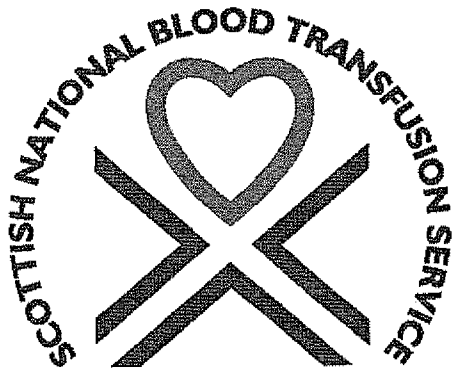
NHS
National
Services
Scotland



PENROSE INQUIRY

Scottish National Blood Transfusion Service

Self-Sufficiency and the Supply of Blood Products in Scotland (With Particular Reference to the Treatment of Haemophilia A)

Author: P R Foster

Date: January 2011 (Revised February 2011)

SNBTS DOCUMENT REQUEST No:

2010/00032

Glossary

albumin	A major protein circulated in the bloodstream. Albumin levels can be low in malnutrition and in diseases of the kidney and liver. Albumin, extracted from blood donations, is used in the treatment of a wide variety of medical conditions
antibody	A protein produced as part of the body's immune response to a 'foreign invader'. Depending on the infectious agent, antibodies may be effective at eliminating a 'foreign invader' (e.g. measles virus) or less effective (e.g. HIV, Hepatitis B and hepatitis C infection). A reactive antibody to a virus, such as hepatitis C virus, means that the person may at some stage have been infected with the virus. It does not necessarily indicate present infection.
anti-D immunoglobulin	A preparation of human anti-rhesus antibodies derived from plasma of selected donors. An important product of plasma fractionation which is used to prevent rhesus disease of the newborn.
anti-haemophilic globulin (AHG)	An older term used to describe factor VIII
cellular constituents	Constituents of blood in the form of cells (eg. red cells, white cells, platelets)
erythrocytes	Red cells
factor VIII	A blood coagulation factor which is lacking in people with haemophilia A. Factor VIII is a protein which is present in trace quantities in the plasma of normal people e.g. accounting for about 6 parts per million (ppm) of the total protein present in normal human plasma.
factor IX	A blood coagulation factor which is lacking in people with haemophilia B.
haemostatic	stopping bleeding
m iu	million international units (one international unit being the biological activity of a coagulation factor present in one millilitre of blood plasma of a normal person).
OAS	Optimal Additive Solution; a mixture of additives designed for the

	suspension of red cells which enabled more plasma to be recovered from a donation of whole blood
plasma	The straw coloured liquid portion of blood. Contains proteins (e.g. albumin, antibodies, clotting factors) as well as hormones, fats and dissolved salts and gasses.
recombinant	A technique in which a specific segment of DNA is isolated and inserted into a bacterium or other new host (e.g. yeast, animal cell) in a form that allows the DNA segment to be replicated as the new host multiplies. The DNA segment is said to have been 'cloned' because it exists free of the rest of the DNA from which it was derived. Used in the modern treatment of haemophilia in the form of recombinant Factor VIII and Factor IX concentrates in which the human coagulation factor is synthesised by hamster cells.
supernatant	The solution remaining after a precipitate has been removed by centrifugation.

CONTENTS

	Summary	7
1.	INTRODUCTION	10
1.1	Therapeutic Proteins from Human Blood Plasma	10
1.2	Blood Products for the Treatment of Haemophilia	10
2.	SELF-SUFFICIENCY	12
2.1	Government Policy	12
2.1.1	The World Health Organisation Recommendation WHA 28.72	13
2.1.2	The Council of Europe Recommendation R 80 (5)	14
2.1.3	The Council of Europe Recommendation R 81 (14)	15
2.1.4	The Council of Europe Recommendation R 83 (8)	15
2.1.5	The Impact of variant Creutzfeldt-Jakob Disease (vCJD)	16
2.2	Policy into Practice	17
2.2.1	Forecasting Product Demand	18
2.2.2	Forecasting Product Yield	18
2.2.3	Supply of Plasma	19
2.2.4	Manufacturing Capability	20
2.3	Management Processes (Scotland)	21
2.3.1	National Management Processes	21
2.3.2	The SNBTS Management Processes	22
2.3.3	The PFC Management Processes	22
3.	FACTOR VIII DEMAND	23
3.1	Forecasts of Demand (United Kingdom)	23
3.2	Forecasts of Demand (Scotland)	24
3.3	Amount of Factor VIII Used in the United Kingdom	24
3.4	Amount of Factor VIII Used in Scotland	26
3.5	Comparisons Between Scotland and the Rest of the UK	27
3.6	Accuracy of Forecasts	28
3.6.1	Long Term Planning	28
3.6.2	Estimates, 1973 to 1977	28
3.6.3	Estimates, 1979 to 1981	30
4.	PROVISION OF PLASMA	30

4.1	Type of Plasma Required	30
4.2	Strategies for Obtaining Fresh Frozen Plasma	31
4.2.1	Increasing the Number of Blood Donations	31
4.2.2	Component Therapy	31
4.2.3	Eighteen Hour Plasma	32
4.2.4	Optimal Additive Solution	33
4.2.5	Plasmapheresis	33
4.2.6	Other Investigations	34
4.3	Provision of Fresh Frozen Plasma by the SNBTS	35
5.	SNBTS MANUFACTURING CAPABILITY	38
5.1	Premises for the Manufacture of Plasma Products	38
5.1.1	The Blood Products Unit	38
5.1.2	The Protein Fractionation Centre	38
5.2	Regional Blood Transfusion Centres	40
5.2.1	Glasgow & West of Scotland RTC	41
5.2.2	Edinburgh & South East Scotland RTC	41
5.3	Know-How for the Preparation of Coagulation Factor Concentrates	41
6.	BLOOD PRODUCTS FOR THE TREATMENT OF HAEMOPHILIA	42
6.1	Introduction	42
6.2	SNBTS Products	44
6.3	Commercial Products	47
7.	YIELD OF FACTOR VIII	51
7.1	Introduction	51
7.2	Factor VIII Content of Plasma	52
7.3	Optimisation of Process Conditions for the Manufacture of Factor VIII Concentrate	53
7.4	Increased Yield and Quality of Factor VIII in Cryoprecipitate by Continuous- Thawing of Plasma	53
7.5	Addition of Calcium During the Manufacture of Factor VIII Concentrate	54
7.6	Addition of Sodium Chloride During the Manufacture of Factor VIII Concentrate	55
8.	SUPPLY OF SNBTS PRODUCTS FOR HAEMOPHILIA A	56
9.	COMMERCIAL PRODUCTS IN SCOTLAND	62

9.1	Commercial Products and Their Regulatory Approval	62
9.2	1977/78 to 1982/83	63
9.3	1983/84 to 1987/88	65
9.4	1988/89 & 1989/90	65
9.5	1990/91 to 1998/99	66
10	OTHER COUNTRIES	68
10.1	England & Wales	68
10.2	Other Countries	70
11.	CONCLUSIONS	71
12.	REFERENCES	73

SUMMARY

Demand for blood and blood products increased strongly in developed countries during the 1970s as a result of medical developments, including advances in the treatment of disorders of the blood such as haemophilia. In 1975, the World Health Assembly of the World Health Organisation advised that all countries should aim to meet their medical needs for blood and blood products from within their own population, taking donations of whole blood or plasma in volumes that were considered to be safe for the donor. Donors should be motivated by altruism and should not be paid as blood from paid donors was known to cause a higher incidence of hepatitis than blood from unpaid donors. This objective, known as self-sufficiency, was based on ethical and safety considerations and was at first strongly supported in principle by successive governments of the United Kingdom. However, in 1990, the UK Government provided a definition, in which self-sufficiency was considered to have been achieved when supplies of domestically sourced products are sufficient to meet the needs of all patients whose clinicians prefer these to other available products.

Although this advice concerned a number of different blood and blood products, the greatest difficulty lay in providing adequate therapy for the treatment of haemophilia A, a serious disorder caused by a deficiency of factor VIII, a protein required for blood clotting. There were a number of reasons for this being so difficult;

- factor VIII is a fragile protein, only a small proportion of which survives the processes used for its extraction and purification,
- factor VIII is a trace constituent and must be obtained from a large number of blood donations to provide treatment sufficient for all patients,
- sophisticated, large-scale manufacturing facilities are needed to extract the fragile protein from large-volumes of blood plasma under pharmaceutical conditions,
- the high demand and low recovery meant that large volumes of plasma were needed for self-sufficiency which exceeded the normal capability of national Red Cross and Blood Transfusion Services,
- provision of the systems and facilities required was far from straightforward and depended on long-term planning,
- the demand for Factor VIII concentrate was much greater and increased more rapidly than had been estimated originally by expert bodies. As treatment became available, clinicians and patients became more exacting in their needs, first requiring home therapy and then prophylaxis regimes.

Commercial Factor VIII concentrates that were obtained by practices (i.e. paid donors with high donation frequency and volume) which did not comply with guidance from the WHO, became available during the 1970s and offered an alternative to domestic concentrates, particularly where the supply of the latter was not sufficient to meet clinical demand. As demand escalated progressively, commercial products came to supply most of the Factor VIII concentrate throughout the world. Despite virtually all countries aspiring to national self-sufficiency, few have ever achieved this objective using donations from unpaid volunteers.

In Scotland, the SNBTS supplied two types of blood product for the treatment of haemophilia A, cryoprecipitate and Factor VIII concentrate, with the concentrate being generally preferred by clinicians and by patients. Estimates of demand were agreed at meetings of SNBTS Directors and Haemophilia Directors in Scotland under the auspices of SHHD. Production levels that would achieve self-sufficiency increased steadily, doubling on average every 4 years.

If cryoprecipitate is accepted as having been suitable for the treatment of haemophilia A when there was a shortfall of concentrate, then sufficient factor VIII was available from the SNBTS to provide a volume of treatment for Scotland which was comparable on a population basis to the actual level of use in the UK, from 1975/76 to 1989/90, with the possible exception of 1982/83, when the amount supplied by the SNBTS equated to about 90% of the average level of use throughout the UK.

If cryoprecipitate is considered to have been unsuitable as an alternative to concentrate when there was a shortfall in the amount of Factor VIII concentrate, then supply from the SNBTS did not fully match the level used in the UK until 1983/84. Despite this apparent shortfall of Factor VIII concentrate, production of Factor VIII concentrate by the SNBTS exceeded the amount of concentrate used in Scotland throughout the period 1979 to 1985, except for 1980, when the amount of concentrate used clinically doubled in one year.

This performance by the SNBTS was achieved by:

- increasing the number of blood donations by over 20% from 1975-1981
- increasing the amount of fresh frozen plasma by over 4-fold from 1975-1984
- increasing the yield of factor VIII in fractionation by over 50% from 1978-1981,
- constructing a new manufacturing facility with sufficient capacity to process all of the plasma supplied, which opened in 1975.

A small proportion of the Factor VIII concentrate used in Scotland during the early 1980s was obtained from commercial suppliers. This was comparable in quantity to an amount of unused SNBTS Factor VIII concentrate which had been released for use by the SNBTS and which was being held in storage at the West of Scotland Regional Blood Transfusion Centre (WRTC) in 1984. Supplies of Factor VIII concentrate from the SNBTS were sufficiently strong thereafter to avoid commercial Factor VIII concentrate being purchased in Scotland until 1988/89, at which point finance was provided to allow the SNBTS to further increase the supply of plasma for fractionation. Some commercial Factor VIII prepared using monoclonal antibody purification continued to be purchased by Haemophilia Directors in the 1990s, as the SNBTS did not prepare a Factor VIII concentrate by this method.

1. INTRODUCTION

Self-sufficiency in the supply of blood products for England & Wales has been considered in depth in reports by the Department of Health (Department of Health, 2006[1]) and by Lord Archer of Sandwell (Archer et al, 2009[2]). Neither of these reports examined Scotland.

In Scotland, a new facility for the manufacture of plasma products for the SNBTS became operational in 1975. By the late-1970s, the SNBTS output of all products was sufficient to meet expected clinical demand, with the exception of Factor VIII concentrate for the treatment of haemophilia A (Grant, et al.1980[3]).

Some twenty different plasma products were manufactured at the Protein Fractionation Centre (PFC) (Foster, 2008[4]). Of these, Factor VIII concentrate presented the greatest challenge to the SNBTS as it was the most difficult product to manufacture and growth in demand was high. Alternative products, from commercial sources, were associated with a greater risk of infection than products supplied by the SNBTS. Therefore, these notes will focus on the provision of Factor VIII for the treatment of haemophilia A, especially in the period before safety of coagulation factor concentrates with respect to transmission of HIV and hepatitis C was achieved.

1.1. Therapeutic Proteins from Human Blood Plasma

The concept that human proteins could be extracted from blood plasma for use in medical therapies was conceived in the USA in 1940 by Edwin J Cohn (Cohn, 1948[§] Surgenor, 2002[§]). As well as laying a foundation for the provision of major plasma proteins such as albumin and immunoglobulin (antibodies) the procedures devised by Cohn for the 'fractionation' of blood plasma (Cohn et al. 1946[§]) also provided a fraction (Cohn Fraction 1) which was effective in the treatment of haemophilia.

1.2. Blood Products for the Treatment of Haemophilia

Infusions of whole blood (Emile-Weil, 1906[§]) or blood plasma (Feissley, 1924[§]) were the first medical treatments that were found to be useful in treating the disorder of haemophilia. However, the volumes needed to stop bleeding in severe haemophilia were so large that neither whole blood nor plasma was able to fully correct the haemostatic defect, causing leading medical experts to conclude *"concentrated*

preparations of A.H.G. [i.e. FVIII] *seem to provide the only practical form of therapy"* (Biggs & MacFarlane, 1957[§]).

In 1959 it was discovered that a residue which remained in the bottle following the transfusion of thawed plasma contained anti-haemophilic factor (factor VIII) activity (Pool & Robinson, 1959[§]). The factor VIII activity that was concentrated in this material, named cryoprecipitate, was able to correct the haemostatic defect in haemophilia A (Pool & Shannon, 1965[§]) and became the mainstay of haemophilia treatment in the UK from 1966 (Forbes & Prentice, 1977[§]).

At the same time, new preparations for the treatment of haemophilia, known as intermediate-purity concentrates, were emerging in the United States (Hershgold et al, 1966;[§] Johnson et al, 1967;[§]) and have been the subject of detailed reviews (Aronson, 1990;[§] Kasper et al, 1993[§]).

Intermediate-purity concentrates were derived from cryoprecipitate or a similar plasma fraction. They were more potent, defined and purified than cryoprecipitate; they could be filtered to remove bacterial contaminants and had a lower incidence of allergic reactions than cryoprecipitate. In contrast to cryoprecipitate they were also amenable to large volume manufacture compliant with good pharmaceutical manufacturing practice (GMP). The fact that they were freeze dried also made them easier, quicker and more convenient to use than cryoprecipitate, which had to be stored frozen. Crucially, they enabled patients to treat themselves at home, giving people with haemophilia access to education and employment which had not previously been possible.

Intermediate-purity concentrates of Factor VIII were developed by a number of commercial companies in the USA and in Europe and were imported into the UK from 1972 (Biggs, 1977[§]). The NHS manufacturers of plasma products in England and in Scotland also developed intermediate-purity concentrates of Factor VIII and Factor IX in the early 1970s for the treatment of haemophilia A and haemophilia B respectively.

Although the availability of these new products opened the way to improved treatment in comparison with cryoprecipitate, the new products carried cost implications. There was also a possible increase in the risk of hepatitis transmission. This was due to each batch being derived from many donations and as a result of commercial concentrates being derived from paid plasma donors in the USA, a category of donor known to have a higher prevalence of infection with hepatitis (Titmuss, 1970[5]).

In 1973, the Department of Health & Social Security (DHSS) established an Expert Group to provide advice on this matter. The terms of reference of the Expert Group were "*To advise the Department on trends in methods of treatment of haemophilia and allied conditions; and to consider possible future requirements for the treatment of the condition and the consequences for the supply of therapeutic agents*".

At its first meeting (DHSS, 1973[6]), the Expert Group confirmed that freeze dried intermediate-purity concentrates were the product of choice for the treatment of haemophilia, despite *"the theoretically increased risk of acquiring hepatitis"*, and recommended that:

- *"the UK should aim to become self-sufficient as soon as possible by increasing home* [i.e. UK] *production of freeze-dried AHG* [i.e. anti-haemophilic globulin or Factor VIII] *concentrate"*.
- *"Regional Transfusion Directors should be consulted ..... in terms of increased demands upon the Blood Transfusion Services ..... decreasing production of cryoprecipitate, increasing production of fresh-frozen plasma for fractionation and possibly increased collection of plasma by plasmapheresis"*.
- *"It was also suggested that the National Medical Director of the Scottish National Blood Transfusion Association and Mr Watt of the Edinburgh BPL (sic) should be invited to join the group"*.

2. SELF-SUFFICIENCY

2.1 Government Policy

The 1973 recommendation from the Expert Group that the UK should aim to become self-sufficient was accepted by the DHSS and was acknowledged formally on 22 January 1975 in a Parliamentary statement by Dr David Owen, the Minister of State for Health. The objective of achieving self-sufficiency in the UK was endorsed by the succeeding government on the 15 of December 1980, in an announcement to the House of Commons by Sir George Young, Under-Secretary of State for Health & Social Security.

The Department of Health has since confirmed (Department of Health, 2006[1]) that the British Government supported recommendations on national self-sufficiency from the World Health Organisation and from the Council of Europe.

2.1.1 The World Health Organisation, Recommendation WHA 28.72

On 29th May 1975 the World Health Assembly adopted Resolution WHA 28.72 on the utilization and supply of human blood and blood products (World Health Assembly, 1975[7]) which included:

- *"being aware of the higher risk of transmitting diseases when blood products have been obtained from paid rather than from voluntary donors,"*
- *"and of the harmful consequences to the health of donors of too frequent blood donations (one of the causes being remuneration),"*

and urged Member States to:

- *"promote the development of national blood services based on voluntary nonremunerated donation of blood;"*
- *"enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and of recipients of blood and blood products;"*

and requested:

- *"cooperation between countries to secure adequate supply of blood products based on voluntary donations;"*

A Group of Experts was established by the World Health Organisation (WHO) to develop this policy further. The Group met on 9-13 December 1975 in conjunction with the League of Red Cross Societies, the International Society of Blood Transfusion and the Council of Europe (World Health Organisation, 1977[8]). The final recommendations of the group included the follow points:

- *"a non-profit national blood transfusion service should rely upon voluntary unpaid donors and relate its activities to the country's need, particularly for erythrocytes. In so doing it could provide most if not all of the plasma needed to prepare albumin, coagulation factors and immunoglobulins. The use of component therapy..... , a sound logistic organization and judicious supplementary use of electrolyte solutions are essential. Plasmapheresis should only be part of a national blood transfusion programme and used to cover any deficit of plasma needed for the preparation of clinically useful derivatives. As in the case of whole blood donation, only voluntary unpaid donors should be recruited for plasmapheresis ....."*
- *"because the plasma protein which is most slowly regenerated after plasma withdrawal appears to be albumin, the interval between plasmapheresis should be long enough to allow the body content of albumin to return to normal well before the next donation. The donation of plasma by a healthy individual should*

therefore not exceed 600 ml on each occasion with a maximum of 15 litres per annum. The interval between two consecutive plasmapheresis should in general not be less than 2 weeks."

- *"as the long-term effects of repeated plasmapheresis and hyperimmunisation on the health of the donor are not well known, both retrospective and prospective controlled studies should be undertaken to identify and evaluate the health hazards that may be inherent in these procedures ……."*
- *"national health authorities should have responsibility of blood transfusion services in all countries……."*
- *"effective legislation should be enacted in all countries regulating blood donation (including the collection of plasma by plasmapheresis), processing, distribution, export and import of blood and blood products. Such legislation should take into account the medical and ethical problems involved, and protect the donors and recipients from commercial exploitation."*

2.1.2 The Council of Europe Recommendation R (80) 5.

On 30th April 1980, the Council of Europe Committee of Ministers to Member States adopted Recommendation R (80) 5 concerning blood products for the treatment of haemophiliacs (Council of Europe, 1980[9]) in which it advised governments of member states to:

- establish *" minimal criteria for the quality, packaging, labelling and control of blood products for the treatment of haemophiliacs;"*
- ensure *" that the available products are put to optimal use from a medical and socio-economic point of view;"*
- inform *" all concerned in haemophilia therapy of the problems arising from the procurement and rational use of blood components concerned in order to balance the needs and resources;"*
- reach *"as far as possible, self-sufficiency of the member states ……..both in respect of antihaemophilia products and blood plasma required for their preparation".*
- increase *" whole blood collections and the development of plasmapheresis –"*
- achieve *"the optimal use of red cell concentrates, albumin and plasma protein solutions ……."*
- limit *"use of fresh-frozen and freeze-dried plasma ……."*
- use *"frozen cryoprecipitate only when other preparations of Factor VIII of controlled potency are not available with satisfactory conditions of efficiency, safety and cost".*

- follow *"the recommendations of WHO and of the League of Red Cross Societies concerning the promotion of voluntary non-remunerated blood and plasma donations"*
- make *"special efforts ..... to reduce the risk of transmission of hepatitis ...."*
- achieve *"a balance ..... between the available resources and the justified needs of haemophiliacs".*

2.1.3 The Council of Europe Recommendation R (81) 14

On 11 September 1981, the Council of Europe Committee of Ministers to Member States adopted Recommendation R (81) 14 concerning the prevention of transmission of infectious diseases by the international transfer of blood products (Council of Europe, 1981[10]) in which it advised governments of member states:

- *".... that the transmission of infections through the international transfer of blood, its components and derivatives represents a constant health hazard for recipients....."*
- *".... that national regulations be established concerning the importation of blood, its components and derivatives with a view to limiting as fully as possible potential health hazards due to the transmission of infectious agents ....."*

2.1.4 The Council of Europe Recommendation R (83) 8.

On 23 June 1983, the Council of Europe Committee of Ministers to Member States adopted Recommendation R (83) 8 concerning the prevention of the possible transmission of AIDS to patients receiving blood or blood products (Council of Europe, 1983[11]) in which it advised governments of member states:

- *"to expose the recipient to a minimum number of donations of blood when the transfusion is of cellular and coagulation factor products,"*
- *"to achieve national self-sufficiency in the production of coagulation factor products from voluntary, non-remunerated donors,"*
- *"to avoid importation of blood plasma and coagulation factor products from countries with risk populations and from paid donors;"*
- *"...to avoid wherever possible the use of coagulation factor products prepared from large plasma pools; this is especially important for those countries where self-sufficiency in the production of such products has not yet been achieved;"*
- *"to pursue rapid and full implementation of Recommendations No. R (80) 5 and No. R (81) 14."*

Despite the strong support of the British Government (Department of Health, 2006[6]) for the 1975 WHO resolution WHA 28.72 and for the recommendations from the Council of Europe, the British Government subsequently adopted a policy that stated:

"*The principle of self-sufficiency therefore means that the supplies of domestically sourced blood products should be sufficient, both in range and quantity, to meet the needs of all patients whose clinicians prefer these to other available products".* (Acheson, 1990[12]).

With this explanation, the UK government provided a new and unique definition of self-sufficiency, such that national supplies from unpaid donors were required only where individual clinicians preferred not to use commercial products from paid donors. The date when this particular definition became UK Government policy is not known.

2.1.5 The impact of variant Creutzfeldt-Jakob Disease (vCJD)

The policy of achieving self-sufficiency within the UK ended in 1998 when, in response to concerns over a theoretical risk of vCJD being transmitted via blood products (Ludlam, 1997[§]), the Department of Health first authorised the importation of plasma for fractionation (Department of Health, 1998[13]) and then banned the manufacture of plasma products from UK-donor plasma (Department of Health, 1998[§]). In addition the Scottish Home & Health Department (SHHD) decided to fully fund the purchase of Factor VIII and Factor IX concentrates manufactured commercially using recombinant technology.

In responding to this decision, the SNBTS replaced plasma from donors in Scotland with imports from Germany and from the USA, obtaining plasma from voluntary non-remunerated donors as far as possible in order to continue to comply with the underlying principles of the WHO and the Council of Europe.

In England, the NHS Bio-Products Laboratory (BPL) replaced UK-donor plasma with paid-donor plasma provided by Life Resources Inc, a company with 24 commercial plasma collection centres in the USA, which was subsequently purchased by the UK Department of Health (Department of Health, 2002[14]) in order to safeguard supplies of plasma to BPL.

In the 12 years since the ban on UK plasma was introduced, only one potential transmission of vCJD via UK plasma products has emerged. In this case, a sample of tissue from a haemophilia A patient, with no symptoms of vCJD, and who died from other causes, tested positive for vCJD at a post-mortem examination. Although none

of the test results from 22 additional tissue samples were able to confirm the original positive result (Peden et al, 2010[15]), this has been accepted as a case of vCJD transmission (Health Protection Agency, 2009[16]).

In 2006, the devolved Scottish Government accepted a recommendation from SNBTS Directors and the Board of National Services Scotland (formerly the Common Services Agency) that the SNBTS should no longer provide Scotland with plasma products, primarily because the move to recombinant coagulation factors, the cost of importing plasma, a reduction in the use of albumin and a requirement for substantial investment in the facility led to the PFC being considered to be no longer economic (Scottish Executive, 2006[17]).

As a result of this decision, the Scottish Protein Fractionation Centre (PFC) was closed and Scotland's plasma products have since been obtained from suppliers who depend mainly on remunerated donors in the USA as a source of plasma; thereby ending Scotland's aspiration to self-sufficiency in plasma products using unpaid volunteer donors.

2.2 Policy into Practice

Achieving national self-sufficiency using local plasma from volunteer non-remunerated donors was not straightforward. A number of different plasma products had to be produced (e.g. Factor VIII concentrate, Factor IX concentrate, Albumin and a range of immunoglobulin products) to pharmaceutical standards and quality comparable to equivalent products from a number of specialist, multinational pharmaceutical companies (e.g. Alpha, Armour, Baxter, Cutter, Immuno).

Although all products had to comply with specifications established by national authorities (e.g. Committee on Safety of Medicines, National Institute for Biological Standards and Control) there were inevitable variations between products from different manufacturers, such as variations in dose size, product potency or reconstitution time.

The dilemma facing clinicians was whether to select the product they believed to have the best characteristics, perhaps Factor VIII from company A, Factor IX from company B, Albumin from company C and immunoglobulin from company D, or to restrict themselves to products from their national organisation, such as a Red Cross or Blood Transfusion Service.

The challenge facing Red Cross and Blood Transfusion Services was not only to provide a range of products which complied with national specifications but also, for each product, to match as far as possible the best characteristics of any product available commercially. Unlike commercial companies, national organisations had to achieve this whilst producing all products in quantities sufficient to treat their whole population, using only unpaid donors from within their own population and with donation volumes specified by WHO[8] and by the Council of Europe. They also lacked a team of sales and marketing representatives to promote their products and offer clinicians support for research and attendance at meetings.

Although most countries supported the 1975 resolution of the World Health Assembly and aspired to national self-sufficiency, little progress was made. Despite growth in the not-for-profit sector, increasing product demand meant that by the mid-1980s about 70% of the world's plasma products were being supplied by the commercial sector using plasma obtained predominantly from paid donors (Foster, 1994[18]). With donation volumes per donor that were unique to the USA, this is a situation which remains essentially the same today (Lamb, 2009[19]).

To understand why the vast majority of countries failed to achieve self-sufficiency using non-remunerated donors, it is necessary to consider a number of different elements that had to be addressed. These included:

2.2.1 Forecasting Product Demand

Long-term forecasting is required because most of the elements needed to achieve self-sufficiency need considerable time and resources to implement. The necessary information can only be provided by knowledgeable doctors responsible for the treatment of patients, such as haemophilia directors. Given the timescales involved, forecasts that were accurate in predicting future needs were necessary for self-sufficiency to be achieved. What was not readily predicted was how the availability of concentrates would change practice and drive up demand.

2.2.2 Forecasting Product Yield

To achieve a specified supply of product, the quantity of plasma required was determined by the yield obtained after manufacture, hence accurate estimates of product yield were needed in order to plan for the provision of suitable quantities of plasma.

2.2.3 Supply of Plasma

During the 1970s plasma for fractionation in the not-for-profit sector (e.g. Blood Transfusion Services and Red Cross organisations) was mainly obtained from donations of whole-blood which had not been used and which had 'out-dated'. This type of plasma was not suitable for the preparation of coagulation factors such as factor VIII, which were too sensitive to survive the length of time involved. Out-dated, or time-expired plasma was suitable for the preparation of albumin and normal immunoglobulin.

Only plasma which had been separated from the cellular constituents shortly after donation, and frozen quickly, was suitable for the preparation of concentrates of Factor VIII and Factor IX used in the treatment of haemophilia A and B respectively.

Plasma obtained in this manner, designated Fresh Frozen Plasma (FFP), was sometimes known as 'recovered' plasma if it was recovered from a donation of whole-blood. An alternative way of obtaining FFP, involves returning the cellular components to the donor, using sterile procedures, known as plasmapheresis. FFP obtained in this manner is known as 'source' plasma and was used predominantly by commercial manufacturers. In the USA, red cells for transfusion must be labelled if obtained from a paid donor. This policy caused the supply of red cells to be restricted to not-for-profit organisations that used unpaid donors. By contrast most plasma collection organisations obtained paid-donor plasma using the technique of plasmapheresis, with no cellular components being provided.

The frequency by which a person can donate whole-blood is limited by the time taken to recover the lost cellular constituents, resulting in donation frequency usually being restricted to two or three times per donor per annum, with typically about 0.5 litres of plasma per annum being obtained per donor.

By contrast more frequent donations of greater volume can be obtained by plasmapheresis, as the limiting factor is the time taken for the donor to synthesise plasma proteins rather than cellular constituents.

In the UK, the volume of plasma that could be obtained by plasmapheresis from a donor was restricted to 12 litres per annum. Regulations in the USA are much less stringent than elsewhere in the world and allowed up to 60 litres per annum per donor; a practice which, together with the size of population and the incentive of donor-

remuneration, enabled the USA to provide the world with most of its plasma products; a situation which continues to this day.

2.2.4 Manufacturing Capability

The preparation of plasma products is a highly specialised field of pharmaceutical manufacturing where, in contrast to the manufacture of conventional pharmaceuticals, a large number of different products are obtained from a common biological feedstock.

The complexity of both the starting material and the resultant products, as well as the multiplicity of different products, means that their preparation, known as plasma fractionation, requires considerable knowledge and expertise from a wide range of scientific and technical disciplines, as well as a close involvement with suitable medical experts.

The facilities required for the fractionation of plasma are equally complex, involving temperature controlled areas for large-scale processing ranging from -5°C to +20°C and from -40°C to +30°C for storage. Processing facilities that are hygienic, with provision for sterilisation of equipment, reagents and materials and with aseptic facilities in which products can be dispensed and sealed in their final container free from bacterial contamination are also required.

In addition to facilities for production, expertise and resources are required for Quality Control and Quality Assurance and for the maintenance of utilities, including plant for refrigeration and air-handling as well as major items of industrial pharmaceutical plant for the sterilisation of process equipment, materials and reagents and for freeze drying products. A research and development capability is also essential to assist in problem solving and to ensure that products and procedures benefit from emerging knowledge.

In the absence of a manufacturing capability, some countries (e.g. Norway) achieved self-sufficiency by arranging for the plasma from their own population to be processed elsewhere, with the resultant products being returned. It is unlikely that dedicated facilities would be available for this purpose, and therefore a risk of mixing with plasma from other sources within the manufacturing plant could not be excluded, making this option somewhat less than ideal prior to the development of virus inactivation technology.

2.3 Management Processes (Scotland)

The provision of blood products for the treatment of people with haemophilia in Scotland was considered at a number of tiers of management.

2.3.1 National Management Processes

Blood product requirements for the treatment of people with haemophilia and related policies were considered at meetings between officials of the SHHD, Haemophilia Directors and SNBTS Directors. These meetings were arranged by the SHHD and were generally held annually, sometimes with a working group to progress matters between annual meetings. No annual meetings took place in 1978, 1979, 1980 and 1982. The SNBTS also obtained information on blood product requirements for the treatment of haemophilia by attending annual meetings of the UK Haemophilia Directors, or by direct communications between the SNBTS National Medical Director and Haemophilia Directors.

Council of Europe Recommendation No. R (80) 5 was considered by Directors of the SNBTS and Haemophilia Directors in conjunction with officials of the SHHD at a meeting in January 1981. At this meeting, the SHHD chairman introduced a paper on the Council of Europe Recommendation which, according to the minute of the meeting "*...broadly set guidelines for the preparation and use of blood products for the treatment of haemophiliacs and urged member states to become self sufficient in these products. After consideration of the various recommendations in the paper members agreed that policy and practice in Scotland were consistent with this document, subject to further consideration of the recommendation on the setting up of a haemophilia register.*" (Scottish Home & Health Department, 1981[20]).

2.3.2 The SNBTS Management Processes

Statutory responsibility for the management of blood transfusion services in Scotland was assigned to the Common Services Agency (CSA) of the Scottish Health Service in 1974. A Blood Transfusion Sub-Committee was established by the CSA in 1978 and operated until 1990, at which point the post of SNBTS General Manager was established.

A meeting of SNBTS Directors was held on a quarterly basis with officials from SHHD in attendance. Additional meetings of SNBTS Directors were held from 1980 to co-ordinate activities on a national basis. Meetings of SNBTS Directors were organised and chaired by the National Medical Director. In the absence of the National Medical

Director during 1976, meetings were chaired by the Regional Director of the Glasgow Centre. The post of SNBTS National Medical Director was vacant from 1977 to 1979; during this period meetings of SNBTS Directors were chaired by the Regional Director of the Glasgow Centre (1977-1978) and by the Regional Director of the Edinburgh Centre (1978-1979).

Prior to 1982, the PFC Director acted on advice from the SNBTS National Medical Director either by direct communication or via meetings of the SNBTS Directors. In January 1982, the National Medical Director established a formal mechanism for the management of coagulation factor developments known as the Factor VIII Study Group. The Group comprised senior staff from across the SNBTS and was chaired and managed by the National Medical Director, who reported progress to the SNBTS Board and the CSA BTS sub-committee. The SNBTS Factor VIII Study Group subsequently encompassed the development of all of the SNBTS plasma products and became known as the SNBTS Product Development Group.

2.3.3 The PFC Management Processes

Prior to the creation of the SNBTS Factor VIII Study Group, the research and development strategy pursued within PFC was determined by the PFC Director in consultation with the PFC Research & Development (R&D) Manager and other senior R&D staff. R&D matters were included in topics that were considered at regular meetings of PFC Heads of Departments, which were attended by the R&D Manager and chaired by the PFC Director.

These communications continued after the creation of the Factor VIII Study Group, in order to provide advice to the PFC Director and to progress nationally agreed strategies as efficiently as possible. This was formalised in 1986 by the creation of the PFC Development Review Group (later named the PFC Development Team) chaired by the PFC R&D Manager which included the PFC Director, the PFC Quality Manager and senior PFC R&D staff.

3. FACTOR VIII DEMAND

3.1 Forecasts of Demand (United Kingdom)

In 1973, the Expert Group on the Treatment of Haemophilia advised that treatment of UK sufferers from haemophilia would require 400,000 donations per annum

(Department of Health & Social Security, 1973[6]). At the same time, a Medical Research Council (MRC) Working Party concluded "*An assessment of the total amount of factor VIII likely to be required for all types of treatment* (i.e. concentrate and cryoprecipitate) *puts the total in excess 500000 blood donations or about 40 million units of factor VIII*" and, in a further review commented that "*the estimate made in the previous report is unlikely to be excessive*" (Biggs et al, 1977[§]). The estimate that 40 million units could be obtained from 500,000 blood donations, suggests that the forecast of the 1973 Expert Group was equivalent to 32 million units per annum.

In 1977 a Working Group on Trends in the Demand for Blood Products "*noted that the commonly accepted target figure for Factor VIII was 1000 iu per annum per 1000 population*" and that it "*.... should be increased by 25%, to meet sudden demands for the emergency treatment of haemophilic patients*" and "*.... whether as concentrate alone or concentrate and cryoprecipitate was yet to be decided.*" (Department of Health & Social Security, 1977[21]).

Subsequently, in 1981, a National Blood Transfusion Service (NBTS) Working Party on plasma supplies for England & Wales noted "*Representatives of the Haemophilia Directors estimate that by the mid-1980's the annual requirement for FVIII will reach 100 M i.u. for the United Kingdom. Forecasting beyond that time could not be accurate but it was considered that by the 1990's the need for FVIII could reach 150 M i.u. per year.*" (Department of Health & Social Security, 1981[22]).

3.2. Forecasts of Demand (Scotland)

In the mid-1970s, the first National Medical Director of SNBTS noted "*The haemophilia population of Scotland is about 400*" and "*The figure of 10,000 units of factor VIII per patient per year can be accepted as a reasonable estimate for the next few years at least.*" (Jeffrey, 1976[23]). This estimate equated to a total of 4 million units of FVIII per annum for Scotland, equivalent to 0.75 units per head of population per annum.

Subsequently, in 1979, the SNBTS proposed a target of 1.8 units per head of population per annum (SNBTS, 1979[24]) then, in 1981, increased this to 2.75 units per head of population per annum by 1986, rising to 3.75 units per head of population by 1996 (Cash, 1981[25]).

3.3. Amount of Factor VIII Used in the United Kingdom

The amount of Factor VIII used each calendar year in the United Kingdom has been monitored by the UK Haemophilia Centre Doctors Organisation (HCDO) since 1969, including the source (i.e. NHS or commercial) and type (i.e. cryoprecipitate or concentrate) of treatment as well as the total consumption. Annual figures for the period 1970 – 1990 are tabled below, together with equivalent information for 1995, 2000 and 2005.

Table 1. Consumption of Factor VIII in the United Kingdom, 1970-2005

Year	Cryoppt (m iu)	Concentrate (m iu) NHS	Concentrate (m iu) Commercial	Total (m iu)	Total (iu per pop)
1970[a]	7.3	0.9	0	8.2	0.15
1971[a]	8.7	3.1	0	11.8	0.21
1972[a]	8.4	1.9	0.7	11.0	0.20
1973[a]	12.5	2.5	0.8	15.8	0.28
1974[a]	15.1	2.7	2.7	20.5	0.36
1975[a]	16.6	3.1	5.1	24.8	0.44
1976[a]	15.7	6.9	11.1	33.7	0.60
1977[a]	15.2	12.9	15.0	43.1	0.77
1978[a]	11.1	14.6	19.3	45.0	0.80
1979[a]	9.4	15.1	26.2	50.7	0.90
1980[a]	8.2	14.4	34.7	57.3	1.02
1981[a]	7.7	22.5	35.5	65.7	1.17
1982[a]	5.2	22.9	45.6	73.7	1.31
1983[a]	4.8	30.0	36.2	71.0	1.26
1984[a]	5.7	40.2	34.0	79.9	1.42
1985[a]	3.3	23.1	50.9	77.3	1.37
1986[a]	3.2	31.5	53.7	88.4	1.56
1987[a]	2.7	26.0	59.2	87.9	1.55
1988[b]	2.0	41.0	55.0	98.0	1.72
1989[b,c]	2.0	65.5	36.5	104.0	1.84
1990[b,c]	2.0	85.0	23.0	110.0	2.03
1995[b,c]	n/a	105	38	152[d]	2.62
2000[c]	n/a	n/a	n/a	210[d]	3.57
2005[c]	n/a	8.5	11.5	283[d]	4.73

[a] from Re-Amended Main Statement of Claim in HIV haemophilia litigation, para. 31 (Snape,1999[53]).

[b] estimated from Rizza at al, 2001.[§]

[c] estimated from UK HCDO Annual Report 2006.

[d] includes recombinant FVIII

A number of points can be noted:

- an almost continual year-on-year increase in the treatment with Factor VIII over a 35-year period,
- a reduction in the use of cryoprecipitate from 1977,
- a marked use of imported commercial concentrates from 1974,
- a year-by-year increase in use of commercial concentrates from 1974 to 1982,
- a decline in the use of commercial concentrates in 1983 and 1984,
- a substantial reduction in the supply of NHS Factor VIII concentrate in 1985 which was associated with the introduction of heat treated Factor VIII (8Y) at BPL (Elstree), as the yield of factor VIII was reduced by about 30% (i.e. from 225 iu per Kg plasma to 160 iu per Kg plasma) in addition to a cessation in the supply of Factor VIII concentrate from BPL for about four months prior to 8Y being introduced,
- a marked increase in the use of commercial concentrates in 1985, reaching a peak of almost 60 m iu in 1987,
- a marked increase in the supply of NHS Factor VIII concentrate in 1989 & 1990 associated with an increase in output from a new BPL facility at Elstree,
- A marked decrease in the amount of commercial Factor VIII concentrate in 1989 & 1990, although the quantities used remained significant.

A reduction in the use of cryoprecipitate was consistent with guidance in the 1970s from expert advisory committees and UK Haemophilia Directors (BMJ Editorial, 1978[26]), whilst importation of commercial Factor VIII concentrates was recommended by Haemophilia Directors (Biggs, 1974;[§] Ingram, 1974;[§] Blackburn, 1974,[§] Dormandy,1974;[§] Jones, 1974[§]) and by the UK Haemophilia Society (Prothero,1974[§]).

3.4. Amount of Factor VIII Used in Scotland

The UK HCDO does not normally provide a breakdown of the treatment of people with haemophilia in different parts of the UK. However the SNBTS was provided with data

for Scotland for the period 1978-1984 in order to assist with forward planning (Rizza & Spooner, 1985[27]).

Table 2. Consumption of Factor VIII in Scotland, 1978-1984

Year	Cryoppt (m iu)	Concentrate (m iu) NHS	Commercial	Total (m iu)	Total (iu per head pop.)
1978	1.35	1.66	0.45	3.46	0.66
1979	1.24	1.76	0.72	3.72	0.71
1980	1.48	3.84	0.97	6.29	1.21
1981	0.90	3.48	1.24	5.62	1.08
1982	0.57	4.79	0.55	5.91	1.14
1983	0.33	5.86	0.38	6.57	1.27
1984	0.30	6.85	0.03	7.18	1.40

These figures show:

- an almost year-on-year increase in the amount of Factor VIII used
- a reduction in the use of cryoprecipitate from 1981
- some use of commercial concentrates.
-

3.5. Comparison Between Scotland and the Rest of the UK

A direct comparison between Scotland and the rest of the UK can be made for the period 1978-1984 as specific data from HCDO on the use of Factor VIII in Scotland are held by the SNBTS. This period is of particular interest as it encompasses the emergence of the epidemic of AIDS and extends to the point when heat treated Factor VIII concentrates began to be introduced in the UK.

The respective amounts of Factor VIII used per million population, together with the proportion provided from NHS sources (i.e. the SNBTS), inclusive of cryoprecipitate, are given in Table 3 below.

Table 3. Comparison Between Scotland and the Rest of the UK on the Amount of Factor VIII Used and its Origin in the Period 1978-1984

Year	Total FVIII (iu per pop)[a]		Proportion from NHS (%)[a]	
	Scotland	UK (excl. Scot)	Scotland	UK (excl. Scotland)
1978	0.66	0.81	87.0	54.6
1979	0.71	0.92	80.6	45.8
1980	1.21	1.00	84.6	33.9
1981	1.08	1.17	77.9	43.0
1982	1.14	1.32	90.7	33.5
1983	1.27	1.26	94.2	44.4
1984	1.40	1.42	99.6	55.5

[a] inclusive of cryoprecipitate

For this particular period, the total amount of factor VIII used to treat haemophilia was 7.5 iu per head of population in Scotland and 7.9 iu per head of population in the rest of the UK, indicating that the overall amount of treatment in Scotland was about 5% lower than the average for rest of the UK.

The difference in the origin of Factor VIII was more substantial, with 88% used in Scotland being obtained from the NHS (i.e. the SNBTS) compared with 44% in the rest of the UK and with 12% and 56% being imported from commercial sources respectively.

3.6 Accuracy of Forecasts

3.6.1 Long Term Planning

Long term planning is needed to create the infrastructure required to deliver national self-sufficiency using unpaid volunteer donors. The accuracy of the forecasts used for planning purposes in the UK is summarised Table 4, where the forecasts that were made are compared to the actual outcome.

Table 4. Forecasts of Factor VIII Requirement Compared with Actual Usage

Year	Source of Forecast	Forecast of FVIII Use	Forecast Exceeded
UK			
1973	DHSS Expert Group	0.6 m iu per 10^6 pop.	1977[a]
1973	MRC Working Party	0.7 m iu per 10^6 pop.	1977[a]
1977	DHSS Working Group	1.2 m iu per 10^6 pop.	1982[a]

Year	Source of Forecast	Forecast of FVIII Use	Forecast Exceeded
1981	Haemophilia Directors	1.8 m iu per 10^6 pop. (by 1985)	1990[a]
1981	Haemophilia Directors	2.6 m iu per 10^6 pop. (by 1990)	1996[a]
Scotland			
1975	SNBTS (H C Jeffrey)	0.8 m iu per 10^6 pop. ("*for the next few years at least*")	1980[b]
1979	SNBTS (J D Cash)	1.8 m iu per 10^6 pop.	1989[a]
1981	SNBTS (J D Cash)	2.7 m iu per 10^6 pop. (by 1986)	1997[a]
1981	SNBTS (J D Cash)	3.7 m iu per 10^6 pop. (by 1996)	2002[a]

[a] based on UK usage reported by UK Haemophilia Centre Directors; inclusive of cryoprecipitate, NHS concentrates and commercial concentrates of plasma and recombinant origin.

[b] based on usage in Scotland according to HCDO.

3.6.2 Estimates, 1973 to 1977

It can be seen that the first set of estimates, either for the UK or for Scotland, failed to anticipate long-term growth in use. Although data on the actual use of Factor VIII were collected annually by the UK HCDO, this was retrospective and only usually available some ten months later. At a time of strong growth in usage, reliance on these data could be misleading. This is illustrated by an editorial in the British Medical Journal (British Medical Journal Editorial, 1978[26]), published in November 1978, which indicated that UK self-sufficiency could be achieved with 40 million iu of Factor VIII. From data provided retrospectively by the HCDO (Table 1), it can be seen that at the time this opinion was published, the actual consumption of Factor VIII in the UK had already reached 45 million iu and was continuing to rise year-on-year.

To calculate the amount of plasma required it was necessary to know the yield of product derived. For example, the MRC Working Party (Biggs et al, 1974[28]) assumed a yield for Factor VIII concentrate of 37% (i.e. 370 iu factor VIII activity per litre of plasma) based on data from the Plasma Fractionation Laboratory (PFL) in Oxford, whilst Jeffrey (1976[23]) in Scotland assumed a yield of 40%.

The actual yield of Factor VIII concentrate in routine manufacture was much less than had been assumed, with the result that the estimates of the amount of plasma to be collected and the processing capacity needed were both about half of what was required before growth in the use of factor VIII which had not been anticipated, was taken into consideration.

There were two principal reasons for the over-estimation of yield. The first was that the original estimates were based on early experience of preparing Factor VIII concentrate at a relatively small-scale, when assay methods for the measurement of factor VIII activity were at an early stage of development and difficulties of large-scale manufacture were not well appreciated. For example, poor stability of factor VIII activity meant that there was a greater loss during the additional time needed to process larger volumes as output was scaled-up.

The second reason, was a change to the method (assay) used in the UK by which the activity of factor VIII was measured. This change was introduced by the National Institute for Biological Standards and Control (NIBSC) in December 1976 in order to increase agreement between different laboratories (Kirkwood et al, 1977[29]). Although a number of modifications were made to the assay, the most significant was a change in the reference material used to calibrate the amount of factor VIII activity, with a national standard composed of freeze dried plasma being replaced by a national standard composed of Factor VIII concentrate. At the SNBTS these changes were associated with an apparent yield reduction of 14% (Foster & Dickson, 1980[30]) whilst in England a reduction of 22% was observed (Rizza & Spooner, 1977[31]).

The net effect at the SNBTS was that instead of a yield of 40% assumed by Jeffrey (1976[23]) the overall routine yield by 1976/77 was only 20% (inclusive of rejected batches and removal of samples for quality control) falling to 15% in 1977/78 (Foster & Dickson, 1980[30]) when the full impact of the change in assay procedure was experienced. This resulted in the amount of plasma needed to meet the target output of Factor VIII being increased 2.6-fold. As the target output was too low, the wrong yield assumption amplified the error considerably.

3.6.3 Estimates, 1979 to 1981

For Scotland, the main consequence was that the demand predicted by the SNBTS in 1975 was exceeded in 1980 and the demand predicted by the DHSS Trends Working Party in 1977 was exceeded in 1982. Although the SNBTS revised its targets in December 1979 it was a number of years before the continuing growth in demand for concentrate was met.

The estimates of 1979 and 1981 from the UK Haemophilia Directors and from the SNBTS were more accurate than the earlier estimates in that both predicted continued

growth in usage over a long period of time. However, in both cases the actual rate of growth was much slower than predicted.

4. PROVISION OF PLASMA

4.1. Type of Plasma Required

Three different types of plasma were supplied for the manufacture of plasma products:

- hyperimmune plasma, collected from donors with a high level of a particular antibody,
- time-expired plasma, recovered from donations of whole blood or plasma which had not been used clinically and which were 'time-expired',
- fresh frozen plasma, obtained either from donations of whole blood or by plasmapheresis and frozen within a few hours of donation.

Of these, only fresh frozen plasma (FFP) was suitable for the preparation of coagulation factors used in the treatment of haemophilia, as the proteins concerned are not preserved sufficiently in plasma recovered from donations of whole-blood which had time-expired. Hyperimmune plasma was not used for the preparation of coagulation factors, either because unwanted antibody (e.g. anti-D immunoglobulin) would co-purify with factor VIII or because the specific antibody concerned was a response to an infection (e.g. hepatitis B). Therefore, to meet the growing demand for plasma products for the treatment of haemophilia, it was necessary for the SNBTS to provide increased quantities of FFP.

4.2. Strategies for Obtaining Fresh Frozen Plasma

There are a number of strategies for increasing the collection of FFP.

4.2.1 Increasing the Number of Blood Donations

Only a small minority of a population are prepared to donate their blood voluntarily without payment. Considerable effort is therefore required to persuade more people to donate blood. In 1974/75, the SNBTS obtained 233,485 blood donations, equivalent to a donation rate in Scotland of 44.6 per 1000 population per annum. The success of efforts to increase the number of donors since 1974/75 is illustrated in Table 5 below.

Table 5. Number of Useable Whole-Blood Donations Obtained by the SNBTS

Year	Number of Useable Donations	Number of Useable Donations per 1000 Population	% Increase from 1974/75
1975/76	247,685	47.3	6.0
1980/81	282,312	54.3	21.7
1986/87	301,259	58.9	32.1
1991/92	314,982	61.9	38.8
1996/97	269,861	52.8	18.4

It can be seen that a 20% increase had been achieved by 1980/81, rising to over 30% by 1986/87. The higher level of 1991/92 was due to an increase in new donors whose motivation was to support British Forces involved in the Gulf War.

4.2.2 Component Therapy

The essence of component therapy is to give the patient only that part of the blood that they lack. Traditionally blood transfusion involved the transfusion of whole-blood. In this situation a patient who required treatment with red cells also received plasma, which was not necessary for their treatment. By separating the red cells from the plasma it became possible to provide red cells for treatment and to supply plasma for the preparation of Factor VIII and other plasma products, such as albumin, immunoglobulin and Factor IX concentrate.

The development of interconnected plastic bags for this purpose enabled the separation to be performed aseptically in a closed system (Gibson, et al. 1960[32]). The use of plastic bags instead of glass bottles also made it easier to freeze plasma to preserve temperature sensitive constituents, such as factor VIII (Vallet, 1973[33]).

The SNBTS began to provide red cells for transfusion in 1960 (Cumming et al, 1965[§]) and by 1975 some 35% of Scotland's donations were processed to separate red cells from plasma (Jeffrey, 1976[23]). In order to meet the growing demand for Factor VIII concentrate a concerted effort was subsequently made by the SNBTS to encourage hospital doctors to always use red cell concentrates instead of whole-blood. This required changes to established clinical practice in hospitals throughout Scotland. Eventually the SNBTS ceased to supply whole-blood routinely, only issuing red cell concentrates even when whole-blood was requested.

Similarly, for many years the SNBTS supplied freeze dried plasma for the treatment of injuries, as commercial albumin was regarded as too expensive to purchase. For example, 6,000 litres of plasma were used by the SNBTS in 1973/74 for the preparation of freeze dried plasma (Jeffrey, 1976[23]). However, once the new SNBTS Protein Fractionation Centre (PFC) became operational in the mid-1970s sufficient albumin was produced (Grant et al, 1980[3]) to enable the preparation of freeze dried plasma to be discontinued, making this plasma available for the preparation of factor VIII as well as factor IX, albumin and immunoglobulin. The freeze drying plant at Glasgow was subsequently used for the preparation of freeze dried cryoprecipitate but was closed following an inspection in 1980 at which it was considered unable to attain the standard of good pharmaceutical manufacturing practice (GMP) then required by the UK Medicines Inspectorate

4.2.3 Eighteen Hour Plasma

Fresh Frozen Plasma is specified as plasma which has been frozen within 6 hours of donation and was designated as suitable for the preparation of Factor VIII concentrate (World Health Organisation, 1978[34]). However, a time limit of 6 hours could be a significant constraint when donations are collected in the evening and/or at locations far removed from the processing laboratories. To overcome this difficulty the SNBTS examined whether or not plasma frozen within 18 hours of donation would be suitable for the preparation of Factor VIII concentrate.

Although the yield of factor VIII activity was almost 15% lower than that obtained with 6 hour FFP, (Foster & Dickson, 1980[30]) the final product met the established specifications for Factor VIII concentrate. This made it possible to hold whole-blood donations overnight to perform the separation the following day without the plasma being classified as 'time-expired'. Consequently, 18 hour FFP was introduced routinely by the SNBTS in 1975 and enabled the supply of plasma for the preparation of Factor VIII concentrate to be increased by about 30%.

4.2.4 Optimal Additive Solution

Red cell concentrates that are very viscous (i.e. thick) may not be suitable for transfusion. Therefore, to avoid this problem, the amount of plasma removed was typically limited to about 200 mL per donation. A solution of additives for the suspension of red cells was devised in Sweden (Högman, et al. 1981[35]) which allowed more plasma to be removed. Use of this Optimal Additive Solution (OAS) enabled the volume of plasma recovered per donation to be increased by about 30%.

A study of the use of OAS was proposed by the National Medical Director of the SNBTS (Cash, 1982[36]) and it was introduced in Edinburgh in the early-1980s and throughout the SNBTS in 1989.

4.2.5 Plasmapheresis

In the technique of plasmapheresis, whole-blood is drawn from a donor, centrifuged to sediment the cellular constituents from the plasma, then the plasma supernatant is removed and the red cells returned to the donor. As the body can replace plasma proteins much more quickly than cells, plasmapheresis can be repeated weekly for many weeks without causing anaemia in the donor.

The extent to which donors can be subjected to plasmapheresis varies from country to country. The USA has the most generous provisions, allowing up to 60 litres per annum per donor, whereas a maximum of about 12 litres per donor per annum is permitted in the UK.

Only about 0.4 litres of plasma is obtained per annum from a donor of whole-blood who donates on average 1.6-times a year, making a donor of whole-blood in the UK some 30-times less productive than a plasmapheresis donor in the UK and 150-times less productive than a commercial plasma donor in the USA.

As well as offering a much higher degree of productivity per donor, plasmapheresis also avoids wastage of red cells when the need for plasma is greater. However, the donation takes longer to obtain and requires specialist facilities and equipment, which are not inexpensive.

In Scotland this was appreciated by the SNBTS, and in 1976 the National Medical Director wrote "*Plasmapheresis is time-consuming for both donor and operator and involves expensive equipment; it is not generally used to obtain normal plasma in this country. The time may come, however, when the requirements for plasma for fractionation considerably exceed the demand for red cells and the regular use of plasmapheresis on a modified scale in a proportion of normal donors will have to be considered.*" (Jeffrey, 1976[23]).

In the early 1980s automated systems became available for the collection of plasma by plasmapheresis and a study of this technology by the SNBTS was proposed (Cash,

1982[36]). Although these studies were completed, funding for the routine collection of normal plasma by plasmapheresis was not available to the SNBTS until 1990.

4.2.6 Other Investigations

A number of other avenues were explored to obtain additional plasma for the preparation of Factor VIII concentrate; these included:

- a proposal in 1979, from Mr Watt, to import plasma from unpaid donors that was surplus to the needs of the Community Blood Center, Kansas was not supported by Medicines Division at the DHSS. Although plasma from Kansas was not used to manufacture Factor VIII concentrate for clinical use, it was utilised to support R&D at PFC thereby enabling more plasma from Scotland to be assigned to the production of Factor VIII concentrate for clinical use.
- the preparation of Factor VIII concentrate from the supernatant (cryosupernatant) which remained after the preparation of cryoprecipitate at RTCs and which contained residual factor VIII activity; an approach that was discontinued after Haemophilia Directors advised that the factor VIII potency of trial batches was too low
- the preparation of cryoprecipitate at RTCs using a thaw-syphon technique (Mason, 1978[37]) to increase yield and thereby release additional plasma for fractionation; an approach which proved to be unsuccessful in routine application, despite promising results from R&D studies (Prowse & McGill, 1979;[38] Mason, et al. 1981[39]).

4.3. Provision of Fresh Frozen Plasma by the SNBTS

As a result of these strategies, the amount of FFP supplied by SNBTS increased greatly from 1974/75. This is illustrated in Table 6 below, where the quantities of FFP used to prepare cryoprecipitate and Factor VIII concentrate are given as well as the total quantity of FFP provided for each financial year from 1974/75 to 1997/98, when SNBTS ceased to use SNBTS-donor plasma for the preparation of Factor VIII concentrate and other fractionated products.

Table 6. Amount of Fresh Frozen Plasma Collected by the SNBTS

Year[a]	Amount of Fresh Frozen Plasma (Kg)[b]			Total FFP
	To Cryoprecipitate[c]	To Concentrate[d]	Total	Kg per 10^6 pop.
1974/75	7,010	3,114	10,124	1,934

Year[a]	Amount of Fresh Frozen Plasma (Kg)[b]			Total FFP
	To Cryoprecipitate[c]	To Concentrate[d]	Total	Kg per 10^6 pop.
1975/76	8,497	5,514	14,011	2,677
1976/77	5,471	10,176	15,647	2,990
1977/78	6,216	12,563	18,779	3,588
1978/79	6,752	12,973	19,725	3,780
1979/80	6,477	17,416	23,893	4,593
1980/81	5,498	21,597	27,095	5,213
1981/82	3,341	30,463	33,804	6,522
1982/83	2,963	35,509	38,472	7,446
1983/84	2,520	42,423	44,943	8,717
1984/85	2,767	41,434	44,201	8,593
1985/86	3,633	40,740	44,373	8,653
1986/87	2,677	44,105	46,782	9,142
1987/88	2,915	42,597	45,512	8,913
1988/89	2,341	49,011	51,352	10,099
1989/90	2,480	59,995	62,475	12,286
1990/91	1,720[e]	70,953	72,673	14,292
1991/92	2,110[e]	73,585[f]	75,695	14,886
1992/93	2,030[e]	67,321[f]	69,351	13,443
1993/94	2,290[e]	71,208[f]	73,498	14,454
1994/95	2,390[e]	73,273[f]	75,663	14,850
1995/96	2,390[e]	72,495[f]	74,885	14,666
1996/97	2,320[e]	67,283[f]	69,603	13,632
1997/98[g]	2,560[e]	63,771[f]	66,331	13,019

a financial year from 1st April to 31st March

b from statistics tabled at meetings of SNBTS Directors; excludes clinical FFP.

c assumes one unit of cryoprecipitate is obtained from 0.2 Kg plasma; cryoprecipitate was used to treat haemophilia A and other disorders of haemostasis

d after deduction of the weight of plastic, which accounted for 6% of the weight.

e mainly for treatment of coagulation disorders other than haemophilia.

f inclusive of plasma collected by plasmapheresis.

g preparation of fractionated plasma products from UK-plasma was banned in 1998.

These data demonstrate both the magnitude of the year-on-year increase in the quantity of plasma obtained and the increasing emphasis on the preparation of Factor VIII concentrate at the SNBTS Protein Fractionation Centre (PFC) instead of cryoprecipitate at Regional Transfusion Centres. This is illustrated in Table 7 below.

Table 7. Annual Trends in the Supply of Fresh Frozen Plasma by the SNBTS

Year	Annual Increase in Total FFP (%)	Annual Increase in FFP to PFC (%)
1975/76	38.4	77.1
1976/77	11.7	84.5
1977/78	20.0	23.5
1978/79	5.0	3.3
1979/80	21.1	34.2
1980/81	13.4	24.0
1981/82	24.8	41.0
1982/83	13.8	16.6
1983/84	16.8	19.5
1984/85	-1.6	-2.3
1985/86	0.4	-1.7
1986/87	5.4	8.3
1987/88	-2.7	-3.4
1988/89	12.8	15.1
1989/90	21.7	22.4
1990/91	17.5	18.3
1991/92	3.6	3.7
1992/93	-9.2	-9.1
1993/94	5.6	5.8
1994/95	2.8	2.9
1995/96	-1.0	-1.1
1996/97	-6.9	-7.2
1997/98	-5.0	-5.2

There were substantial increases in the amount of FFP for the preparation of Factor VIII concentrate:

- during 1975-1978, following the opening of the new PFC facility and an increase in the use of red cell concentrates,
- during 1979-1984, by an increased use of red cell concentrates, a reduction in the use of cryoprecipitate, and the introduction of OAS at the Edinburgh RTC .
- during 1988-91, by introduction of OAS at other RTCs, the introduction of plasmapheresis for the collection of normal plasma and an increased number of blood donations associated with the Gulf War.

5. SNBTS MANUFACTURING CAPABILITY

5.1 Premises for the Manufacture of Plasma Products

5.1.1 The Blood Products Unit (1950-1974)

Under the Scottish National Blood Transfusion Association (SNBTA) a facility for the preparation of blood plasma products in Scotland, known originally as the Blood Products Unit (BPU), was established at the Royal Infirmary of Edinburgh in the 1950s under the management of the Edinburgh & South East Scotland Blood Transfusion Centre. The first plasma products prepared here included immunoglobulin for the prevention of measles, and Cohn Fraction I for the treatment of haemophilia (Cumming et al, 1965;[§] Foster, 2008[4]).

By the late-1960s the range of products supplied by the SNBTA BPU had expanded to include albumin for the treatment of injuries, specific immunoglobulins for the prevention of rhesus disease of the newborn, for the prevention of infection with rubella (German measles), for the treatment of tetanus infection and for the prevention of smallpox and a Prothrombin Complex concentrate for the treatment of haemophilia B (Watt et al, 1972[40]). Intermediate-purity concentrates of Factor VIII and Factor IX were developed in the early 1970s (Foster, 2008[4])

The growing importance of plasma products to modern medicine was recognised during the 1960s; growth in demand was anticipated and planning of a larger-scale pharmaceutical facility was begun in 1965. It was envisaged that this new Centre would have the capability of meeting not only the future needs of Scotland for plasma products, but also those of northern England (Foster, 2001[41]).

5.1.2 The Protein Fractionation Centre (1975-2008)

A new SNBTS facility for the manufacture of plasma products was opened in 1975, on a dedicated site, situated at Liberton in south Edinburgh. Although designed to process 1,500 litres of plasma per week, the centre was initially equipped and financed to process up to 1,000 litres per week, pending agreement on processing plasma from England.

Although production trials using plasma from England & Wales were completed successfully at the PFC (Cash, 1982[42]), the DHSS decided not to utilise the PFC for the fractionation of plasma from England & Wales as this was judged, wrongly, to be more expensive than the construction of a larger new facility at the BPL (Department of

Health & Social Security, 1982[43]). The DHSS instead proposed that the fractionation of plasma for Northern Ireland be transferred from the BPL to the PFC. Consequently, the PFC began the fractionation of plasma from Northern Ireland in 1982.

The construction of the PFC was based on a building design which had been essentially completed in 1970. Government guidance on the construction of, and operation of facilities for, the manufacture of pharmaceuticals in the UK was first published in 1971 (DHSS, 1971[44]) and was substantially revised in 1977 (DHSS, 1977[45]).

A number of modifications were subsequently made to the PFC facility in order to comply with the most recent Medicines Control Agency (MCA) guidance and to increase the capability of the centre, including:

- internal modifications during the early 1980s to re-route process streams and to enhance the environment,
- construction of an extension, with specialist laboratories for microbiology, virology and a pilot-scale research laboratory, which was completed in 1982/83,
- construction of an extension in the early 1990s, with increased capacity for cold storage, aseptic dispensing, product inspection, labelling and packaging, product storage, engineering workshops, information technology and general warehousing.

Further equipment was installed to increase processing capacity, including:

- new equipment in 1981 for thawing plasma for the preparation of Factor VIII concentrate (Foster, et al. 1982[46]),
- new freeze driers in 1979 and in 1983 for the processing of coagulation factor concentrates,
- new equipment in the mid-1980s with increased capacity for the fractionation of plasma for the preparation of albumin and immunoglobulin (Foster, et al, 1986[47]),
- specialist ovens in mid-1985 for controlled, dry heat treatment of coagulation factor concentrates,
- automated equipment in 1987 for the formulation of albumin products,
- new equipment in the early 1990s for the preparation of high-purity Factor VIII concentrate, including equipment specially designed for virus inactivation by solvent/detergent treatment,
- new production equipment in 1998, to replace items potentially contaminated with the agent responsible for vCJD and which were not suitable for decontamination.

The PFC closed in 2008.

5.2 Regional Blood Transfusion Centres

Responsibility for the recruitment and selection of donors, the collection and testing of donations, the separation and storage of plasma for fractionation and the preparation of cryoprecipitate lay with Regional Blood Transfusion Centres (RTCs). There are five RTCs located throughout Scotland, viz:

- Aberdeen & North East Scotland, based at Forresterhill Hospital, Aberdeen,
- Dundee & East Scotland, Based at Ninewells Hospital Dundee,
- Edinburgh & South East Scotland, based at the Royal Infirmary of Edinburgh,
- Glasgow & West of Scotland, based at Law Hospital, Carluke (until 2001),
- Inverness & Northern Scotland, based at Raigmore Hospital, Inverness.

All of these RTCs were situated in established hospital premises whose development was under the management of the relevant regional Health Board.

The requirement for increased quantities of FFP to meet the amount estimated to achieve self-sufficiency increased the workload of these RTCs considerably. This is illustrated in Table 8 below, where the quantity of FFP prepared at each RTC is given for the years 1974/75, 1978/79 and 1983/84.

Table 8. Fresh Frozen Plasma Provided by Regional Transfusion Centres,1975-84

RTC	Quantity of Fresh Frozen Plasma, Kg (%)[a]		
	1974/75	**1978/79**	**1983/84**
Aberdeen	228 (2)	1,308 (6)	3,114 (6)
Dundee	379 (4)	1,129 (6)	2,912 (6)
Edinburgh	3,203 (31)	5,602 (27)	13,389 (26)
Glasgow	5,373 (52)	11,000 (54)	28,525 (56)
Inverness	1,140 (11)	1,514 (7)	3,077 (6)
All	10,323 (100)	20,553 (100)	51,077 (100)

[a] inclusive of FFP for cryoprecipitate

It can be seen that about 80% of the FFP was provided by the RTCs of Edinburgh and Glasgow combined, therefore it is these centres where the greatest increase in workload was experienced.

5.2.1 Glasgow & West of Scotland RTC

Glasgow & West of Scotland RTC was situated at Law Hospital at Carluke, Lanarkshire, which opened in 1939 and comprised a large number of prefabricated buildings in an open rural location. The RTC was sited in a detached, dedicated building complex at the boundary of the site, with room for limited development without interfering with any of the hospital premises. The Glasgow RTC re-located in 2001 to newly constructed premises at Gartnavel Hospital, Glasgow.

5.2.2 Edinburgh & South East Scotland RTC

The Edinburgh & South East Scotland RTC was situated at the Royal Infirmary of Edinburgh (RIE), Lauriston Place, Edinburgh. Although the main hospital dated from 1879, new premises which integrated with the established building were provided for the Edinburgh RTC in 1950. Plans to modernise the RIE were under consideration for many years (a new hospital eventually opening at Little France, Edinburgh in 2003). In order to undertake its increased workload during this period the Edinburgh RTC utilised a number of different premises owned by Lothian Health Board, in addition to the main premises at RIE, namely:

- buildings in Archibald Place adjacent to the main RIE,
- the area within the main RTC which was vacated when the manufacture of plasma products was re-located to PFC at Liberton, Edinburgh in 1975,
- Livingstone House (formerly Livingston Memorial Hospital), Cowgate, Edinburgh,
- facilities in phase I of the new RIE, Lauriston Place, Edinburgh
- release of space for routine activities by the purchase of property at Bristo Place, Edinburgh, for the establishment of an SNBTS R&D laboratory.

5.3 Know-How for the Preparation of SNBTS Coagulation Factor Concentrates

The development of the first Factor VIII concentrate by the SNBTS (Cohn Fraction I) was based on information obtained from the laboratory of Dr Cohn in the early 1950's by Dr Drummond Ellis, head of the SNBTS BPU. Dr Ellis subsequently joined BPL (Elstree) and was replaced at the SNBTS BPU by Mr John G Watt in 1967.

A chance meeting in 1966, in Australia, between Mr John G Watt (soon to be appointed head of the SNBTA BPU/PFC) and Dr Alan J Johnson, a leading USA academic expert in the preparation of coagulation factors, resulted in advice being provided to the PFC by Dr Johnson on the preparation of intermediate-purity concentrates of Factor VIII and Factor IX, with the preparation of the former being based on methodology devised by Dr Johnson (Newman, et al. 1971[§]).

In addition to on-going communications with Dr Johnson and his colleagues at New York University Medical Center (NYU), the R&D staff of PFC and SNBTS obtained specialist knowledge by a number of routes, including:

- undertaking their own R&D,
- communicating with other plasma fractionation organisations, especially
  - BPL (Elstree) and PFL (Oxford), England,
  - Commonwealth Serum Laboratories, Melbourne,
  - Central Laboratory of the Netherlands Red Cross, Amsterdam,
  - Cutter Laboratories (Bayer), USA,
  - Regional Transfusion Centre at Lille, France (with SNBTS methods for the preparation of high-purity concentrates of Factor VIII and Factor IX being based on methods devised at Lille RTC).
- attending relevant symposia and conferences,
- searching and reading relevant medical and scientific journals,
- interacting with university researchers including the sponsorship of PhD students,
- interacting with relevant experts at haemophilia centres,
- interacting with relevant experts at the UK National Institute for Biological Standards & Control.

6. BLOOD PRODUCTS FOR THE TREATMENT OF HAEMOPHILIA

6.1. Introduction

People with haemophilia lack a specific protein that is essential for blood to clot properly. There are two types of haemophilia, designated A and B respectively, with the former being due to an absence of the protein factor VIII and the latter to the absence of the protein factor IX. In a similar disorder of coagulation known as von Willebrand's disease (vWD) the missing protein is known as the von Willebrand factor (vWF).

In each of these disorders, replacement of the missing protein enables blood to clot normally. However the level of these proteins in normal blood or plasma is too low to raise the level in the patient to that needed to control bleeding. Proper treatment of these disorders has only been possible using blood products in which the necessary protein has been extracted from blood plasma donations and concentrated by processing to obtain a pharmaceutical product suitable for administration.

Generally the more concentrated or potent the product the faster the level can be raised in the patient which, in an emergency, can be critical. Normally, the more pure the product (expressed as iu of factor activity per mg protein) the easier it is to increase the product potency (expressed as iu of factor activity per ml of injection).

In the UK, the composition of Factor VIII concentrate for the treatment of people with haemophilia is specified in the British Pharmacopœia. For example, in December 1980 it was specified that the resulting solution should "*contain not less than 3.0 Units per ml and not less than 0.1 Units per mg of protein*" (British Pharmacopœia, 1980[48]) values that were increased in 1981 to "*not less than 6.0 Units per ml and not less than 0.2 Units per mg*" (British Pharmacopœia, 1981[49]).

However, additional processing needed to increase purity causes a reduction in yield (expressed as iu factor per litre plasma). For manufacturers who were aiming for national self-sufficiency, where yield was paramount, it was necessary to find a suitable balance between yield and purity. By contrast, for those manufacturers who were not aiming for self-sufficiency the balance between yield and purity was a commercial marketing consideration. Consequently, commercial products often tended to be somewhat more concentrated and more potent than those prepared by national manufacturers.

Subsequently, knowledge was gained which could be used to either increase yield or to allow additional processing to be undertaken without a large reduction in yield. This coincided with developments in virus inactivation technology and was used to introduce this new technology without substantial loss of yield.

Technologies for the preparation of very highly purified concentrates of coagulation factors were devised in the late-1980s and products of this type became available from the early 1990s, however further yield penalties were incurred such that additional FFP was required to maintain output.
The various types of blood products which have been used in the UK for the treatment of people with haemophilia are classified on this basis in Table 9

Table 9. Different Types of Blood Product Used in the Treatment of Haemophilia A

Purity	Product Type	Specific Activity[a] (iu per mg protein)

Purity	Product Type	Specific Activity[a] (iu per mg protein)
Very low purity	Plasma	0.02
Low purity	Cohn Fraction I	0.10
	Cryoprecipitate	0.20
Intermediate Purity	NHS (e.g. NY, Z8,8A, HL, CRV)	0.50 to 1.0
	Commercial	0.50 to 1.50
High Purity	NHS (e.g. 8Y)	2.0 to 5.0
	Commercial	2.0 to 8.0
Very High Purity	NHS (e.g. Liberate, Replenate)	100 to 2000[b]
	Commercial	50 to 3000[b]

[a] typical average value

[b] *discounting albumin added as a stabiliser (about 10 IU per mg otherwise).*

As the concept of purity has changed over time it is necessary to use the measured specific activity of any given product to establish the correct classification of purity.

6.2. SNBTS Products

A preparation of Cohn Fraction I (Cumming, et al. 1965[§]) was introduced by the SNBTS (then the Scottish National Blood Transfusion Association) in 1956 for the treatment of haemophilia and was the first concentrated form of factor VIII (AHG) available in Scotland. An early Factor IX concentrate for the treatment of haemophilia B, containing factors II, VII, IX & X, was introduced in 1968.

However, supplies of this early Factor VIII concentrate were limited (Watt, et al, 1972[40]) and most treatment was provided by cryoprecipitate which was prepared at Regional Transfusion Centres from 1966 (Cash & Spencely, 1976;[50] Forbes & Prentice, 1977[§]).

Whilst the new SNBTS Protein Fractionation Centre (PFC) was under construction, modern intermediate-purity concentrates of Factor VIII (called NY) and Factor IX (called DEFIX) for the treatment of haemophilia A and B respectively, were developed by the PFC in its facility (formerly known as the Blood Products Unit) at the Royal Infirmary of Edinburgh, in collaboration with a leading authority, Dr A J Johnson of New York University Medical Center.

It was expected that the intermediate-purity coagulation factor concentrates would be included in the range of products to be prepared at the new PFC facility being planned. However, the quantities to be manufactured were not known, as requirements for the treatment of haemophilia were uncertain (Scottish Home & Health Department, 1973[51]), especially in light of the dominant role being played by cryoprecipitate, which was prepared at Regional Transfusion Centres.

The development of freeze dried cryoprecipitate was explored at the Glasgow and West of Scotland Regional Transfusion Centre (Milligan, et al. 1981[52]) but was discontinued after Medicines Inspectors advised that the equipment and procedures did not reach the standard of Good Manufacturing Practice (GMP) expected in the UK.

Although the SNBTS continued to supply frozen cryoprecipitate on demand, its use in the treatment of severe haemophilia A was largely replaced by freeze dried Factor VIII concentrates, as this was the product of choice of haemophilia doctors and of patients and their representatives.

The different coagulation factor products supplied by the SNBTS for the treatment of people with haemophilia are listed in Table 10 below, with their date of introduction.

Table 10. SNBTS Coagulation Factor Products for the Treatment of Haemophilia

Date	Product	Purpose
1956[a]	Factor VIII concentrate (Cohn Fraction I), freeze dried.	Treatment of haemophilia A
1966[b]	Cryoprecipitate, frozen	Treatment of haemophilia A and other disorders of coagulation
1968[a,c]	Factor II,VII,IX&X concentrate (PPSB), freeze dried.	Treatment of haemophilia B and other disorders of coagulation
1971[a,c]	Factor II,IX&X concentrate (DEFIX) of intermediate-purity, freeze dried	Treatment of haemophilia B Treatment of haemophilia A with inhibitors to factor VIII
1974[a,c]	Factor VIII concentrate (NY) of intermediate-purity, freeze dried	Treatment of haemophilia A
Dec 1984[c]	Factor VIII concentrate (NY) of intermediate-purity, freeze dried, dry heat treated for 2 hours at 68°C	Treatment of haemophilia A

Date	Product	Purpose
Aug 1985[c]	Factor II,IX&X concentrate (modified DEFIX) of intermediate-purity, freeze dried, dry heat treated for 72 hours at 80°C	Treatment of haemophilia B
Sep 1985[c]	Factor VIII concentrate (modified NY) of intermediate-purity, freeze dried, dry heat treated for 24 hours at 68°C	Treatment of haemophilia A
April 1987[c]	Factor VIII concentrate (Z8) of intermediate-purity, freeze dried, dry heat treated for 72 hours at 75°C or 80°C	Treatment of haemophilia A
1991[d]	Factor VIII concentrate of high-purity, solvent/detergent treated	Treatment of haemophilia A
1992[e]	Factor VIII concentrate (Liberate) of high-purity, solvent/detergent treated	Treatment of haemophilia A
1993[e]	Factor IX concentrate (HIPFIX) of high-purity, solvent-detergent treated and dry heat treated for 72 hours at 80°C	Treatment of haemophilia B
1996[e]	Factor VIII concentrate (Liberate) of high-purity, solvent-detergent-treated and dry heat treated for 72 hours at 80°C	Treatment of haemophilia A

[a] prepared at the Blood Products Unit/ Protein Fractionation Centre at The Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh.

[b] prepared at Regional Transfusion Centres in Aberdeen, Dundee, Edinburgh, Glasgow and Inverness.

[c] prepared at the Protein Fractionation Centre, Ellen's Glen Road, Edinburgh

[d] prepared for SNBTS at the Centre Regionale Transfusion Sanguine, Lille, France from partially purified factor VIII solution prepared at PFC; the date of introduction is when the product was approved for clinical evaluation

[e] prepared at PFC; the date of introduction is when the product was approved for clinical evaluation.

6.3. Commercial Products

So great was the impact of treatment with coagulation factor concentrates that the demand exceeded the availability of products prepared by the NHS and created a market for imported concentrates produced by commercial manufacturers,

predominantly from paid-donor plasma, contrary to the WHO policy (World Health Assembly, 1975[7]).

Commercial products have been approved by the Committee on Safety of Medicines since 1973 (Snape, 1999[53]). Commercial Factor VIII concentrate was recommended by UK Haemophilia Directors (Biggs, 1974;[§] Ingram, 1974;[§] Blackburn, 1974;[§] Dormandy; 1974;[§] Jones, 1974[§]) and by the UK Haemophilia Society (Prothero, 1974[§]) who urged that finance be provided for the purchase of commercial Factor VIII concentrate, pending sufficient local product being available. It was only following this advice that the use of commercial Factor VIII concentrate began to increase significantly (Table 1) indicating that the finance requested had been made available by the UK Government.

The principal commercial Factor VIII concentrates approved for use in the UK from 1973 to 2000 are listed in Table 11.

Table 11. Commercial Factor VIII Concentrates in the UK (from human plasma)

Company / Product Name	**Purity (iu per mg)[a]**	**Virus Inactivation**	**UK Licence From**	**To**
Alpha Therapeutic[b]				
Profilate	0.5	none	May 1975	n/k[c]
Profilate HT	0.5	60°C/24h, dried powder suspended in organic solvent	Feb 1985	Aug 1989
Alpha VIII	6-8 (20-30[d])	S/D[e]	Dec 1992[f]	n/k[c]
Alphanate	20 (100[d])	S/D[e]	May 2000[f]	n/k[c]
Armour[f]				
Factorate	0.5 – 1.0	none	Mar 1976	n/k[c]
Factorate Gen II	2 - 3	none	Sep 1979	n/k[c]
HT Factorate	0.5 – 1.0	Dry heat; 60°C/30h	Feb 1985	1986
Monoclate P	10 (3000[d])	Heat in solution, 60°C/10h	Dec1989[f]	2005[f]
Baxter[g]				
Hemofil	1.5	none	Feb 1973	n/k[c]
Hemofil T	1.5	Dry heat, 60°C/72h	Feb 1985	1989[f]
Hemofil M	11 (2000[d])	S/D[e]	Jun 1994[f]	2009[f]

Company / Product Name	Purity (iu per mg)[a]	Virus Inactivation	UK Licence From	To
Cutter Biologicals[h]				
Koate	0.5 – 1.0	none	Jul 1976	1988[l]
Koate HT	1.0	Dry heat, 68°C/72h	Feb 1985	1992[l]
Koate HP	9 – 22 (50[d])	S/D[e]	Jun 1994[l]	n/k[c]
Immuno Ltd[f]				
Kryobulin	1.0	none	Mar 1973	n/k[c]
Kryobulin TIM	1.0	Steam, 60°C/10h	Feb 1985	1992[l]
Speywood[j]				
Humanate[k]	1.0	none	Aug 1976	1986

[a] international units of factor VIII activity per milligram of protein, approximate values.

[b] formerly Abbot Laboratories; later the Green Cross Corp, Yoshitomi; now Grifols.

[c] date not known to the SNBTS

[d] discounting added albumin.

[e] treated with solvent/detergent for virus inactivation.

[f] later Centeon, Rhone-Poulenc Rorer, Aventis, Aventis Behring; now CSL Behring.

[g] also known as Hyland, Travenol or Fenwall.

[h] also known as Miles, Bayer; now Talecris (in the process of being acquired by Grifols).

[i] now Baxter.

[j] also known as Porton International; now Ipsen.

[k] Koate (Cutter), product purchased by Speywood (Wrexham) and sold in UK as Humanate.

[l] information provided by MHRA; this Crown copyright material is reproduced by permission of the Medicines and Healthcare products Regulatory Agency (MHRA) under delegated authority from the Controller of HMSO.

The extent to which these different products were used in the UK can be estimated from the market share of sales enjoyed by each company.

Table 12. % Share of UK Supply of Factor VIII Concentrate Held by Different Commercial Companies (Marketing Research Bureau, 1994[54])

Company[a]	1978	1980[e]	1981	1984	1987	1990	1993
Alpha	1	3	3	11	39	3	15
Armour	18	34	23	28	2	13	21
Baxter	19	11	12	4	1	2	
Behring							5
Cutter			11	15	26	1	
Immuno	5	12	12	3		1	
Speywood[b]	13[d]	1					
ALL[c]	56	71	61	61	68	20	41

[a] commercial products only; the remaining share was provided by NHS suppliers, BPL and SNBTS

[b] excluding porcine-derived Factor VIII concentrate which was used in the treatment of patients who had developed antibodies (inhibitors) to human factor VIII.

[c] total share of UK Factor VIII concentrate supply provided by commercial companies

[d] factor VIII concentrate derived from human-plasma; involved the commercial preparation of Factor VIII concentrate in the UK using imported cryoprecipitate.

[e] based on data released by Department of Health under Freedom of Information (see Breakdown of Brands of Factor VIII concentrate Used in UK Haemophiliacs 1980 and 1981, www.taintedblood.info/timeline) and Snape (1999[53])

The 1975 WHO policy on self-sufficiency specified that blood or plasma should be obtained from unpaid donors, as it was well established that paid donors were more likely to be infected with blood borne agents, such as the hepatitis viruses (Domen, 1995[55]). However, commercial plasma products are derived predominantly from plasma collected from paid donors in the USA where the volume of donation allowed was much greater than elsewhere, causing Titmuss to describe such donors as a "*blood proletariat*" (Titmuss, 1970[5]).

In May 1983, the Director of the Communicable Disease Surveillance Centre (Galbraith, 1983[56]) and the Association of Scientific Technical and Managerial Staff (Veitch, 1983[57]) proposed a ban on the importation of Factor VIII concentrates from the USA because of a risk of transmission of the Acquired Immune Deficiency Syndrome (AIDS). However, the Haemophilia Centre Directors (HCDO, 1983;[58] Bloom, 1983[59]) the Committee on Safety of Medicines (Committee on Safety of Medicines, 1983[60]) and the UK Haemophilia Society (Tanner, 1983;[61] Haemophilia Society, 1983a;[62]

Glenarthur, 1983a;[63] Glenarthur 1983b[64]) recommended continued importation and opposed a ban on commercial concentrates from the USA, with the Haemophilia Society advising its members that *"the risk of AIDS is tiny compared to the risks from untreated bleeding episodes"* (Haemophilia Society, 1983b[65]).

HIV infection of people with haemophilia in the UK has been largely correlated with the use of commercial concentrates (Melbye, et al. 1984;[66] Moffat, et al. 1985[67]), presumably because they were prepared from plasma collected in the USA at a time when the epidemic of HIV infection was more advanced there than elsewhere.

There is further evidence for this in the extent to which antibodies to HIV were detected in immunoglobulin prior to donor screening, with 16 of 17 batches of immunoglobulin from US commercial plasma testing positive (Gocke, et al. 1986[68]) compared with none of 56 batches derived from donors in Scotland (SNBTS unpublished results).

Following the development of a test for screening donors for infection with hepatitis C, a USA study found 10.5% of commercial plasma donors and 0.8 % of unpaid donors positive for antibodies to hepatitis C (Dawson, et al. 1991[69]), whereas the proportion of donors in Scotland who tested positive was 0.09% (Crawford, et al. 1994[70]).

This much greater prevalence of hepatitis C infection amongst USA paid plasma donors was reflected in the different levels of hepatitis C antibody detected in plasma pools from which coagulation factor concentrates used in the UK were prepared, with 89% of plasma pools from commercial manufacturers positive for antibody to hepatitis C compared with none for UK-donor plasma (Minor, 1990[71]). There is evidence of continued hepatitis transmission in England & Wales by commercial Factor VIII concentrates, after the introduction of 8Y by BPL in 1985 (Craske, 1987[72]).

Commercial products which were not free from the risk of hepatitis transmission continued to be purchased in the UK until at least 1990. For example, Profilate HT from Alpha had been shown to transmit NANBH (Kernoff, et al. 1987[§]) but still represented 39% of the Factor VIII concentrate supplied in the UK in 1987, falling to 3% in 1990. Although the UK licence for Armour's HT Factorate was withdrawn in October 1986 because of the risk of HIV transmission (Williams, et al. 1990[§]) the product appears to have retained 2% of the UK market share in 1987. By 1990, some 7% of the Factor VIII supplied in the UK consisted of commercial products which were not free from the risk of transmission of hepatitis C. It is not until 1993 that data on

market share show that all of the commercial Factor VIII concentrate purchased in the UK was essentially safe with respect to hepatitis C transmission.

More recently, following the 1998 ban on fractionation of UK-donor plasma, the SNBTS has imported some plasma from commercial as well as non-commercial sources and has therefore been in a position to obtain comparative data. Donations which had tested negative for antibody to hepatitis C by the supplier were tested by the SNBTS for the presence of HCV by the more sensitive Nucleic Acid Amplification (NAT) test. One in 6000 paid donations and one in 140,000 unpaid USA donations were found to be positive, compared with none of two million donations collected in Scotland that had been tested in this manner (SNBTS, unpublished results). These observations are consistent with findings elsewhere (van der Poel, et al. 2002[73]).

7. YIELD OF FACTOR VIII

7.1 Introduction

Obtaining the amount of plasma needed to satisfy demand for Factor VIII was a major challenge to transfusion services. However, the quantity of plasma required to meet a given demand is dependent on yield of factor VIII activity produced; hence any increase in yield reduced the amount of plasma required.

Following the commissioning of the PFC in 1975, factor VIII yield became a major focus of study for the SNBTS, especially when changes to the method for measuring factor VIII activity, made by NIBSC in December 1976, were associated with an apparent reduction in yield (see section 3.6 above). The extent to which factor VIII yield was increased by the SNBTS as a result of its research is illustrated in Table 13 below, in which the annual yield of factor VIII activity is given for the 7-year period 1977/78 to 1983/84.

Table 13. Changes in the Yield of Factor VIII, 1977/78 - 1981/82

Year[a]	Plasma (litres)[b]	FVIII Produced (m iu)[c]	FVIII Yield (iu/l)	Increase in Yield from 1977/78 (%)
1977/78	11,816	1.81	153	
1978/79	13,439	2.25	168	9.8
1979/80	15,063	3.32	220	43.8
1980/81	19,337	4.64	240	56.9
1981/82	22,716	6.00	264	72.5
1982/83[d]	34, 163	8.16	239	56.2
1983/84[d]	54,709	13.90	254	66.0

[a] financial year from 1st April – 31st March,

[b] estimated volume of fresh frozen plasma entering processing during each financial year, from which the specified Factor VIII concentrate was manufactured,

[c] amount, in million international units of factor VIII activity produced, after the removal of samples for quality control.

[d] includes plasma from Northern Ireland

It can be seen that factor VIII yield increased each year from 1977/78 to 1981/82 with an overall improvement of about 60 %, at the same time that the volume of plasma processed increased 4.5-fold. A number of factors contributed to this increase in yield.

7.2 Factor VIII Content of Plasma

Normal plasma contains 1.0 iu of factor VIII activity per millilitre by definition, reducing to 0.90 – 0.95 when collected into anticoagulant. However, the journey from the arm of a donor to the start of fractionation provides many opportunities for factor VIII activity to be lost. An intensive study of the factor VIII content of frozen plasma prior to fractionation was undertaken by the SNBTS. The principal discovery was that of two different anticoagulant solutions that were being used in Scotland, the plasma from one had a mean factor VIII content of 0.84 iu/ml compared with 0.60 iu/ml with the other (Prowse, et al. 1981[§]). Use of the latter anticoagulant was therefore discontinued by the SNBTS.

The possibility of collecting plasma in a reduced concentration of sodium citrate for anti-coagulation was also explored by the SNBTS as a means of increasing the stability of factor VIII in plasma (Prowse et al, 1987[74]). Despite encouraging results, the

technique was not implemented due to concern over the potential for increased thrombogenicity of factor IX concentrate.

7.3 Optimisation of Process Conditions for the Manufacture of Factor VIII Concentrate

Although the preparation of Factor VIII concentrate by the SNBTS was based on the method of Johnson (Newman, et al. 1971[§]), specific items of equipment had to be selected and the optimal conditions of operation determined at each step of the process. Numerous studies were undertaken, both in the research laboratory and by monitoring production procedures directly (Foster, et al. 1984[75]). Features optimised included:

- the type of centrifuge used for collecting cryoprecipitate and its temperature control
- the type of agitator (mixer) used for re-suspending cryoprecipitate,
- the pH at which extraction of factor VIII from cryoprecipitate was maximised,
- the proportion of aluminium hydroxide that had to be added to remove unwanted proteins without excessive removal of factor VIII.

7.4 Increased Yield and Quality of Factor VIII in Cryoprecipitate by Continuous-Thawing of Plasma

The production of cryoprecipitate is the first step in the process from which Factor VIII concentrate is manufactured and was identified as the point of principal yield loss during the monitoring of the SNBTS production process on which optimisation was based (Prowse, et al. 1981[§]). As well as being the point of principal loss of yield, the outcome of this step also influences the composition and quality of the final product.

Loss of factor VIII was considered to be due to two factors; to damage occurring to the protein during the time taken to thaw the frozen plasma and to particles of cryoprecipitate re-dissolving after partial-thawing had taken place. To avoid this behaviour it was necessary to reduce the thawing time considerably whilst at the same time avoiding any overheating of the solution, as the extent to which factor VIII would re-dissolve is temperature dependent. To achieve these aims, a process for thawing plasma continuously was devised (Foster & White, 1978[76]) to provide both faster thawing and better temperature control than was obtained with conventional batch-thawing.

Evaluation of pilot-scale equipment which had been designed for this purpose was begun in March 1979. Factor VIII yield was increased by 40% (Foster & Dickson, 1980[30]) leading to the established process of batch-thawing being replaced by pilot continuous-thawing from July 1979.

Large-scale equipment was designed and constructed (Foster, et al. 1982[46]) and was introduced in January 1981. The increase in yield compared with batch-thawing was sustained, now being of the order of 50%. In addition, the capacity of the process was enhanced, enabling greater quantities of plasma to be processed relatively easily without loss of yield. The solubility (reconstitution time), the purity (specific activity) and the potency of the resultant Factor VIII concentrate were all increased (Foster et al, 1982[46]) bringing these characteristics closer to those of commercial Factor VIII concentrates that were being marketed in the UK at the time.

Additional discoveries were made concerning the preservation of factor VIII activity which subsequently enabled further processing to be introduced, such as heat treatment and increased purification, without a very high reduction in yield.
These discoveries included:

7.5 Addition of Calcium During the Manufacture of Factor VIII Concentrate

Monitoring the preparation of a large number of production batches led to the discovery that almost 20% of the factor VIII activity was being lost over the latter stages of processing (Prowse, et al. 1981[§]). In investigating the mechanisms responsible for loss of yield it was surprisingly found in late-1980 that the chemical, sodium citrate, which was generally added during processing to stabilise factor VIII by preventing coagulation (Hynes et al, 1969;[77] Newman et al, 1971[§]), was responsible for making factor VIII even more unstable.

It was considered that this might be due to the preferential binding of calcium to sodium citrate, as this was known to be the mechanism by which citrate acts as an anti-coagulant, suggesting that removal of calcium might destabilise the factor VIII molecule. This was consistent with an observation that calcium was involved in linking together the sub-units of the factor VIII molecule (Fass et al, 1982[78]).

As the addition of citrate was necessary to prevent coagulation, the possibility of adding calcium to replace ionised calcium that had been removed was explored. It was discovered that the loss of factor VIII activity that had been observed was almost

completely prevented, leading to the addition of calcium becoming an important ingredient in the mixture of chemicals used to formulate factor VIII solutions (Foster et al, 1983;[79] Foster et al, 1988[§]).

Although this discovery was made in the early 1980s, further research was undertaken to confirm the observation and to ensure that the addition of calcium would not have any harmful effects (Foster, et al. 1988[§]).

Calcium addition was not used in the preparation of unheated factor VIII concentrate, but was used by the SNBTS in the preparation of pilot batches of its pasteurised Factor VIII concentrate, ZHT, and in its Factor VIII concentrate, Z8 that was dry heated for 72 hours at 75/80°C (McIntosh et al, 1987[§]). Hence the contribution made by calcium addition to self-sufficiency was to reduce the degree of yield loss experienced by the introduction of severe heat treatment from 1987, rather than to increase output per se.

Information on calcium addition was shared with the BPL who utilised this in the preparation of their severely heat treated Factor VIII concentrate 8Y (Smith, 1986[80]). The technique was also one of the changes made by Behringwerke in their modified version of pasteurised Factor VIII concentrate, Haemate P (Heimburger et al, 1986[§]). The addition of calcium to stabilise factor VIII has since become widely used in the preparation of Factor VIII concentrates, both from plasma and by recombinant technology.

7.6 Addition of Sodium Chloride During the Manufacture of Factor VIII Concentrate

In experiments performed during 1985, SNBTS researchers discovered that the coagulant activity of factor VIII in solution was lost when the concentration of sodium chloride fell below a critical level (McIntosh & Foster, 1990[81]). A small increase in ionic strength using a low concentration of sodium chloride can also increase protein solubility (Cohn & Ferry, 1943[82] Foster, 1994[§]). Therefore, sodium chloride was added to the formulation of the new SNBTS product Z8 to increase both the stability of factor VIII and the solubility of the product (McIntosh, 1987[§] McIntosh & Foster, 1990[81]).
This procedure is now widely used in the formulation of Factor VIII concentrates both from plasma and recombinant technology.

8. SUPPLY OF SNBTS PRODUCTS FOR HAEMOPHILIA A

The SNBTS produced two products for the treatment of haemophilia A, cryoprecipitate and Factor VIII concentrate and, as the SNBTS was funded centrally, both products were supplied to the NHS in Scotland free of charge. The choice of which product with which to treat a particular patient was the responsibility of the prescribing doctor; Factor VIII concentrate being generally preferred by UK haemophilia directors. However, as significant quantities of cryoprecipitate were used to treat haemophilia A in the 1970s and because it remained an option as an alternative to concentrate during the 1980s, the amounts of cryoprecipitate produced by the SNBTS from 1975 up to 1990 are shown in table 14. Also shown is the quantity of Factor VIII concentrate issued from the PFC to the Regional Transfusion Centres in Scotland up to the year 2000, by which time recombinant Factor VIII concentrate had largely replaced plasma-derived factor VIII. The amount of SNBTS factor VIII issued per head of population is also shown in Table 14, both for Factor VIII concentrate and cryoprecipitate combined and for Factor VIII concentrate alone.

Table 14. Supply of SNBTS Products Suitable for the Treatment of Haemophilia A, Scotland 1975/76 to 1999/2000

Year[a]	Cryo (m iu)[b]	FVIII Conc. (m iu)[c]	Total Incl. Cryo (m iu)	Total Incl. Cryo (iu /pop)	Total Excl. Cryo (iu/pop)
1975/76	3.97	0.94	4.91	0.94	0.18
1976/77	2.80	1.36	4.16	0.79	0.26
1977/78	3.15	1.74	4.89	0.93	0.33
1978/79	3.52	1.86	5.38	1.03	0.36
1979/80	3.02	2.21	5.23	1.00	0.42
1980/81	2.60	3.58	6.18	1.19	0.69
1981/82	1.78	4.70	6.48	1.25	0.91
1982/83	1.29	4.86	6.15	1.19	0.94
1983/84	1.16	7.23	8.39	1.63	1.40
1984/85	1.27	6.85	8.12	1.58	1.33
1985/86	1.68	5.53	7.21	1.41	1.08
1986/87	1.28	7.45	8.73	1.71	1.46
1987/88	1.39	8.37	9.76	1.91	1.64
1988/89	1.16	7.93[d]	9.09	1.79	1.56
1989/90	2.48	7.42	9.90	1.95	1.46
1990/91	nil[e]	8.96	n/a[f]	n/a	1.76
1991/92	nil	10.69	n/a	n/a	2.10

Year[a]	Cryo (m iu)[b]	FVIII Conc. (m iu)[c]	Total Incl. Cryo (m iu)	Total Incl. Cryo (iu /pop)	Total Excl. Cryo (iu/pop)
1992/93	nil	11.02	n/a	n/a	2.17
1993/94	nil	12.60	n/a	n/a	2.48
1994/95	nil	11.91	n/a	n/a	2.34
1995/96	nil	14.45	n/a	n/a	2.84
1996/97	nil	11.68	n/a	n/a	2.30
1997/98	nil	8.45	n/a	n/a	1.66
1998/99	nil	7.46	n/a	n/a	1.47
1999/00	nil	4.72	n/a	n/a	0.93

[a] year from 1st April to 31st March

[b] assumes 100 iu FVIII per unit of cryoprecipitate; figures refer to the total amounts of factor VIII activity issued by the SNBTS Regional Transfusion Centres in the form of cryoprecipitate; cryoprecipitate was supplied on demand for the treatment of haemophilia A and other disorders of haemostasis.

[c] issue of Factor VIII concentrate from PFC to the SNBTS Regional Transfusion Centres; excludes stock stored at PFC

[d] 1 m iu of SNBTS Factor VIII concentrate returned from Northern Ireland for use in Scotland in exchange for commercial Factor VIII concentrate.

[e] cryoprecipitate considered unsuitable as an alternative to Factor VIII concentrate, as a hepatitis C safe FVIII concentrate from a commercial source was licensed and available in UK from Dec 1989.

[f] not appropriate

As the use of Factor VIII was increasing year-on-year in an unplanned manner, the extent to which output from the SNBTS was sufficient to meet clinical demand can be estimated by comparing year-by-year output from the SNBTS per head of population with the average year-by-year use of Factor VIII per head of population. The monitoring of Factor VIII use was undertaken on a UK basis by the UK HCDO, therefore data obtained by HCDO can be transformed to the amount of Factor VIII per head of population and compared with the amount supplied by the SNBTS. This comparison is shown in Table 15 both for cryoprecipitate and Factor VIII concentrate combined and for Factor VIII concentrate alone.

Table 15. The Degree to Which the Supply of Factor VIII by SNBTS Matched Clinical Use of Factor VIII in the Treatment of Haemophilia A, 1975/76 to 1999/2000

Year[a]	Average use of FVIII in UK[b] (iu per head population)		Proportion of Clinical Use Matched by SNBTS FVIII Supply[c] (% average UK use per pop)	
	Incl. Cryo	Excl. Cryo	Incl. Cryo	Excl. Cryo
1975/76	0.48	0.19	196	95
1976/77	0.64	0.32	123	81
1977/78	0.77	0.39	121	85
1978/79	0.83	0.63	124	57
1979/80	0.93	0.77	107	54
1980/81	1.05	0.91	113	76
1981/82	1.20	1.08	104	84
1982/83	1.30	1.21	91	78
1983/84	1.30	1.21	125	116
1984/85	1.40	1.31	113	101
1985/86	1.42	1.36	99	79
1986/87	1.56	1.50	110	97
1987/88	1.59	1.55	120	106
1988/89	1.75	1.71	102	91
1989/90	1.85	1.75	105	83
1990/91	n/a	1.99		88
1991/92	n/a	2.26		93
1992/93	n/a	2.49		87
1993/94	n/a	2.49		100
1994/95	n/a	2.64		89
1995/96	n/a	2.51		113
1996/97	n/a	2.43		95
1997/98	n/a	2.28		73
1998/99	n/a	1.88		78
1999/00	n/a	1.74		53

[a] year from 1st April to 31st March

[b] estimates for the financial year derived from annual (Jan – Dec) data from HCDO, excluding recombinant FVIII which obtained European approval in 1993.

[c] calculated from the supply of factor VIII given in Table 13; excludes stock of SNBTS FVIII concentrate stored at PFC.

The data from the SNBTS is normally reported for the financial year (ie. April to March), whilst data from the UK HCDO are for the calendar year. In Table 15, the average UK use of Factor VIII concentrate for each financial year has been estimated from data

published for the calendar year.

The amount of Factor VIII concentrate used in Scotland has been reported in Appendix 1 of the Preliminary Report of the Penrose Inquiry, for each calendar year from 1980 to 1991. In order to make an accurate comparison between production of Factor VIII concentrate by the SNBTS and the amounts of Factor VIII concentrate used in Scotland, data have been obtained from individual records of every batch of Factor VIII concentrate produced by the SNBTS from 1979 to 1985. The amounts produced at PFC for use in Scotland are compared with the amounts used clinically for each calendar year from 1979 to 1985 (Table 16).

Table 16. Production of Factor VIII Concentrate by SNBTS and Clinical Use of Factor VIII Concentrate in Scotland, 1979 to 1985

Year	Amount of FVIII Produced by the SNBTS[a] (m iu)	Amount of SNBTS FVIII used Clinically[b] (m iu)	Amount of commercial FVIII used[b] (m iu)	Total Amount of FVIII used Clinically[b] (m iu)
1979	2.74	1.76[c]	0.72[c]	2.48
1980	3.73	3.87	0.96[d]	4.83
1981	5.58	3.48	1.22	4.70
1982	6.68[a]	4.75	0.52	5.27
1983	9.81[a,e]	5.73	0.39	6.12
1984	8.18[a,f]	6.89	0.05	6.94
1985	6.73[a]	5.67	nil	5.67

[a] production of Factor VIII concentrate for Scotland (i.e. amounts produced have been adjusted to exclude the production at PFC of Factor VIII concentrate for Northern Ireland).

[b] figures derived from Appendix 1 of the Preliminary Report of the Penrose Inquiry (September 2010).

[c] data[27] from Table 2, page 26.

[d] excludes commercial Factor VIII concentrate (Koate) used at Glasgow Royal Infirmary (data not given in the Preliminary Report of the Penrose Inquiry).

[e] includes 1.59 m iu of Factor VIII concentrate that was distributed to BPL (England) in 1984.

[f] includes 0.54 m iu of Factor VIII concentrate that was distributed to BPL (England) in 1984.

In order to maintain supplies of essential treatment at a time when demand was uncertain, the SNBTS supply chain comprised stocks of Factor VIII concentrate stored

at the Regional Transfusion Centres (RTCs) and a reserve stock held at the PFC, in addition to stocks held at the haemophilia centres and at the homes of individual patients.

Stocks of Factor VIII concentrate held at the RTCs are included in the amounts of Factor VIII concentrate supplied by the SNBTS given in Table 15. However, Tables 15 and 16 do not include the stock of Factor VIII concentrate in storage at PFC which requires to be taken into consideration when assessing the extent to which output from the SNBTS was sufficient to meet demand. The stock of Factor VIII concentrate held in storage at PFC at 31 March each year from 1975/76 to 1988/89 is given in Table 17 expressed both in units of activity and in terms of the number of months supply available.

Table 17. Stock of SNBTS Factor VIII Concentrate Stored at PFC

Year	Stock of FVIII Concentrate[a]		Supply at Current rate of Use[b] (months)
	(m iu)	(iu per pop)	
1975/76	0.18	0.03	1.9
1976/77	0.37	0.07	2.6
1977/78	0.33	0.06	1.8
1978/79	0.42	0.08	1.5
1979/80	1.40	0.27	4.2
1980/81	1.56	0.30	4.0
1981/82	1.21	0.23	2.5
1982/83	3.15	0.61	6.0
1983/84	1.60	0.31	3.1
1984/85	6.54[c]	1.27	11.6
1985/86	5.90	1.15	10.1
1986/87	5.30	1.04	8.3
1987/88	1.50	0.29	2.2

[a] amount of finished product in storage at PFC on 31st March.

[b] estimated according to average rate of use in the UK according to HCDO returns.

[c] excludes distribution of 2.1 m iu of SNBTS Factor VIII concentrate to BPL to avoid out-dating of unused product.

It is important to appreciate that these stock figures are cumulative and represent the total stock available at the year end, not the change in stock. Nevertheless, the figures suggest that SNBTS Factor VIII concentrate was available if required, in addition to that

issued to RTCs. An estimate of the availability of Factor VIII at each year from 1975/76 to 1987/88, taking the PFC stock into account, is given in Table 18.

Table 18. Amounts of Factor VIII Available from the SNBTS Compared with the Amounts Used Clinically, 1975/76 – 1987/88

Year	Total SNBTS FVIII Available[a] (m iu per pop)		Proportion of Clinical Use Matched by Available FVIII from SNBTS (% average UK use per pop)	
	Incl. Cryo	Excl. Cryo	Incl. Cryo	Excl. Cryo
1975/76	0.97	0.21	202	111
1976/77	0.86	0.33	134	103
1977/78	0.99	0.39	129	100
1978/79	1.11	0.44	134	70
1979/80	1.27	0.69	136	89
1980/81	1.49	0.99	141	109
1981/82	1.48	1.14	123	105
1982/83	1.80	1.55	138	129
1983/84	1.94	1.71	149	142
1984/85	2.85	2.60	204	197
1985/86	2.56	2.23	180	163
1986/87	2.75	2.50	177	166
1987/88	2.20	1.93	138	125

[a] amount of factor VIII available at each point in time (year), not every year as product withdrawn from stock one year would reduce the amount available subsequently

The data in Table 18 indicate that at any point in time the SNBTS had available sufficient Factor VIII to meet average UK clinical practice, if cryoprecipitate was considered to be suitable to supplement Factor VIII concentrate. If cryoprecipitate is excluded then, with exception of the two year period 1978/79 -1979/80, the availability of Factor VIII concentrate from the SNBTS was sufficient to meet average UK clinical use throughout this period.

9. COMMERCIAL PRODUCTS IN SCOTLAND

9.1. Commercial Products and Their Regulatory Approval

Despite governmental support of national self-sufficiency, commercial products were licensed and marketed in the UK (Table 11) and were available for clinicians to

purchase. Information held by the SNBTS, prior to the publication of the Preliminary Report of the Penrose Inquiry, on the purchase of commercial Factor VIII concentrate in Scotland is summarised in Table 19.

Table 19. Plasma-Derived Factor VIII Concentrates in Scotland from Sources Other than the SNBTS

Year	Amount of FVIII [a] (m iu)	Proportion of Total FVIII in Scotland (%)[b]	
		Incl. Cryo	Excl. Cryo
1977/78	0.50[c]	9.3	22.3
1978/79	0.86[d]	13.8	31.6
1979/80	0.98[d]	15.8	30.7
1980/81	1.37[d]	18.1	27.7
1981/82	1.40[d]	17.8	22.9
1982/83	1.04[d]	14.5	17.6
1983/84	0.11[d]	1.3	1.5
1884/85	0.03[e]	0.4	0.4
1985/86	0.11[e]	1.5	1.9
1986/87	0.17[e]	1.9	2.2
1987/88	0.13[e]	1.3	1.5
1988/89	1.72[f]	15.9	17.8
1989/90	1.24[f]	11.1	14.3
1990/91	0.79[f]	n/a[h]	8.1
1991/92	0.46[f]	n/a	4.0
1992/93	1.24[g]	n/a	10.1
1993/94	0.98[g]	n/a	7.2
1994/95	0.81[g]	n/a	6.4
1995/96	1.07[g]	n/a	6.9
1996/97	1.04[g]	n/a	8.2
1997/98	0.70[g]	n/a	7.6
1998/99	0.01[g]	n/a	0.1
1999/00	0.85[g]	n/a	15.3

[a] amount purchased in the financial year; excludes recombinant FVIII; does not necessarily equate to use in the corresponding period, except for 1992/93 to 1999/00 – see footnote [f].

[b] based on FVIII issued by the SNBTS in the corresponding financial year; excludes stocks of Factor VIII concentrate stored at the PFC.

[c] estimate

[d] obtained from Haemophilia Directors/Pharmacists

[e] obtained from the SHHD

[f] obtained from Chief Administrative Pharmaceutical Officers

[g] use of FVIII obtained from Haemophilia Directors; does not necessarily equate with purchases in the corresponding period

[h] not appropriate; assumes that cryoprecipitate would no longer be considered suitable for the treatment of haemophilia A, as a hepatitis-safe concentrate from a commercial source was approved in the UK in December 1989.

9.2. 1977/78 to 1982/83

Information on the purchase of commercial Factor VIII concentrates was not collected centrally in Scotland. However, figures obtained by the SNBTS from Scotland's Haemophilia Directors and from hospital pharmacies (Table 19) are consistent with the use of commercial Factor VIII concentrates in Scotland recorded by HCDO (Table 2), especially as each batch of coagulation factor concentrate had a 2-year shelf-life and would therefore not necessarily have been used in the same year that it was purchased.

A breakdown of the purchase of commercial Factor VIII concentrate in Scotland by region is available for the period 1978/79 to 1982/83 and is shown in Table 20. This is based on information held by the SNBTS prior to the publication of the Preliminary Report of the Penrose Inquiry.

Table 20. Regional Purchase of Commercial Factor VIII Concentrate, 1978/79-1982/83

Year[a]	Purchase of Commercial Factor VIII Concentrate (m iu)[b]					
	Aberdeen	**Dundee**	**Edinburgh**	**Glasgow**	**Inverness**	**All Regions**
1978/79	0.01	nil	nil	0.85	nil	0.86
1979/80	nil	nil	nil	0.98	nil	0.98
1980/81	nil	nil	0.46	0.91	nil	1.37
1981/82	nil	nil	0.73	0.67	nil	1.40
1982/83	nil	0.03	0.46	0.55	nil	1.04
Total	0.01	0.03	1.65	3.96	nil	5.65

[a] financial year, 1st April to 31st March

[b] information obtained by SNBTS Directors from Haemophilia Directors and Pharmacists

Of the total amount of commercial Factor VIII concentrate purchased by the Scottish Health Service at this time, 29% was purchased by the Edinburgh region and 70% by the Glasgow region. It has been reported that 38 people with haemophilia were treated at Glasgow Royal Infirmary with commercial Factor VIII concentrates some of whom were infected with HIV (Melbye, et al.1984;[66] Madhok, et al, 1985[§]), whilst at the Royal Hospital for Sick Children in Glasgow, imported Factor VIII concentrate was used until 1984 (Scottish Home & Health Department, 1984[83]).

In the period 1977-1979 the incidence of overt NANBH associated with the use of commercial concentrates was reported as being from 4 to 20 times greater than with NHS products (Craske, 1981[84]), whilst for the period 1980-1982 the SNBTS Factor VIII concentrate was associated with the lowest degree of overt transmission of NANBH in the UK (Craske, 1983[85]).

A review of stock levels of SNBTS Factor VIII concentrate at RTCs and at PFC undertaken in November 1983 (Perry, 1983[86]) noted that in November 1982 the stock stood at approximately 5 m iu and had risen to approximately 7 m iu by November 1983. In May 1984, a review of stocks held at Regional Transfusion Centres disclosed that a stock of 4.5 million iu of SNBTS Factor VIII concentrate was available at the Glasgow Regional Transfusion Centre (Hopkins, 1984[87]), a quantity which exceeded the total amount of commercial Factor VIII that had been purchased by the Glasgow region since 1978/79.

The stock of SNBTS Factor VIII concentrate in Scotland was so high, that SNBTS transferred 2.1 million iu to BPL in 1984 to avoid batches outdating and to reduce the amount of commercial Factor VIII concentrate needed in England & Wales at a time when the risk of HIV transmission via commercial products was at its highest.

9.3. 1983/84 to 1987/88

Factor VIII purchased during this period is believed to have been of porcine origin to treat patients with inhibitors (antibodies) to human factor VIII. It is believed that little or no commercial Factor VIII concentrate of human origin was purchased in Scotland during this 6-year period, even though the issue of Factor VIII concentrate from the PFC to the RTCs fell some 20% below the UK average use of concentrate in 1985/86 (Table 15).

9.4. 1988/89 and 1989/90

For the first time since 1982/83, a significant amount of commercial Factor VIII concentrate was purchased by Scotland's Haemophilia Directors (Table 19). This occurred at a time when there was a marked increase in average use of Factor VIII concentrate in the UK (Table 1).

Supply of Factor VIII concentrate (Z8) by the SNBTS was not sufficient to meet this level of use, as factor VIII yield had been reduced by heat treatment, manufacturing difficulties had occurred before stocks had been established to cover contingencies and there had been little or no increase in the provision of plasma for fractionation since 1983/84 (Table 6).

Although cryoprecipitate remained available as an alternative to concentrate for at least some clinical situations, all Scottish Haemophilia Centres purchased commercial Factor VIII concentrate in 1988/89, whilst both Edinburgh and Glasgow made further purchases in 1989/90 (Table 21) with commercial products averaging about 16% of supply. In order to minimise exposure in patients not previously treated with imported products, Haemophilia Directors arranged to transfer about 1 m iu of commercial Factor VIII concentrate to Northern Ireland in exchange for Factor VIII concentrate (Z8) that had been manufactured by the SNBTS for Northern Ireland.

Table 21. Factor VIII Concentrates Purchased in Scotland, 1988/89 and 1989/90

Year[a]	Product	Factor VIII Concentrate Purchased (m iu)[b,c]					
		Aberdeen	Dundee	Edinburgh	Glasgow	Inverness	All
1988/89	Monoclate P[d]			0.17			0.17
	Profilate HT[e]	0.15	0.92	0.40	0.85	0.05	2.37[h]
	All Products	0.15	0.92	0.57	0.85	0.05	2.54[h]
1989/90	Monoclate P[d]			0.13	0.05		0.18
	Profilate HT[e]			0.45	0.52		0.97
	Hemofil M[f]			0.05			
	Octa8[g]			0.04			0.04
	All Products			0.67	0.57		1.24

[a] financial year, 1st April to 31st March

[b] excludes purchase of activated Factor IX concentrate (FEIBA, Immuno) and porcine Factor VIII (Hyate:C, Speywood) for the treatment of inhibitors (antibodies) to factor VIII.

[c] excludes purchase of 8Y (BPL) for the treatment of von Willebrand's Disease

[d] high-purity Factor VIII concentrate (Armour); pasteurised for 10 hours at 60°C to inactivate viruses; licensed in UK 13th December 1989

[e] intermediate-purity Factor VIII Concentrate (Alpha); lyophilised powder heat treated in an organic solvent suspension for 24 hours at 60°C to inactivate viruses; risk of transmission of NANBH (Kernoff, et al. 1987[§]); licensed in UK from 1985 to 1989.

[f] high-purity Factor VIII concentrate (Baxter); treated with solvent/detergent to inactivate viruses; licensed in UK 6th June 1994.

[g] high-purity Factor VIII concentrate (Octapharma); treated with solvent/detergent to inactivate viruses; licensed in UK 28th July 2005.

[h] includes approximately 1 m iu of Factor VIII concentrate subsequently exchanged for Factor VIII concentrate (Z8) that had been supplied by the SNBTS to Northern Ireland.

9.5. 1990/91 to 1998/99

A Factor VIII concentrate from commercial sources which could be considered as essentially safe with respect to hepatitis C was first licensed in the UK in December 1989 (Monoclate P, Armour) providing an alternative to SNBTS Factor VIII concentrate that could be considered to be safer than cryoprecipitate.

As demand for Factor VIII concentrate continued to increase year-on-year, the SNBTS responded by extending the use of OAS and by introducing plasmapheresis to obtain normal plasma for fractionation by this route (see section 4.2), with a 45% increase in FFP over the two years 1989/90 -1990/91 (Table 6). Despite these efforts, it proved difficult to keep pace with the increase in use of Factor VIII concentrate in the UK (Table 15).

During this period Scotland's Haemophilia Directors continued to purchase small quantities of Factor VIII concentrate from sources other than the SNBTS, ranging from 4% to 10% per annum (Table 19). With the exception of 1990/91, when 0.05 m iu of an intermediate-purity Factor VIII concentrate was obtained, all purchases of human Factor VIII concentrate, known to the SNBTS, concerned high purity products prepared by immuno-purification using monoclonal antibodies, i.e. Monoclate P (Armour) and Replenate (BPL).

Although immuno-purified concentrates were regarded as safe with respect to

hepatitis C, they are believed to have been purchased primarily because of a belief that they might have a therapeutic advantage in HIV-seropositive patients (Gomperts, et al.1992;[88] Watson & Ludlam, 1992[89]). Although a high-purity Factor VIII concentrate had been introduced by the SNBTS in 1991 (Table 10), this was not immuno-purified and, unlike immuno-purified concentrates, had not been the subject of clinical studies concerning immune–modulation. The theory that immuno-purified concentrates were superior in this respect was later shown to be incorrect (Mannucci, et al. 1992[90]), with viral infection being found to have been responsible for immunological abnormalities rather than the degree of protein purification (Berntorp, 1994[91] Berntorp, 1996[§]), which had been hypothesized by proponents of immuno-purified concentrates.

Recombinant Factor VIII concentrate was granted a European licence in 1993 and its uptake was faster in Scotland than elsewhere in the UK, resulting in a reduction in the proportion of Factor VIII concentrate being provided by the SNBTS (Table 15). In 1998, the Scottish Department of Health decided to fully fund the purchase of recombinant Factor VIII concentrate as a precaution against the then theoretical risk of vCJD transmission.

At the same time the use of UK donor plasma for the preparation of plasma products was banned (Department of Health, 1998[§]) for the same reason, thereby eliminating the possibility of national self-sufficiency and making patients in the UK dependent on products manufactured from plasma collected elsewhere. Prior to the closure of the PFC, the SNBTS obtained most of this plasma from unpaid donors with volumes of donation comparable to those allowed in the UK.

10. OTHER COUNTRIES

10.1 England & Wales

The situation in England & Wales has been considered in detail in reports from the Department of Health (Department of Health, 2006[1]) and in the report of the inquiry conducted by Lord Archer of Sandwell (Archer et al, 2009[2]).

It was not until 1981 that the true scale of demand for Factor VIII concentrate was recognised (see Table 4). It was then estimated that 400,000 litres of plasma would have to be collected and processed per annum to meet this demand.

The principal problem in meeting these objectives was that the processing capacity of the existing BPL plant at Elstree was 150,000 litres of plasma per annum, yielding only about 40% of the Factor VIII concentrate required (The Baroness Trumpington, 1985[92]). This estimate was made prior to the development of heat treatment which reduced yield and, on the introduction of 8Y, resulted in a substantial reduction in the output of Factor VIII concentrate from BPL, prior to the new BPL facility coming on-stream in 1988.

The absence of the necessary fractionation capacity delayed the drive by Regional Transfusion Centres in England & Wales to collect the quantity of plasma needed. This is illustrated in Table 21 in which the amount of plasma collected on a population basis is compared to that of Scotland for the period 1982/83 to 1988/89.

Table 22. The Amount of Fresh Frozen Plasma Collected in England & Wales Compared with Scotland, 1982/83 to 1988/89.

Year	Amount of Fresh Frozen Plasma (Kg per million population)	
	England & Wales	Scotland
1982/83	3,000	7,446
1983/84	3,800	8,717
1984/85	4,850	8,593
1985/86	6,100	8,653
1986/87	6,200	9,142
1987/88	7,250	8,913
1988/89	7,550	10,650

In 1982 the British Government decided to construct a new facility at BPL with a capacity to process 500,000 litres of plasma per annum rather than to utilise spare capacity at PFC or to develop PFC further (DHSS, 1982[43]), although it had been estimated by the SNBTS that the PFC could process 100,000 kg of plasma for NBTS on an interim basis and 270,000 kg plasma per year with an investment of £1.2 M beyond that needed for Scotland and Northern Ireland (Cash, 1982[42]). When the new BPL facility opened in 1987/88, the amount of plasma being collected was still somewhat lower than the pre-heat treatment target of 400,000 litres per annum (equivalent to about 7,800 litres per million population). The yield of factor VIII with 8Y was only 130 iu per kg plasma and about 30% of the factor VIII concentrate needed continued to be obtained from commercial sources (DHSS, 1988[93]).

The impact of this situation on the provision of Factor VIII concentrate in England & Wales is illustrated by the experience of the West Midlands Area Heath Authority, a region with a population equivalent in size to that of Scotland.

Table 23. Use of Factor VIII Concentrate by the West Midlands Regional Health Authority (from Laird, 1988[94])

Year[a]	FVIII Used (m iu)	FVIII Used (iu per pop)[b]	BPL %	Commercial %
1980	4.1	0.80	32	68
1981	5.4	1.06	52	48
1982	6.4	1.25	41	59
1983	6.2	1.22	52	48
1984	7.5	1.47	53	47
1985	6.5	1.27	14	86
1986	9.7	1.90	25	75
1987	11.0	2.16	15	85

[a] calendar year from 1st January to 31st December.

[b] based on a population of 5.1 million

Key points to note are:

- a maximum contribution from BPL to the West Midlands of little over 50% in 1983 and 1984; when equivalent figures for the SNBTS supply to Scotland were 94% and over 99% respectively (see Table 3).
- a marked increase in use of Factor VIII concentrate in 1986, following the introduction of heat treated products in 1985.
- a very high proportion of commercial Factor VIII concentrate in 1985, 1986 and 1987; a period when commercial products were not safe from transmission of HCV and when there was little or no commercial Factor VIII concentrate used in Scotland.

Prior to 1985, when commercial coagulation factor concentrates carried the greatest risk of infection from NANBH and from HIV, the proportion of Factor VIII concentrate supplied to England & Wales by BPL never exceeded 50%. Subsequently supply from BPL was at its lowest during 1985-1987, during the transition to heat treatment and the introduction of 8Y (Table 1), falling as low as 14% and 15% in the West Midlands Region in 1985 and 1987 respectively (Table 23).

Although 8Y was subsequently shown to be safe with respect to transmission of NANBH (Colvin, et al.1988[§]) and HCV (Colvin, 1990;[§] Pasi, et al. 1990;[§] Rizza, et al. 1993[§]), patients continued to be infected with hepatitis (Craske,1987[72]) as a significant amount of commercial Factor VIII was still being used (Table 1). The first commercial Factor VIII concentrate that was safe from transmission of HCV (Monoclate P) was not approved for use in the UK until December 1989 (Table 11).

10.2 Other Countries

The state of self-sufficiency for blood and plasma products in Europe was reviewed for the Council of Europe in 1989 (van Aken, 1993[95]). The use of Factor VIII concentrate in different countries varied from 0.4 to 6.0 iu per inhabitant, with an average in 1986 of 1.5 iu per inhabitant. It was concluded that self-sufficiency could be achieved with 40-60 donations of whole blood per 1000 inhabitants, if there was rational use of blood products and optimal use of plasma products, with a lower threshold of whole blood donations if plasmapheresis was used. The performance of different countries is illustrated in Table 24 for 1986.

Table 24. Self-Sufficiency: Performance of European Countries, 1986 (based on van Aken, 1993[95])

Country	Blood Donations per 1000 pop	Plasma (Litres per 10^6 pop)	Plasma by 'apheresis (%)	FVIII Use (iu per pop)
Scotland	59	9,019	nil	1.7[a]
England/Wales	42	6,000	1.1	1.7[a]
Belgium	64	23,664	50.2	2.4
Denmark	79	15,365	4.5	6.0
France	60	11,091[b]	2.2[b]	1.7
German[c]	42	8,837[d]	27.8[d]	3.0
Greece	37	2,000	nil	0.6
Ireland	40	4,350	20.8	1.0
Italy	38	1,821	2.0	0.9
Luxembourg	61	21,067	31.6	3.4
Netherlands	50	10,916	6.1	2.5
Portugal	15	2,033[d]	1.6[d]	0.7
Spain	22	2,447	1.0	1.8

[a] UK average
[b] data for 1988
[c] Federal Republic of Germany
[d] data for 1989

Of the 13 countries listed, Scotland ranked 5th in the number of whole blood donations collected and 6th in the amount of plasma provided, despite being virtually unique in having no contribution from plasmapheresis at that time.

The survey noted that in 1989 about 30% of the Factor VIII used in Europe was imported from the USA, with estimates being: Germany (100 m iu), Spain (40 m iu), the United Kingdom (30 m iu), Italy (27 m iu), the Netherlands (3 m iu) and Austria (unknown).

By 1989, Belgium, Denmark, Finland, France, Luxembourg, Norway and Switzerland reported being self-sufficient according to WHO criteria; whilst countries reporting that they had not reached self-sufficiency were Germany, Greece, Italy, The Netherlands, Portugal and Spain. The United Kingdom reported being self-sufficient according to its own definition that "*The principle of self-sufficiency therefore means that the supplies of domestically sourced blood products should be sufficient, both in range and quantity, to meet the needs of all patients whose clinicians prefer these to other available products*". (Acheson, 1990[12]). However, according to the WHO definition, England & Wales never achieved self-sufficiency at any time.

Of those countries reported as achieving self-sufficiency, Belgium (SNBTS, 1981[96]) and Switzerland, had both depended predominantly on freeze dried cryoprecipitate, a product which was discontinued by the SNBTS on advice from the Medicines Inspectors. Following the development of heat treated Factor VIII concentrates, continued use of unheated freeze dried cryoprecipitate in Switzerland was associated with HIV infection in 67 haemophiliacs. The Director of the Swiss Red Cross was later found guilty of allowing HIV-infected blood products to be distributed to haemophiliacs and was given a suspended prison sentence (New York Times, 1999[97]).

In Denmark, pressure in the early 1980s from patients and the media led to very high levels of Factor VIII concentrate being used to treat patients with an inhibitor (antibody) to factor VIII. Known as the "Bonn protocol", the large amounts of Factor VIII involved meant that supplies of domestic product were severely depleted. Commercial concentrates were therefore imported from the USA and were prescribed not only to

inhibitor patients but to many other haemophiliacs; subsequently 64% of Danish haemophiliacs were found to have been infected with HIV (Albæk, 1999;[98]) with infection being correlated with the consumption of commercial Factor VIII concentrate imported from the USA (Melbye, et al. 1984[66]).

11. CONCLUSIONS

Virtually all developed countries in the world aspired to national self-sufficiency in the provision of blood products using only donations from unpaid volunteers, yet few have ever achieved this objective. The supply of blood products for the treatment of haemophilia presented the greatest challenge, as demand increased dramatically from the mid-1970s once the benefits of treatment with Factor VIII concentrates were realised. Treatment evolved from hospital-based therapy, to home treatment of incipient bleeds to current routine baseline factor VIII replacement (prophylaxis).

Some countries, such as Belgium and Switzerland, aimed for self-sufficiency by supplying cryoprecipitate for the treatment of most people with haemophilia A. In other countries, such as the UK, Factor VIII concentrate became the treatment of choice of most clinicians. In Scotland, the SNBTS provided both cryoprecipitate and Factor VIII concentrate, with supply of concentrate exceeding that of cryoprecipitate by 1980/81.

If cryoprecipitate is accepted as having been suitable for the treatment of haemophilia A when there was a shortfall of Factor VIII concentrate, then sufficient factor VIII was supplied by the SNBTS to provide treatment at the average UK level throughout the period from 1975/76 to 1989/90, except for 1982/83 when only about 90% of the UK level was supplied (Table 15), although reserve stock was available (Table 18).

If cryoprecipitate is considered to have been unsuitable as an alternative to concentrate when there was a shortfall in the amount of Factor VIII concentrate from the SNBTS, then supply from the SNBTS did not fully match the level used in the UK until 1983/84. Despite this apparent shortfall in supply of Factor VIII concentrate, production of Factor VIII concentrate at PFC exceeded that amount of concentrate used throughout during 1979 to 1985, except for 1980 when the amount used double in one year. A considerable amount of Factor VIII concentrate, which had been issued from PFC to the RTCs, remained unused by 1984. Most commercial Factor VIII purchased in Scotland in the early 1980s was obtained by haemophilia centres in

Glasgow and was comparable in quantity to the unused stock of SNBTS Factor VIII concentrate that had accumulated at the Glasgow Regional Transfusion Centre.

Supplies of Factor VIII concentrate from the SNBTS were sufficiently strong thereafter to avoid commercial Factor VIII concentrate being purchased in Scotland until 1988/89, at which point finance was provided to allow the SNBTS to increase the supply of plasma for fractionation.

The SNBTS was virtually unique amongst European countries in not utilising plasmapheresis during the 1980s to enhance the supply of normal plasma for fractionation. The strong performance of the SNBTS was achieved despite this by:

- estimating future growth in demand for Factor VIII concentrate more accurately than had been achieved previously in the UK,
- increasing the number of donations of whole blood,
- recovering plasma from all donations by rigorous implementation of component therapy,
- the possession of a fractionation facility with a capacity to process all of the plasma provided,
- the possession of the knowledge and expertise necessary to manufacture Factor VIII concentrate.
- substantially increasing the yield of factor VIII by applying knowledge gained from research & development activities.

After 1989/90, small quantities of commercial Factor VIII concentrate continued to be purchased in Scotland for the treatment of some patients, for whom the product in question was considered by the treating physician to be more beneficial than that available from the SNBTS.

12. REFERENCES

§ denotes a reference which is cited in: Foster PR & Bienek C (2008). Fractionated products. In, *Transfusion Medicine*, eds JAJ Barbara, FAM Regan & MC Contreras. Cambridge University Press, pp.259-303. (see addendum).

1. Department of Health (2006). *Self-Sufficiency in Blood Products in England and Wales. A Chronology from 1973 to 1991.* London, Department of Health.
2. The Right Hon Lord Archer of Sandwell, Jones N & Willetts J (2009). *Independent Public Inquiry Report On NHS Supplied Contaminated Blood and Blood Products.* Published 23 February 2009 (www.archercbbp.com).
3. Grant W, Patterson MR & Foster PR (1980). Supply of plasma fractions in Scotland. *Proceedings of the 9th Conference of the National Blood Transfusion Service*, Southampton, 7th-9th September 1979. Southampton, National Blood Transfusion Service.
4. Foster PR (2008). Plasma fractionation in Scotland. *Scottish National Blood Transfusion Service BloodLetter*, Spring 2008, pp.21-23.
5 Titmuss RM (1970). *The Gift Relationship, From Human Blood to Social Policy.* London, George Allen & Unwin Ltd.
6. Department of Heath & Social Security (1973). *Expert Group on the Treatment of Haemophilia, Note of the meeting held at DHSS on 20th March 1973.* London, Department of Health and Social Security (Department of health FOI release on safety of blood and blood products, document number 60).
7. World Health Assembly (1975). Utilization and supply of human blood and blood products (WHA.28.72). *Twenty-Eighth World Health Assembly, Geneva, 13-30 May 1975.*
8. World Health Organisation (1977). Meeting on the utilization and supply of human blood and blood products, December 9-13, 1975. *Vox Sanguinis,* **32**, 367-373.
9. Council of Europe (1980). *Recommendation No. R (80) 5 concerning blood products for the treatment of haemophilia. Adopted by the Committee of Ministers on 30 April 1980.* Strasbourg, Council of Europe.
10. Council of Europe (1981). *Recommendation No. R (81) 14 on preventing the transmission of infectious diseases in the international transfer of blood its components and derivatives. Adopted by the Committee of Ministers on 11 September 1981.* Strasbourg, Council of Europe.
11. Council of Europe (1983). *Recommendation No. R (83) 8 on preventing possible transmission of acquired immune deficiency syndrome (AIDS) from affected blood donors to patients receiving blood or blood products. Adopted by the Committee of Ministers on 23 June 1983.* Strasbourg, Council of Europe.
12. Acheson D (1990). *Letter to Mr D G Watters, Secretary, The Haemophilia Society, 1 November 1990.* London, Department of Health.

13. Department of Health (1998). Further precautionary measures in blood products announced. *Press Release 98/076,* 26th February 1998. London, Department of Health.

14. Department of Health (2002). Department of Health secures guaranteed long-term supplies of plasma for NHS patients. *News Release, 17 December 2002.* London, Department of Health.

15. Peden A, MCCardle L, Head MW, Love S, Ward HJY, Cousens SN, Keeling DM, Millar CM & Ironside JW (2010). Variant CJD infection in the spleen of a neurologically asymptomatic UK adult patient with haemophilia. *Haemophilia*, **16**, 296-304.

16. Heath Protection Agency (2009). *Variant CJD and plasma products, 27 July 2009.* London, Health Protection Agency (www.hpa.org.uk).

17. Scottish Executive (2006). Changes in blood processing activities. *News Release*, 26th June 2006. Edinburgh, Scottish Executive.

18. Foster PR (1994). Fractionation: Blood plasma fractionation. In: *The Kirk-Othmer Encyclopedia of Chemical Technology*, 4th edition, volume 11, pp. 990-1021.

19. Lamb M (2009). Source plasma: future outlook. *Transfusion*, **49**, 1520-1526.

20. Scottish Home & Health Department (1981). *Meeting of Directors of the Scottish National Blood Transfusion Service and Haemophilia Directors in St Andrew's House, Friday 30 January 1981.* Edinburgh, Scottish Home & Health Department.

21. Department of Health & Social Security (1977). Working Group on Trends in the Demand for Blood Products. *Minutes of the second meeting held on 13th July 1977 at the Department of Health and Social Security.* London, Department of Health & Social Security (Department of Health, FOI release on safety of blood and blood products, document no. 1497).

22. Department of Health & Social Security (1981). Working Party to Advise on Plasma Supplies for Self-Sufficiency. Preliminary Report, June 1981. *Advisory Committee on N.B.T.S.* (Department of Health FOI release on safety of blood and blood products, document number 2138)

23. Jeffrey HC (1976). Problems of supply and demand. In *Blood Transfusion and Blood Products, ed. JD Cash, Clinics in Haematology,* **5** (no. 1), pp.13-31.

24. SNBTS (1979). *Minute of Directors meeting held at the Protein Fractionation Centre, Edinburgh on Tuesday 11 December 1979.* Edinburgh, SNBTS.

25. Cash JD (1981). *Notes for Scottish Health Service Haemophilia Centre/Transfusion Service Directors' Meeting, January 1981.* Edinburgh, SNBTS.

26. British Medical Journal Editorial (1978). Freeze dried factor VIII concentrate and the NHS. *British Medical Journal,* **2**, 14501451.

27. Rizza CR & Spooner RJD (1985). *Treatment of patients by Haemophilia Centres in Scotland.* 17th December 1985. Oxford, Oxford haemophilia Centre

28. Biggs R, Rizza CR, Blackburn EK, Cleghorn TE, Cumming R, Delamore IW, Dormandy KM, Douglas AS, Grant J, Hardisty RM, Ingram GIC, Kekwick RA, Maycock Wd'A & Wallace

J (1974). Factor VII concentrates made in the United Kingdom and the treatment of haemophilia based on studies made during 1969-72. Report of the Medical Research Council's Blood Transfusion Research Committee Working Party on the Cryoprecipitation Method of Preparing AHF Concentrates. *British Journal of Haematology*, **27**, 391-405.

29. Kirkwood TBL, Rizza CR, Snape TJ, Rhymes IL & Austen DEG (1977). Identification of sources of inter-laboratory variation in factor VIII assay. *British Journal of Haematology,* **37**, 559-568.

30. Foster PR & Dickson I (1980). A review of factor VIII recovery at PFC. *PFC R&D Report No. 81*, September 1980.

31. Rizza CR & Spooner RJ (1977). Home treatment of haemophilia and Christmas disease: five years' experience. *British Journal of Haematology*, **37**, 53-66.

32. Gibson JG, Pond JC & McManus TJ (1960). Viability of red cells of ACD blood aseptically separated from plasma in a closed plastic system. *New England Journal of Medicine*, **263**, 634-637.

33. Vallet L (1973). Freezing plasma in 5-litre bags for storage and thawing for use. *Vox Sanguinis,* **24**, 550-559.

34. World Health Organisation (1978). Requirements for the collection, processing and quality control of human blood and blood products. *WHO Expert Committee on Biological Standardization, Twenty-ninth Report, WHO Technical Report Series 626,* Annex 1, p.81. Geneva, World Health Organisation.

35. Högman CF, Hedlund K & Sahlesström Y (1981). Red cell preservation in a protein-poor media. III. Protection against in vitro hemolysis. *Vox Sanguinis,* **41**, 274-281.

36. Cash JD (1982). A proposal to increase the production of factor VIII concentrate in order to achieve self-sufficiency in Scotland for the next decade, *Paper submitted to the meeting of the Common Services Agency BTS sub-committee held on 24th February 1982.* Edinburgh, SNBTS.

37. Mason EC (1978). Thaw-siphon technique for factor VIII cryoprecipitate. *Lancet,* **ii**, 636-637.

38. Prowse CV & McGill A (1979). Evaluation of the 'Mason' (continuous-thaw-siphon) method for cryoprecipitate production. *Vox Sanguinis*, **37**, 235-243.

39. Mason E, Pepper DS & Griffin B (1981). Production of cryoprecipitate of intermediate purity in a closed system thaw-siphon process. *Thrombosis & Haemostasis*, **46**, 543-546.

40. Watt JG, Smith JK, Grant & Turnbull C (1972). New developments in large-scale plasma fractionation. *Proceedings of the Royal Society of Edinburgh (B),* **71** (Supplement), 3, pp.s15-s34.

41. Foster PR (2001). Planning of plasma fractionation in Scotland, A synopsis of meetings held from 1965-1973. *SNBTS Memorandum,* July 2001.

42. Cash JD (1982). *Notes on "An Interim Report on a Study of the Continuous Fractionation of Plasma" by JG Watt, November 1981*. Edinburgh, SNBTS

43. Department of Health & Social Security (1982) Blood Products Laboratory: Redevelopment. Ministerial briefing paper, copied to SHHD on 2 September 1982. (released by the Department of Health under FOI on the safety of blood and blood products, File HIM 22/1, Volume 78, Document Ref No. 11).

44. Department of Health & Social Security (1971). *Guide to Good Pharmaceutical Manufacturing Practice*. London, Her Majesty's Stationery Office.

45. Department of Health & Social Security (1977). *Guide to Good Pharmaceutical Manufacturing Practice 1977*. London, Her Majesty's Stationery Office.

46. Foster PR, Dickson AJ, McQuillan TA, Dickson IH, Keddie S & Watt JG (1982). Control of large-scale plasma thawing for recovery of cryoprecipitate factor VIII. *Vox Sanguinis,* **42**, 180-189.

47. Foster PR, Dickson AJ, Stenhouse A & Walker EP (1986). A process control system for the fractional precipitation of human plasma proteins. *J Chemical Technology & Biotechnology,* **36**, 461-466.

48. British Pharmacopoeia (1980) Dried Factor VIII Fraction. *British Pharmacopœia 1980,* Volume II, pp.847-848. London, Her Majesty's Stationery Office.

49. British Pharmacopœia (1981). Dried Factor VIII Fraction. *British Pharmacopœia 1980, Addendum 1981*. p. 78. London, Her Majesty's Stationery Office.

50. Cash JD & Spencely M (1976). Haemophilia A and the blood transfusion service: a Scottish study. *British Medical Journal,* **2**, 682-884.

51. Scottish Home & Health Department (1973). Note of meeting to consider the development of plasma fractionation facilities at Elstree and Edinburgh, March 1973. Edinburgh, Scottish Home & Health Department (see ref 41).

52. Milligan G, Graham R, Hanratty S, Muir W & Mitchell R (1981). Production of freeze-dried human antihaemophilic cryoprecipitate. *Journal of Clinical Pathology*, **34**, 1091-1093.

53. Snape TJ (1999). Hep C. *BPL Facsimile Transmission to Dr Bob Perry SNBTS,* 26 August 1999.

54. Marketing Research Bureau (1994). *The Plasma Fractions Market in Europe 1993, Volume A (United Kingdom)*. Laguna Beach, California.

55. Domen RE (1995). Paid-versus-volunteer blood donation in the United States: a historical review. *Transfusion Medicine Reviews,* **9**, 53-59.

56. Galbraith NS (1983). Action on AIDS. *Letter to Dr I Field, Department of health & Social Security, 9th May 1983.* London, Communicable Disease Surveillance Centre, Public Health Laboratory Service.

57. Veitch A (1983). Aids-free blood centre 'starved by cash limits'. *The Guardian,* 6 May 1983. (Department of health FOI release on safety of blood and blood products, document number 2555)

58. Haemophilia Centre Directors Organisation (1983). *Minute of Special Meeting of Haemophilia Reference Centre Directors held at St Thomas Hospital on 13.5.83.* Oxford, Haemophilia Centre Directors Organisation (Department of Health FOI release on safety of blood and blood products, document number 2580)..

59. Bloom AL (1983). *Letter to Dr FE Bolton, Deputy Director, Regional Blood Transfusion Service, Edinburgh, 23rd May 1983.* Cardiff, Department of Haematology, University Hospital of Wales.

60. Committee on Safety of Medicines (1983). *Minute of the meeting of the sub-committee on biological products held on 13 July 1983,* London. Committee on Safety of Medicines.

61. Tanner AJ (1983). *Letter to Members, 4 May 1983.* London, The Haemophilia Society (Department of Health, FOI release on safety of blood and blood products, document number 2548).

62. The Haemophilia Society (1983a). *Letter to the Department of Health and Social Security, 15th August 1983.* London, The Haemophilia Society (Department of Health, FOI release on safety of blood and blood products, document number 2722).

63. Glenarthur (1983a). *Letter to Mr Clive Jenkins Esq., General Secretary, Association of Scientific Technical and Managerial Staffs, 26th August 1983.* London, Department of Health & Social Security (Department of Health, FOI release on safety of blood and blood products, document number 2734).

64. Glenarthur (1983b). *Letter to The Baroness Masham of Ilton, 30 August 1983.* London, Department of Health & Social Security. (Department of Health, FOI release on safety of blood and blood products, document number 2735).

65. The Haemophilia Society (1983b). *HÆMOFACT A.I.D.S. Release No. 2, 22 September 1983.* London, The Haemophilia Society. (Department of Health, FOI release on safety of blood and blood products, document number 2764).

66. Melbye M, Froebel KS, Madhok R, Biggar RJ, Sarin PS, Stenbjerg S, Lowe GDO, Forbes CD, Goedert JJ, Gallo RC & Ebbesen P (1984). HTLV-III seropositivity in European haemophiliacs exposed to factor VIII concentrate imported from the USA. *Lancet,* **ii**, 1444-1446.

67. Moffat EH, Bloom AL & Mortimer PP (1985). HTLV-III antibody status and immunological abnormalities in haemophilic patients. *Lancet*, **i**, 935.

68. Gocke DJ, Raske K, Pollack W & Schwartzer T (1986). HTLV-III antibody in commercial immunoglobulin. *Lancet*, **i**, 37-38

69. Dawson GL, Lesniewski RR, Stewart JL, Boardway KM, Gutierrez RA, Pendy L, Johnson RG, Alcalde X, Rote KV, Devare SG, Robey WG & Peterson DA (1991). Detection of

antibodies to hepatitis C virus in U.S. blood donors. *Journal of Clinical Microbiology,* **29**, 551-556.

70. Crawford RJ, Gillon J, Yap PL, Brookes E, McOmish F, Simmonds P, Dow BC & Follett EA (1994). Prevalence and epidemiological characteristics of hepatitis C in Scottish blood donors. *Transfusion Medicine,* **4**, 95-97.

71. Minor P, Pipkin P, Thorpe R & Thomas D (1990). Antibody to hepatitis C virus in plasma pools. *Lancet*, **336**, 188.

72. Craske J (1987). *UK Haemophilia Hepatitis Working Party Report for 1986/87, 15 September 1987.* Report Presented at the 19th Meeting of the UK Haemophilia Centre Directors held at the Royal Free Hospital London on 25th September 1987. Oxford, Haemophilia Centre Directors Organisation.

73. van der Poel CL, Seifried E & Schaasberg WP (2002). Paying for blood donations: still a risk? *Vox Sanguinis*, **83**, 285-293.

74. Prowse CV, Waterston YG, Dawes J & Farrugia A (1988). Studies on the procurement of blood coagulation factor VIII, in vitro studies on blood components prepared in half-strength citrate anticoagulant. *Vox Sanguinis*, **52**, 257-264.

75. Foster PR, Dickson AJ & Dickson IH (1984). Improving yield in the manufacture of factor VIII concentrates. *Scandinavian Journal of Haematology,* **33** (Suppl. 40), 103-110.

76. Foster PR & White BJ (1978). Thaw-siphon technique for factor VIII-cryoprecipitate. *Lancet*, **ii**, 574.

77. Hynes HE, Owen CA, Bowie EJW & Thompson JH (1969). Citrate stabilization of chromatographically purified factor VIII. *Blood*, **34**, 601-609.

78. Fass DN, Knutson GJ & Katzmann JA (1982). Monoclonal antibodies to porcine factor VIII coagulant and their use in the isolation of active coagulant protein. *Blood,* **59**, 594-600.

79. Foster PR, Dickson IH & McQuillan TA (1983). Stability of factor VIII during the preparation of an intermediate-purity factor VIII concentrate. *British Journal of Haematology*, **53**, 343.

80.Smith JK (1986). *Letter to Dr DS Pepper,* SNBTS , 26th February. Oxford, Plasma Fractionation laboratory

81. McIntosh RV & Foster PR (1990). The effect of solution formulation on the stability and surface interactions of factor VIII during plasma fractionation. *Transfusion Science*, **11**, 55-66.

82. Cohn EJ & Ferry JD (1943). The interaction of proteins with ions and dipolar ions. In, *Proteins, Amino Acids and Peptides*, (eds. EJ Cohn & JT Edsall), pp.586-622. New York, Reinhold Publishing Corporation.

83. Scottish Home & Health Department (1984). *Notes of Meeting of Haemophilia Directors and SNBTS Representatives on 29 November 1984 in St Andrew's House.* Edinburgh, Scottish Home & Health Department.

84. Craske J (1981). Haemophilia Centre Directors Hepatitis Working Party Report For Year 1980-81. *Report to the 12th Meeting of UK Haemophilia Centre Directors held at the Royal Free Hospital London,* 9th October 1981.

85. Craske J (1983). Haemophilia Centre Directors Hepatitis Working Party Report For Year 1982-83. *Report to the 14th Meeting of the UK haemophilia Centre Directors held at the Oxford Regional health Authority,* 17th October 1983.

86. Perry RJ. FVIII-Supply and Demand. *Memorandum to J Watt, W Grant & P Foster,* 18 November 1983. Edinburgh SNBTS Protein Fractionation Centre.

87. Hopkins DF (1984). *Letter to Dr R Perry, SNBTS Protein Fractionation Centre*, 3rd May 1984. Carluke, Glasgow and West of Scotland Blood Transfusion Service.

88. Gomperts ED, de Biasi R & De Vreke R (1992). The impact of clotting factor concentrates on the immune system in individuals with hemophilia. *Transfusion Medicine Reviews,* **6**, 44-54.

89. Watson HG & Ludlam CA (1992). Immunological abnormalities in haemophiliacs. *Blood Reviews,* **6**, 26-33.

90. Mannucci PM, Gringeri A, de Biasi R, Baudo F, Morfini M & Ciavarella N (1992). Immune status of asymptomatic HIV-infected hemophiliacs: randomized, prospective, two-year comparison of treatment with a high-purity or an intermediate-purity factor VIII concentrate. *Thrombosis Haemostasis,* **67**, 310-313.

91. Berntorp E (1994). Impact of replacement therapy on the evolution of HIV infection in hemophiliacs. *Thrombosis Haemostasis*, **71**, 678-683.

92. The Baroness Trumpington (1985). *Letter to The Baroness Masham of Ilton, 22nd October 1985.*London, Department of health & Social Security (Department of Health, FOI release on blood safety, document no. 4385).

93. Department of Health & Social Security (1988). Blood Products Laboratory and factor VIII requirement. *Memorandum from Dr RJ Moore, 29 September 1988.* London, Department of Health & Social Security

94. Laird RA (1988). A review of the RHA's funding and consumption of factor VIII, *Report to the Regional Management Team of the West Midlands Regional Health Authority.* 27 April 1988. Birmingham, West Midlands Regional health Authority.

95. van Aken WG (1993). The collection and use of human blood and plasma in Europe. Strasbourg, Council of Europe Press.

96. SNBTS (1981). *Minutes of Directors' Meeting held in the SNBTS Headquarters Unit on Tuesday 22 September 1981.* Edinburgh, SNBTS.

97. New York Times (1999). Alfred Hassig, 78; Target of Tainted-Blood Trial. *New York Times,* 20th November 1999.

98. Albæk E (1999). The never-ending story? The political and legal controversies over HIV and the blood supply in Denmark. In, *Blood Feuds. AIDS, Blood, and the Politics of Medical Disaster, eds. EA Feldman & R Bayer, pp. 161-189.* Oxford, Oxford University Press.

ADDENDUM

This addendum includes those references which have been denoted § and which are cited in Foster PR & Bienek C (2008). Fractionated products. In, *Transfusion Medicine*, eds JAJ Barbara, FAM Regan & MC Contreras. Cambridge University Press, pp.259-303.

Aronson DL (1990). The development of the technology and capacity for the production of factor VIII for the treatment of hemophilia A. *Transfusion*, **30**, 748-758.

Berntorp E (1996). Why prescribe highly purified factor VIII and IX concentrates. *Vox Sanguinis*, **70**, 61-68.

Biggs R (1974). Supply of blood-clotting-factor VIII for treatment of hæmophilia. *Lancet*, **i**, 1339.

Biggs R & McFarlane RG (1957). *Human Blood Coagulation and its Disorders,* second edition. Oxford: Blackwell Scientific Publications

Biggs, R (1977). Haemophilia treatment in the United Kingdom from 1969 to 1974. *British Journal of Haematology*, **35**, 487-504.

Blackburn EK (1974). *Treatment of hæmophilia. Lancet, **ii**, 105.*

Cohn EJ (1948). The history of plasma fractionation. In *Science in World war II. Advances in Military Medicine made by American Investigators working under the Sponsorship of the Committee on Medical Research, volume 1,* eds. E.C.Andrus, C.S. Keefer, D.W. Bronke, *et al.*, pp. 364- 443. Boston: Little, Brown & Co.

Cohn EJ, Strong CE, Hughes WL, Mulford DJ, Ashworth JN, Melin M & Taylor HL (1946). Preparation and properties of serum and plasma proteins IV: a system for the separation into fractions of the protein and lipoprotein components of biological tissues and fluids. *Journal of the American Chemical Society*, **68**, 459-475.

Colvin BT (1990). Prevention of hepatitis C infection in haemophiliacs. *Lancet*, **335**, 1474.

Colvin BT, Rizza CR, Hill FGH, Kernoff PBA, Bateman CJT, Bolton-Maggs P, Daley HM, Kenny MW, Taylor PC, Mitchell VE, Wensley RT, Whimore DN, Lane RS & Smith JK (1988).

Effect of dry-heating of coagulation factor concentrates at 80 degrees C for 72 hours on transmission on non-A, non-B hepatitis. Study Group of the UK Haemophilia Centre Directors on Surveillance of Virus Transmission by Concentrates. *Lancet*, **ii**, 814-816.

Cumming RA, Davies SH, Ellis D & Grant W (1965). Red cell banking and the production of a factor VIII concentrate. *Vox Sanguinis*, **10**, 687-699.

Department of Health (1998). *Committee on Safety of Medicines Completes Review of Blood Products,* press release no. 98/102. London: Department of Health.

Dormandy KM (1974). Blood fractions for hæmophilia. *Lancet*, **ii**, 155.

Emile-Weil P (1906). Etude du sang chez les hémophiles. *Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris*, **23**, 1001-1018.

Feissley R (1924). Recherches sur la pathogénie at la thérapeutique des états hémophiliques. *Schweizerische Medizinische Wochenschrift*, **55**, 81-84.

Forbes CD & Prentice CRM (1977). Mortality in haemophilia – a United Kingdom survey. In *Unsolved Therapeutic Problems in Hemophilia,* eds. J.C.Fratantoni & D.L.Aronson, pp. 15-22. Washington: US Department of Health, Education, and Welfare, DHEW publication no. (NIH) 77-1089.

Foster PR (1994). Protein precipitation. In *Engineering Processes for Bioseparation*, ed. L.R. Weatherley, pp. 73-109. Oxford:Butterworth-Heinemann.

Foster PR, Dickson IH, McQuillan TA, *et al.* (1988). Studies on the stability of VIII:C during the manufacture of a factor VIII concentrate for clinical use. *Vox Sang*, **55**, 81-89.

Heimburge N, Wormsbacher W & Kumpe G (1986). *Process for the production of a pasteurized isoagglutinin-free Factor VIII preparation from a cryoprecipitate.* European Patent no. EP0173242.

Hershgold EJ, Pool JG & Pappenhagen AR (1966). The potent antihemophilic globulin concentrate derived from a cold insoluble fraction of human plasma: characterization and further data on preparation and clinical trial. *Journal of Laboratory and Clinical Medicine*, **67**, 23-32.

Ingram GIC (1974). Blood fractions for treatment of hæmophilia. *Lancet*, **ii**, 56-57.

Johnson AJ, Newman J, Howell MB & Puszkin S (1967). Purification of antihemophilic factor (AHF) for clinical and experimental use. *Thrombosis Diathesis Haemorrhagica*, **26** (Suppl.), 377-381.

Jones P (1974). Blood fractions for hæmophilia. *The Lancet*, **ii**, 155.

Kasper CK, Lusher JM, Silberstein CE, *et al.* (1993). Recent evolution of clotting factor concentrates for hemophilia A and B. *Transfusion*, **33**, 422-434.

Kernoff PBA, Miller EJ, Savidge GF, Machin SJ, Dewar MS & Preston FE (1987). Reduced risk of non-A, non-B hepatitis after a first exposure to 'wet heated' factor VIII concentrate. *British Journal of Haematology*, **67**, 207-211.

Ludlam CA (1997). New-variant Creutzfeldt-Jakob disease and treatment of haemophilia. *Lancet*, **350**, 1704.

Madhok R, Melbye M, Lowe GD, Forbes CD, Froebel KS, Bodner AJ & Biggar RJ (1985). HTLV-III antibody in sequential plasma samples: from haemophiliacs 1974-84. *Lancet*, **i**, 524-525.

McIntosh RV, Docherty N, Fleming D & Foster PR (1987). A high yield factor VIII concentrate suitable for advanced heat treatment. *Thrombosis and Haemostasis*, **58**, 306.

Newman J, Johnson AJ, Karpatkin MH & Puszkin S (1971). Methods for the production of clinically effective intermediate- and high purity factor VIII concentrates. *British Journal of Haematology*, **21**, 1-20.

Pasi KJ, Evans JA, Skidmore SJ & Hill FGH (1990). Prevention of hepatitis C infection in haemophiliacs. *Lancet*, **335**, 1473-1474.

Pool JG & Robinson J (1959). Observations on plasma banking and transfusion procedures for haemophilic patients using a quantitative assay for antihaemophilic globulin (AHG). *British Journal of Haematolgy*, **5**, 24-30.

Pool JG & Shannon AE (1965). Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. Assay in vitro and in vivo. *New England Journal of Medicine*, **273**, 1443-1447.

Prothero JL (1974). Blood fractions for hæmophilia. *Lancet*, **ii**, 300-301.

Prowse CV, Griffin B, Pepper DS, Dickson AJ, McQuillan TA, Dickson IH & Foster PR (1981). Changes in factor VIII complex activities during the production of a clinical intermediate-purity factor VIII concentrate. *Thrombosis Haemostasis*, **46**, 597-601.

Rizza CR, Fletcher ML & Kernoff PBA (1993). Confirmation of viral safety of dry heat treated factor VIII concentrate (8Y) prepared by Bio Products Laboratory (BPL): a report on behalf of UK haemophilia centre directors. *British Journal of Haematology*, **84**, 269-272.

Rizza, C.R., Spooner, R.J.D. & Giangrande, P.L.F. (2001) Treatment of haemophilia in the United Kingdom 1981-1996. *Haemophilia*, **7**, 349-359.

Surgenor, D.M, (2002) Edwin J. Cohn and the Development of Protein Chemistry. Boston: Centre for Blood Research, Inc.

Williams MD, Skidmore SJ & Hill FGH (1990). HIV seroconversion in haemophilia boys receiving heat treated factor VIII concentrate. *Vox Sanguinis,* **58**, 135-136.