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The manufacture of blood plasma products in Scotland: a brief history

Peter R Foster

Abstract

A number of essential clinical products are derived from human blood plasma, including immunoglobulin products for the treatment of infections and disorders of immunity; albumin for protein and fluid replacement and coagulation factors for the treatment of haemophilia and other disorders of haemostasis. For many years, these protein pharmaceuticals were manufactured by the Scottish National Blood Transfusion Service (SNBTS) at its Scottish Protein Fractionation Centre (PFC) in Edinburgh, a contribution which ended with the closure of the PFC in 2008. The origins and development of plasma fractionation in Scotland are summarised in this article, as well as issues which contributed to the closure of the PFC.

Keywords

Plasma fractionation, blood products, Protein Fractionation Centre, transfusion medicine, protein pharmaceuticals

1941–1950

The origin of plasma fractionation in Scotland lies in a decision to produce freeze-dried plasma in Edinburgh during World War II.[1,2] In 1941, the Medical Research Council advised that there should be two facilities for the preparation of freeze dried plasma in the UK, with one situated "*in the north*". The Scottish National Blood Transfusion Association proposed that this facility be sited in Edinburgh, with a plasma freeze drying unit[3] being constructed at the Royal Infirmary of Edinburgh (RIE). Funding of £3750 was approved by the War Emergency Expenditure Committee and a donation of £560 was made by the pupils and staff of the Mary Erskine School for Girls. The unit operated on a 24-h basis, from March 1943 to March 1945, producing 10,126 bottles of dried plasma.

Subsequently, Dr Edwin Cohn's studies on the fractionation of plasma[4] led the new Director of the Edinburgh Transfusion Service, Dr A C McRae, to propose that the unit be extended to accommodate "*Plasma Fractionation and the drying of products so obtained*". Despite the sudden death of Dr McRae in 1947, his successor Dr Robert Cumming continued the project, locating a Blood Products Unit (BPU) within new premises for the Edinburgh Blood Transfusion Service, which were completed at RIE in 1950.

1950–1974

Dr Drummond Ellis was appointed deputy to Dr Cumming in 1950 with a remit of establishing plasma fractionation technology. After a period of study in Cohn's laboratory at Harvard University, Dr Ellis designed and installed equipment to produce normal immunoglobulin for the prevention and treatment of measles; produced from 1952, it was Scotland's first plasma product (Figure 1). Further products were developed[5] (Figure 2) including a factor VIII concentrate[6] and a fibrinogen concentrate in 1956, and human albumin and anti-vaccinia immunoglobulin in 1965.

By the mid-1960s, the demand for plasma products had begun to exceed the capacity of the BPU. A new centre was planned, primarily to meet the demand for albumin which, unlike plasma, was pasteurised and therefore free from the risk of hepatitis transmission.[5] Dr Ellis moved to the Blood Products Laboratory (BPL) at Elstree and was replaced, in 1967, by

Formerly Development Manager, SNBTS Protein Fractionation Centre, UK

Corresponding author:
Peter R Foster, 6 GRO-C
Email: peterrfoster@ GRO-C

Mr John G Watt who appointed biochemist Dr James K Smith to assist him. New products continued to be introduced[5] including: anti-D immunoglobulin in 1968; prothrombin complex concentrate for the treatment of haemophilia B, anti-tetanus immunoglobulin and anti-rubella immunoglobulin in1969; plasma protein fraction in1971; a Factor II, IX & X concentrate[7] in 1972 for the treatment of haemophilia B and, in 1974, anti-hepatitis B immunoglobulin and intermediate-purity Factor VIII concentrate.

The Scottish BPU was officially renamed the Scottish Protein Fractionation Centre (PFC) in 1970 and relocated to newly constructed premises at Ellen's Glen Road, Edinburgh at the end of 1974, with Dr Smith moving to the Plasma Fractionation Laboratory at Oxford in 1975.

Figure 1. Normal Immunoglobulin, 1950's (© Antonia Reeve).

1975–1983

Design of the new PFC was centred on a computer-controlled, continuous-flow, small-volume mixing (CSVM) cold-ethanol fractionation process for mainstream fractionation of plasma[8]; a technical innovation which offered online monitoring and control, shorter processing times and a high capacity. Multi-stage fractionation was performed using a series of mobile processing modules (Figure 3) located in a +4°C process hall (Figure 4), that was constructed in stainless steel for ease of cleaning, with newly designed refrigerated centrifuges for the recovery of protein precipitates.

The new centre was designed to accommodate plasma from the north of England as well as from Scotland, but was equipped initially for Scotland's needs only. Meeting demand for albumin was the first challenge. The high capacity of the CSVM process quickly enabled a stockpile of 30,0001 of plasma to be processed to satisfy Scotland's requirements for albumin. Despite this achievement, processing of plasma from England did not come to fruition, leaving the PFC's CSVM process operating well below its potential capacity.[9]

Anti-hepatitis B and anti-zoster immunoglobulin solutions were introduced in 1975. Factor VIII

Figure 2. Early freeze dried Products (a) Plasma, (b) Albumin, (c) Fibrinogen, (d) Factor VIII (AHF) Concentrate (© Antonia Reeve).

Figure 3. Module for continuous-flow plasma fractionation, 1975 (© Antonia Reeve).

Figure 4. Main process cold-room at PFC (© Antonia Reeve).

concentrate was so successful in treating haemophilia A that demand exceeded all estimates, presenting SNBTS with a major challenge. A technical innovation at PFC[10] simultaneously increased factor VIII yield and purity and the capacity of the manufacturing process. These advances, together with a substantial increase in supply of fresh frozen plasma, enabled SNBTS to meet Scotland's demand for Factor VIII concentrate by 1983, making Scotland the first country to meet its essential blood product needs using unpaid donors from its own population. The year 1983 also saw the introduction of immunoglobulin products against mumps, measles and cytomegalovirus as well as a normal immunoglobulin suitable for intravenous administration (IV IgG).

Although covered by Crown Immunity, PFC was granted a Manufacturer's Licence by the Medicines Control Agency in 1976 and Product Licences for Factor VIII and Factor IX concentrates in 1978 and 1979 respectively. An extension to the PFC building was completed in 1982 to provide on-site facilities for virology and microbiology, as well as an R&D pilot plant. Mr Watt left at the end of 1983 and was replaced as Director by Dr R J Perry.

1984–1994

Further advances followed. Heat treatment of Factor VIII concentrate began in November 1984, within days of a report that HIV might be inactivated by this procedure and with stocks obtained from donations obtained from late-1983 being heat treated. Calcium was added to stabilise factor VIII during processing,[11] a technique now widely used in the preparation of both recombinant and plasma-derived Factor VIII concentrates. Further research led to the introduction of a new Factor VIII concentrate in 1987 which could be heated at an even higher temperature,[12] and eventually confirmed as effective against hepatitis C virus (HCV). A modification to Factor II, IX & X concentrate in 1985 enabled heat treatment to be applied which was effective against both HIV and HCV, with product being issued as soon as studies on freedom from thrombogenic reactions had been completed.[13]

A high purity Factor VIII concentrate and a fibrin sealant kit were both developed in 1992 and high purity Factor IX and a heat-treated fibrinogen concentrates in 1993. The demand for plasma products continued to increase with use of Factor VIII concentrate doubling and output of IV IgG increasing 10-fold during this period.

There were developments in process equipment too. The CSVM fractionation process was upgraded in 1986,[14] with fractionation modules containing microprocessors (Figure 5) to replace the main-frame computer employed previously for process control. In-line orifice-mixers were designed to produce oscillatory flow patterns to mix adherent proteins and to aggregate protein precipitate particles to enhance recovery by centrifugation.[15] (Figure 6). Other equipment innovations included design of an automated, multi-stage

Figure 5. Module for continuous-flow plasma fractionation, 1986 (© Antonia Reeve).

Figure 6. Refrigerated centrifuges for the recovery of precipitated protein fractions (© Antonia Reeve).

protein-chromatography unit in 1985, and in 1987 automated diafiltration/ultrafiltation (Figure 7) was introduced to reduce the aluminium content of albumin solutions.[16]

A therapeutic monoclonal antibody to hepatitis B was developed in 1990 using continuous cell culture. Although clinical evaluation of the product had begun, the project was abandoned in 1993 because of the increased cost of new regulatory requirements.

Crown Immunity was removed by the government in 1991 and new applications were submitted for a Manufacturers Licence and for Product Licences.

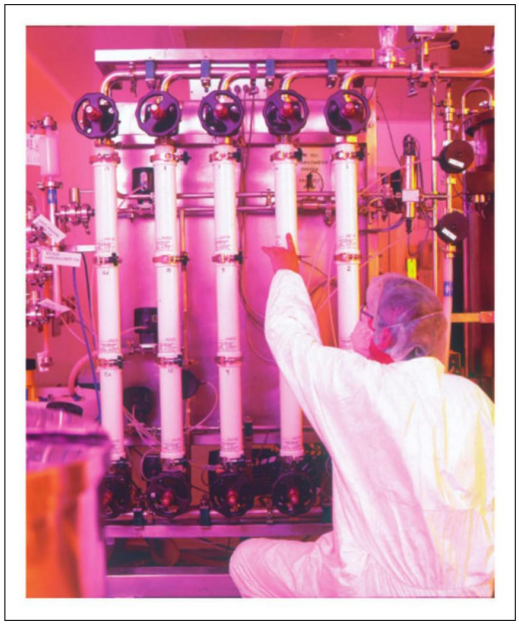

Figure 7. Formulation of albumin by ultrafiltration (© Antonia Reeve).

In 1994, a £4.5 m extension was completed with enhanced facilities for aseptic dispensing, heat treatment, inspection, labelling, packaging, warehousing and cold-storage.

1994–2007

Transmissions of hepatitis A, hepatitis B, hepatitis C and HIV by plasma products used in Germany in 1994 caused European regulators to advise that an additional virus inactivation step be incorporated into the manufacture of coagulation factor concentrates.[17] Additional virus inactivation steps were introduced into the manufacture of each of PFC's relevant products in 1996, all of which had to undergo new clinical trials. A defined virus inactivation step was also added to all immunoglobulin products for intramuscular administration at the request of European regulators,[17] despite the fact that no virus transmissions had ever been associated with PFC products of this type. Again, new clinical trials were required to obtain regulatory approval. Also in 1996, a thrombin concentrate and a solution (liquid) dose form of intravenous immunoglobulin (IV IgG) (Figure 8) were approved for clinical trial and a simplified method for the preparation of Human Albumin was introduced.

Three events in 1998 had major consequences for PFC. First, plasma products derived from UK donations were banned as a precaution against the

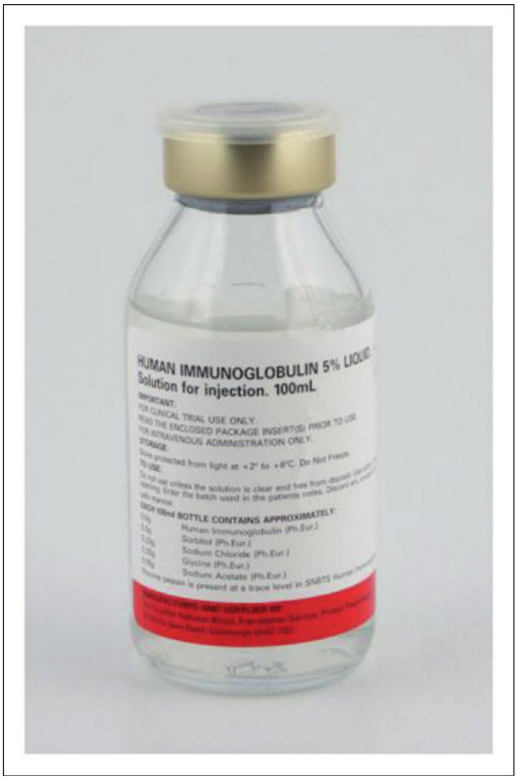

Figure 8. Intravenous Immunoglobulin (liquid) (© Antonia Reeve).

theoretical risk of transmitting variant Creutzfeldt-Jakob disease (vCJD); second, plasma-derived coagulation factors for the treatment of haemophilia were substantially replaced in Scotland by recombinant products as a precaution against vCJD. Third, the demand for Human Albumin fell sharply following a report[18] that it was harmful to treat critically ill patients with Human Albumin, a conclusion that was not supported in a subsequent clinical trial designed to address this issue.[19]

Importation of plasma was begun in 1998, but before it could be processed, the PFC facility had to be treated to eliminate any contamination with vCJD that might conceivably be present. Equipment unable to tolerate severe treatment was replaced, resulting in continuous fractionation modules being replaced by batch-tanks. Imported plasma was obtained from unpaid donors as far as possible and products from UK-plasma were recalled as soon as stocks could be replaced. During this transition, established products were given precedence over those in development, with clinical trials being suspended until new clinical trial authorisations were obtained due to the change in source of plasma, causing new product developments to be delayed by two years.

Following the concern that the agent of vCJD might have entered plasma pools, research was undertaken on the extent to which prion agents might be removed by processes used in the preparation of plasma products.[20,21,22]

To compensate for the decrease in demand for Human Albumin and coagulation factor concentrates, contract processing was undertaken for biotechnology companies. Contracts were also established to fractionate plasma for Taiwan and to transfer fractionation technology to Taiwan and Egypt, the latter projects eventually being discontinued. Intravenous Immunoglobulin was supplied to Regional Health Authorities in England and surplus Human Albumin was sold in India at production cost.

The development of immunoglobulin-based products for bio-defence was begun in 1998, in collaboration with the Ministry of Defence (MoD). As part of that project, an anti-botulinum toxin from animal plasma was modified to be well tolerated in humans for both MoD and civilian use.

In 2004, the PFC Director Dr Perry, was seconded to assist in the management of SNBTS and was replaced by Dr Katherine Reid (Acting Director, 2004–2006), Mr Richard Blythe (Interim Director, 2006–2007) and Dr Ronald McIntosh (Director, 2007–2008).

By 2006, the cost of importing plasma accounted for half of the operating costs of PFC, resulting in the centre being considered uneconomic. A decision to close PFC was taken in 2007, by which time PFC had a portfolio of 27 plasma products (Table 1 and Figure 9), and granted patents for prion removal,[23,24] intravenous immunoglobulin (liquid),[25] fibrinogen[26] and thrombin,[27] the latter products also comprising a fibrin sealant kit (Figure 10). The centre held a Manufacturer's Licence, a Good Manufacturing Practice (GMP) Certificate, a Manufacturer's Specials Licence, a Manufacturer's Authorisation for Investigational Medicinal Products (IMP) and Good Laboratory Practice (GLP) accreditation.

2008–2015

The Penrose inquiry

In April 2008, the Scottish Government established a Public Inquiry into the infection of patients with hepatitis C and HIV by NHS treatment with blood and blood products. In its assessment of the performance of the PFC, the Inquiry concluded[28]:

> *It was the ability of Scottish scientists to pursue their own research that resulted in the development of effective heat inactivation at the end of 1984, enabling the SNBTS*

Table 1. PFC products and their regulatory status, 2007.

Plasma product	Dose form	Dose size	UK regulatory status
Immunoglobulin products			
Normal immunoglobulin for intravenous administration	Freeze dried	3 g, 5 g and 10 g protein	Product Licences
Normal immunoglobulin for intravenous administration	Liquid	5 g and 10 g protein	Clinical Trial Authorisation Product Licences pending
Normal immunoglobulin for intramuscular administration	Liquid	250 mg protein	Product Licence
Anti-D immunoglobulin	Liquid	250 IU & 500 IU	Product Licences
Hepatitis A immunoglobulin	Liquid	500 IU	Product Licence
Hepatitis A immunoglobulin	Freeze dried	5000 IU	Manufacturer's Specials Licence
Tetanus immunoglobulin	Liquid	250 IU	Product Licence
Tetanus immunoglobulin	Freeze dried	2500 IU	Manufacturer's Specials Licence
Varicella-Zoster immunoglobulin	Liquid	250 mg protein	Product Licence
Cytomegalovirus immunoglobulin	Freeze dried	1.5 g protein	Manufacturer's Specials Licence
Botulinum Toxin immunoglobulin (Ovine)	Freeze dried	700 mg protein	Manufacturer's Specials Licence
Albumin			
Human Albumin, 4.5% protein solution	Liquid	100 ml and 400 ml	Product Licences
Human Albumin, 20% protein solution	Liquid	50 ml and 100 ml	Product Licences
Coagulation factor concentrates			
High Purity Factor VIII concentrate	Freeze dried	500 IU	Product Licence
High Purity Factor IX concentrate	Freeze dried	500 IU	Product Licence
Factors II, IX and X concentrate	Freeze dried	360 IU (FIX)	Product Licence
Prothrombin complex concentrate	Freeze dried	500 IU (FIX)	Clinical Trial Authorisation.
Fibrinogen concentrate	Freeze dried	225 mg and 1 g protein	Clinical Trial Authorisation
Thrombin concentrate	Freeze dried	1000 IU	Clinical Trial Authorisation
Fibrin Sealant Kit	Freeze dried	225 mg Fibrinogen and 1000 IU Thrombin	Clinical Trial Authorisation Product Licence pending

Figure 9. Final portfolio of PFC plasma products (© Antonia Reeve).

Figure 10. Fibrin sealant kit (© Antonia Reeve).

to provide the first comprehensive national supply of heat treated Factor VIII in the world.

... a safe NHS product was available many years before commercial manufacturers supplied Factor IX concentrates that were safe from the transmission of NANB Hepatitis/HCV.

There is no basis for criticism of the PFC and its scientists over the period ending with the introduction of Z8 [a Factor VIII concentrate] *for routine clinical use in April 1987. On the contrary, they achieved outstanding results, as evidenced by the fact that Scotland appears to have been the first country in the world that was able to supply all of its haemophilia patients with a Factor VIII product that did not transmit hepatitis C.*

Lord Penrose also concluded:[28]

With the closure of the PFC, Scotland lost many of the skill sets associated with Fractionation.

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