



**EVENTS CONCERNING THE SAFETY OF
BLOOD AND BLOOD PRODUCTS WITH
SPECIAL REFERENCE TO THE TREATMENT
OF HAEMOPHILIA**

Scottish National Blood Transfusion Service

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AIDS	ACQUIRED IMMUNODEFICIENCY SYNDROME
ALT	ALANINE AMINOTRANSFERASE
BPL	BLOOD PRODUCTS LABORATORY, ELSTREE
CDC	CENTERS FOR DISEASE CONTROL, USA
COPFS	CROWN OFFICE AND PROCURATOR FISCAL SERVICE
CPMP	COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS
CSA	COMMON SERVICES AGENCY FOR THE SCOTTISH HEALTH SERVICE
CSL	COMMONWEALTH SERUM LABORATORIES, AUSTRALIA
DHSS	DEPT OF HEALTH & SOCIAL SECURITY
DOH	DEPARTMENT OF HEALTH
ELISA	ENZYME-LINKED IMMUNOSORBENT ASSAY
FDA	FOOD AND DRUG ADMINISTRATION, USA
GMP	GOOD MANUFACTURING PRACTICE
HAV	HEPATITIS A VIRUS
HBsAG	SURFACE ANTIGEN OF THE HEPATITIS B VIRUS
HBV	HEPATITIS B VIRUS
HCCC	HEALTH AND COMMUNITY CARE COMMITTEE
HCDO	HAEMOPHILIA CENTRE DIRECTORS ORGANISATION
HCV	HEPATITIS C VIRUS
HIV	HUMAN IMMUNODEFICIENCY VIRUS
IU	INTERNATIONAL UNIT
JPAC	JOINT PROFESSIONAL ADVISORY COMMITTEE
MCA	MEDICINES CONTROL AGENCY
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
NANBH	NON-A NON-B HEPATITIS
NHS	NATIONAL HEALTH SERVICE
NIBSC	NATIONAL INSTITUTE FOR BIOLOGICAL STANDARDS AND CONTROL
NSS	NHS NATIONAL SERVICES SCOTLAND
PFL	PROTEIN FRACTIONATION LABORATORY, OXFORD
PHLS	PUBLIC HEALTH LABORATORY SERVICE
SNBTS	SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
TTI	TRANSFUSION TRANSMISSIBLE INFECTION
WFH	WORLD FEDERATION OF HAEMOPHILIA
WHO	WORLD HEALTH ORGANISATION

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INTRODUCTION

Blood-borne infectious agents present naturally in the human population are an inherent risk in treatment with blood products and pose a major challenge to Transfusion Medicine. The risk is greatest when an infectious agent is new or unknown since many patients may be infected before the viruses responsible can be identified.

Haemophilia affects about one person per thousand in the population. People with haemophilia who depend on treatment with blood products are especially at risk from blood-borne infectious agents. Nevertheless advances in the treatment of haemophilia have been remarkable. Before treatment with blood products, a person with haemophilia was not expected to survive beyond childhood. As recently as 1974, the average age of death in the UK was 34 years for a person with haemophilia B and 42 years for a person with haemophilia A; most were badly crippled as a result of their disorder.

In contrast a person born with haemophilia in the UK within the last 20 years should enjoy a normal life expectancy and be free from disability and from infection by blood borne viral pathogens. This achievement is the result of scientific and medical advances that occurred in the 1970s and 1980s.

SNBTS contributed to these advances by:

- achieving self-sufficiency in Factor VIII supply for Scotland (in 1983)
- the prompt introduction of dry-heat treatment to destroy HIV (in 1984)
- making key discoveries in the development of a more severe dry-heat treatment, that was shown subsequently to destroy the hepatitis C virus

As a result of these achievements:

- SNBTS Factor VIII issued from December 1984 was HIV-safe. This included the recall and heat treatment of all remaining product manufactured prior to December 1984
- Scotland was the first country in the world to supply HIV-safe Factor VIII in sufficient quantity for the treatment of all of its patients
- SNBTS Factor VIII was safe from hepatitis C two years before the virus responsible was discovered and before it was known that the hepatitis C virus (HCV) could be destroyed by severe dry-heat treatment
- Scotland was three years ahead of any other country in the world in supplying HCV-safe Factor VIII sufficient for the treatment of all of its patients

1. Background Information

1.1 The Scottish National Blood Transfusion Service (SNBTS)

The SNBTS (formerly the Scottish National Blood Transfusion Association) was created in 1940 and has been a division of the Common Services Agency for the Scottish Health Service (CSA) since April 1974. The CSA is known as NHS National Services Scotland (NSS) and is a Non-Departmental Public Body constituted under the National Health Service (Scotland) Act 1978. The CSA is accountable to the Scottish Government and its statutory duties include the provision of supplies of human blood for blood transfusion and the production of blood products (see Article 3(a) of the National Health Service (Functions of the Common Services Agency)(Scotland) Order 1974). The Accountable Officer for all NSS Divisions, including SNBTS, is the Chief Executive of NSS.

The role of the SNBTS is the production and supply of human blood and blood products. Responsibility for the treatment of patients lies, in the main, with Health Boards. SNBTS medical staff provide advice on the selection and use of blood components and plasma and, since 2005, SNBTS has operated the NHSScotland Better Blood Transfusion Programme.

At the time the CSA was created, the post of SNBTS National Medical Director was established to co-ordinate the activities of Regional Transfusion Centres in Aberdeen, Dundee, Edinburgh, Glasgow and Inverness and the Protein Fractionation Centre (PFC) in Edinburgh, where SNBTS plasma products were manufactured.

The Regional Transfusion Centres were responsible for recruiting and managing donors, collecting and testing donations and preparing and distributing blood components, including whole blood, red cells, platelets, cryoprecipitate and plasma for clinical use. Plasma for fractionation was separated from cellular components at Regional Transfusion Centres and sent to the PFC for the manufacture of plasma products.

Plasma products have been prepared by the SNBTS since the 1950s, first on a relatively small-scale within the Royal Infirmary of Edinburgh and later on a large-scale in a purpose built manufacturing facility in Edinburgh, the PFC, which opened in 1975.

In late 2005 following an extensive strategic review, the SNBTS Management Board recommended to the NSS Board that the PFC should be sold or closed. The principal reasons behind this decision were that the PFC was no longer an instrument of National self sufficiency nor was it economically viable. Following the banning of UK plasma as a vCJD precautionary measure, plasma was bought from Germany and the USA for fractionation and, with the total replacement of Coagulation factors by recombinant products, the economics of fractionating the plasma compared to buying plasma products was adversely affected. In addition there was a requirement for considerable investment to renew ageing plant. This recommendation was accepted by the NSS Board and subsequently Scotland's Health Minister, who decided in June 2006 that

Scotland would obtain its plasma products from elsewhere. Following this decision, the PFC continued to operate at a reduced capacity to manufacture a novel bio-defence product for the Ministry of Defence. This contractual commitment was fulfilled in April 2008, following which the PFC was decommissioned and closed.

1.2 Blood Products

A number of medicinal products are manufactured from human blood. They fall into two categories: (a) blood components, such as red cells, platelets, cryoprecipitate and plasma and (b) bio-pharmaceutical proteins (also referred to as plasma products), such as albumin, immunoglobulins and coagulation factors, that are derived from human plasma using highly specialised manufacturing processes (see tables below).

Principal Blood Components Derived from Human Blood and their Medical Applications

Blood Components	Medical Applications
Red cells	Acute anaemia (due to haemorrhage) and chronic anaemia
Platelets	Prevention or treatment of bleeding due to chemotherapy; Management of major bleeding in surgery, trauma or obstetrics
Plasma	Treatment of deficiency of coagulation proteins when no specific plasma or recombinant product is available; Management of major bleeding in surgery, trauma or obstetrics
Cryoprecipitate	Treatment of deficiency of fibrinogen associated with major bleeding, for example in post partum haemorrhage; Formerly used in UK as a source of factor VIII for treatment of bleeding due to haemophilia (still used in some countries for this indication)

Principal Products Derived from Human Blood Plasma and their Medical Applications

Plasma Product	Medical Applications
Albumin	Restoration of blood volume; protein replacement
Immunoglobulin (polyvalent)	Treatment of immune deficiencies and immune disorders
Immunoglobulin (anti-D)	Prevention of RhD immunisation in RhD negative women
Immunoglobulin (other specificities)	Prevention & treatment of specific infections e.g. tetanus, hepatitis B, varicella/zoster, rabies, cytomegalovirus (CMV).
Factor VIII concentrate	Treatment of haemophilia A
Factor IX concentrate	Treatment of haemophilia B
Fibrin Sealant (fibrinogen + thrombin)	Haemostasis
Prothrombin Complex Concentrate (PCC)	Treatment of haemophilia B; Reversal of coumarin (Warfarin) anti-coagulant therapy

Blood-borne infections present naturally in the human population represent an inherent risk to recipients of human blood products, with those who require extensive treatment being at greatest risk. Blood components could not, until the recent advent of pathogen reduction systems, be treated to eliminate viruses and their safety depended on the selection and testing of blood donors.

Plasma products can be treated to eliminate viruses during their manufacture. Coagulation factor concentrates used in the treatment of haemophilia are the most sensitive of the plasma products and are the most difficult to treat in this respect. Despite these difficulties, technologies suitable for the virucidal

treatment of coagulation factor concentrates were developed successfully during the 1980s and represented a major advance in the treatment of haemophilia.

1.3 Treatment of Haemophilia

There are two types of haemophilia, type A caused by a deficiency of coagulation Factor VIII and type B, caused by a deficiency of coagulation Factor IX.

The treatment of most people with haemophilia is undertaken in specialist haematology departments that have been designated for this purpose and which are managed in Scotland by territorial Health Boards. The Haemophilia Centre Doctors Organisation (HCDO) monitors haemophilia in the UK and provides advice on treatment.

Without medical treatment, the average life-expectancy of a person with haemophilia was 14 years.¹ Those surviving into adulthood would, without medical treatment, face crippling disability.

Treatment of haemophilia by transfusion with blood or fresh plasma was introduced in the first half of the 20th century and succeeded in raising the life-expectancy of a haemophiliac in the UK to about 40 years.¹

Cryoprecipitate, a more concentrated form of Factor VIII, was introduced for the treatment of haemophilia A in the mid-1960s. Although this enabled a greater quantity of Factor VIII to be administered, there was no apparent reduction in mortality in the UK, with cerebral haemorrhage being the leading cause of death and 30% of patients dying before the age of 21.¹

For the period 1969-1974, the average age at death in the UK was 42 years for a person with haemophilia A and 34 years for a person with haemophilia B. Of 62 haemophilia deaths during this period, 5 (8%) were from hepatitis, with 4 of these infected via cryoprecipitate.²

From the mid-1970s, Factor VIII and Factor IX concentrates increasingly replaced cryoprecipitate and plasma for the treatment of haemophilia A and haemophilia B respectively. These concentrates were made from pools of sometimes many thousands of individual donations.

For the period 1977-1999 the median life expectancy in the UK for haemophiliacs who were not infected with HIV was 63 years for severe haemophilia and 75 years for moderate/mild haemophilia.³

Today, most people with haemophilia are treated with recombinant coagulation factors which are prepared in animal cells by genetic engineering to avoid the use of human blood donations. The impact of this change on life expectancy of people with haemophilia has still to be determined.

1.4 Hepatitis

The possibility that hepatitis could be transmitted by blood plasma products has been known since the 1930s, with transmissions by Factor VIII concentrate in the UK first reported in 1963.⁴

Two types of hepatitis were recognised at this time; one with an incubation period of 20-40 days which was transmitted by the faecal-oral route and known as 'infectious hepatitis' and another with an incubation period of 60-180 days which was transmissible by blood serum and known as 'serum hepatitis'. These two types of hepatitis were designated hepatitis A and hepatitis B respectively in 1947.

The virus responsible for hepatitis B infection (HBV) was identified in 1967 and isolated in 1970, whilst the virus responsible for hepatitis A (HAV) was discovered in 1973. Despite these discoveries a type of hepatitis that could not be accounted for by either HAV or HBV continued to be transmitted via transfusion of blood and blood products, leading to the designation non-A, non-B hepatitis (NANBH). A virus responsible for most cases of NANBH, named the hepatitis C virus (HCV), was identified in 1989.

The risk of hepatitis transmission by blood products, including coagulation factor concentrates, was included in advice issued by the Department of Health in 1973⁵ and in a book published in 1974 which was written specifically for patients and was distributed by the Haemophilia Society.⁶

Warnings of a risk of hepatitis transmission were issued with coagulation factor concentrates. For example, in 1978 five warnings concerning hepatitis were issued with coagulation factor concentrates prepared by the SNBTS; two in the patient information leaflet issued with the product, two on the box containing vials of product and one on the product label attached to each vial.

Hepatitis warnings were also issued with commercial products and the SNBTS holds samples of early product literature, with hepatitis warnings, issued by Hyland (1975, 1977), Cutter (1978), Immuno (1979) and Alpha Therapeutics (1979). Hepatitis warnings continued to be included in product literature after the development of heat treatment.

An information leaflet of 1978 from one USA manufacturer includes the statement "*The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequences of withholding it, particularly in persons with few previous transfusions of blood and plasma products.*"⁷

The risk of hepatitis transmission via coagulation factor concentrates has been described in numerous medical publications since the 1960s and was the subject of television and press reports in the 1970s.

Information on the risk of contracting hepatitis was presented to regular meetings of patient organisations, such as the World Federation of Hemophilia (WFH), of which the UK Haemophilia Society is a founder member. For example, the first evidence that patients with haemophilia were infected with non-A, non-B hepatitis (NANBH) was presented initially to a meeting of the WFH in 1975.⁸ Also, during the 1970s and 1980s the WFH listed medical papers concerning the risk of hepatitis in its regular Bulletin.

The risk of hepatitis was considered at annual meetings of the UK Haemophilia Centre Directors Organisation (HCDO), which were attended by representatives of the UK Haemophilia Society from the mid-1970s.

Open symposia were sometimes arranged in conjunction with meetings of the HCDO. For example, in September 1975 there was a presentation entitled “*Virus hepatitis complicating replacement therapy*” at an open symposium in Glasgow,⁹ whilst similar symposia, held in Glasgow¹⁰ in 1980 and in Manchester¹¹ in 1982, included major sessions on hepatitis.

Hepatitis was also discussed with haemophilia organisations at a grass-roots level as, for example, with a clinician at a local meeting¹² of the Scottish Haemophilia Forum (formerly known as The Haemophilia Society – Scottish Group) held in March 1980.

Although blood product manufacturers issued warnings with their products, it is the treating physician who is responsible for advising individual patients of risks associated with their treatment.

A handbook was supplied for patients on home therapy which contained the warning “*There is always a risk of hepatitis virus being present in blood products and so all the materials you use could be contaminated.*” The final draft of this document¹³ was considered at a meeting of the UK Haemophilia Centre Directors on 24th October 1977, which was attended by representatives of the UK Haemophilia Society.

Patients were also informed directly via the Haemophilia Society. For example, a letter of 4th May 1983 concerning AIDS contains the statement “*We are no strangers to infective diseases, such as hepatitis, which can be transmitted by factor concentrates.*”¹⁴

1.5 Acquired Immunodeficiency Syndrome (AIDS)

The epidemic of AIDS emerged amongst homosexual men in Los Angeles and New York in late-1980 and was first reported by the USA Centers for Disease Control in 1981.^{15,16} A number of theories were proposed to explain the disease,¹⁷ but reports during 1982 concerning three people with haemophilia^{18,19} and an apparent transmission via a blood transfusion²⁰ led credence to the hypothesis that the syndrome was caused by an infectious agent that was blood-borne.²¹

At the time, about 50% of the Factor VIII concentrate used in the UK was imported and derived from USA-donor plasma. Concerns were expressed during 1983 over the continued importation of these products. Nevertheless, the Government was advised to continue importation by both the Committee on Safety of Medicines²² and by the Haemophilia Society.²³ The Haemophilia Society and the World Federation of Haemophilia both published information for patients concerning AIDS, in which people with haemophilia were advised to continue treatment with USA-derived coagulation factor concentrates.^{14,24,25}

A retrovirus, later named the human immunodeficiency virus (HIV), was found to be responsible for the disease. It was initially designated human T-lymphotrophic virus type III (HTLV3) and is referred to as such in early literature. HIV was first isolated²⁶ by researchers associated with the Institute Pasteur in Paris in 1983 but was not proven to be the agent responsible for AIDS until 1984.²⁷ This discovery, and the development of methods for culturing the virus, enabled a blood screening test to be developed (see section 5.2) and methods for the inactivation of the virus in coagulation factor concentrates to be devised (see section 3.1).

The development of a blood-screening test also enabled patients to be tested, demonstrating that many people with haemophilia had been infected before the introduction of heat treated concentrates and donor- screening.²⁸ In Scotland about 80 people with haemophilia were infected, about 20 of whom are understood to have been treated only with SNBTS Factor VIII²⁹ and are presumed to have been infected via that route. How other patients were infected is not known to the SNBTS.

Whether or not consent for HIV-testing should be obtained from patients was the subject of ethical debate within the medical profession. This was eventually resolved at the annual meeting of the British Medical Association in July 1988 where it was decided that consent should be obtained and that patients should be informed of the result.³⁰

1.6 Supply of Plasma Products

Plasma products were obtained by the NHS either from NHS manufacturers or from commercial companies. The UK NHS manufacturing facilities were:

- the Blood Products Laboratory (BPL), Elstree (still in operation),
- the Plasma Fractionation Laboratory (PFL), Oxford (closed 1992 and absorbed into BPL), and
- the Protein Fractionation Centre (PFC), Edinburgh (closed 2008).

In the period 1969-1974, haemophilia A in the UK was treated mainly by cryoprecipitate, with Factor VIII concentrate (from both NHS and commercial manufacturers) representing only 23% of the Factor VIII used.

By contrast, during the same period, 80% of Factor IX therapy, used in the treatment of haemophilia B, was in the form of NHS concentrate with plasma making up the remainder. (Haemophilia B is much less common than haemophilia A and so less plasma needs to be processed to supply all patients.)

Commercial Factor VIII concentrates were first licensed for use in the UK in 1973. Supply of NHS Factor VIII concentrate was insufficient to meet growth in demand, causing leading haemophilia doctors³¹⁻³⁵ and the UK Haemophilia Society³⁶ to press for the purchase of commercial products on the grounds that 90% of patients were receiving sub-optimal treatment and that failure to purchase commercial products was unethical.

In the decade that followed (1975-1984) use of Factor VIII in the UK increased almost 4-fold, with imported commercial Factor VIII providing half of the total quantity administered during this period.³⁷ The predicted UK requirement² of 40 million units per annum for all types of treatment (including cryoprecipitate) was exceeded in 1977. Total Factor VIII usage continued to increase thereafter, reaching 80 million units per annum in 1984,³⁷ 160 million units per annum in 1994 and 280 million units per annum by 2004.³⁸

Central DHSS contracts were established for the purchase of commercial Factor VIII concentrates and authority to place orders was restricted to the Directors of Haemophilia Centres, or their nominees.³⁹ The central DHSS contracts for supply of Factor VIII expired on 30th April 1979 and were not renewed. Individual authorities were advised to make their own arrangements for purchase from 1st May 1979, with the Demanding Authorities for purchase being Haemophilia Centre Directors or their nominees.⁴⁰

The SNBTS distributed its own products, which were supplied to the NHS without charge.

2. Self-Sufficiency

2.1 General

The 28th meeting of the World Health Assembly in 1975 urged that member states should aim to be self-sufficient in the supply of blood products based on voluntary, unpaid donations as it had been shown that the viral marker rate within such a donation system was lower than within the paid donor system. Member states were specifically urged to “*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 the recipients of blood and blood products.*” (Resolution WHA 28/72).

In order to achieve national self-sufficiency, the following elements were required.

- an accurate forecast of demand
- a sufficient supply of plasma for fractionation
- the necessary manufacturing know-how and skills
- a sufficient manufacturing capacity

For a given forecast of demand, both the quantity of plasma for fractionation and the manufacturing capacity required are determined by the yield of the manufacturing process. An accurate estimate of product yield is therefore a critical factor in planning for self-sufficiency.

A commitment to achieving UK self-sufficiency was announced on 22nd January 1975 by the Secretary of State for Health and Social Security with further announcements on 25th February 1975 and on 6th May 1975 concerning the allocation of funding and its distribution.

The objective of UK self-sufficiency was later endorsed by the Under-Secretary of State for Health and Social Security on 15th December 1980, during a parliamentary debate on the Blood Transfusion Service, and additional funding of £1.25M to increase output of Factor VIII from BPL was provided.

An account of the measures taken to increase output of Factor VIII from BPL throughout this period is available.⁴¹ Annual output of Factor VIII from BPL increased over 3-fold between 1975-1977 and then doubled again between 1980-1983.

2.2 Scotland

The SNBTS provided cryoprecipitate and Factor VIII concentrate for the treatment of haemophilia A. Cryoprecipitate was available on demand, but by the late 1970s use of Factor VIII concentrate exceeded output from the SNBTS.

Considerable efforts were made by the SNBTS to meet the increasing demand for Factor VIII concentrate and Scotland ultimately became one of few countries to ever achieve self-sufficiency from unpaid volunteer donors. How this was achieved is summarised according to each of the elements noted above.

Forecast of demand

The original estimate from the early 1970s of UK demand² of 40 million units of Factor VIII per annum (equivalent to 0.8 units per head of population) was accepted in Scotland for planning purposes. However, by the late-1970s, it became evident from retrospective data on actual usage that demand had not plateaued at 40 million units and was continuing to rise. A fresh analysis was undertaken by the SNBTS which forecast a rise to 2.5-3.0 units per head of population,⁴² (equivalent to a UK demand of up to 160 million units per annum). The SNBTS targets for increasing the supply of plasma for fractionation were revised accordingly.

Plasma supply

There are two ways in which plasma can be obtained, either from a whole blood donation or by taking only plasma from a donor and returning red cells to them by a process known as plasmapheresis (the procedure still used to collect commercial, paid donor, plasma in the USA).

The latter procedure was introduced in the USA in the 1960s. A critical factor about the USA is not the use of plasmapheresis per se, but the volume of plasma that USA regulations allow to be collected from each donor. Formerly 1.2 litres per week i.e. up to 60 litres per donor per year, it is even more now. This allowed the USA to produce very large quantities of plasma derivatives and is why most of the world still depends on the USA as its source of plasma products. Other countries limit plasma collections because of concerns about the health of donors. The UK Guidelines for the Blood Transfusion Services in the UK permit a maximum of 24 donations (about 12 litres) per year. The Council of Europe Guidelines for the Preparation, Use and Quality Assurance of Blood Components permit up to 33 procedures or a maximum of 25 litres of plasma per year.

The collection of large volumes of plasma depends on the donors being motivated by payment. Despite these differences between countries in the treatment of donors, Regulatory Authorities generally approve the plasma products derived from USA paid donors who supply manufacturers in the USA and elsewhere with plasma for fractionation.

In the UK, most donations are taken in the form of whole blood. Plasmapheresis for special donors with high levels of antibodies was used and its use for 'normal' plasma was considered, but did not replace whole blood collection as the major form of donation. All UK donations adhere strictly to national and international guidelines concerning the volume and frequency of donation. All UK donations were, and continue to be, from unpaid volunteers.

Factor VIII is unstable in plasma. Therefore, plasma must be frozen to preserve factor VIII activity, preferably within 6 hours of donation. Consequently whole blood donations must be processed soon after donation, leaving plasma-depleted

red cells for transfusion instead of whole blood, a practice known as component therapy.

Use of whole blood was standard hospital practice during the 1970s and the concept of component therapy represented a significant change to established medical practice. The attempt to move to component therapy, in order to release plasma for the preparation of Factor VIII, challenged blood transfusion services and hospital practices world-wide.

The SNBTS was unusual in targeting 100% component therapy. This was achieved, first by education of hospital doctors and then by meeting all requests for whole blood with a red cell concentrate, unless whole blood was specifically approved by a SNBTS clinician.

At no time, prior to 1998, did the SNBTS import plasma from other countries for the manufacture of its products. From 1998 the SNBTS imported plasma because of a ban on the fractionation of UK plasma, as a precaution against vCJD. This plasma was obtained from unpaid donors as far as possible in order to comply with World Health Organisation (WHO) guidance. The objective of achieving UK self-sufficiency ended with this vCJD precautionary measure. Imports of plasma for fractionation ended with the closure of PFC.

Manufacturing know-how

Early coagulation factor concentrates were devised mainly by companies in the USA and essential know-how concerning manufacturing methods was held confidential for commercial reasons.

A chance encounter in 1966 between John Watt, Director of PFC and Dr Alan Johnson, an academic expert from the USA, led to a collaboration from which the SNBTS introduced new intermediate-purity concentrates of Factor VIII (in 1974) and Factor IX (in 1972). This knowledge was shared with PFL & BPL and the Commonwealth Serum Laboratories (CSL) in Australia, enabling these centres and PFC to be the first plasma fractionators in the not-for-profit sector to be capable of manufacturing these products.

Manufacturing capacity

By the mid-1960s it was recognised that increased supplies of plasma products would be required as a result of medical advances and that the SNBTS facilities for plasma fractionation would not be adequate. Planning for a new centre in Scotland (PFC Liberton) was begun and was co-ordinated with plans for the construction of a major extension to BPL Elstree. The new BPL extension opened in 1972 and the new PFC facility opened in 1975.

The design of both PFC and BPL was based primarily on the production of albumin as this was the product in greatest demand at that time and the UK requirement for coagulation factor concentrates had still to be defined. Once the

commissioning of PFC was complete, the SNBTS was soon able to meet Scotland's demand for albumin and concentrated on increasing the supply of Factor VIII, as demand in Scotland had begun to exceed the output planned from PFC.

PFC had been designed with a flexible capacity in order to accommodate plasma from the North of England as well as future growth in demand. The fractionation of plasma for England did not come to fruition, leaving PFC well positioned to accommodate unplanned growth in demand.

Factor VIII yield

In order to calculate the quantity of plasma to be collected and the fractionation capacity required it was necessary to estimate the output envisaged from the full-scale manufacturing operation. In Scotland, initial planning assumed a yield of 40% (i.e. 400 units of Factor VIII per litre of plasma),⁴³ similar to the UK assumption.²

Once PFC had been commissioned, the actual yield turned out to be less than half of this value. There were a number of reasons for this:

- there was less Factor VIII activity in plasma than expected, due to the instability of Factor VIII,
- process yield was less than expected due to the instability of Factor VIII and to difficulties of manufacture in large-scale production,
- product yield was less than expected because of the relatively large volume occupied by samples taken to comply with Good Manufacturing Practice (GMP) guidelines.
- the assay method used in the UK to determine the amount of Factor VIII in each vial was changed in December 1976 to improve accuracy. Although the new assay method was much more reproducible, the amount of Factor VIII activity measured was lower than had been obtained with the previous methods, effectively reducing product yield.

In order to increase yield of Factor VIII, a programme of research was undertaken at PFC which involved careful optimisation of process conditions⁴⁴ and the development of a new technology for the efficient recovery of cryoprecipitate on a large-scale.⁴⁵

Subsequently, a new means of stabilising Factor VIII activity was discovered at PFC⁴⁶ which was to enable further processes to be developed for the inactivation of the hepatitis C virus and to increase purity without an unacceptable loss of yield (the method was also used subsequently by other manufacturers to stabilise Factor VIII concentrates, both plasma-derived and recombinant).

Meeting demand

The volume of fresh frozen plasma provided by the SNBTS for fractionation was increased by 3.7-fold between 1977 and 1983. Over the same period, Factor VIII yield per litre of plasma was increased by more than 60%.

These achievements, taken together, not only enabled the SNBTS to meet Scotland's demand for Factor VIII concentrate by 1983 but also allowed a stock of Factor VIII concentrate to be established that would support the early introduction of heat treatment.

This is illustrated in the table below which gives the quantity of Factor VIII concentrate used in the UK per head of population; the quantity provided by the SNBTS to Scotland per head of population and the relative proportion of concentrate provided by the SNBTS each year from 1978 to 1988.

The Total Amount of Factor VIII Concentrate Used in the UK and the Amount of SNBTS Factor VIII Concentrate Supplied to Scotland, 1978-1988 (measured in International Units (IU))

Year	Amount used in UK³⁷ (IU/head pop.)	Amount issued to Scotland by SNBTS (IU/head pop)	Amount issued to Scotland by SNBTS (% UK use)
1978	0.60	0.36	60
1979	0.72	0.42	58
1980	0.86	0.63	73
1981	1.01	0.87	86
1982	1.20	0.95	79
1983	1.17	1.20	103
1984	1.32	1.36	103
1985	1.29	1.17	91
1986	1.48	1.07	72
1987	1.47	1.78	121
1988	1.63	1.83	112

Notes:

- (i) Factor VIII concentrates have been produced by the SNBTS since 1956 and production data are available from that date.
- ii) The figures exclude the use and supply of cryoprecipitate for the treatment of haemophilia A.
- (iii) In addition to the amounts of Factor VIII concentrate issued by the SNBTS that are shown in this table, the SNBTS held stocks of finished product at PFC to provide cover for emergencies and contingencies.
- (iv) Factor VIII concentrates have a shelf-life of two years and may therefore not be used in the year of issue.
- (v) International Units (IU) are a measurement of biological (functional) activity (e.g. factor VIII activity) based on a comparison with a defined international standard preparation.

It can be seen from the table that supply of SNBTS Factor VIII concentrate fell in 1985, following the introduction of heat treatment, and in 1986 during the transition to the more severely heat treated SNBTS Factor VIII concentrate, Z8, before increasing beyond UK use in 1987-1988. To the best of SNBTS knowledge, no commercial Factor VIII concentrate was purchased by Scotland's Health Boards during 1985-86, suggesting that Scotland remained self-supporting during this period. By contrast the majority of Factor VIII concentrate used in England & Wales prior to 1989 was imported.³⁷

The UK Haemophilia Centre Doctors Organisation (HCDO) holds detailed information on the treatment of haemophilia³⁷ but does not normally provide

separate information for different areas of the UK (i.e. England, Scotland, N. Ireland & Wales). However, the SNBTS has obtained information from HCDO for Scotland for the period 1978 – 1984. Products used in the treatment of people with haemophilia A and von Willebrand’s disease are given in the table below and include cryoprecipitate, supplied on-demand by the SNBTS and imported concentrates from commercial suppliers as well as from the SNBTS.

Factor VIII Products Used in Scotland, 1978-1984

Year	SNBTS Cryoprecipitate Million IU FVIII (% total)	SNBTS Concentrate Million IU FVIII (% total)	Commercial Concentrate Million IU FVIII (% total)	Total Million IU
1978	1.35 (39)	1.65 (48)	0.45 (13)	3.45
1979	1.24 (33)	1.76 (47)	0.72 (20)	3.72
1980	1.48 (24)	3.84 (61)	0.97 (15)	6.29
1981	0.90 (16)	3.48 (62)	1.24 (22)	5.62
1982	0.57 (10)	4.79 (81)	0.55 (9)	5.91
1983	0.33 (5)	5.86 (89)	0.38 (6)	6.57
1984	0.30 (4)	6.89 (95)	0.05 (1)	7.24

It can be seen that the total amount of factor VIII administered to patients in Scotland doubled over this period with a substantial reduction in the use of cryoprecipitate and a marked increase in the use of SNBTS Factor VIII concentrate.

Although the SNBTS supplied cryoprecipitate on-demand for the treatment of haemophilia A and von Willebrand’s disease, the type of treatment given to patients (e.g. cryoprecipitate or concentrate) was determined by the treating physician, not by the SNBTS.

Supply of Factor IX Concentrate for the Treatment of Haemophilia B

The number of people with haemophilia B is about one tenth of those with haemophilia A; consequently provision of Factor IX concentrate by transfusion services was less difficult as the volumes required were much lower. The SNBTS supplied sufficient Factor IX concentrate for the treatment of haemophilia B from the late-1960s; nevertheless, of the total Factor IX concentrate used in Scotland in the early 1980s, some was commercial (i.e. 8.1% in 1980, 2.6% in 1981 and 1.3% in 1983). Some commercial heat treated Factor IX concentrate was also used in Scotland from April 1985 as the SNBTS ceased the supply of unheated Factor IX concentrate pending the introduction of SNBTS heat treated Factor IX concentrate in October 1985.

3. Development of Heat Treatment

3.1 International

Background

Eliminating the risk of hepatitis transmission via blood products has been the subject of research since the 1940s. Despite numerous investigations concerning a range of physical and chemical methods of virus inactivation, no suitable procedures were found that could be applied to coagulation factor concentrates.²⁸

Renewed efforts were made to solve this problem following the recognition during the 1970s that hepatitis was still being transmitted, despite blood donations being tested for the hepatitis B virus (HBV).

Coagulation factor concentrates were unstable and composed of heat sensitive proteins. Therefore inactivation of hepatitis virus(es) by heat without causing serious damage to the coagulation factors was not thought feasible until a report emerged from Germany in 1981 about a method for the pasteurisation (wet heat in solution) of Factor VIII.⁴⁷

The yield of factor VIII from this process was only 8% and was much too low to be viable for the general production of Factor VIII concentrate, but the fact that 50% of the factor VIII activity appeared to survive the pasteurisation step was sufficient to encourage further research.

The concept of applying heat treatment to Factor VIII concentrate after it had been freeze dried followed.⁴⁸ It was found that established products, or variants of them, could withstand heating at 60-68 °C for a number of hours before being damaged irreversibly. However, by early-1983, it had been found that heating in this manner at these temperatures was insufficient to inactivate the agent(s) of non-A, non-B hepatitis.⁴⁹

Risk of inhibitors to Factor VIII

The development of antibodies (inhibitors) to factor VIII is a very serious complication in the treatment of haemophilia, that may cause a patient to be almost impossible to treat, or to require extremely large doses of factor VIII. The possibility that factor VIII might be altered (damaged) by heat treatment and generate inhibitors⁵⁰ was an important consideration. In the absence of any evidence of benefit to the patient, there was concern that the administration of a heated product might do more harm than good. This remained the view of some experts⁵¹ even when evidence had become available⁵² that HIV might be inactivated by heat treatment procedures that had failed to inactivate the agent(s) of non-A, non-B hepatitis.

Subsequently, two heat treated products prepared in Europe were withdrawn from use after patients developed a high level of inhibitors,^{53,54} demonstrating

that concerns over possible adverse reactions to heat treated products were justified.

Factor VIII made safe from HIV by heat treatment

Evidence that HIV could be inactivated by heat treatment of Factor VIII concentrate was first obtained by the USA Centers for Disease Control (CDC) and Bayer in preliminary experiments undertaken in the Autumn of 1984.⁵⁵ Results from heating experiments at 68°C were summarised by CDC in a report⁵² that was published in the USA on 26th October 1984 and published in peer-reviewed journals in June and August 1985.^{56,57}

The SNBTS introduction of heat treatment

Data from these experiments were presented⁵⁸ by CDC on 2nd November 1984 at a conference in the Netherlands, at which the SNBTS was represented. As a result, the SNBTS decided to immediately dry-heat treat its established Factor VIII concentrate at 68°C, the highest temperature that its own or any other established Factor VIII concentrate had been shown to withstand.

Sufficient heat-treated Factor VIII concentrate for all patients was distributed by the SNBTS throughout Scotland and Northern Ireland on 10th December 1984. Unheated Factor VIII concentrate was re-called and all product stocks heat-treated. A stock of SNBTS Factor VIII concentrate of some 8 million units of factor VIII was available as a result of the increases in product yield and plasma supply discussed above. Heat-treatment of this stock enabled Factor VIII concentrate obtained from donations collected as early as October 1983 to be made HIV-safe.

The information from CDC caused many countries to decide to move to products that were dry-heat treated at 60-68°C. The UK Medicines Control Agency licensed commercial heat treated coagulation factor concentrates from February 1985, but the time required to manufacture, re-stock and distribute the new concentrates meant that unheated products from other suppliers continued to be used well into 1985 in the UK⁵⁹ and in other countries.⁶⁰ Clinical evidence demonstrating that HIV had not been transmitted by a Factor VIII concentrate from the USA which was dry-heated for 72 hours at 60 °C was first published in February 1985.⁶¹ No transmission of HIV via SNBTS coagulation factor concentrates took place after the introduction of heat treatment by the PFC in December 1984.

Inactivation of the agent of non-A, non-B hepatitis (HCV)

Although dry heating at 60 to 68 °C was sufficient to make products safe from HIV (with the exception of H.T. Factorate manufactured by Armour Pharmaceuticals) further advances were required to remove the risk of hepatitis infection and research was being progressed on a number of fronts

internationally. Of these, the low-yielding method of pasteurisation, pioneered in Germany, was the only procedure to have given encouraging results in patients.⁶²

The alternative method of heating, dry-heat treatment, was limited to temperatures in the range 60-68°C. It was unexpected therefore, when researchers at PFL (Oxford) found that a more highly purified preparation of Factor VIII concentrate⁶³ survived dry-heating at 80°C.⁶⁴ It was viewed with some astonishment by other fractionators at the time.⁶⁵ The principal objective of PFL/BPL was to supply a Factor VIII concentrate free from the risk of HIV transmission. Whether or not agent(s) responsible for NANBH would be destroyed was not known. Evidence that this product (8Y) did not transmit hepatitis required careful monitoring of recipients and the necessary study was only completed in 1988.⁶⁶

8Y was issued routinely in England from 18th September 1985, but output prior to 1989 was only able to meet about 30% of the Factor VIII concentrate needed in England & Wales, with commercial imports, that were not necessarily safe from hepatitis, continuing to provide the remainder.³⁷

Dry-heating of Factor VIII concentrate at 80°C was an extremely difficult technology to master and was not achieved, at this time, by any of the commercial companies, who continued to provide products heated at 60-68°C.⁶⁷

The commercial products which were approved for use in the UK at this time (information provided by Medicines and Healthcare products Regulatory Agency (MHRA)) are listed below.

Company	FVIII Concentrate	Method of Virus Inactivation	UK Approval Ceased
Alpha	Profilate-HT HT-Profilate	60°C/24h, suspension 60°C/24h, dry	1989
Armour	HT Factorate	60°C/36h, dry	1986
Baxter	Hemofil T	60°C/72h, dry	1989
Bayer	Koate	none	1988
	Koate HT	68°C/72h, dry	1992
Behringwerke	Haemate HS	60°C/10h, solution	1996
	Haemate P	60°C/10h, solution	
Immuno	Kryobulin TIM	60°C/10h, steam	1992

Because of the difficulty of heating Factor VIII concentrate at 80°C, most commercial companies turned instead to a chemical method for virus inactivation (solvent- detergent treatment) which was proven to be effective against non-A, non-B hepatitis in 1988.⁶⁸ New commercial products prepared using this chemical treatment⁶⁷ were subsequently approved for use in the UK.

The success of these developments^{69,70} is illustrated by the fact that in a large study in the USA no person with haemophilia tested positive for HIV if born after 1984, nor for HCV if born after 1992, nor for HBV if born after 1993.⁷¹

Equivalent information for Scotland is not held by the SNBTS, other than that supplied to the investigation undertaken by the Scottish Executive in 2000. This disclosed that six people with haemophilia A contracted hepatitis C during the period September 1985 to December 1987, of whom two had been treated with cryoprecipitate, one with cryoprecipitate and SNBTS Factor VIII concentrate and three with SNBTS Factor VIII concentrate.

3.2 Development of Heat Treatment by the SNBTS

A detailed and comprehensive account of the development of heat treatment by the SNBTS was provided to an investigation undertaken by the Scottish Executive in 1999/2000. This account and a response to additional questions raised by the Scottish Executive are both available in the Scottish Parliament Information Centre (SPICE). These documents are included as Appendices A and B to this submission.

The chronology of key events was as follows:

1970s

- i. The SNBTS has been involved in research aimed at removing viruses from coagulation factors since 1970.

1981

- ii. SNBTS scientists began research on pasteurisation of coagulation factors in 1981 and then on dry-heat treatment also. Results were shared with scientists at PFL/BPL.

1983

- iii. Pilot batches of a pasteurised Factor VIII concentrate (named ZHT) were released by the SNBTS for clinical evaluation in 1983 and given to three patients, one of whom suffered an adverse reaction regarded as “*unacceptable*” by his clinician.

1984

- iv. It was concluded that a higher degree of purification was needed and research was begun for this purpose in collaboration with experts in the USA.
- v. In October 1984, 15 haemophilia patients who had been treated only with SNBTS Factor VIII concentrate tested positive for antibodies to HIV,²⁹ indicating that HIV had entered Scotland’s blood supply in donations used to manufacture batches of Factor VIII.
- vi. As soon as it was known that HIV might be inactivated by dry-heat treatment at 68°C,⁵⁸ PFC applied heat treatment at 68°C for 2 hours to Factor VIII concentrate and, following clinical evaluation, immediately (on 10th December 1984) distributed sufficient heat treated Factor VIII concentrate for all patients in Scotland and in Northern Ireland. A shelf-stock of some 8 million units of Factor VIII concentrate was also heat treated, enabling factor VIII from donations collected as early as October 1983 to be made HIV-safe. Unheated Factor VIII concentrate was recalled, heat treated and re-issued. Although it was later found that there had been HIV positive donations in some of the plasma pools associated with the first products that were heat treated, no HIV infections were transmitted, illustrating the importance of this very rapid introduction of heat treatment by the SNBTS.

1985

- vii. As a result of its research the SNBTS was able to modify the formulation of newly prepared batches of Factor VIII concentrate, enabling the time of heating to be extended from 2 hours to 24 hours to provide a greater margin of safety. Production of the revised product commenced in January 1985.
- viii. SNBTS scientists continued to carry out research to discover if dry- heat treatment of Factor VIII concentrate could be extended to a higher temperature.

- ix. This breakthrough was first achieved by researchers in England at PFL/BPL,^{63,64} who believed that the reason why an experimental preparation of Factor VIII concentrate could withstand heating at 80°C for 72 hours was because the preparation was some 10-times more pure than established Factor VIII concentrates.
- x. In order to implement this technology BPL had to develop a new product (8Y) and design, install and commission a new bio-pharmaceutical manufacturing process. Evidence that 8Y could be prepared successfully in routine, large-scale manufacture, and the resultant product tolerated clinically, was not available until late-1985.

NHS scientists at the BPL were first in the world to develop a Factor VIII concentrate that could withstand dry-heating at 80°C. Although this product was issued routinely by BPL from September 1985, output was insufficient and patients in England remained largely dependent on imported Factor VIII concentrates heated at 60-68°C, which continued to be available in the UK until October 1992 (see section 3.1 (table)).

- xi. SNBTS research on increasing purity (see point iv above) advanced quickly during 1985, promising a product 10-times more pure than 8Y and the possibility that temperatures beyond 80°C could be applied, should this be necessary to inactivate hepatitis viruses.
- xii. In October 1985, as a result of a joint development, the SNBTS and BPL both introduced Factor IX concentrates which were dry-heat treated at 80°C for 72 hours after the established products had been reformulated and critical safety studies in animals⁷² had been completed. This SNBTS product was named HT DEFIX. The unheated version of the SNBTS Factor IX concentrate (DEFIX) was recalled.
- xiii. In October-November 1985, SNBTS researchers discovered that it was not its purity *per se* that had enabled BPL's new Factor VIII concentrate (8Y) to tolerate heating at 80°C, but the way that the product had been freeze dried (later found by SNBTS researchers to be specifically due to the formation of a particular ice-crystal structure which had occurred by chance during the freezing process).
- xiv. Also in late-1985, information emerged that HIV had been transmitted by an imported, commercial dry-heat treated Factor VIII concentrate, causing the HIV-safety of dry-heated products to be questioned.

1986

- xv. Continuing concern over HIV, together with the knowledge that freeze drying, rather than a high degree of purity, was the key to heating Factor VIII concentrate at 80°C, resulted in a decision that research on increasing the purity of factor VIII be suspended and that a lower-purity product, that could withstand heating for 72 hours at 80°C, be developed as quickly as possible.

- xvi. This meant a new product had to be developed and a new biopharmaceutical manufacturing process designed, installed and commissioned. In order to achieve this as quickly as possible, the SNBTS designed a process similar to that of BPL, using procedures already familiar to the SNBTS and compatible with existing SNBTS operations. Pilot-scale experiments were completed in mid-1986 and full-scale manufacture of the product (Z8) was begun in August 1986 with batches of Z8 released for clinical trial in December 1986.

Scotland was second in the world to develop severe dry-heat treatment technology successfully. The SNBTS was able to produce sufficient Factor VIII concentrate for all patients in Scotland, enabling Scotland to lead England (and all other countries) by a number of years in providing sufficient Factor VIII concentrate for the treatment for its haemophilia patients that was safe with respect to hepatitis C.

- xvii. Preliminary clinical evidence that 8Y might be hepatitis-safe was presented to a meeting of the UK Haemophilia Centre Directors Organisation in October 1986.⁷³

[Note: This clinical trial was completed in 1988⁶⁶ but did not meet international guidelines⁷⁴ for studies of this type (see section 4.4). The clinical trial of 8Y was therefore repeated, with recipients being tested for hepatitis C, instead of markers of NANBH. This second clinical trial was completed in 1990⁷⁵ and confirmed the safety of 8Y with respect to hepatitis C.]

1987

- xviii. Clinical trials to establish the tolerability and efficacy of Z8 were completed in April 1987 and the product was issued routinely thereafter. Clinical evidence confirming that Z8 was safe with respect to transmission of HCV was available in 1993.⁷⁶

- xix. In order to reduce the risk of hepatitis infection, patients in Scotland had been allocated specific batches of Factor VIII concentrate to minimise exposure to multiple donors. As the safety of Z8 had still to be confirmed, it was agreed that this system of batch dedication should be retained. In order to accommodate this safety measure, patients already being treated with a specific batch of 68°C heated Factor VIII concentrate continued with this product until the batch in question was completed.

1988

- xx. Some early batches of Z8 could not tolerate heating at 80°C and were heated at 75°C instead, as this was superior to all alternative products that were available in Scotland. Laboratory virus inactivation studies supported this approach.

- xxi. Scottish demand for Factor VIII concentrate continued to increase, requiring a greater output of Factor VIII from the SNBTS. Heating Factor VIII concentrate at 80°C was an immense challenge and some additional technical difficulties emerged during routine production which prevented the SNBTS from increasing its output of Z8 temporarily. Some commercial product continued to be purchased by Haemophilia Directors in Scotland to provide the additional supplies required to satisfy the increased demand.

1991

- xxii. The SNBTS went on to develop a new high-purity Factor VIII concentrate (Liberate[®]) to supersede Z8. This utilised solvent-detergent treatment⁶⁸ to inactivate HIV and HCV and was introduced successfully in 1991.

4. Evaluation of Heat Treated Products

4.1 Background

In order to develop procedures for the production of virus-safe coagulation factor concentrates for the treatment of haemophilia it was necessary to establish that:

- the product could be manufactured successfully
- the product was clinically effective and well tolerated
- virus(es) of concern were destroyed by the procedure

Much research was undertaken before the viruses of concern had been discovered. The nature, properties and characteristics of the infective agents were not known, nor was it known how much virus an inactivation procedure would have to destroy in order to make a product safe. These limitations restricted investigators to the following approaches.

4.2 Experiments with Model Viruses

Studies were undertaken in research laboratories using viruses that it was hoped would behave in a manner similar to the agents responsible for hepatitis C or AIDS. Such studies involved small-scale experiments performed in suitably equipped microbiological containment facilities and are commonly described as ‘spiking’ studies i.e. adding marker viruses to a sample to allow measurements of reduction after treatment. Studies of this type have been required for process validation by European regulatory authorities since 1992.²⁸

There were two reservations associated with this type of study. First, the marker viruses selected might not perfectly represent the unknown virus of concern. Second, the small-scale procedure might not simulate industrial-scale manufacture accurately.

The SNBTS utilised ‘spiking’ studies with marker viruses to investigate possible heat treatment procedures from 1982 and subsequently performed studies of this type for BPL, which did not have a specialist facility for this purpose.

This work was strictly controlled by the SNBTS and was performed either off-site or in a specialised containment laboratory removed from manufacturing areas. Because of these tight controls there was no possibility that a virus used in such ‘spiking’ studies could inadvertently contaminate the preparation of clinical products. On no occasion was any virus added to clinical products.

4.3 Animal Studies

The SNBTS has never undertaken hepatitis infectivity studies in chimpanzees, nor in any other animal.

A pedigree serum (i.e. a pool of serum with a defined amount of non-A, non-B hepatitis (NANBH) infectivity that had been established by infectivity studies in chimpanzees) for NANBH was established in 1979 in the USA and opened the way for infectivity experiments to be undertaken in susceptible animals. The chimpanzee was the established model, but few animals were available and there were ethical concerns over the use of primates in experiments in which positive controls were necessary.

Studies in chimpanzees were undertaken by a number of organisations using Factor VIII concentrate prepared from plasma to which pedigree NANBH sera was added. Three heat treatment procedures that were effective in preventing infection in chimpanzees failed to prevent NANBH infection in humans who were treated with a comparable product prepared from normal plasma (see table).

Virus Inactivation Method	Chimpanzees infected/treated	Humans infected/treated
Dry-heat in solvent, 60°C/24h	0 / 4 ⁷⁷	5 / 18 ⁷⁸
Dry-heat, 60°C/30h	0 / 3 ⁷⁹	2 / 2 ⁸⁰
Dry-heat, 60°C/72h	0 / 4 ⁸¹	11 / 13 ⁸²

Although the reason for this discrepancy was not known, it was concluded that the chimpanzee was not a suitable model for studies of this type.

4.4 Monitoring Patients

The SNBTS does not treat patients with haemophilia and does not have access to their medical records. Therefore, issues relating to individual patients required to be addressed to their treating clinicians. However, there are some general comments that can be offered.

Monitoring patients for infection from established products

Where a medicinal product is associated with a known side-effect or complication, the prescribing doctor is expected to monitor the health of the patient in this regard.

When Factor VIII concentrates were first introduced, the importance of monitoring patients for evidence of hepatitis infection was stressed by the International Society of Thrombosis and Haemostasis.⁸³ Monitoring recipients of blood plasma products for evidence of a transfusion transmitted infection is standard practice today and is required by regulatory authorities.

Tolerability and efficacy of new products

Before a new or modified product can be introduced it must be shown to be clinically effective in the treatment of haemophilia and to be well tolerated in recipients.

The SNBTS arranged for such studies to be undertaken on its products via Haemophilia Directors, with the understanding that informed consent would always be obtained. Obtaining consent was a matter for the relevant Haemophilia Director. However, SNBTS protocols made it clear that consent was needed.

Monitoring new products in previously untreated patients

By the early 1980s, the monitoring of liver function in haemophiliacs had shown that almost every patient who was treated with established Factor VIII concentrates would be infected with NANBH on their first infusion.^{84,85}

These observations, together with the failure of the chimpanzee model, led to the view that the only way in which it could be discovered if products treated to destroy viruses were hepatitis-safe was by monitoring patients who had not previously been treated with a blood product and whose physician had determined that treatment with Factor VIII concentrate was required. Such a patient was referred to as a 'previously untreated patient'.

A trial protocol was drawn up in 1984 for this purpose by the International Society for Thrombosis and Hemostasis. It was recommended that 10 batches of a treated product should be administered to 20 patients, with each batch being assigned to two patients and liver function tests performed for 6 months. The rationale for this protocol and the difficulties associated with such studies have been reviewed.⁷⁴

SNBTS products were not entered into a 'previously untreated patient' study until 1987, when there was a high degree of confidence that the products concerned (Z8 and HT DEFIX) would be safe with respect to NANBH. This study was completed in 1993 and confirmed that both Z8 and HT DEFIX were safe with respect to hepatitis C.⁷⁶

5. Selection of Donors and Testing of Donations for Markers of Hepatitis Viruses and Human Immunodeficiency Virus (HIV)

5.1 Selection of Donors

Questioning prospective donors about possible exposure to transfusion transmissible infection (TTI) is of vital importance to the safety of blood and blood products. This remains the case even when a highly sensitive and specific test for a given infectious agent is in place, since a period of time elapses between exposure to the infection and the test becoming positive (the "window period").

In March 1983, before any specific test for the AIDS virus was available, the USA Centers for Disease Control identified groups of people at increased risk of AIDS.²¹ Persons in these 'high-risk' categories were asked to refrain from giving blood. The SNBTS adopted this approach and initiated a series of actions, including preparing and issuing information to donors during May/June 1983.⁹⁵

SNBTS continued to develop new methods of donor screening for high risk behaviour as better epidemiological evidence became available, and in 1992 began the phased introduction of private, personal interviews for new donors, some years before the rest of the UK adopted this practice. The beneficial impact of effective donor screening became apparent when testing for anti-HCV was introduced. The prevalence in Scottish blood donors was found to be only 10% of that of the general population in Scotland.

Criteria for the selection of donors are now established nationally in the UK by the Joint Professional Advisory Committee (JPAC); they conform with EU legislation (transformed into UK law as the Blood Safety and Quality Regulations), and are kept under continuous review.

5.2 Testing for HIV

In 1984, 1000 unselected UK blood donors were tested for antibodies to HIV in a research study, all of whom were seronegative⁹⁶ Although the HIV test that was used had been developed by researchers in the UK, they had used material from the USA that had been supplied for research only. The UK Department of Health requested permission from the USA to use this test for routine screening of NHS blood donors, but the USA government insisted that test kits should be obtained from one of the USA companies to whom commercial licences had already been awarded.⁹⁷

Of the USA companies licensed to commercialise a screening test for HIV, first approval from the USA Food and Drug Administration (FDA) was granted to Abbott in March 1985, but at that time the supply position for the UK was not clear⁹⁸.

The decision on when to begin testing was taken by the DOH where it had been decided that all test kits should be evaluated by the Public Health Laboratory

Service (PHLS). Thereafter selected kits would be field-tested by BTS prior to a suitable kit(s) and a date of introduction being decided. PHLS did not complete their first phase evaluation until end-July. Field testing by BTS then took a few weeks; hence the start date of 14th October 1985. SNBTS centres began testing earlier to ensure that all SNBTS blood components issued from that date were from donations screened for HIV.

As had been the case when testing for hepatitis B was introduced in 1970, SNBTS committed to the "lookback" procedure when HIV testing began (in common with the other UK transfusion services). This meant that attempts were made to trace, inform and offer testing to patients who had been transfused with components donated prior to the introduction of testing by donors now discovered to be positive for HIV antibodies. In Scotland this led to the discovery of 9 such patients.

Plasma products which utilised appropriate processing technology (e.g. heat treatment) were regarded as safe from HIV transmission prior to the introduction of donation testing. Therefore no attempt was made by regulatory bodies to prevent the release of essential products obtained from untested donations for some time after the development of HIV tests. This meant that products from HIV untested donations, but processed and regarded as safe e.g. by heat treatment, remained on the market for some years. However, regulations were slowly introduced by the European Pharmacopoeia (EP) to require that products placed on the market were exclusively derived from donations tested for HIV. No HIV transmissions have been associated with SNBTS plasma products released during this period.

These HIV-screening tests were based on detection of antibody to HIV and were not sufficiently sensitive to reliably identify contaminated batches of Factor VIII or Factor IX concentrates. This is because both pooling of donations and product purification leads to the dilution of antibodies. The SNBTS used the HIV-ELISA (Enzyme-linked immunosorbent assay) to screen batches of Factor VIII concentrate routinely when the test became commercially available, although the test had been designed and licensed for testing samples of blood plasma or serum, not plasma products. Earlier batches of SNBTS Factor VIII concentrate were also tested using the HIV-ELISA, including batches implicated in the transmission of HIV. No positive batches were ever detected (SNBTS unpublished results).

Detection of HIV in concentrates required the development of more advanced analytical technology, which was not achieved until 1991.^{99,100}

Tests for antibody to HIV have progressively increased in sensitivity since 1985, but still cannot detect the very earliest evidence of infection. Thus some individuals may donate during the period (typically a few weeks from exposure) before antibodies are detectable ("window period"). One patient in Scotland is known to have been infected with HIV from such a donation of platelets that contained no detectable antibody to HIV, even though that donation had been tested.

In January 2003 the SNBTS additionally implemented routine screening of every donation for the genetic material of HIV, thereby reducing the duration of the “window period” and the risk of failing to detect the virus to a level that is approaching the irreducible.

5.3 Testing for Hepatitis

5.3.1 Hepatitis B

The SNBTS introduced Hepatitis B screening of blood donations from late 1970, ahead of most of the rest of the UK transfusion centres. The initial test used a fairly insensitive technique (electroimmunopheresis). Even though this assay was fairly insensitive, it was still highly effective in identifying infectious donations. Experience with more sensitive radioimmunoassays for the surface antigen of the HBV virus (HbsAg), led to the SNBTS introducing these assays ahead of most blood services in the world. The SNBTS was regarded as expert in HBsAg testing and commercial companies such as Abbott used the SNBTS as expert testers to evaluate these more sensitive assay techniques. Today, the SNBTS uses the acknowledged most sensitive HBsAg assay (Abbott Prism) for screening blood donations.

5.3.2 Hepatitis C

The SNBTS had begun a dialogue with Ortho Diagnostics Systems Ltd, the company developing the HCV test, in July 1988 and was advised by the company that the test could be available for use towards the end of 1989. In planning for the introduction of the HCV test the SNBTS was also in dialogue with the SHHD, and was notified by the SHHD in August 1989 that decisions concerning the introduction of a HCV test would be taken by the Department of Health. There was an understanding on the part of the SHHD that if the HCV test was to be introduced for use, this would be effected simultaneously across the UK. When a test became available the SNBTS advised the CSA BTS Sub-committee (in late 1989) that it expected that the test would be introduced in mid-1990; costings for purchase and use of the test were provided by the SNBTS to the CSA/SHHD in November 1989. The SNBTS was preparing to introduce the HCV test as soon as it was authorised to do so and the necessary funding had been provided. The SNBTS has documentary evidence of these events.

The SNBTS was notified in August 1991 that the Minister of State for Scotland had agreed to the introduction of routine testing of blood donations for HCV from 1st September 1991. The necessary funding had already been made available to the SNBTS. The UK (including the SNBTS) introduced routine donation testing for hepatitis C on 1st September 1991. This is later than several other countries which used the first generation of commercial HCV tests, despite its limitations. The date for introducing a HCV test was a UK Departments of Health decision and all UK transfusion centres were expected to adhere to this date. The West of Scotland (Glasgow) BTS was one of six UK centres which participated in an evaluation of both the first and second generation tests, with the latter evaluation taking place some months

prior to acceptance of the second generation test for routine use. The UK was one of the first countries to utilise the second-generation test and SNBTS centres other than Glasgow began testing about one month prior to 1st September 1991 to ensure that their systems were working properly. All positive donations detected during these trials were removed by the SNBTS and blood components issued by the SNBTS from 1st September 1991 were derived only from tested donations.

Plasma products manufactured using the processing methods available in the early 1990's were regarded as having low risk of HCV transmission prior to the introduction of donation testing. Despite this low risk, the European regulators, the Committee for Proprietary Medicinal Products (CPMP) decided that products from non HCV tested donations should not be released for issue after 31 December 1992. However, regulatory authorities allowed the stock of essential products from untested donations to continue to be used until the end of 1995. No HCV transmissions have been associated with SNBTS plasma products released in this manner.

5.3.2.1 Hepatitis C Look-back

In the run-up to the introduction of testing for hepatitis C, a Working Party established by SNBTS Directors was asked to prepare guidelines on the counselling and management of donors with positive tests (report dated February 1991). The Working Party in its report advised that the lookback procedure should be implemented, as was standard practice for hepatitis B and HIV. This was a subject of intense controversy at the time, however, the scant information available about HCV suggested that it was a relatively benign condition in the great majority of those infected. Additionally, there was great concern about the numbers of positive donors anticipated, and the potential resource implications of what might be a massive lookback exercise. In the event, most countries, including the UK, at that time, adopted a policy of not implementing lookback.

In South East Scotland BTS, however, lookback was initiated as soon as testing commenced, and this "pilot study", the results of which were published in 1994⁸⁶, established the feasibility and effectiveness of the process, and led to the adoption of systematic lookback as UK national policy in 1995. In Scotland, when the outcome of lookback was reviewed by the SHHD and the DoH in 1998, the total number of patients whose HCV status was discovered through the lookback process was 133. (Haemophiliacs, renal unit patients and bone marrow transplant recipients had been already screened routinely and were therefore excluded from the final results).

5.4 Testing for Raised Liver Enzymes (ALT)

Before the hepatitis C virus was discovered, it was suggested that a test for general inflammation of the liver, such as the level of the enzyme ALT (alanine aminotransferase), might be an indirect (surrogate) marker for non-A, non-B hepatitis (NANBH).

Many factors could result in a raised ALT value, such as obesity, alcohol consumption and taking pharmaceutical drugs such as the contraceptive pill, in addition to a viral infection. Accuracy of the test was poor⁸⁷ and there were concerns that only a minority of donors infected with NANBH would be discovered and that a large number of healthy donors would wrongly test positive.

The topic was the subject of considerable international and national debate throughout the 1980's and was reviewed by a committee of experts for the Council of Europe in 1987 which concluded that "*The committee cannot give a general recommendation on the introduction routinely of non-specific tests for evidence of NANB infectivity of blood donors.*"⁸⁸ Some countries introduced surrogate testing, but most decided against.

During this debate the SNBTS proposed that ALT testing should be introduced in the UK because of its interpretation of the forthcoming Consumer Protection Act, describing this view as "*irrational, perhaps, but inescapable*" in a letter to the Lancet.⁸⁹

On the advice of experts no decision was taken by the UK Departments of Health to use the ALT test as it was believed that the loss of so many healthy donors would disrupt the blood supply and do more harm than good. Applications for funds to perform this test made by the SNBTS to SHHD during 1986 and 1987 were not supported.

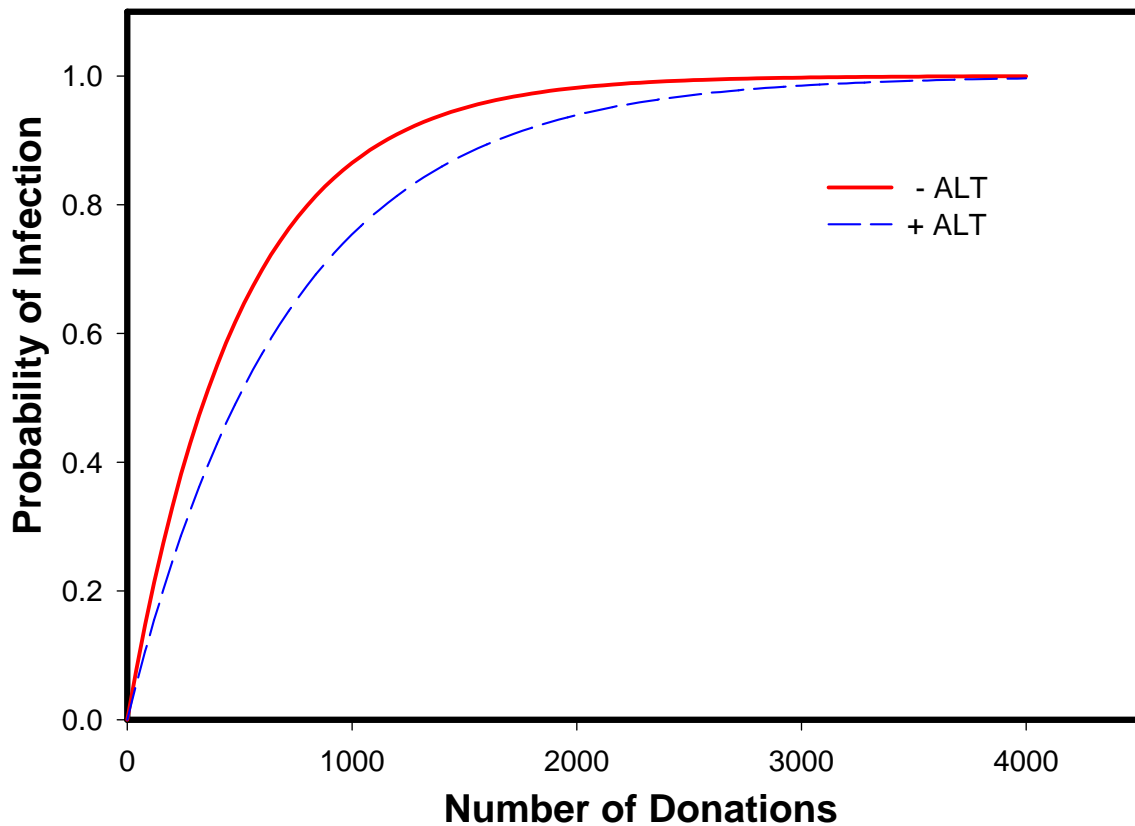
Had the test been used in the UK and performed as well as its advocates hoped, the risk of infection to people with haemophilia would not have been reduced because of the very large numbers of donations required for their treatment

The risk of a patient being infected is related to the amount of treatment, specifically the number of donor exposures, with blood products. This is illustrated in the figure below, in which the probability⁹⁰ of a recipient being exposed to an agent responsible for NANBH, with and without ALT testing, is shown against the amount of treatment received (calculated assuming a prevalence of NANBH in the blood donor population of 0.3%). It should be noted that a typical person with severe haemophilia is treated with 2000 IU of Factor VIII thirty times per annum, throughout their life. By the 1980s, each batch of SNBTS Factor VIII concentrate was prepared using plasma from over 2000 donations.

Treatment with cryoprecipitate at a level employed in Scotland in 1974⁹¹ involved exposure of adult haemophiliacs to over 300 donations per annum,

giving an estimated 60% probability of infection with NANB after 12 months and 85% after 24 months treatment.

Effect of ALT testing of blood donations on the probability of a recipient of a blood product being infected with hepatitis C



The SNBTS is not aware of any evidence of a lower incidence of hepatitis C in people with haemophilia in those countries that did undertake ALT testing.

Direct comparisons of ALT testing with testing for HCV have shown that many donors with hepatitis C were not detected using this approach and that the majority who tested positive by ALT did not have hepatitis C.⁹²⁻⁹⁵

However in 1991, the SNBTS carried out a study on the effectiveness of ALT testing. It was discovered that about 50% of donations that tested positive for HCV might also have been detected by ALT testing.

5.5 Collection of Blood Donations in Prisons

In the 1960s and 1970s people in prison were allowed to contribute to society by donating blood, a practice that was encouraged by the Home Office and employed in most advanced countries.

The SNBTS had already begun to phase out collections in prisons during the early 1980s, when the practice was questioned by the UK Medicines Inspectorate. Current data held shows that this process was completed by March 1984. Prisoners were known to have a higher risk of hepatitis. The UK Chief Medical Officer acknowledged this in a letter copied to transfusion directors in 1975¹⁰² but advised that blood should still be collected from prisons if the donations were tested appropriately. One reason for this advice was the view that this practice was important in helping to rehabilitate prisoners back into society and it was strongly encouraged by the Home Office.

It should be noted that:

- prison inmates were not amongst the ‘high-risk’ groups for AIDS identified by United States Centers for Disease Control in March 1983,²¹ nor in January 1985.¹⁰³
- a recommendation from the FDA that blood should not be collected in prisons was first published in June 1995¹⁰⁴ and to the best of SNBTS knowledge is the only guidance to have been published on this matter by any regulatory authority.

5.6 Collection of Blood Donations from US Military Personnel

The SNBTS followed national and international policy in the selection of donors, which included the collection of blood from healthy volunteer USA citizens resident in the UK, including military personnel.

USA military donors were rejected if they exhibited high-risk behaviour or if they failed in some other way to meet the standards required for donation.

Epidemiological data indicate that the prevalence of hepatitis C amongst American navy personnel was comparable to that of the normal population of Scotland.¹⁰⁵

The prevalence of hepatitis C in Scotland meant that infection of heavily treated patients, such as people with haemophilia, was virtually inevitable via donations taken from the normal population.

6. Regulation and Control of Plasma Products

6.1 Introduction

Plasma products are prescription-only-medicines which are regulated under the UK Medicines Act of 1968 by the Medicines and Healthcare Products Regulatory Agency, (MHRA) (formerly the Medicines Control Agency and Medicines Division of the DHSS). According to these requirements, facilities for the preparation of plasma products must possess a manufacturer's licence and be subjected to regular inspection by MHRA.

Each product must also be approved for medicinal use by the granting of a product licence. Clinical studies required to support a product licence application for plasma products were authorised by MHRA using its CTX (clinical trial exemption) scheme.

In addition, products from each manufacturer are assessed by the National Institute for Biological Standards and Control (NIBSC), which is the National control authority for the UK and which authorises the release of each batch for clinical use.

6.2 First UK Licences for Factor VIII Concentrate

Early Factor VIII concentrates were approved by MHRA as follows:

Organisation	Product	Application	Approval
Baxter	Hemofil	December 1972	February 1973
Immuno	Kryobulin	December 1972	March 1973
Abbot	Profilate	August 1974	May 1975
Armour	Factorate	March 1975	March 1976
Cutter	Koate	October 1975	July 1976
NHS (BPL)	FVIII (8A)	April 1976	February 1978
NHS (PFC)	FVIII (NY)	March 1978	September 1978

6.3 Crown Immunity

The facilities at BPL (Elstree), PFL (Oxford) and PFC (Edinburgh) were operated within the NHS and were therefore under Crown Immunity and not legally subject to the 1968 Medicines Act. Crown Immunity was removed on 1st April 1991.

The position of the PFC with regard to the UK regulatory authority is described below.

6.4 The SNBTS Protein Fractionation Centre

Manufacturer's licence

The PFC opened at Liberton in Edinburgh in 1975. The Director of the PFC was a member of the UK Committee on Safety of Medicines and strongly

advocated that licences should be obtained to demonstrate that appropriate standards were being maintained. It was uncertain if Crown Immunity applied in Scotland and it was decided that, in any case, an application should be submitted by the PFC for a manufacturer's licence.

An application for a manufacturer's licence for the PFC was submitted in March 1976 and was granted in May 1976 for a period of five years, covering 18 human blood plasma products and 7 crystalloid products (these did not contain material of human origin).

Renewal was due in May 1981. However, fresh legal opinion supported the view that Crown status did apply to Scotland and no application for renewal was necessary. It was made clear by the SHHD that no such renewal application should be made.

Despite this, communications with MHRA continued, with informal inspections to ensure that appropriate standards were maintained. Documentation on the chronology of these visits exists.

When it was known that Crown Immunity was going to be removed, an application for renewal of the manufacturer's licence was submitted. The application was approved by MHRA in September 1991 after a 6 month formal transition period.

A manufacturer's licence for the PFC was held continuously from that time, with the most recent renewal being after an MHRA inspection in January 2008.

As a result of the decision to close the PFC, the manufacturer's licence was withdrawn in March 2008.

Product licences

When the PFC opened in 1975, advice was sought from the MHRA concerning the licensing of products. The MHRA advised that applications for Factor VIII and Factor IX concentrates should be submitted first. These were therefore the first PFC products to be approved by the MHRA.

Factor VIII concentrate

An application for a product licence for the SNBTS intermediate-purity Factor VIII concentrate (named NY) was submitted in March 1978 and was granted in September 1978 for a period of five years. This was renewed on 26th September 1983 for a period of five years. From 26th September 1988, SNBTS intermediate-purity Factor VIII concentrate (now named Z8) was released under Crown Immunity and, from 1st April 1991, was approved for use by MHRA under a formal transitional arrangement for the removal of Crown Immunity. This product was superseded by a high-purity Factor VIII concentrate (Liberate[®]) which was awarded a product licence by the MHRA in March 1992.

Factor IX concentrate

An application for a product licence for SNBTS intermediate-purity Factor IX concentrate (named DEFIX) was submitted in October 1978 and was granted in July 1979 for a period of five years. This licence was renewed by MHRA in July 1989, the product having been released under Crown Immunity in the period July 1984 to July 1989.

As a result of the decision to close the PFC, all product licences were withdrawn by the SNBTS in March 2008.

Regulatory inspections

Pharmaceutical manufacturing facilities are inspected regularly by the MHRA to ensure compliance with Good Manufacturing Practice (GMP).

GMP evolves continually and inspections are used by the MHRA to promote and progress programmes of continual improvement. Reports of inspections are not a 'balanced-scorecard', but are invariably critical as their purpose is to identify improvements required and to establish a timescale for their introduction.

Guidance on the standards expected is contained in the *Guide to Good Pharmaceutical Manufacturing Practice* provided by the UK Medicines Inspectorate. The first edition was published in 1971, before any formal inspections had been carried out by MHRA. This Guide was substantially revised in 1977 following wider experience of medicines manufacture by the Inspectorate.

Construction of the PFC facility was completed in 1974. However, despite requests from the SNBTS, the centre was not inspected by the MHRA until January 1980 due to the conflicting priorities of the MHRA. The first inspection of the PFC was performed against the 1977 edition of the GMP guide, not the 1971 edition which had been current when the PFC was designed. A number of changes were required and a phased programme for these was agreed with the MHRA.

The PFC has been subjected to numerous MHRA inspections since its inception and has always sought to implement improvements recommended. After the recommendation to sell or close the PFC in November 2005, and following an MHRA inspection in January 2006, manufacturing was suspended by management to enable upgrades to be made to the Quality Management System, which were successfully completed prior to eventual closure.

7. Formal Investigations in Scotland Concerning HCV & HIV

7.1 Scottish Executive Investigation into Hepatitis C (2000)

An investigation into hepatitis C and heat treatment of blood products for haemophiliacs was undertaken by the Scottish Executive following allegations made to the media in August 1999 by the Scottish Haemophilia Forum.

The SNBTS provided written evidence to the Investigation, which is appended to this paper (Appendices A and B). Haemophilia doctors were interviewed by those conducting the investigation.

None of the allegations made against the SNBTS, nor any of those made against haemophilia doctors, were upheld.

The investigation concluded that “*SNBTS made very reasonable progress in developing products with reduced viral risk, relative to activity elsewhere.*”

The final report of the investigation is available:

www.scotland.gov.uk/Resource/Doc/158690/0043060.pdf

7.2 Scottish Parliament Investigation into Hepatitis C (2001)

The Health & Community Care Committee (HCCC) of the Scottish Parliament undertook a review of the Investigation by the Scottish Executive and examined further allegations made by the Scottish Haemophilia Forum and the Haemophilia Society.

The SNBTS provided written evidence and answered questions put to it by the committee at a public hearing.

The proceedings of the committee, the evidence provided and the findings of the committee are available:

www.scottish.parliament.uk/business/committees/historic/health/reports-01/her01-17-01.htm

7.3 Lord Ross Expert Group on Financial and Other Support (2003)

In response to the recommendation from the HCCC (2001), the Scottish Executive established an Expert Group under Lord Ross to consider “*...the circumstances in which a system of financial and other support might be available to people who have been harmed by NHS treatment in Scotland in circumstances in which there is unlikely to be liability on the part of NHS Scotland.*”

Membership of the Expert Group included the Chairman of the Scottish Haemophilia Forum, a Solicitor representing patients claiming to have been infected with hepatitis C via NHS treatment and the Chief Executive of Action for Victims of Medical Accidents.

The SNBTS was not a member of the Expert Group, nor were any doctors who were either responsible for or experienced in the treatment of haemophilia.

The final report of the Expert Group is available:
www.scotland.gov.uk/Resource/Doc/47034/0024918.pdf

The recommendation of the Lord Ross Expert Group led to the Skipton Fund being established throughout the UK.

7.4 Investigation by the Crown Office and Procurator Fiscal Service (2005)

A number of applications for Fatal Accident Inquiries concerning hepatitis C infection by blood products were made to the Procurator Fiscal Service.

The SNBTS was approached for information by the Procurator Fiscal Service and co-operated as fully as was possible without having access to all relevant medical records.

None of the applications for a Fatal Accident Inquiry was approved by the Lord Advocate.

7.5 Scottish Parliament Investigation into Hepatitis C (2006)

The HCCC returned to the topic of hepatitis C infection via blood products in 2006.

The Scottish Haemophilia Forum, a number of individual patients and a Solicitor representing patients claiming to have been infected with hepatitis C via NHS treatment were invited by the HCCC to make written and oral submissions.

The SNBTS was not invited to give evidence to the HCCC, either orally or in writing, nor was the SNBTS questioned by the HCCC on the issues raised.

At the conclusion of its hearings, the HCCC decided:

- *“to ask the Scottish Executive to establish an independent judicial inquiry examining the treatment of people who were infected with hepatitis C through NHS treatment and examining the “look-back” procedure employed to trace them.”*

The Minister for Health & Community Care declined this request.

SNBTS comments on the matters considered by the committee are included in Appendix C.

8. Concluding Remarks

- Haemophilia is an incurable, life-threatening disorder. One hundred years ago, no-one with haemophilia was expected to live for more than a few years. By the early 1970s the life expectancy of a person with haemophilia in the most advanced countries was only about 40 years, with most being badly crippled by their disorder.
- Factor VIII concentrate transformed this bleak out-look. The threat of sudden death was removed. So great were the life benefits that the amount of treatment with coagulation factor concentrates exceeded all predictions, leaving blood transfusion services unable to satisfy the demand for treatment.
- The value of treatment with concentrates was generally accepted to greatly outweigh the known risk of hepatitis infection.
- The emergence of AIDS, a new and devastating blood borne infection, presented transfusion services worldwide with unique challenges. These were overcome by heat treatment of plasma products before it was possible to test for the virus and by antibody testing of donations after the virus was identified.
- Despite the profound setback in the treatment of people with haemophilia which resulted from the emergence of AIDS, progress continued to be made. Plasma-derived concentrates were made safe both from AIDS and from hepatitis C; the viruses responsible for these diseases were discovered and tests for screening blood donors were developed. Factor VIII was purified in the research laboratory and subsequently bio-synthetic products were genetically engineered by recombinant technology.
- To selectively destroy viruses without harming complex and sensitive coagulation proteins was a significant achievement allowing plasma-derived concentrates required for the treatment of haemophilia to be made safe.
- The relatively long incubation periods of these diseases meant that all haemophiliacs infected with hepatitis C and the vast majority infected with HIV were exposed before the viruses responsible had been discovered and before testing of blood donors was possible.¹⁰⁷
- It is 25 years since the virus responsible for AIDS was discovered. Yet, to-date, no vaccine has been developed, there is no cure, spread of the disease has not been halted and 40 million people have been infected world-wide. By contrast, blood products were made safe within months of the virus responsible being discovered. Scotland was the first country in the world to make heat treated Factor VIII safe from HIV available to its whole population.
- The virus responsible for hepatitis C was discovered 20 years ago. Yet, to-date, no vaccine has been developed, few have been cured, spread of the

disease has not been halted and 170 million people have been infected worldwide. By contrast, SNBTS Factor VIII and Factor IX concentrates were made safe before the virus responsible was discovered. Scotland was the first country in the world to make heat treated Factor VIII safe from HCV available to its whole population.

- Authority for the introduction of testing of donations for both HCV and HIV was given by UK Departments of Health and the SNBTS introduced these tests promptly after permission was given.
- The SNBTS was at the forefront of these medical advances, enabling Scotland to lead the world in making safe products for the treatment of haemophilia widely available.

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10. Appendices

APPENDIX A

SNBTS Evidence to the Scottish Executive Investigation

into

**Hepatitis C and Heat Treatment of Blood Products for
Haemophiliacs in the mid 1980s**



**THE DEVELOPMENT OF
HEPATITIS-SAFE FACTOR VIII CONCENTRATE BY THE SCOTTISH
NATIONAL
BLOOD TRANSFUSION SERVICE**

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1. INTRODUCTION

- 1.1 The most significant advances in the treatment of haemophilia A have been:
 - The provision of Factor VIII concentrate
 - The provision of HIV-safe Factor VIII concentrate
 - The provision of hepatitis-safe Factor VIII concentrate.
- 1.2 Scotland is believed to have been the first country in the world to become self-sufficient in the provision of Factor VIII concentrate obtained from unpaid volunteer blood donors.
- 1.3 Scotland is believed to have been the first country in the world to be able to provide sufficient HIV-safe Factor VIII concentrate for all of it's people with haemophilia A.
- 1.4 Scotland is believed to have been the first country in the world to be able to provide sufficient hepatitis-safe Factor VIII for all of it's people with haemophilia A.

How this was achieved is outlined below.

2. FACTOR VIII

- 2.1 Factor VIII is a plasma protein which is necessary for blood to clot normally. Individuals deficient in Factor VIII suffer from Haemophilia A, a disorder which can result in a painful crippling condition and early death, if left untreated.
- 2.2 Factor VIII concentrates for the treatment of Haemophilia A became available from the early 1970's and revolutionised the lives of haemophilia sufferers who with this treatment were able to lead a relatively normal life for the first time.
- 2.3 As soon as the benefits of this treatment were appreciated, the demand for Factor VIII increased beyond all expectations.
- 2.4 The preparation of Factor VIII is a highly specialised activity which was initially attempted by only a small number of commercial pharmaceutical manufacturers, based largely in the USA, and some blood transfusion services.
- 2.5 In the UK this activity was undertaken by the NHS blood transfusion services, with production of Factor VIII concentrate taking place in centres in Edinburgh (The Protein Fractionation Centre), Oxford (The Plasma Fractionation Laboratory) and Elstree (The Blood Products Laboratory), with the PFC operating within SNBTS and PFL/BPL operating under the aegis of the blood transfusion services of England and Wales.

- 2.6 At this time, Factor VIII was identifiable only by its ability to correct the defective coagulation of haemophilic plasma (ie. it's biological 'activity'). Little was known of the molecular, physical and chemical characteristics of Factor VIII. In addition, Factor VIII activity was unstable and tended to co-purify with Fibrinogen and Fibronectin, which are particularly difficult proteins to deal with in pharmaceutical processing because of their poor solubility and adherent nature.
- 2.7 Most methods for preparing Factor VIII concentrates were based on work that had been carried out during the 1960's at New York University Medical Center, under the direction of Dr Alan J Johnson¹. SNBTS (PFC) collaborated with Dr Johnson in order to introduce this technology into the UK.
- 2.8 Despite assistance from Dr Johnson, the product was found to be extremely difficult to manufacture, because of the instability of Factor VIII activity and the poor processing characteristics of the other proteins present. Consequently processing was always problematic, Factor VIII yields were low, capacity was very limited and there was insufficient Factor VIII available to meet patient needs.
- 2.9 Manufacturers world-wide experienced similar problems, however commercial companies increased their output by purchasing increasing quantities of plasma from paid donors, a practice which was favoured in the USA where limits on the volumes of plasma that could be taken from an individual donor were much more lenient than in Europe.
- 2.10 As a result, the NHS requirement for Factor VIII concentrate was met increasingly by commercial products imported from the USA.
- 2.11 In order to increase its output of Factor VIII, the SNBTS undertook a programme of R&D aimed at resolving the scientific and technical problems which were constricting output and also sought to obtain more plasma for fractionation by changing the way in which blood donations were being used clinically.
- 2.12 From this research, we discovered the cause of Factor VIII instability in the PFC process²⁻⁴ and why yield was being lost⁵⁻⁷. New equipment was designed and constructed and other technical improvements made, resulting in a substantial increase in both yield and capacity⁸⁻¹⁰.
- 2.13 These advances enabled Scotland to have available, from it's own blood donor population, sufficient Factor VIII for the treatment of all people in Scotland with haemophilia A according to UK clinical practice (ie. to be self-sufficient in Factor VIII concentrate derived from unpaid blood donors).

2.14 The knowledge obtained from this work also provided the foundation necessary for future developments in virus inactivation and Factor VIII purification.

3. HEPATITIS AND FACTOR VIII

3.1 The risk of hepatitis transmission has been associated with the clinical use of human blood products since their inception over 50 years ago. A specific screening test for hepatitis B infection was introduced for blood donors in the early 1970's, following the identification of the hepatitis B virus, which was believed to be the agent responsible for post-transfusion hepatitis.

3.2 By the late-1970's it became evident, from liver function tests, that haemophiliacs were contracting another form of hepatitis¹¹⁻¹³ which became known as non-A, non-B hepatitis (NANBH). Usually there were no clinical symptoms and the illness was generally regarded as mild and non-progressive^{14,15}. However, by the mid-1980's, there was growing evidence that NANBH may be a more serious disease^{16,17}.

3.3 It was not until 1989 that the hepatitis C virus was identified¹⁸ and appropriate screening tests were developed subsequently.

3.4 SNBTS worked throughout the 1970's to try and remove the risk of hepatitis from coagulation factor products, collaborating on research into methods for removing viruses from Factor VIII¹⁹ and Factor IX concentrates²⁰⁻²².

3.5 This work was superseded in the early 1980's by research into heat treatment, as soon as we became aware of developments in this area²³.

4. HEAT TREATMENT OF FACTOR VIII

4.1 A heat treatment process (pasteurisation of the solution at 60°C), whereby Human Albumin products could be made hepatitis-safe was developed in the 1940's in the USA and was employed by SNBTS for its Albumin products. However, Albumin was considered to be unique amongst plasma products in its ability to withstand heating to this degree²⁴.

4.2 Factor VIII concentrates were highly sensitive to damage by a variety of mechanisms. The notion that conditions might be obtained under which Factor VIII could be heat treated to inactivate hepatitis virus(es) was a concept which only emerged in the early 1980's, when two different approaches to the heat treatment of Factor VIII were reported, one from Germany and one from the USA.

4.3 Research in Germany by Behringwerke involved pasteurisation at 60°C (ie. heating as a liquid) of a more highly purified form of Factor VIII, which had been partially stabilised using a high concentration of

sucrose, which then had to be removed to make the product suitable for administration to patients²⁵.

- 4.4 There were two major problems evident. Firstly, although experiments carried out in chimpanzees indicated that hepatitis B infectivity had been eliminated, it was not clear if this was due to removal of virus by the purification process or inactivation of virus by pasteurisation. Whether or not the process would be effective against the agent of NANB hepatitis was not known.
- 4.5 The second problem concerned the need to separate Factor VIII from the added stabilisers once pasteurisation had been completed. This was necessary in order to be able to provide the final product in a dose form which was pharmaceutically acceptable. The procedures used initially for this purpose were technically difficult and very inefficient resulting in a high loss of Factor VIII, with the overall yield²⁶ being less than 25% of that being achieved at PFC at that time.
- 4.6 Although the Behringwerke process did not appear to be viable immediately (because of the very low yield) and despite uncertainty over the effectiveness of the heating procedure, we believed that the possibility that heat treatment could be applied to Factor VIII deserved very serious attention. Therefore, to resolve these problems, the SNBTS began in 1981 to undertake research on the pasteurisation of Factor VIII, as soon as we became aware of the progress being made in Germany.
- 4.7 A second approach to the heat treatment of Factor VIII emerged in August 1982 and concerned heating of the product after it had been freeze dried. It was reported at a meeting in Hungary, that 50% of the Factor VIII activity could survive heating at 80°C for 10 hours²⁷, but the product had such a poor solubility that it was suitable for clinical use only when heated at lower temperatures (eg. 60°C)²⁸. No information was available on the ability of this procedure to inactivate hepatitis viruses or any other viruses.
- 4.8 Differences between Factor VIII products prepared by different manufacturers meant that the degree of 'dry' heat treatment that a product was able to tolerate varied from manufacturer to manufacturer (eg. from 60°C for 24h for Factor VIII manufactured by Alpha, to 68°C for 72h for Factor VIII manufactured by Bayer)²⁹.
- 4.9 Some USA manufacturers reported data from chimpanzee studies that claimed to show a reduction of hepatitis infectivity following 'dry' heat treatment^{30,31}. However, such products continued to transmit hepatitis in clinical use^{32,33}, suggesting that none of them could be considered to be hepatitis-safe.
- 4.10 Uncertainty over the findings of studies in animals³⁴ meant that the hepatitis-safety (or risk) of a product could only be determined

following detailed evaluation in patients. In 1984, concern over the validity of such studies led to a protocol (the ICTH protocol) being drawn up for this purpose by an international committee of experts. This required the assessment of up to 10 batches of a product in up to 20 susceptible patients who had not been treated previously with a blood product; with each patient being monitored for evidence of sub-clinical NANBH, at frequent intervals, for up to 6 months³⁵.

5. INITIAL SNBTS R&D ON HEAT TREATMENT OF FACTOR VIII

- 5.1 To achieve self-sufficiency in the supply of Factor VIII from unpaid donors, the SNBTS Factor VIII concentrate at that time (named 'NY') was a high yielding product which was consequently somewhat less purified than most of the commercial products. We found that NY could withstand dry heat treatment for up to 24 hours at 60°C or for up to 2 hours at 68°C before becoming insoluble.
- 5.2 Because of the lack of evidence concerning the ability of dry heat treatment to inactivate hepatitis and the relatively low tolerance of the NY concentrate to this type of treatment, the SNBTS R&D programme remained focused on pasteurisation, for which there was preliminary evidence from studies in animals and patients that it might be effective against hepatitis³⁶.
- 5.3 At PFC a number of discoveries were made in our attempt to develop pasteurisation of Factor VIII into a viable process³⁷⁻³⁹ and, although there were considerable difficulties remaining, sufficient progress was made during 1983 that we were able to prepare a pilot batch of pasteurised Factor VIII for clinical evaluation. Unfortunately the first patient treated suffered an adverse reaction, the clinical study was abandoned and we had to revise our R&D programme.
- 5.4 Our prototype pasteurised product (named 'ZHT') was less purified than that being trialled in Germany and we decided that further purification was needed both to avoid reactions in patients and to resolve the major technical problems being encountered on scale-up of the process.
- 5.5 Therefore, we began to undertake R&D on a high-yielding chromatographic method for the purification of Factor VIII in collaboration with Dr Alan J Johnson at New York University Medical Center⁴⁰, in the belief that a higher degree of purification would improve the pasteurisation process and perhaps enable a much greater degree of heat treatment to be applied, should this be needed to inactivate hepatitis viruses.
- 5.6 We learned much later that Behringwerke had experienced similar processing problems to ourselves which had severely restricted their ability to manufacture pasteurised Factor VIII. These problems were partially resolved by the incorporation⁴¹ of a novel formulation

procedure to stabilise Factor VIII, which had been discovered as a result of R&D at PFC, and a chromatographic procedure similar to that invented by Dr Johnson. In addition, we are aware of one major USA manufacturer (Bayer) who took seven years to develop a similar process for the pasteurisation of Factor VIII⁴², which was later abandoned²⁹.

6. AIDS AND FACTOR VIII

- 6.1 In mid-1982 it was reported that two haemophiliacs in the USA had contracted a new illness, which subsequently became known as AIDS. By early 1983 further cases had occurred in recipients of Factor VIII and it seemed possible that this disease may be being caused by a blood borne virus.
- 6.2 As AIDS was occurring predominantly in the USA, the continued use of Factor VIII concentrates imported from the USA was a major concern. The use of locally produced Factor VIII was seen as a first line of defence, but with a recognition that the disease might be caused by a blood borne virus and that if so, it may just be a matter of time before the UK blood supply became contaminated.
- 6.3 It was a matter for conjecture whether or not this putative 'AIDS virus' might be inactivated by any of the procedures being studied for the inactivation of hepatitis viruses.
- 6.4 HIV was isolated in the USA during 1984 and this enabled an HIV screening test to be developed, as well as sufficient stocks of virus to be grown for laboratory experiments to be undertaken on the heat inactivation of HIV in the presence of Factor VIII.
- 6.5 During October 1984, in one of the first applications of the new HIV screening test, samples were tested from haemophiliacs being treated at the Edinburgh Centre. We were quickly informed that a number of Scottish haemophiliacs who had only ever been treated with SNBTS products were HIV positive, indicating that contamination of the Scottish blood supply with HIV was already taking place.
- 6.6 Studies on the effect of heat treatment on HIV were being done in the USA by the Center for Disease Control, in conjunction with commercial manufacturers. Preliminary results were first reported on 2nd November 1984 at a meeting in the Netherlands at which SNBTS scientists were present.
- 6.7 The data presented demonstrated that a substantial degree of inactivation of HIV was obtained after 'dry' heating Factor VIII at 68°C for 1 hour; we already knew from our own studies that the SNBTS NY product could tolerate heating at 68°C for 2 hours.

- 6.8 PFC production had been suspended during the period October-December 1984, in order to complete a previously planned upgrade of the facility. Therefore, we decided to 'dry' heat treat at 68°C for 2 hours, all of the SNBTS Factor VIII already manufactured in order to have an immediate supply of product which would be HIV-safe. By heat treating the existing stocks of product, representing almost 12 months supply, we were able to ensure that all Factor VIII issued by SNBTS from December 1984 onwards would be HIV-safe. Furthermore, in this way sufficient heat treated, HIV-safe Factor VIII was available to treat all patients in Scotland.
- 6.9 At the same time, further R&D led us to discover how to prepare Factor VIII in a manner that would allow 68°C heat treatment to be extended beyond 2 hours, to provide a greater margin of safety. Experiments were undertaken using samples retained from our earlier studies on Factor VIII stability⁴, resulting in a change to the formulation of NY being discovered that allowed heating at 68°C to be extended from 2 hours to 24 hours.
- 6.10 This work was completed in time for 24 hour heat treatment of FVIII to be introduced as soon as PFC production was begun again in January 1985.
- 6.11 At the same time, studies were being undertaken on the 'dry' heat treatment of Factor II, IX & X concentrate (named 'DEFIX'), which was used to treat haemophilia B. Changes to the DEFIX process were discovered which enabled the product to be modified to withstand heating at 80°C for 72 hours. However, as Factor IX concentrates were known to carry a risk of causing thrombosis, it was necessary to carry out suitable safety studies in animals^{43,44} prior to infusing the new heat treated concentrate into humans. This precaution, delayed the clinical trial and introduction of heat treated DEFIX until October 1985.
- 6.12 Some years later, as the result of an HIV 'look-back' study it was discovered that two of the first batches of NY heated in November 1984 and two of the first batches of modified NY heated in January/February 1985, had each been prepared using a donation infected with HIV. Contaminated batches were subsequently found to have not transmitted HIV⁴⁵, confirming the effectiveness of the heat treatment processes used and the critical importance of introducing 68°C heat treatment immediately.

7. THE DEVELOPMENT OF 80°C HEAT TREATMENT OF FACTOR VIII

- 7.1 NHS colleagues at PFL Oxford were investigating the ability of a variety of preparations of Factor VIII to withstand different heat treatment procedures. During 1984, they discovered that one of their experimental preparations was able to withstand 'dry' heat treatment at 80°C for 72 hours.

- 7.2 This was a unique achievement, which was expected to provide a greater margin of safety against the risk of HIV transmission⁴⁶. The preparation was some 10-times more purified than the SNBTS NY product and this was believed to be the reason why the PFL product (named '8Y') was able to withstand heat treatment at 80°C.
- 7.3 At this time there was no information to indicate if 80°C 'dry' heat treatment would have any effect on hepatitis viruses. By contrast, there was strong evidence from clinical studies, as well as from animal studies, that the pasteurisation process developed by Behringwerke might be effective against hepatitis viruses^{36,47} (although these studies did not comply with the ICTH protocol and had to be repeated⁴⁸).
- 7.4 Consequently SNBTS continued to work on the development of pasteurisation, with studies at this stage focusing on increasing Factor VIII purity to resolve the problems that had been encountered earlier (an approach which we now know that Behringwerke also took at this time).
- 7.5 Our work using chromatography to increase the purity of Factor VIII was already well underway resulting in material some 150-times more pure than NY. By the Autumn of 1985 we were able to prepare sufficient of this highly purified Factor VIII to begin studies on the freeze drying of this type of material.
- 7.6 We discovered that the standard method used to freeze dry Factor VIII was inappropriate for such a highly purified product and a new method of freeze drying had to be devised. However, once we had determined how to freeze dry this highly purified material, we discovered that it did not withstand 'dry' heat treatment at 80°C, suggesting that increased purity might not be the reason why 8Y could tolerate heating at 80°C.
- 7.7 By contrast, samples of the relatively impure NY product, that had been included in this set of experiments as controls, were found to withstand heat treatment at 80°C.
- 7.8 It became clear from these experiments, that it was the nature of the freeze drying process rather than the purity of the product *per se* which was critical to achieving 'dry' heat treatment at more severe conditions⁴⁹. We therefore shelved our work on increasing purity and concentrated instead in adapting our existing technology to be able to introduce 80°C 'dry' heat treatment to Factor VIII to increase the margin of safety with regard to HIV, as this remained the overriding concern at this point in time⁵⁰⁻⁵². This change in strategy was endorsed by SNBTS Management in February 1986.
- 7.9 The new freeze drying cycle that we had devised took much longer to complete than the standard cycles used in production therefore, to make this process practicable it was necessary to reduce the volume of

solution per vial by introducing a degree of purification and concentration into the product. Although we were able to adapt methods which we had already researched, these required to be fine-tuned and production equipment had to be designed, purchased and evaluated.

- 7.10 In September 1986, preliminary clinical data were reported by PFL/BPL⁵³ providing evidence that their 80°C 'dry' heat treated 8Y product had a reduced risk of hepatitis transmission and recommending that this pilot study be followed by a formal prospective clinical trial with a stricter protocol.
- 7.11 At PFC we had already decided to cease manufacture of 68°C/24 hour heated NY, so that the introduction of SNBTS 80°C heated Factor VIII (named 'Z8') could be accelerated by making production resources and facilities available to assist completion of the development work. We did so, knowing that we had sufficient stocks of heat treated HIV-safe NY to ensure continuity of supply while we worked on the new product. Consequently, the first full-scale production trial batches of Z8 were processed in August 1986.
- 7.12 On transferring Z8 to the production freeze driers a further key discovery was made concerning the importance of the crystalline structure of the product after freezing. A special freezing technique was devised to enable the uniform crystal structure required to be achieved reproducibly in all vials throughout all of the different production freeze driers^{54,55}.
- 7.13 Further fine-tuning of the process was required at full production scale, as some of the initial batches of Z8 were unable to tolerate heating at 80°C and were instead heated at 75°C for 72 hours.
- 7.14 The development of 8Y at PFL Oxford was undertaken using an early model of freeze drier which operated in a unique manner. In retrospect it is possible to see that the particular composition of 8Y, together with its FVIII content, specific activity, dose size and vial size, resulted in a volume of solution which when processed in this particular freeze drier, achieved both the necessary ice crystal structure and the appropriate drying conditions required for the product to then withstand 80°C heat treatment.

8. DIFFERENCES BETWEEN SNBTS (Z8) AND BPL (8Y) PROCESSES

- 8.1 The Z8 process developed by SNBTS⁵⁴ was essentially a simplified version of the 8Y process developed at PFL Oxford⁵⁶, which had itself been derived from the earlier ZHT (para 5.4) pasteurisation process being developed by SNBTS³⁷⁻³⁹.
- 8.2 In both the 8Y and Z8 processes Factor VIII was prepared from cryoprecipitate, followed by a precipitation step to remove

contaminating proteins. This step was followed by the concentration and formulation of Factor VIII prior to freeze drying and heat treatment.

- 8.3 In the 8Y process the first precipitation step used a relatively high concentration of heparin as precipitant⁵⁶ whereas in the Z8 process we used zinc combined with a low concentration of heparin⁵⁷. There were two main reasons for this:

Firstly heparin, at high concentrations, interferes with the Factor VIII assay method used by PFC at that time and additional development of assays would have caused a significant delay.

Secondly, and most importantly, we had discovered that the degree of purification obtained by the 8Y process was not necessary for 80°C 'dry' heat treatment to be achieved. Therefore, by using the zinc/heparin precipitation procedure, with which we already familiar, we were able to avoid a major area of additional work that would have been needed to implement 80°C heat treatment at PFC.

- 8.4 In the 8Y process, Factor VIII was concentrated by precipitation/centrifugation and the recovered precipitate resuspended then formulated using gel filtration. We had studied the same precipitation procedure during our work on pasteurisation but had found ultrafiltration to be a superior technology for this purpose, both in performance and ease of operation.

We had no experience of gel filtration of Factor VIII but, as formulation could also be achieved using ultrafiltration, our preference for ultrafiltration at the concentration step obviated the need for the extra stage in the process using unfamiliar gel filtration technology.

- 8.5 We judged, therefore, that rather than begin work on a new product with new process steps, we could introduce an 80°C heat treated product more rapidly by adapting existing SNBTS developments for this purpose.

- 8.6 In early 1985, there was no readily available equipment that could be purchased immediately for the heat treatment stage. At PFC, equipment which we had designed for the pasteurisation of Albumin at 60°C was able to operate at up to 70°C and this was utilised to enable the heat treatment of Factor VIII at 68°C to be introduced promptly.

- 8.7 During this period, PFL Oxford developed a specialised heat treatment oven for heating dried products, in conjunction with a manufacture experienced in this technology. PFC collaborated in this development and purchased equivalent ovens from the same manufacturer as soon as they became available.

9. INTRODUCTION OF 80°C HEAT TREATED FACTOR VIII BY SNBTS

- 9.1 Full-scale production of Z8 was begun at PFC during the Autumn of 1986. However, before the product could be issued routinely it was necessary to undertake a clinical evaluation to ensure that the product was effective and well tolerated.
- 9.2 Although 8Y appeared to be well tolerated, Z8 was a less purified product. There were concerns in the medical literature that heat treatment of Factor VIII may cause adverse reactions in patients⁵⁸ which, taken with our earlier experience of pasteurisation (see para 5.3), meant that freedom from adverse reactions could not be assumed. In addition, careful evaluation of the pharmacokinetics of heat treated concentrates was strongly advised⁵⁹. Therefore, a clinical trial to establish the tolerability and effectiveness of Z8 was regarded as critical before the product could be issued routinely.
- 9.3 Before the clinical trial of Z8 could be undertaken, it was necessary to complete the fine-tuning of the process at full-scale (see para 7.13) and then to prepare a number of batches of the definitive product for clinical evaluation (with each batch taking about 2-3 months to complete manufacture and testing).
- 9.4 The clinical evaluation of tolerability and effectiveness of 80°C heated Z8 was undertaken in March-April 1987, with satisfactory results enabling the product to be available for routine clinical use from April 1987.
- 9.5 During 1987, a number of batches of Z8 were prepared which could not withstand heating at 80°C and were heated at 75°C instead. A thorough investigation discovered the problem to be related to the use of plasma which had been held in a temporary cold storage facility. Further work was undertaken to adjust the Z8 process conditions to make the product more robust to variations of this type.
- 9.6 Additional data on the safety of 8Y were published in 1988⁶⁰ and these were consistent with the interim results reported in 1986⁵³. Further clinical studies have since confirmed both 8Y and Z8 to have been free from the risk of hepatitis transmission⁶¹⁻⁶⁴.

10. CONCLUDING REMARKS

- 10.1 The development of 8Y was a major achievement by NHS colleagues in England. This was the first 80°C heat treated Factor VIII product in the world and a number of patients in the UK were the first to benefit from this advance.
- 10.2 SNBTS scientists worked closely with their colleagues in England throughout this period, co-operating on the development of both Factor VIII and Factor IX concentrates

- 10.3 Although the development of 8Y was described at a number of international conferences during 1985/86, we believe that PFC was the first manufacturer other than PFL/BPL to have been able to achieve 'dry' heat treatment of Factor VIII at such high temperatures. We are aware of at least two other manufacturers who attempted and failed to achieve 80°C heating of Factor VIII before the key method that we devised for freezing and freeze drying of the Factor VIII solution was reported⁵⁴.
- 10.4 Many countries continued to use 60-68°C heated Factor VIII concentrates up to the early 1990's. Analysis of patient data has suggested that the use of such products reduced the incidence of HCV(NANBH) infection in haemophilia patients by about 75% in France⁶⁵, 83% in Finland⁶⁶ and 94% in Italy⁶⁷.
- 10.5 In the USA, these early heat treated products accounted for 90% of the Factor VIII usage in 1987 and some were still available in late-1989⁶⁸.
- 10.6 In 1986/87, commercial imports (which were predominantly heated at 60-68°C) accounted for about 70% of the Factor VIII used in England & Wales. By contrast there was little or no imported Factor VIII used in Scotland.
- 10.7 An imported Factor VIII concentrate, which had been 'dry' heat treated at 60°C, was withdrawn from the UK market in October 1986, following the transmission of HIV to a number of patients in the UK⁶⁹ and elsewhere^{70,71}.
- 10.8 When a specific test for HCV became available, plasma and Factor VIII concentrates were found to have a much greater frequency of contamination with HCV when obtained from paid USA donors rather than UK donors⁷²⁻⁷⁴.
- 10.9 In 1987, the use in England & Wales of Factor VIII prepared by PFL/BPL fell by about 25%, co-incident with the introduction of 8Y and there was an increased use of commercial imports commensurate with this.
- 10.10 Factor VIII concentrates imported into the UK during this period continued to be associated with hepatitis transmission^{75,76}.
- 10.11 Most commercial manufacturers exporting plasma products to the UK did not achieve hepatitis-safe FVIII before 1988-1990²⁹.
- 10.12 In Scotland, hepatitis-safe Factor VIII concentrate was introduced by SNBTS in April 1987 without any disruption to Factor VIII supplies.

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APPENDIX B

**SNBTS Response to Further Questions From The
Scottish Executive Inquiry**

**into
Hepatitis C and Heat Treatment of Blood Products for
Haemophiliacs in the mid 1980s**



**INVESTIGATION CONCERNING EVENTS SURROUNDING THE
INTRODUCTION OF HEAT TREATMENT FOR BLOOD PRODUCTS
IN THE MID 1980's**

ADDITIONAL INFORMATION REQUESTED BY THE SCOTTISH EXECUTIVE

**Scottish National Blood Transfusion Service
Edinburgh**

February 2000

1. INTRODUCTION

In December 1999, the Scottish National Blood Transfusion Service (SNBTS) submitted a report to the Scottish Executive describing the development of hepatitis-safe Factor VIII concentrate by SNBTS. Subsequently, additional information was requested by the Scottish Executive (letter from C Dora to F Gibb, 14 February 2000). Our response to this request is provided below, with each item being dealt with in the order listed by the Scottish Executive. Reference numbers for cited literature are those given in the original report. Copies of references not cited previously are appended.

2. QUESTIONS CONCERNING THE SNBTS SUBMISSION OF DECEMBER 1999

2.1 **Question**

“Paragraphs 2.6 and 5.1 Can more information be provided on the “purification” of FVIII (ie. in lay terms, what is being removed in order to “purify” the product?) When did SNBTS make the findings about the behaviour of NY under heat treatment?”

Response

FVIII is a trace component of human blood plasma, accounting for less than 0.001% by weight of the protein present. The objectives of the fractionation process are to separate this material from plasma and provide it to the patient in a concentrated dose form which is stable, convenient and as safe as possible.

In the preparation of FVIII concentrate, FVIII is separated from most of the plasma proteins by being concentrated into insoluble (solid) material which remains when frozen plasma is thawed at low temperatures. This solid material or fraction, known as cryoprecipitate, can be redissolved to form an impure solution of FVIII which is composed mainly of Fibrinogen and Fibronectin, proteins which tend to co-purify with FVIII.

Fibrinogen and Fibronectin are poorly soluble, adherent proteins which prevent cryoprecipitate from being filtered to remove bacterial contaminants and solutions of FVIII from being concentrated into a convenient dose size.

In addition, some liquid plasma is inevitably carried over with the cryoprecipitate and certain other proteins (enzymes) present in this material can degrade FVIII leading to product instability.

The first generation of FVIII concentrates resolved these problems by further purifying the redissolved cryoprecipitate to specifically remove both the least soluble protein and the damaging enzymes.

In the 1970's, the purification methods available for this purpose also resulted in significant loss of FVIII. For those manufacturers aiming to achieve self-sufficiency, yield was considered most important; whilst some commercial companies chose to increase purity at the expense of yield in order to provide a greater product solubility, the convenience of which was attractive for marketing purposes.

The purity of different products is characterised by their “specific activity”; that is, the FVIII activity (in International Units) divided by the total protein content (in milligrams of protein). Some examples are given below for first generation concentrates, together with the degree of dry heat treatment that each product was able to withstand before becoming insoluble and unsuitable for use.

PRODUCT	FVIII SPECIFIC ACTIVITY (IU/mg)	DRY HEAT TOLERATED (°C, hours)
Plasma	0.02	
Cryoprecipitate	0.2	
FVIII Concentrates:		
SNBTS, NY	0.4	68, 2h 60, 24h
Alpha, Profilate	0.5	60, 24h
Armour, Factorate	0.5 - 1.0	60, 36h
Cutter, Koate	1.0	68, 72h
Baxter, Hemofil	1.5	60, 72h

During 1983 we learned that Baxter and Armour were both investigating dry heat treatment of FVIII at 60°C. Preliminary studies on dry heat treatment of NY were carried out by SNBTS in November 1983, indicating that NY could tolerate heating to a similar degree before becoming insoluble, but the degree of virus inactivation measured at the same time was lower than we had obtained in our studies of pasteurisation (heating in a liquid state).

By the Autumn of 1984 we were aware that the causative agent of AIDS had been identified and that its sensitivity to heat was being investigated in the USA. In order to better define the options available, should HIV be found to be sensitive to dry heat treatment, we decided to make further measurements on the behaviour of NY under heat treatment. These measurements were completed in October 1984.

The first indication that HIV might be inactivated by dry heat treatment of FVIII at 68°C was published in the USA on 26 October (Morbidity Mortality Weekly Report, 33, 589-591, 1984) with more detailed information being presented on 2 November 1984 at a conference in the Netherlands at which SNBTS staff were present. A programme to implement dry heat treatment of NY at 68°C for 2 hours was initiated immediately by SNBTS.

As a result of research undertaken during November/December 1984 we discovered that heating of NY at 68°C could be extended from 2 hours to 24 hours by the addition of carbohydrate to the final product formulation. This change to the

manufacture of NY was implemented in January 1985. Research continued on dry heat treatment of NY during 1985 in an attempt to further extend these heating conditions, but no further changes were identified.

2.2 Question

“Paragraph 2.12

When was the new equipment designed and constructed”

Response

New equipment was designed and constructed in order to thaw plasma and recover cryoprecipitate in a more rapid and controlled manner than the established technology in the belief that this would reduce loss and degradation of FVIII at this step. This concept and how it might be achieved were explained by SNBTS in September 1978 (Lancet 2, 574, 1978).

Two items of equipment were designed, the first being a prototype (pilot) unit that was constructed for evaluation in production and the second being the finalised unit, the design of which was based on information gained from the operation of the prototype.

Design and construction of the prototype unit were undertaken in the period August - December 1978. Following commissioning trials in early 1979, the unit was introduced into production in March 1979 and operated in parallel with the established equipment in order to compare the performance of the different systems. By June 1979 sufficient data were available to demonstrate a marked increase in FVIII yield with the new equipment and the older procedure was discontinued.

The prototype was used to evaluate a number of aspects of the process and to provide the information required to specify and construct a definitive and larger unit in anticipation of increased volumes of plasma becoming available. The design and construction of this second unit were completed in the latter half of 1980 with the larger unit replacing the prototype in January 1981.

Each of these units performed in a similar manner, both providing a 40% increase in FVIII yield, as well as increased specific activity and product solubility. However the greater capacity of the definitive unit was more suited to processing the increased quantities of plasma supplied subsequently. This equipment was used for thawing all plasma at PFC for the next 17 years. In mid-1998, new equipment was introduced following the ban on the processing of plasma from UK donors. Construction of the new unit was based on the original design.

2.3 Question

“Paragraph 2.12

When (month and year) did Scotland become self-sufficient in Factor VIII concentrate derived from unpaid blood donors?”

Response

In paragraph 2.12, self-sufficiency is defined as having available “sufficient Factor VIII for the treatment of all people in Scotland with haemophilia A according to UK clinical practice”. To estimate when this was achieved it is necessary to examine year by year the quantity of FVIII concentrate used in the UK per head of population and to compare this with the quantity of Factor VIII concentrate produced for use in Scotland by SNBTS per head of population. Information available to SNBTS on the purchase of commercial imports is also listed. This information is shown below for the period 1978-1988.

YEAR TO 31 DEC	QUANTITY OF FACTOR VIII CONCENTRATE (IU/head of population)		
	UK USAGE NHS+COMMERCIAL	ISSUED BY SNBTS FOR USE IN SCOTLAND	COMMERCIAL IMPORTS SCOTLAND
1978	0.60	0.36	N/A
1979	0.72	0.42	N/A
1980	0.86	0.63	0.20
1981	1.01	0.87	0.27
1982	1.20	0.95	0.27
1983	1.17	1.20	0.20
1984	1.32	1.36	0.02
1985	1.29	1.17	0.01
1986	1.48	1.07	0.02
1987	1.47	1.78	0.04
1988	1.63	1.83	0.03

These data indicate that it was in 1983 that SNBTS produced, for the first time, a quantity of Factor VIII concentrate sufficient to treat all patients in Scotland at the level of treatment being practiced in the UK. The subsequent fall in the purchase of commercial products is consistent with this.

It should be appreciated that these estimates are not precise measurements and that calculations on a monthly basis would not be meaningful, as data on the UK usage of Factor VIII and on the purchase of commercial concentrates are only available on an annual basis.

2.4 Question

“Paragraph 3.1

When was a screening test for hepatitis B introduced?”

treats haemophilia patients nor holds their medical records we are unable to provide the evidence requested.

2.7 Question

“Paragraphs 5.4, 5.5, 5.6 I think it would be useful to our investigation to have dates as precisely as possible.”

Response

These paragraphs describe our work on a new method of purification of FVIII that was aimed at resolving the difficulties that we had encountered in attempting to develop a pasteurised FVIII concentrate, the similar approach taken by Behringwerke in Germany and the length of time taken by Bayer in the USA to develop a pasteurised FVIII concentrate.

SNBTS

We first learned that Professor Johnson was working on a new method of FVIII purification on 27th June 1983 at the Stockholm Congress of the World Federation of Hemophilia when, in a private discussion following an SNBTS presentation, he enquired if we might be interested in working on this project with him as he believed that we were thinking along the same lines as himself.

His procedure was claimed to be capable of producing FVIII with a specific activity of over 100 IU/mg, to be high-yielding and relatively simple to adopt. The potential value of this in resolving the technical difficulties that we were experiencing in the development of pasteurisation was immediately appreciated; we agreed to collaborate with Professor Johnson and formal agreements were drawn up for this purpose.

In January 1984 we were advised by Dr Ludlam that our pilot batch of pasteurised FVIII which had been infused in September, October and November 1983 had produced “significant and unacceptably adverse reactions in the recipient”. Although the cause of these reactions was not known, this response provided another reason for seeking the very substantial increase in purity offered by Professor Johnson’s procedure.

Professor Johnson was planning to exploit his discovery to fund his research group at New York University Medical Centre and, due to commercial concerns over secrecy, he was unable to provide SNBTS with details of the procedure immediately. Further information was eventually supplied to SNBTS at a meeting in his laboratory on 14th June 1984.

The information disclosed indicated that the procedure utilised high concentrations of carbohydrate and calcium stabilisation, similar to our ZHT process. However, although the method seemed very promising, the specific procedures and reagents proposed by Professor Johnson possessed insufficient capacity for large-scale production. To address this problem, we arranged a meeting between Professor Johnson and Pharmacia AG, Europe’s leading supplier of the type of purification reagent and equipment used in Johnson’s process. This meeting was held in Munich on 14th July, during the Congress of the International Society of Blood Transfusion.

Pharmacia identified one of their products under development as a potential candidate for this purpose and agreed to supply samples for evaluation; these were received by SNBTS on 22nd August and we began work immediately. By October 1984, we had initial results from small-scale experiments, which suggested that this new material was effective and that the early stages of our ZHT process could be integrated into Johnson's process. Some of these data were included in Johnson's patent application which was filed on 1st February 1985 (ref 40).

In moving to a new purification reagent, it was necessary to redefine all of the processing conditions, and to investigate scale-up of all of these operations. In April 1985 three members of SNBTS staff were sent to the laboratories of Pharmacia in Sweden to receive training in scale-up and in the large-scale operation of the new purification technology as well as to discuss the performance of the purification reagent and further potential developments. Equipment for operating the purification technology in production was specified by SNBTS in October 1985 with delivery being completed by Pharmacia by mid-1986.

It was also necessary to design a stable dose form for the highly purified final product. It was whilst working on this latter aspect that on 21st October 1985 we discovered a set of freeze drying conditions which allowed a control preparation of lower purity FVIII to tolerate dry heat treatment at 80°C.

Previously, the nature of the freeze drying cycle had not been considered to be particularly important for achieving 80°C dry heat treatment and the relevant conditions had not been included by BPL in their patent application for 8Y. After completing further experiments to confirm our results, details of the freeze drying process used for 8Y were requested from BPL. This information was received on 17th December and indicated that the freeze drying conditions used for 8Y were comparable to those discovered by ourselves, confirming to us that freeze drying was indeed the key process stage for achieving 80°C dry heat treatment, rather than FVIII purification per se. On 23rd December 1985 we reviewed all of this information and decided to begin development of an 80°C dry heat treated FVIII concentrate without the use of extensive purification.

Behringwerke

On 31st August 1984 Behringwerke filed a patent application (ref 41) concerning the use of calcium stabilisation of FVIII during pasteurisation and the use of a purification method for the recovery of FVIII following pasteurisation that was similar to that developed by Johnson's group. This was published (in German) on 6th March 1986. According to this application, Behringwerke were following a similar route to ourselves, presumably because they were having similar technical difficulties with their own process of pasteurisation. The experiments described in the patent application were carried out at a relatively small-scale (ie. 2.5 litres of plasma); when large-scale application was achieved is not known.

Bayer

A patent application concerning the pasteurisation of FVIII was originally filed by Bayer (Cutter Laboratories) on 5th March 1980 based on discoveries made in their research laboratory during 1978/79. This process was very similar to the original pasteurisation process of Behringwerke. The final version of the patent (ref 42) was published on 3rd April 1984 and the product (Koate HS) was approved for clinical use by the FDA in April 1986 (ref 29). This was superceded by a chemically (solvent /detergent) treated FVIII concentrate (Koate HP) which was licensed by the FDA in March 1989 (ref 29).

2.8 Question

“Paragraph 6.12

“Some years later” - when?”

Response

A total of six batches of NY-HT prepared prior to the introduction of HIV screening were subsequently found to have been prepared from plasma containing an HIV-positive donation. These batches were heat treated in November 1984 (two batches), January 1985, February 1985, May 1985 and June 1985 and were issued for use in December 1984 (two batches), March 1985 (two batches), August 1985 and September 1985.

Following the introduction of HIV testing, SNBTS tested archive samples of earlier donations for any donor found to be HIV-positive and the fate of these previous donations was traced. The date at which this information became available depended on the date at which these individuals returned to donate blood following the introduction of HIV screening. The dates on which it was learned that HIV-positive donations had been processed ranged from 29th January 1986 to 7th December 1988.

Products found to have been prepared using an HIV-positive donation were recalled immediately this information was available. No haemophilia patient who was treated with any of these batches was infected with HIV as a consequence.

2.9 Question

“Paragraph 8.7

When were ovens obtained and put to use?”

Response

The process of specifying a high accuracy heat treatment cabinet for use by SNBTS was begun in January 1985. The first cabinet that we purchased was received and commissioned in July 1985 and was used immediately thereafter for the dry heat treatment of Factor VIII concentrate at 68°C and Factor IX concentrate at 80°C.

3. GENERAL QUESTIONS

3.1 Question

“The document sets out a very useful explanation of events. To supplement this, would it also be possible for SNBTS to provide in table form a basic chronology (a kind of “at a glance guide” to what happened with dates)?”

Response

A basic chronology in tabular form is given in table 1.

3.2 Question

“What was SNBTS expenditure on R&D each year 1980-1990?”

Response

During the period 1980-1990, SNBTS did not record its expenditure on R&D as a specific category of expenditure.

In 1992 an internal audit of R&D was undertaken in which expenditure for the financial year 1990/91 was documented. This exercise only covered non-medical staff employed wholly in an R&D capacity, excluding medical staff and those employed in a “service” capacity who might also contribute to R&D activities. According to this audit, the total SNBTS revenue expenditure on R&D for 1990/91 was £1.22M, representing 5.9% of the SNBTS revenue budget for that year. The addition of relevant clinical staff, plus “service” staff contributing to R&D would probably have increased this figure to about 7.5% of the total SNBTS revenue budget. These sums do not include funding for the implementation of service developments arising from R&D programmes (eg. to implement the manufacture of hepatitis-safe FVIII).

Despite being a relatively small organisation, SNBTS was able to develop hepatitis-safe coagulation factor concentrates well before most other manufacturers in the world, including most of the large commercial companies operating in this field. This achievement demonstrates that it is the quality of the R&D which is most important, rather than the size of the R&D budget.

3.3 Question

“What are the details of the history of donor selection policy in the 1970’s and 1980’s?”

3.4 Question

“What screening methods were used between what dates from 1970 to 1990? How did this compare with international measures?”

3.5 Question

“We understand that SNBTS did not export any blood products at the time, but was any whole blood exported, and if so what testing was undertaken before export?”

Response

The information requested in questions 3.3, 3.4 and 3.5 will be provided separately in a specific document.

TABLE 1
KEY EVENTS AND DATES IN THE DEVELOPMENT OF
HEPATITIS SAFE FACTOR VIII CONCENTRATE BY SNBTS

EVENT	DATE
• SNBTS introduces Hepatitis B screening of plasma	1970
• SNBTS introduces FVIII concentrate “NY”	1974
• First published information (Behringwerke, Germany) on “pasteurisation” of FVIII for virus inactivation	1981
• “Dry” heat treatment of FVIII first proposed	1982
• First postulated that AIDS may be caused by a blood borne virus	1983
• Scotland “self sufficient” in SNBTS FVIII NY	1983
• Adverse report from clinical study on SNBTS prototype pasteurised FVIII	January 1984
• HIV isolated	March 1984
• Bayer (USA) publish patented method for pasteurisation of FVIII	April 1984
• First HIV tests on Scottish patients	October 1984
• First report of HIV being sensitive to 68°C dry heat for 1 hour	November 1984
• All SNBTS FVIII (NY) heat treated at 68°C for 2 hours	December 1984
• SNBTS begins FVIII (NY) heat treatment at 68°C for <u>24</u> hours	January 1985
• USA introduces HIV screening of plasma	March 1985
• All PFL (Oxford) FVIII heat treated - some at 80°C	March 1985
• All BPL (Elstree) FVIII heat treated - some at 80°C	May 1985
• All PFL/BPL FVIII (25% of England and Wales requirement) heat treated at 80°C	September 1985

EVENT	DATE
<ul style="list-style-type: none"> • UK introduces HIV screening of plasma 	October 1985
<ul style="list-style-type: none"> • SNBTS achieves sufficient stocks of NY 68°C 24 hours to stop production but still maintain supplies 	July 1986
<ul style="list-style-type: none"> • First production trial batches of SNBTS 80°C 72 hour heat treated FVIII (Z8) 	August 1986
<ul style="list-style-type: none"> • Preliminary clinical report that 8Y 80°C 72 hour heat treatment may prevent transmission of NANBH 	September 1986
<ul style="list-style-type: none"> • Clinical trial of SNBTS FVIII (Z8) 80°C 72 hours 	March 1987
<ul style="list-style-type: none"> • SNBTS introduces Z8 FVIII product 	April 1987
<ul style="list-style-type: none"> • Scotland “self sufficient” in SNBTS Z8 product 	1987
<ul style="list-style-type: none"> • ALT (quasi surrogate measure of NANBH) screening of plasma introduced in USA 	1987
<ul style="list-style-type: none"> • Publication of results confirming 80°C 72 hours heat treatment of 8Y prevents NANBH transmission 	1988
<ul style="list-style-type: none"> • First publication of clinical trial results showing solvent/detergent treatment prevents HIV and NANBH transmission 	1988
<ul style="list-style-type: none"> • Hepatitis C Virus (HCV) identified. NANBH has been subsequently shown to be caused by HCV 	1989
<ul style="list-style-type: none"> • HCV screening of plasma introduced in UK 	September 1991
<ul style="list-style-type: none"> • HCV screening of plasma introduced in USA 	late 1991
<ul style="list-style-type: none"> • Withdrawal of UK marketing authorisation for last commercial heat treated but <u>non</u> HCV safe product 	October 1992
<ul style="list-style-type: none"> • Published results on clinical safety of 8Y from HCV transmission 	1993
<ul style="list-style-type: none"> • Published results on clinical safety of Z8 from HCV transmission 	1993

APPENDIX C

**SNBTS Comments on Matters Considered by The Scottish
Parliament Health & Community Care Committee (2006)**



HEPATITIS C AND BLOOD PRODUCTS SUPPLIED BY SNBTS

FACT SHEET

1. BACKGROUND

There is always a risk that donated blood will contain viruses that exist naturally in the human population.

Hepatitis C is a blood-borne virus which has existed in the human population for a long period of time. Currently over 170 million people are infected world-wide, presenting blood transfusion services with a major challenge.

In Scotland, hepatitis C is spread mainly by illicit use of intravenous drugs, by tattooing, piercing, and sexual transmission (risk is extremely low) is also involved. About 3% of cases are from transfusions received prior to donation testing in 1991.

2. DONOR SELECTION

Criteria for selecting blood donors are established nationally in the UK; they conform with EU guidelines and undergo continual review.

SNBTS has always strived to exclude donors whose health, medical history or lifestyle indicate that they may have a higher than normal risk of carrying an infection which could be passed on to patients receiving their blood. Prospective donors who represent a higher risk are excluded even when specific screening tests are in place because of the possibility that their infection may be undetectable at the time of donation (window period).

While placing restrictions on donors to prevent transmission of infection by transfusion, the transfusion services must continue to provide sufficient blood to meet essential medical need.

In the 1960's and 1970's people in prison were allowed to contribute to society by donating blood, a practice that was encouraged by the

Home Office and employed in most advanced countries. SNBTS stopped collections in prisons in the early 1980's when there was growing evidence from other countries that prisoners represented a higher risk.

SNBTS has always collected blood from unpaid volunteer donors in Scotland. It has never imported whole blood. However, as a precaution against vCJD, blood plasma has been imported since 1998. This plasma is obtained from Centres in the USA and in Germany which have been inspected by SNBTS and approved by the Medicines and Healthcare products Regulatory Authority (MHRA). No plasma is obtained from prisons.

3. HEPATITIS

- 3.1 The transmission of hepatitis by blood products has been recognised as a risk of transfusion since 1938.

Means of detecting the hepatitis B virus was discovered in 1968. The virus itself was first isolated in 1970 and was believed, at the time, to be the main cause of transfusion transmitted hepatitis.

SNBTS introduced screening of blood donors for hepatitis B in 1970 and was amongst the first to do so.

By the mid-1970's it was observed that hepatitis was still being transmitted by certain blood products; unknown viruses were presumed to be responsible.

- 3.2 SNBTS continued to undertake research on hepatitis, in an attempt to discover the viruses responsible, to devise and evaluate possible screening tests and to devise a way of removing viruses from coagulation products used to treat haemophilia.

4 TESTING FOR HEPATITIS C (NON-SPECIFIC)

- 4.1 Before the hepatitis C virus was discovered, tests for inflammation of the liver [ALT test] were studied to see if they could be used to identify infected donors.
- 4.2 Accuracy was poor and there was concern that a significant number of healthy donors would wrongly test positive, while only a minority of donors genuinely infected would be discovered.
- 4.3 There was considerable international debate on this issue, with some countries deciding to employ this testing but most deciding against.
- 4.4 During this debate, SNBTS experts proposed that this [ALT] testing should be introduced because of its concern over interpretation of the Consumer Protection Act, describing its view as “*irrational, perhaps, but inescapable*”.
- 4.5 The decision taken by the Departments of Health with advice from experts, was **not** to use this test as it was believed that the loss of so many healthy donors would disrupt the blood supply and do more harm than good.
- 4.6 Had the test had been used and performed as well as its advocates hoped, the risk to haemophiliacs would **not** have been reduced due to the very large numbers of donations required for their treatment. Even if cryoprecipitate had been used rather than Factor VIII concentrates, the great majority of people with haemophilia would still have been exposed to HCV because of the number of donation exposures.
- 4.7 Recent studies have shown that most donors with hepatitis C would **not** have been detected using this approach and that most of those who tested positive with ALT would **not** have had hepatitis C.

This topic was considered by the Health and Community Care Committee in 2001. (see transcript of HCCC meeting, 14th March 2001 and follow-up written evidence of the Scottish National Blood Transfusion Service.

<File://H:\HCCC\Health and Community Care Committee.htm>)

5. TESTING FOR HEPATITIS C (SPECIFIC)

5.1 Following the discovery of the hepatitis C virus a specific test for screening blood donors was developed in the USA. This was introduced for screening donors in the UK in 1991.

5.2 The date for introducing the test was decided by the UK Departments of Health, with advice from experts. To achieve uniform standards and avoid a “post-code lottery” it was decided that all Transfusion Centres in the UK should begin routine testing on the same date.

5.3 In order to ensure that its systems were working properly, SNBTS commenced testing of all donors prior to the date mandated for the routine introduction of hepatitis C screening.

5.4 One Transfusion Centre in England implemented routine screening independently, and publicised this action. This was the subject of a letter from Dr Cash to Dr Lloyd which was raised at the meeting of the Health & Community Care Committee on 18th April 2006.

5.5 At that time, Transfusion Centres in England were funded on a regional basis, not centrally as in Scotland. It was this absence of central funding, as well as the independent position taken by Dr Lloyd, that caused Dr Cash to use the term “*shambles*”.

5.6 Today England enjoys a centrally managed Transfusion Service, due in no small part to the advocacy of Dr Cash for a centralised administration.

5.7 Although sometimes there were differences of opinion between transfusion professionals within the UK, the UK Transfusion Services have worked together closely at all times. The claim that Scotland somehow lagged behind England is incorrect. In fact, by working closely with scientists at the University of Edinburgh, SNBTS was one of the first Transfusion Services in the world to have a test that could detect the hepatitis C virus directly (the PCR test) as a back-up confirmatory test. This development subsequently provided the basis for a programme of research on hepatitis C which advanced fundamental knowledge of the virus.

6. TRACING INFECTED PATIENTS

6.1 Following the introduction of testing for hepatitis C, SNBTS commenced a 'look-back' programme. This meant that where a donor was found positive for hepatitis C, earlier donations were traced to discover the blood products that had been derived and to identify the recipients of these products.

6.2 SNBTS was the first in the UK to begin a look-back exercise, which was started within SNBTS at the earliest possible moment. Results from this study carried out in Edinburgh provided the basis for a look-back exercise to be carried out throughout the UK. This also encouraged other countries to undertake similar programmes.

6.3 SNBTS was first in the UK to begin a look-back exercise and went further than most other countries. For example, the USA only began look-back in 1998, and France has never adopted this policy.

6.4 The SNBTS look-back has covered all prospective donors since testing began and will continue to operate indefinitely.

6.5 The administrative work peaked in the period 1995-1997, due to the backlog of cases being traced and ensuring that every effort had been

made to trace patients who might have had been affected. At this point it was concluded that a number of patients could not be traced either because the individual could not be located or because necessary hospital records were not available.

6.6 It is claimed that 3 500 patients have been infected in Scotland by blood transfusion. This was an estimate of the number of blood components that had been prepared in the past, using donations from people who had subsequently tested positive for hepatitis C. The number of patients infected will be lower than this, because:

- this estimate was made when a higher proportion of donors were being found with hepatitis C, because testing had just been introduced
- blood components are issued to hospitals in case they are needed and are only used when necessary. Although issued, blood components are often not used; therefore it is probable that many of the components implicated in the look-back would not have been used.
- where implicated components were used and recipients traced, 60% were no longer alive. Of those tested, some (20%) were found not to be infected.

6.7 It has been suggested that all donors should have been tested, including lapsed donors. This would have involved tracing some 500 000 individuals to obtain consent for testing (ie. about 10% of the Scottish population) and then testing some 3.6 million archive samples. Even if feasible, this would have taken several years to complete, would have cost many £million and would have severely disrupted the work of SNBTS. We know of no country which took this approach.

7. COUNSELLING OF INDIVIDUALS FOUND WITH HEPATITIS C

- 7.1 Donors who are tested by SNBTS and who are found to have hepatitis C are counselled by SNBTS medical staff. This involves a discussion in private, the provision of written information and advice that they should consult their GP. With the agreement of the donor and GP, SNBTS often arranges referral for specialist care.
- 7.2 Where SNBTS is able to identify a blood product which was previously derived from a donor who subsequently tested positive for hepatitis C, it provides details to the hospital where the product was distributed.
- 7.3 Hospital records are then used to trace the patients treated.
- 7.4 Recipients who are traced are informed and counselled, either by their hospital doctor or by their GP as appropriate. SNBTS medical staff provide assistance when the patient's own doctor requests their expert help.
- 7.5 Although the look-back undertaken by SNBTS was extensive, it was impossible to trace all recipients. Therefore it is important that anyone who received a blood product prior to 1991, who believes that they could have hepatitis C, should visit their GP for advice. Testing is readily available and all doctors have been notified of this by the Chief Medical Officer in a letter sent out when look-back became national policy in 1995.

8. WARNINGS

- 8.1 Coagulation factor products supplied by SNBTS for the treatment of haemophilia all carried warnings of the risk from hepatitis. A warning was printed on the label attached to each vial and on the box containing the product. The patient information leaflet issued with

- 8.2 As SNBTS does not treat patients, it is the treating physician who must inform patients of the risks associated with their treatment.
- 8.3 Today, all plasma products provided by the SNBTS are issued with a leaflet for patients which describes the risks associated with the product.

9. HEAT TREATMENT (OF COAGULATION FACTORS)

- 9.1 It is claimed that Scotland introduced heat treatment several years later than England. This was not the case.
- 9.2 In 1970, SNBTS put in place a programme of research aimed at removing hepatitis from coagulation factors used in the treatment of haemophilia.
- 9.3 SNBTS initiated research aimed at applying heat treatment to coagulation factors in 1981 and shared this information with colleagues at the Blood Products Laboratory (BPL) in England, who subsequently began their own programme of research.
- 9.4 At that time no method had been devised that could destroy hepatitis viruses without, at the same time, damaging the fragile coagulation proteins necessary to treat haemophilia. Research on this problem was being carried out throughout the world using a number of approaches.
- 9.5 Experts were concerned that heat treatment might alter factor VIII and cause patients to produce antibodies against factor VIII that would stop it from working. As it can be very difficult to treat haemophilia patients

who have antibodies to factor VIII [known as inhibitors], doctors were concerned that heat treated Factor VIII might do more harm than good.

- 9.6 At the same time, the emergence of AIDS posed a new and even more serious threat to patients than hepatitis.
- 9.7 Achieving self-sufficiency became even more important to avoid the use of commercial Factor VIII from the USA as the USA was at the centre of the AIDS epidemic.
- 9.8 By 1983, as a result of immense efforts by SNBTS, Scotland was supplied with sufficient Factor VIII from its own volunteer blood donors; one of few countries in the world ever to achieve this objective.
- 9.9 Evidence that the AIDS virus could be destroyed using a level of heat treatment that coagulation factor products could withstand, became available in November 1984.
- 9.10 Previously, there had been a concern that heat treatment might have limited benefit in inactivating human viruses. With any new process there is the possibility of increasing the risk of adverse reactions. The benefit of heat treatment now outweighed this risk. Therefore, SNBTS immediately implemented heat treatment, using the highest temperature its product could withstand, and distributed heat treated Factor VIII for all patients on 10th December 1984. This prompt action resulted in Scotland being first in the world to supply sufficient HIV-safe Factor VIII for all its patients.
- 9.11 SNBTS recalled unheated Factor VIII and heated all stocks, resulting in Factor VIII prepared from donations collected as early as October 1983 being made safe (ie. 8 months **before** HIV was discovered).
- 9.12 In England, many Haemophilia Centres continued to use unheated Factor VIII in 1985. Heat treated Factor VIII was issued routinely from

BPL from September 1985. Unheated Factor VIII was not recalled, either by BPL or by commercial suppliers, due to shortages of supply and it is believed that some patients received unheated concentrate up to 1987.

- 9.13 SNBTS was heating its Factor VIII at the highest temperature that it could withstand; a level of heating that had been shown to destroy HIV, even though it was not sufficient to destroy hepatitis.
- 9.14 Researchers at BPL had found that Factor VIII prepared by a new method could withstand heating at an even higher temperature. This product (8Y) was introduced in September 1985.
- 9.15 Initially, 8Y was very difficult to produce as it was not clear why it could withstand heating at such a high temperature. Production difficulties resulted in a fall in output from BPL and more of England's requirement being made up of commercial Factor VIII, imported from the USA.
- 9.16 In its review of this achievement at BPL, The Lindsay Tribunal in Ireland stated "*It was viewed with some astonishment by other fractionators at the time.*"
- 9.17 There was no evidence, at this time, that hepatitis would be destroyed at this higher temperature and The Lindsay Tribunal concluded "*there was no basis for assuming that heating at 80 degrees would prevent the transmission of non-A non-B hepatitis.*"
- 9.18 In late 1985, researchers at SNBTS discovered the reason why the new BPL product could be heated to this temperature. This knowledge enabled SNBTS to begin to develop a similar product and helped BPL to manufacture 8Y more efficiently.

- 9.19 SNBTS started production of its new product in the Autumn of 1986. It was April 1987 before this could be issued for routine use because of the time taken to manufacture a batch of Factor FVIII (about 3 months), the need to maintain continuity of supply to avoid use of imports and the time required for clinical evaluation of the new product.
- 9.20 Preliminary evidence that these heating conditions might destroy hepatitis became available in October 1986 (i.e. after SNBTS had started production) but was not confirmed for a number of years.
- 9.21 Output from SNBTS was sufficient to treat all patients in Scotland with hepatitis–safe Factor VIII (some 2 years **before** the hepatitis C virus was discovered). This was not the case in England where most Factor VIII continued to be imported and was not heated to the higher temperature achieved by BPL and SNBTS. For example, 70% of the Factor VIII used in England from 1986-1988 was from commercial sources, with almost 90% used in 1987 being commercial.
- 9.22 Imported Factor VIII, that was not fully safe from hepatitis C, remained available in England until 1992 and there are reports of haemophiliacs contracting hepatitis up to at least 1990.
- 9.23 It was not until the early 1990's that most countries were able to supply all of their patients with hepatitis-safe Factor VIII.
- 9.24 Therefore Scotland led the world in providing its haemophilia patients with Factor VIII that was safe, first with respect to HIV and then with respect to hepatitis C.

This topic was considered by the Health & Community Care Committee at its meeting on 14th March 2001 (see section 4 above).

Revised 17th July, 2007

