SNBTS 'Blood Letter', Spring 2008, 21-23

feature

Plasma Fractionation in Scotland

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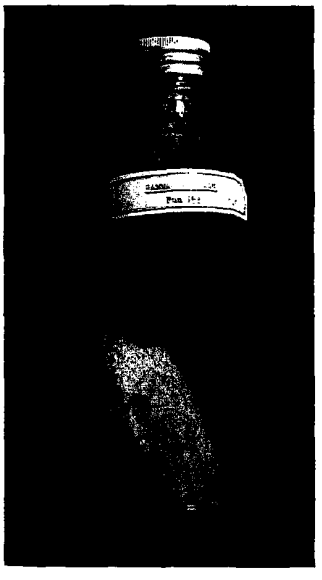
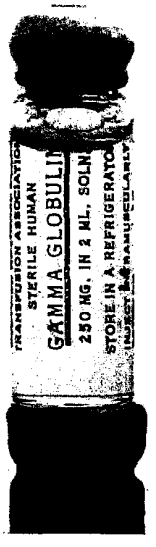
1941-1950

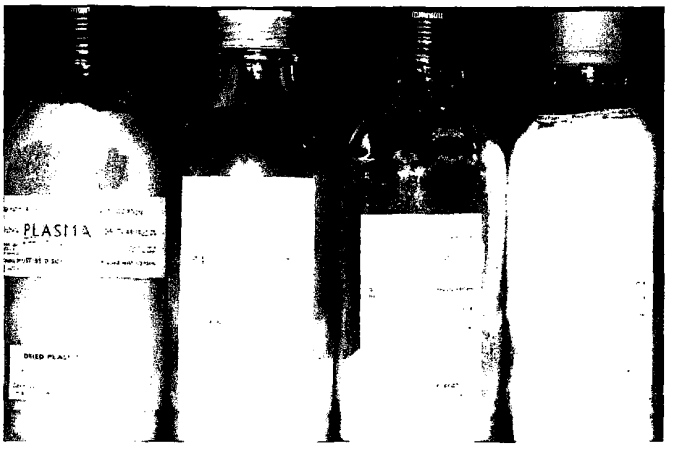
The origin of PFC began with a decision taken in 1941 by the Treasury War Emergency Expenditure Committee to finance two facilities in the UK for the preparation of freeze-dried human plasma, one of which was to be situated "in the north". This resulted in a unit for drying plasma being constructed in an underground site at the Royal Infirmary of Edinburgh (RIE). After the war, it was proposed that the unit be extended to accommodate "Plasma Fractionation and the drying of products so obtained", as "There is only one plant of this kind in Britain at the Lister Institute and it is unlikely that it will be able to meet all demands". This recommendation led to premises at RIE being provided for the Edinburgh & SE Scotland BTS with construction beginning in June 1948 and with the centre being opened by the Queen in September 1950. Dr Robert Cumming was appointed Director of Edinburgh & SE Scotland BTS in 1948 and Dr Drummond Ellis, a biochemist, was appointed his deputy in 1950 with special responsibility for the development of plasma fractionation.





1951-1974

Dr Ellis first travelled to the United States to study plasma fractionation at the Harvard laboratory of Edwin Cohn, where a method for fractionating human plasma by precipitating proteins using cold-ethanol had been devised during World-War II. On his return, Dr Ellis planned the installation and designed much of the equipment to produce Scotland's first fractionated plasma product, normal immunoglobulin for the prevention of measles infection (1952). This was followed in 1956 by an early version of factor VIII (Cohn Fraction I) for the treatment of haemophilia A and fibrinogen to stop bleeding. In addition, Human Albumin and anti-vaccinia immunoglobulin were produced from 1965.



Throughout this period demand for plasma products in Scotland continued to increase. The capacity of the BPU was expanded in 1961, with an expectation that further expansion would be required in 10 years time. By the late-1960s planning was underway for a new purpose-built centre designed to operate at an industrial-scale. Dr Ellis moved to the Blood Products Laboratory (BPL) at Elstree and was replaced by Mr John Watt who had previously worked on the fractionation of animal plasma at the Royal Dick Veterinary College. Dr James K Smith, a biochemist from the Clinical Chemistry department at RIE was appointed to assist him. New products continued to be introduced including: anti-D immunoglobulin (1968); prothrombin complex (factors II,VII,IX&X) concentrate for the treatment of haemophilia B, anti-tetanus and anti-rubella immunoglobulin (1969); Plasma Protein Fraction (1971); intermediate-purity factor IX concentrate (1972); and anti-hepatitis B immunoglobulin and intermediate-purity factor VIII concentrate (1974). Close collaboration with Dr Alan Johnson of New York University Medical Centre was invaluable in the development of intermediate-purity coagulation factor concentrates. On the 1st April 1970, the BPU was officially renamed the Scottish Protein Fractionation Centre (PFC). Construction of new facilities for PFC at Ellen's Glen Road, Liberton began in 1971 and completed at the end of 1974.

1975-1983

35 staff moved from RIE and a further 90 were appointed to operate the new centre. Dr Smith left during 1975 to join the Plasma Fractionation Laboratory (PFL) at Oxford. Design of the new PFC facility was centred on a computer-controlled, continuous-flow, small-volume mixing (CSVM) cold-ethanol fractionation process; a technical innovation, which promised a high throughput, with on-line monitoring and automatic control. A further innovation involved the development of a refrigerated multi-chamber centrifuge (in conjunction with Westphalia Ltd) which was integrated with the CSVM process and represented such an advance that this type of centrifuge was subsequently utilised widely by the plasma fractionation industry.

Although the PFC facility was designed to accommodate plasma from the north of England as well as from Scotland, it was equipped initially for Scottish needs only. Satisfying Scotland's demand for albumin from its own donor

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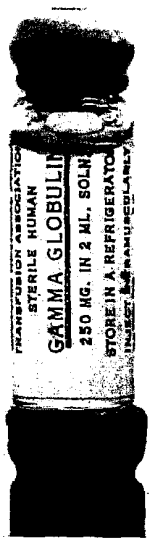

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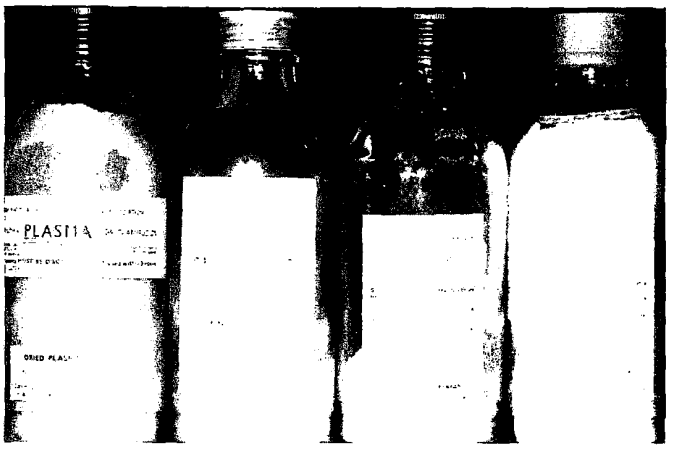

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Plasma Fractionation in Scotland - continued

population was the first challenge, to avoid the need to purchase costly imports. 30,000 litres of plasma had been stockpiled by SNBTS and this, combined with the high capacity of the CSVM process, enabled PFC to quickly meet Scotland's needs for albumin. Despite this success, plans to process plasma from England did not come to fruition and plasma from Northern Ireland was provided instead, leaving PFC with insufficient plasma for the CSVM process to operate to its full potential.

The success of factor VIII concentrate led to demand greatly exceeding all projections. The UK Government objective of achieving national self-sufficiency as recommended by the World Health Organisation presented a major challenge. Technical innovations at PFC enabled process yield and production capacity to be increased simultaneously which, together with a substantial increase in the provision of fresh frozen plasma by SNBTS, enabled Scotland, in 1983, to become the first country in the world to achieve self-sufficiency in supply of factor VIII concentrate from volunteer donor plasma. Also in 1983, PFC became one of the first fractionators to produce immunoglobulin suitable for intravenous administration (IV IgG); a product which was so successful, that it was eventually to replace factor VIII concentrate as the lead product of plasma fractionation.

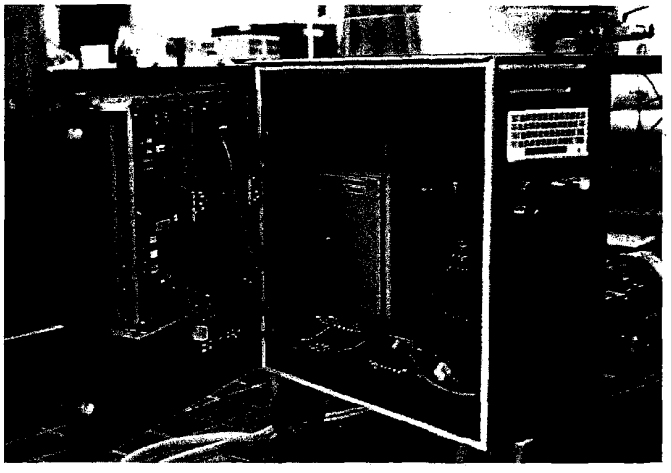
Although covered by crown immunity, PFC applied for and was granted a Manufacturer's Licence by the Medicines Control Agency in 1976; with Product Licences being granted for factor VIII and factor IX concentrates in 1978 and 1979 respectively. An extension to PFC was completed in 1982 to provide virology and microbiology laboratories as well as an R&D pilot plant. At the end of 1983 the PFC Director, Mr Watt, left SNBTS and was replaced by Dr Bob Perry, formerly head of Quality at PFC.

1984-1994

Further advances followed; heat treatment of factor VIII began in November 1984, within days of reports from the USA that HIV might be inactivated by this procedure. SNBTS stocks of factor VIII were heat-treated, effectively back-dating heat treatment and enabling factor VIII prepared from donations collected as early as October 1983 to be made safe from HIV transmission. Further research discoveries led to the introduction of a new factor VIII concentrate in 1987 that could withstand heating at an even higher temperature, eventually confirmed as effective against hepatitis C virus (HCV) also. Equivalent heat treatment was applied to factor IX concentrate in 1985, as soon as critical animal safety studies had been completed. As a result of these advances, Scotland became not only the first country to supply factor VIII concentrate sufficient for its haemophilia population that was safe from HIV, but also first with respect to HCV also. The stabilisation of factor VIII by addition of calcium was developed at PFC at this time; a method that is now used universally in the preparation of factor VIII concentrates, both recombinant and plasma-derived.

Additional product developments included high purity factor VIII concentrate and fibrin sealant (1992) and high purity factor IX and heat-treated fibrinogen (1993). Product demand continued to increase, with use of factor VIII concentrate doubling and output of IV IgG increasing 10-fold during this period.

There were developments to process equipment too. The CSVM fractionation process was re-designed in 1986, with local microprocessors replacing the central, main-frame computer and with new in-line mixers, specially designed using orifice sections to mimick oscillatory-flow to mix poorly soluble, adherent proteins effectively and to aggregate protein precipitates prior to centrifugation. Other equipment innovations included the design of the first automated, multi-stage protein-chromatography system in conjunction with with Pharmacia (1985) and design of the first automated protein-ultrafiltration system in conjunction with Amicon (1987).



A therapeutic monoclonal antibody to hepatitis B was developed using a 20-litre fed-batch bioreactor. Although clinical evaluation had begun, the project was discontinued in 1991 because of escalating estimate of costs, due in part to new regulatory requirements. A number of monoclonal blood grouping reagents were also developed at PFC at this time, providing a foundation for a reagents production unit within SNBTS, later to be sold as Alba BioScience.

Crown Immunity was removed in April 1991 and new

applications had to be submitted for a Manufacturers Licence and for Product Licences for every product. A substantial undertaking, which was completed successfully.

A second extension to PFC was completed in 1994; costing £4.5M it provided increased capacity for aseptic dispensing, heat treatment, inspection, labelling packaging, warehousing and cold-storage as well as enhanced engineering workshops and computer (IT) facilities.

1994-2008

Transmissions of hepatitis A, hepatitis B, hepatitis C and HIV by a number of different commercial plasma product used in Germany during 1994 caused European regulatory authorities to urge manufacturers of plasma products to incorporate additional virus inactivation steps into their processes. PFC responded by introducing an extra virus inactivation step into the manufacture of all of its coagulation factor products (1996) each of which had to undergo new clinical trials. Thrombin, prepared with two virus inactivation steps, was also introduced in 1996. In addition, virus inactivation was incorporated into the preparation of immunoglobulins for intramuscular administration(1998), encompassing normal immunoglobulin and a range of specific immunoglobulins, despite the fact that no virus transmissions had ever been associated with PFC products of this type. Again, new clinical trials were required in order to obtain regulatory approval. A simplified method for the preparation of Human Albumin was also developed.

Three events occurred in 1998 which had major consequences for PFC.

- First, the fractionation of plasma from UK donors was banned as a precaution against the theoretical risk of variant Creutzfeldt-Jakob disease (vCJD) being transmitted via plasma products. Plasma from Scotland's donors was replaced by SNBTS with imports from the USA and from Germany, using unpaid donors as far as possible. New equipment had to be purchased to avoid any possible contamination from UK-donor plasma, resulting in the CSVM fractionation process being replaced with lower capacity, traditional (batch tank) technology that was more readily available.

- Second, Scotland decided to fund recombinant coagulation factor concentrates for the treatment of haemophilia as a precaution against the theoretical risk of vCJD being transmitted by products from non-UK human plasma, despite the relatively high cost and increased incidence of inhibitors (antibodies to factor VIII) in patients.

- Third, demand for Human Albumin in the UK fell sharply following a major article in the British Medical Journal which claimed that albumin was harmful in many of the clinical situations in which it was being used, a conclusion that was eventually shown to be incorrect.

To compensate for the fall in Scottish demand for coagulation factors and albumin, contract work was undertaken for biotechnology companies, such as PPL Ltd and Viragen Ltd in order to generate commercial income. Contracts were established to fractionate plasma for Taiwan and to transfer PFC fractionation technology to Taiwan and to Egypt, with the latter projects eventually being discontinued. Surplus albumin was sold inexpensively to developing countries.

In 1998, contracts were established with the Ministry of Defence for the development and manufacture of immunoglobulin based products. Innovative technology was developed to produce a high yield of anti-botulinum antitoxin, modified to be well-tolerated in humans, even though derived from animal plasma. The resultant product has been used to treat civilians as well as for bio-defence purposes and is currently the world's leading product of this type.

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

When the decision was taken to close PFC, the centre held a Good Manufacturing Practice (GMP) Certificate, GLP accreditation and 15 Product Licences for pharmaceutical proteins, with six new products at an advanced stage of development, making it one of the most successful manufacturers of pharmaceutical proteins in the UK.

Although it is 10 years since fractionation of UK-donor plasma was banned, there is still no evidence of vCJD having been transmitted by plasma products either in the UK or elsewhere, a situation consistent with results of research from PFC and other plasma fractionators.

John Watt strongly advocated processing plasma from England at PFC, as he believed that Scotland was too small to sustain a plasma fractionation facility; a view that was ultimately proven to be correct.

Peter R Foster
Development Manager (PFC)