from human viruses, and the purification should be simple (similar to the purification of milk) and inexpensive. Theoretically, they should be available in very large quantities. Due to the high concentration of transgenic protein in the milk of transgenic animals, there is the potential to produce very large quantities of factor concentrates at very low cost. However, these advantages are purely theoretical at present. It remains to be seen if transgenic production would result in an endless supply of inexpensive concentrate. In the early 1990s there was an expectation that recombinant technology would create an inexpensive and endless supply of concentrate. The supply is neither endless nor inexpensive. Another potential disadvantage is safety in relation to the transmission of animal viruses.

2. Gene Therapy

Gene therapy remains an exciting possibility and holds out the prospect of a partial or complete cure for haemophilia. There are many technical obstacles to overcome, but it is encouraging to see that clinical trials for both factor VIII and factor IX gene therapy have begun. The questions that the haemophilia community wants answered with regard to gene therapy are:

- When will it be available?
- What will it cost?
- Will it be available globally?

None of these questions can be answered at the moment. It is clear, however, that gene therapy will not be available on any widespread basis for several years. It should be remembered that factor concentrates have been available for 25 years now but only 25 per cent of people with haemophilia have access to them. There is no guarantee that gene therapy, when available, will be accessible globally within a reasonable period of time.

Haemophilia Care 2000-10

I would like to end by setting out some of my thoughts on the future directions for haemophilia care over the next decade. In developed countries, I believe there will be an increased reliance on and use of recombinant factor concentrates. This trend will probably be accelerated by the imminent arrival of second-generation recombinant factor VIII concentrates, which will not be stabilised with human albumin, and by the currently available recombinant factor IX concentrate, which is not stabilised with human albumin. I hope that we will see the introduction of gene therapy.

In developed countries there is a danger of retrenchment in haemophilia treatment, as the governments in many countries will come under pressure to decrease healthcare costs. Health expenditure as a percentage of gross domestic product has been increasing in many countries for several years. If the cost of treatment per person for haemophilia continues to increase, governments may cap the amount of funding for haemophilia care.

In developing countries, most of which do not have access to modern haemophilia care, the introduction of modern haemophilia treatment will best be served by the availability of inexpensive plasma-derived concentrates. In many countries, I believe we will see the per capita use of concentrate increase using inexpensive plasma-derived concentrates. This process would be assisted by the maintenance of plasma collection facilities in countries that have switched to recombinant products. If transgenic product is introduced and is available in large quantities at

an inexpensive price, then this has the potential to revolutionise the availability of therapy for people with haemophilia in many developing countries. To achieve better care we need to take a global view. Industry, governments, regulators, and the haemophilia community should look at the situation globally and in the long term. I strongly encourage national haemophilia organisations to develop a sense of haemophilia care throughout the world and not confine themselves to their own country or region. We need to maximise use of available plasma resources. Each country should have a national plan for the development of haemophilia care, which sets out in measurable and practical steps the proposed development of haemophilia care from the current level of therapy to an achievable and realistic level of therapy. Government commitment to providing, maintaining, and improving haemophilia care should be sought. It will be facilitated by building a national coalition between the haemophilia organisation and clinicians.

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