

ENGLAND AND WALES SELF-SUFFICIENCY IN BLOOD PRODUCTS: A CHRONOLOGY FROM 1973-1985

Introduction

Purpose of the report

① About 3000 haemophilia patients treated with blood products in the 1970s and early 1980s were infected with hepatitis C, many with HIV. A number of MPs have suggested that this might have been avoided had the UK achieved self-sufficiency in blood products, a policy the Government initiated in 1975, and Ministers have asked officials to investigate this. This report is the result of a review of surviving documents from 1973 (when a decision was made to pursue self-sufficiency for England and Wales) to 1985 (when viral inactivation was introduced for all the Blood Products Laboratory (BPL)¹ products). It contains a chronology of events (at Annex A) and an analysis of the key issues, including:

- the developing understanding of the seriousness of Non A Non B hepatitis
- the evolving understanding of the viral risks associated with pooled blood products, both domestically produced and imported, and how this influenced policy
- the development of policy on UK self-sufficiency in blood products, the factors that influenced it and the reasons why it was never achieved;
- the developing technologies to enable viral inactivation of blood products and the timing of their introduction in the UK
- the ability of BPL to produce the volumes of products required.

Haemophilia

② There are two types of haemophilia – A and B. Haemophilia A is a genetically inherited bleeding disorder which results from lack of the coagulation Factor VIII in the blood. In patients with this deficiency, any untreated episode of bleeding is usually prolonged and often fatal.

Treatment for bleeding episodes in haemophilia

Initially there was no treatment for haemophilia apart from transfusion of whole blood and later plasma. Then in the 1960s, the use of cryoprecipitate began in hospitals and it was the preferred form of treatment for Haemophilia A up to about 1972/73.

③ Cryoprecipitate does not contain Factor IX, and patients suffering from Haemophilia B continued to be treated with fresh frozen plasma until a process was developed to fractionate Factor IX from the supernatant resulting from the production of cryoprecipitate from plasma.

④ By the early 1970s, freeze-dried concentrates of Factor VIII (for Haemophilia A) and of factor IX (for Haemophilia B) complex made by pharmaceutical companies from large pools of plasma became widely available in the United States. The custom of repeated plasmapheresis of paid normal donors allowed the United States to produce

concentrates in abundance for domestic use and to become the world's major exporter of concentrates abroad. These products were in use in England in the 1970s and 1980s, together with some which were produced within the NHS.

5 The introduction of Factor VIII concentrate revolutionised the treatment of haemophiliacs and improved the outlook for the severely affected haemophiliac. Factor VIII activity was much greater in the concentrates and was much more predictable than cryoprecipitate. Since it could be stored in a domestic fridge, many patients were able to treat themselves at home and, were able to self-inject immediately at the onset of a haemorrhage, without depending on a visit to a hospital or GP. Major operations on haemophiliac patients became easier. These factors, together with the advent of prophylaxis (the prevention of bleeds) later on, particularly for children, and the longer life expectancy of haemophiliacs led to an increased usage.

6 This report concentrates on blood products for the treatment of Haemophilia A, since it is the more common form of haemophilia and there were particular difficulties in relation to self-sufficiency in Factor VIII. With the exception of a brief period of time when BPL was evaluating the safety of its heat treated Factor IX, BPL has largely been able to meet all the demands made on it for Factor IX concentrate. The risk of viral infection was greater with factor concentrates than with other plasma derivatives – for example immunoglobulin preparations – and for albumin preparations, where any viruses were inactivated by pasteurisation.

Developing knowledge of Non A Non B Hepatitis (NANBH) – later known as Hepatitis C

7 With the development of tests for Hepatitis A and B in the 1970s, it became clear that other viruses could be transmitted by blood and these were termed Non A Non B hepatitis (later isolated and fully identified in 1989 as Hepatitis C). (Ref 1 in Main)

8 On 3 August 1974, Dr Prince and others identified in the Lancet this new strain of hepatitis. On 2 August 1975, in the Lancet, Dr Craske and others linked an outbreak of hepatitis (some cases were classified as non-B) between April and June 1974 to intravenous injections of Factor VIII commercial concentrate in the previous six months.

9 In 1975 Professor Zuckermann was interviewed on "Blood Money" and warned that hepatitis linked to the factor concentrates ranged in severity from very mild to a disabling illness lasting several weeks, and in some cases progressing to chronic liver damage and cirrhosis of the liver.

10 A PHLS paper in 1980 on the epidemiology of Factor VIII and IX associated hepatitis in the UK stated that NANBH was an acute illness which was clinically mild and clinically indistinguishable from Hepatitis A and B. Of a total of 138 cases where transfusion history was known, 103 had been associated with first transfusion of Factor VIII or IX concentrate. They published evidence of the existence of at least two types of the virus; one with US sourced commercial products; one with NHS Factor VIII and European products, probably related to the different fractionation

processes. There was therefore a high risk from the use of Factor VIII or IX concentrate that the patient would contract the virus.

11 Also in 1980, Professor Zuckermann warned on "Blood Brothers" that the incidence of hepatitis amongst patients with haemophilia was increasing, and suspected that the reason for this was because the imported products may have carried a higher risk of infection. He also said that NANBH was associated with continuing liver damage, and thought that potentially this was a serious situation. An internal DH memo said on 15 September 1980 that this form of hepatitis could be rapidly fatal (particularly when acquired by patients with pre-existing liver disease) or could lead to progressive liver damage.

12 On 4 July 1981 the BMJ ran an article on post-transfusion hepatitis (PTH). This stated that NonA NonB agents were then thought to be the main cause of chronic liver disease in patients with haemophilia – as was shown by Seef's review (1981) of post-transfusion hepatitis in the US since the introduction of screening for HbsAg. In the absence of specific markers for NonA NonB hepatitis, they said that overall protection against hepatitis appeared remote. A more likely possibility was that hepatitis-free blood products would become available, three recent reports suggesting that viral contamination may be removed by specific processing by chemicals, ultraviolet light or heating.

13 From the papers we have examined, it does not appear that the Advisory Group on Hepatitis began to consider NANBH until 1981, and even then they recommended that research was undertaken in the UK to determine the extent and severity of PTH due to NonA NonB hepatitis viruses.

14 After June 1982, further studies were published which showed that NANBH was more serious than previously thought. For example, the American Public Health Association reported in 1985 that chronic Non-A Non-B hepatitis may progress to cirrhosis but more often improves clinically after 2-3 years. Despite intensive efforts, serologic tests suitable for a diagnosis had not been developed. They concurred that it was more common when paid donors were used. Recipients of blood transfusions and parenteral drug abusers were, they said, at the highest risk.

15 As late as 1985, an article in the Lancet (Hay et al) postulated that progressive liver disease in haemophiliacs who had received clotting factor concentrates was an understated problem. The article stated that serial liver biopsies of 21% of haemophiliacs in a study treated with clotting concentrates showed that they had chronic active hepatitis (mainly NANBH) or cirrhosis and that this had progressed from chronic persistent hepatitis. Therefore this was not as benign as had previously been thought. Again, they said that the patients appeared clinically well and thought that liver disease in haemophiliacs would become an increasing clinical problem in the future.

16 Professor Roger Williams said in 1990 in evidence against HIV Haemophilia Litigation that it has been known for more than 10 years that untreated coagulation factor concentrates such as factor VIII provide the greatest risk of transmission on NonA NonB. He went on to say that the overriding problem facing haemophiliacs

was the need to pool donations to make the specialised factor concentrates. Before 1978, the pool size of NHS Factor VIII was restricted to less than 3000 donations but since then some donor pools have exceeded 10k. This had been considered necessary to maintain the uniform quality of factors.

17 However, at the Hepatitis C Litigation against the National Blood Authority in 2000, Dr John Barbara said it was vital to balance the concept of maximum safety with the need for continuity of blood supply. While there was an inadequate knowledge of the prevalence of NANBH in the late 1980s, enough was known about the incidence. NANBH was perceived as a relatively mild condition in the 1980s. Professor Dusheiko said while it was accepted that in the mid 1980s it was recognised that NANBH could lead to chronic liver disease, he agreed that the prevalence and percentage that could progress to severe illness was unknown.

18 A Scottish review in 2000 of the understanding of the risks of Hepatitis C before the heat treatment of products included interviews with Haemophilia Centre Directors. Their views were that until the late 1980s perceptions were that NANBH was a mild, non-progressive condition, the first serious study on liver biopsy having been undertaken in 1985. The Scottish review also looked at the scientific literature in the late 1970s and early 1980s, and concluded that there was no real consensus on the progression of any disease caused by the Hepatitis C virus at the time.

✓ 19 Even today, Hepatitis C usually runs a milder course than Hepatitis B and many patients show no symptoms of hepatitis. However, although the disease is often mild, there is a tendency for chronic liver damage in up to 50% of patients, varying from mild persistent abnormality of liver function and chronic hepatitis to cirrhosis. *Text etc.*

20 The time for development of chronic disease with serious liver damage may be 15 years or even longer. Therefore, if the NANBH problem started in 1972 with the introduction of large amounts of clotting concentrate then the potential seriousness of the condition would not have been appreciated until the mid to late 1980s. This appears to have been the case with the wider application of liver biopsy and the closer testing of the levels of substances known as transaminases. Tests for the Hepatitis C antibody were not introduced until 1991, after the isolation of the virus in 1989.

Levels of NANBH virus in the products

21 Plasma products, such as clotting factors, consist of donations from tens of thousands of individuals. If just one of the donations used in the manufacturing pool for clotting factor is infected with Hepatitis C, there is a risk to the whole batch made from that pool, and to all recipients of that batch of products. It is possible now to identify the presence of the virus in pools or in individual donations.

22 Blood products in the late 1970s were known to transmit viral infections, in particular Hepatitis B and NANBH and this has been well documented (Barker et al 1973). The products produced in the UK were not immune from hepatitis but since they used a smaller number of volunteer donors who were also unpaid the risks were decreased. However, the US fractionators produced the first high purity Factor VIII products and many of the haemophilia clinical specialists in the UK justifiably wished to use these

products.

Throughout the mid to late 1970s, scientific papers (for example Craske et al 1975) discussed liver function abnormalities in haemophiliacs, and postulated that they might be related to treatment with blood products, particularly Factors VIII and IX. This was largely thought to have arisen in relation to commercial concentrate because the large donor pools used to produce these products would increase the risks of any viruses present. In most of the reports, the illness was stated to be mild and short lived.

In 1981, the Lancet said that paid blood donors were more likely to transmit hepatitis than unpaid donors. At the meeting of UK Haemophilia Centre Directors on 9 October 1981, it was reported that there was a 4-20 times higher incidence of overt NANBH associated with US commercial concentrate than NHS.

However, studies published in 1983 (notably Fletcher et al) confirmed that patients who had not previously been exposed to concentrates would have a high risk of developing NANBH after their first exposure to concentrates which had not been subjected to viral inactivation. This applied whether these concentrates were commercial or produced by BPL. This was confirmed by Kernoff et al in 1985, and showed that all concentrates, whether from paid or volunteer donors, carried a risk of nearly 100% of causing hepatitis when transfused into patients who had never before been transfused, or only infrequently transfused.

Products were heat treated in the 1980s and by 1985 BPL heat treated product became available which led to inactivation of the viruses (please see the later section on heat treatment). However, in a 1990 letter to Vox Sang Professor Hill and others noted HIV seroconversion in 4 sexually immature haemophiliac boys following the use of a dry heated commercial Factor VIII concentrate, which was heated at 60°C for 30h (a lower temperature than NHS Factor VIII). One of the boys seroconverted between September 1985 and September 1986. This led the company to voluntarily withdraw the product from the British market in 1986.

Risks of using the concentrates vs no treatment

It is likely that clinicians who prescribed clotting factors in the 1970s and early 1980s would have been aware of the viral risks attached to the use of Factor VIII. However, the prevailing view seems to have been that these risks were worth taking given the beneficial impact of clotting factors on the quality of patients' lives. A World in Action programme in 1975 dealt with the problem in detail and included interviews with patients who continued to use the concentrate despite knowing the risks. Although Dr Craske recommended in 1975 a return to the use of cryoprecipitate for routine treatment (which was not without its own risks), by then the majority of patients were self-injecting at home, and cryoprecipitate could not be used in this way.

As late as 18 May 1983, the Sun reported on that the Haemophilia Society had appealed to the Government not to ban American blood supplies. The Society said that without the US imports – which account for 2/5 of Britain's blood needs – there

would be a sharp rise in deaths among haemophiliacs. In August 1983, the Society was informing Ministers of its opposition to any move to ban American Factor VIII. Similarly, on 19 November 1984 the Guardian printed an article on a haemophiliac's death from Aids after transfusion. The Haemophiliac Society again urged its members to continue the use of factor VIII.

In 1990, Professor Bloom, reviewing the literature and editorial comments in publications such as the British Journal of Haematology and the Lancet, concluded that it was clear that the use of both domestic and imported concentrates was reasonable and accepted good medical practice during the period 1972 to 1987. The review includes a paper by Rizza and Spooner (1983) which states that between 1976 and 1980 cerebral haemorrhage was the commonest cause of death for UK haemophiliacs (29%) and that there were two deaths from hepatitis (2%). In fact, the yearly incidence of hepatitis remained at about the same level from 1969 to 1980, apart from a rise to 5.2% during 1974-1975 (roughly when commercial concentrates were widely used).

English and Welsh sufficiency in Factor VIII

Development of DHSS Policy

It became apparent in early 1973 that production of Factor VIII concentrate in the UK was insufficient to meet the stated needs of clinicians. The indication was that considerably more of the concentrate would be used if it were available. Consequently, England and Wales relied on expensive imported commercial Factor VIII. Health Authorities spent £500,000 between November 1973 and March 1975 on the purchase from commercial firms of imported Factor VIII concentrate.

The Department therefore decided to convene an expert group to assess the possible future requirements for treatment and the consequence for the supply of therapeutic agents, including human Factor VIII concentrate. It was anticipated that this would lead to realistic planning for the future, and could lead to the possibility in the slightly longer term of producing sufficient material in the UK to meet the need.

The expert group reported in March 1973 and recommended that the NHS should become self-sufficient as soon as possible in the production of Factor VIII. They also recommended that 400,000 donations of blood would be required to treat UK haemophiliacs (including Factor VIII equivalent to 275,000 donations), and more if efforts were made to clear surgical waiting lists, and if home or prophylactic treatment of haemophilia became acceptable. They recognised that as a result there would need to be a substantial increase in the amount of plasma reaching BPL from the Regional Transfusion Centres (RTCs) for the preparation of Factor VIII. This would involve the RTCs in additional expenditure on blood collection and initial processing.

As a result, it was decided that an allocation of funds would be made to Regions, largely to be spent on building and equipping plasma separation rooms and paying for the staff to run them. Early in December 1974, the Minister of State for Health earmarked central funds of up to £0.5m (about half of which would be recurring). This would be used to increase the output of plasma in RTCs to the equivalent of

275,000 blood donations annually for the preparation of Factor VIII and 100,000 donations for cryoprecipitate.

The primary aim of the allocation was to make the NHS self-sufficient in Factor VIII concentrate within two to three years. The reason for seeking to achieve self-sufficiency was to reduce the cost of importing products. Although several of those we interviewed gave the reason for pursuing self-sufficiency as a need to reduce the risk of patients contracting hepatitis from the concentrates, there is no indication in the Departmental papers that safety was a consideration at this point.

However, an internal minute on 10 July 1978 does say that "there is doubt about the circumstances in which the plasma is collected abroad which largely influenced Ministers (so I understand) to enunciate the doctrine of NHS self-sufficiency in blood products." In addition, a January 1980 Sunday Times article states that the Department was concerned about using imported blood products because of the attendant risk of passing on infectious diseases, particularly hepatitis, although we have found no written evidence of this.

In an Adjournment Debate on 15 December 1980, Sir George Young replied for the Government that the Government fully endorsed the principle of self-sufficiency. In doing so, he referred to the risk of contracting hepatitis from imported products, although he did not specifically mention NANBH, and the only other reference in his speech is to Hepatitis B.

On 29 April 1976, the Department issued a Press Release re-affirming that the UK was aiming to become self-sufficient in the supply of blood products by mid-1977. It strongly supported the World Health Organisation (WHO) resolution passed in May 1975 that each country should be able to supply its own blood and blood products to meet clinical needs. The Department also supported the Council of Europe recommendation R(80)5 which recommended that member states pursue the goal of self-sufficiency of anti-haemophilia products and blood plasma for their preparation.

The Central Committee of the National Blood Transfusion Service (NBTS)² met on 2 November 1976, where they heard that the supply of plasma was increasing in line with the target, but that some clinicians believed the target should be set at to 50 million international units per annum (iu pa). The group felt that it was difficult to accurately estimate demand. It was decided therefore to set up an expert group "to consider the likely trends in the demand for blood products over the next 5 to 10 years, taking into account the practicabilities of supply".

The production target for Factor VIII set for June 1977 was attained. However, as already outlined new opportunities in the treatment of haemophilia and associated disabilities had been developed which made further clinical demands for Factor VIII. In addition, the original estimate was based on numbers of severely affected haemophiliacs and did not include those who were moderately or mildly affected. There was still therefore a deficit which was continuing to be met by purchase of concentrate from commercial sources. The Department stated that England and Wales were still aiming for self-sufficiency.

The Working Group on Trends in the Demand for Blood Products reported in December 1977. It confirmed the estimated requirement for 1000 iu of Factor VIII per 1000 population pa (this translated to about 50 million iu per annum). They further recommended that the Department encourage research which would lead to a reduction of the loss of Factor VIII in collection, storage and processing, and that there should be a complete transfer from the use of cryoprecipitate to fractionated freeze dried concentrate in the long-term. They concluded that additional fractionation capacity was needed, estimating that the present UK capacity was for less than half of the requirements for Factor VIII, which would need to double over the next 5-10 years. The report led to the Department concluding that the organisation of the NBTS should be reviewed, particularly in relation to the demand for blood and blood products, and its ability to meet this demand.

The Standing Medical Advisory Committee (SMAC) later confirmed that these were likely to be reliable estimates of future need and supported planning to increase supply accordingly. They felt that the estimates were probably somewhat low for Factor VIII, since increasingly major orthopaedic surgery was undertaken to replace or mobilise damaged joints. Large amounts of Factor VIII was needed to control bleeding in relation to this.

By September 1980, the projected requirements for Factor VIII consumption by the mid 1980s were 90 million iu per annum. However, there was a feeling that these would need to be revised in the face of recent evidence indicating that UK clinicians were coming under pressure to step up the dosage regime for the home treatment of haemophilia.

At a meeting between Ministers and the Haemophilia Society on 21 October 1981, the Government assured the society of its support for the principle of self-sufficiency in blood products though it stressed that this had to be a long-term aim as the present BPL was not able to manufacture sufficient Factor VIII to obviate the need to import blood products. The Haemophilia Society accepted that self-sufficiency should only be aimed for if it could be shown to be economic to do so.

In 1983, evidence emerged that US haemophiliacs were contracting AIDS. Although the mechanism of the infection was not known, it was presumed that it had been transmitted through the use of blood products such as Factor VIII. The Government wrote to the Haemophilia Society to reassure them of the Government's commitment to self-sufficiency in blood products.

Meanwhile it acknowledged that England and Wales continued to be dependent upon additional material to make up the shortfall in the home-produced supply and that this was imported primarily from the USA. In considering whether the imports should cease it was necessary to weigh the possible risks of infection from AIDS against the obvious risks from not having enough Factor VIII. Self-sufficiency was still the target in 1985.

By 1990, the Departmental policy was that while Britain promoted the aim of self-sufficiency in blood products, it acknowledged that clinicians were free to prescribe whatever product they considered appropriate for the patient. This was

linked to BPL's loss of Crown Privilege and cross-charging for products. It was left to BPL to promote its product and for clinicians to make the choice.

This policy was then developed further in 1993, when England and Wales' domestically sourced products had about 75% of the Factor VIII market. At this time, it was felt that there were dangers in absolute self-sufficiency leading to a reliance on a sole supplier of blood products. This would override clinical freedom, stifle new developments (many of which were from the commercial sector), and expose England and Wales to the possibility of inadequate volumes of product for effective treatment, and the risks to supply inherent on relying on a sole manufacturer. The Department aimed to achieve self-sufficiency through products sourced from unpaid donations, but clinicians should not be prevented from using other products where necessary for appropriate treatment. Groups representing haemophiliacs were considered to be strongly against self sufficiency being pursued by limiting the volume of products available and restricting access to new treatments.

Resourcing

There is no evidence that there was insufficient allocation of resources towards achievement of self-sufficiency. These events occurred at a time of financial cuts when budgetary pressures were extreme. The pressure for capital spending on other forms of medicine and other forms of Government expenditure was very considerable. The Department acted reasonably in devoting substantial capital expenditure to achieving production targets in the NHS which it considered would be sufficient to avoid the need to import commercial blood products.

It is moreover true to say that the Central Blood Laboratories' allocations compared very favourably with those of other health authorities during this period, reflecting the importance the Government attached to the development of the blood products service. The growth in revenue allocations increased by 33.5% for the period 1978/79 to 1982/83, compared with 4.9% for other Health Authorities.

Plasma production

The expert group estimated initially that 275,000 donations of blood would be required to achieve self-sufficiency in Factor VIII. Draft Regional Health Authority targets for achieving this objective (by diverting donations used for the preparation of cryoprecipitate and increasing the number of donations used for Factor VIII) were fixed provisionally on 4 March 1975. Bids were submitted and accepted showing an estimated time schedule for the build up of production, the latest date being 30 June 1977.

Although the 1977 target was achieved, it was realised that it would be necessary for the NHS to increase considerably the volume of fresh frozen plasma and the capacity of the processing plants in order to meet the increasing demand for Factor VIII. The Trends Working Group report in December 1977 accepted an estimate for Factor VIII requirements of 1000 international units per thousand population per annum. This could be achieved by an increase in the annual rate of blood collection to 50 donations/1000 population, planning for a possible rise to 60 in the next 10 years,

although expressing caution about a possible excess of red cells.

At a meeting of the RTDs it was stated that the majority of RTCs had reached their capacity to separate plasma given the present state of clinical acceptance locally of plasma depleted blood, and physical constraints at the RTCs. In addition, BPL was nearing its stated capacity. BPL said that it was possible with relatively minor changes to increase the production capacities to 24m iu of Factor VIII. The Department asked BPL to prepare development plans, based on agreed production targets of 50m iu of Factor VIII pa.

In July 1979, BPL highlighted the difficulty Regions were meeting in producing the necessary volumes of fresh plasma. RTDs in general considered that the present policy of distributing Factor VIII to Regions in proportion to the number of haemophiliacs treated and irrespective of the amount of plasma the Region had sent to BPL was a disincentive for Regions to produce more plasma. It was agreed to move towards a system where Regions would receive BPL products on the basis of the amount of plasma the Region had sent to BPL.

A new system was introduced from 1 April 1981 whereby Regions received from BPL blood products containing fractions in quantities proportional to the amount of plasma sent for processing, account being taken of the yield from each batch of plasma.

The Advisory Committee to the National Blood Transfusion Service set up a Working Party on Plasma Supply to consider the plasma requirements for self-sufficiency in blood products in England and Wales. It made its report in mid 1981. It contained the central calculation that demand for Factor VIII would increase to 100 million iu by the mid 1980s, largely due to predicted changes in the pattern of treatment for haemophiliacs.

In 1982 Ministers decided that to enable the UK to proceed to self-sufficiency in blood products, there would need to be a major expansion of the capacity of the Blood Products Laboratory to process plasma. Estimates of the foreseeable needs in the late 1980s for blood products resulted in calculations that 435,000 kg per annum of fresh frozen plasma would be needed to be produced by the NBTS to enable a new BPL unit to function to full capacity. This would enable England and Wales to meet the future requirements for Factor VIII. This plasma would also produce 200g of albumin per 1000 population.

Regions were asked to ensure that sufficient funds were set aside to achieve the plasma procurement targets of 435,000 kg per annum. Regional targets were originally set for 1984/85 but were revised in 1984 to allow for a phased increase by 1987/88 to allow time for the levels of production at the new plant to increase. It was left to Regions to decide how best to achieve these targets and to determine priorities from within their resource allocations.

The March meeting of the Advisory Committee on the NBTS received a paper which showed the following supply of fresh frozen plasma to BPL (it is unclear whether these are financial or calendar year ends):

1979: 76,527 kg
1981 (provisional): 109,403 kg
The national target for 1982 was 131,648 kg.

There was therefore a large growth in plasma supplied during this period. It would appear that until about 1981 BPL had the capacity to process more plasma than the RTCs were supplying.

Further plasma increases were planned, to allow the new BPL plant to open on schedule. At the RTDs meeting on 8 October 1985, BPL presented the following information on plasma supply in relation to the target figures:

<u>Financial year</u>	<u>Max target (t)</u>	<u>Min target (t)</u>	<u>Actual (t)</u>
1983/84	150	150	154
1984/85	205	180	192
1985/86	285	230	240 (estimated)

Factor VIII production/usage

Table 1 overleaf (supplied by Terry Snape, former BPL employee) shows the amount of Factor VIII produced by the NHS and commercially by year.

This shows an increase in the amount of both commercial and NHS Factor VIII used between 1973 and 1982. The increase over several years showed no sign of falling off, and the predictions of a total requirement of 100 m iu by the mid-1980s still seemed valid.

Points to note are:

- Only 15% more Factor VIII (approximately 15m iu) was issued for the year 1977 ending than in 1976;
- Virtually all the increase in Factor VIII usage between 1980 and 1981 was accommodated by increased NHS production (from 14m to 22.5mu), there being little increase in usage of commercial products.

In 1983, for the first time since 1974, more NHS concentrate than commercial concentrate was used. However by 1985 the position was reversed. This was partly because production of non heat-treated Factor VIII stopped during the course of the first quarter of 1985 while rapid preparations were made to introduce a safer heat-treated product.

Sketchy figures are available of the amount of expenditure for the purchase of commercial Factor VIII. However the following figures are:

<u>Year ending March</u>	<u>Cost (approx)</u>
1977	£1,180,000

1979	£1,244,477
1981	Between £3m and £4m

Because detailed costings of individual blood products produced within the NHS were not readily available no estimate of the potential reduction in public expenditure could be made.

Table 1. Annual consumption of factor VIII in UK (including N.I.) in Million International Units (Miu)

Source: BPL

HT3 = terminal heat-treatment of the freeze-dried product at 80°C for 72 hours

Year	NHS Miu factor VIII	Comm. Miu factor VIII
1969	1.025	0
1970	0.884	0
1971	3.071	0
1972	1.939	0.095
1973	2.481	0.875
1974	2.732	2.681
1975	3.085	5.152
1976	6.915	11.069
1977	12.949 (increase reflects David Owen spend at BPL)	15.017
1978	14.600	19.273
1979	15.092	26.178
1980	14.364	34.749
1981	22.472 (increase reflects spend at BPL)	35.5
1982	22.892	45.644
1983	30.018	26.217
1984	40.192	34.003
1985	23.097 (decrease reflects introduction of HT3 at BPL)	50.902
1986	31.483	53.754
1987	25.982	59.186

Table 2. Factor VIII issued by BPL in Million International Units (Miu)

Source: BPL annual reports for these years.

Year	Factor VIII issued by BPL (Miu)
1981/2	21.53
1982/3	22.10
1983/4	27.08
1984/5	27.95
1985/6	8.00 (unheated, intermediate purity concentrate) 17.55 (HT3 heated factor VIII type 8Y)
1986/7	21.87 (all HT3 from now on)

1987/8	24.06
1988/9	52.75

Heat Treatments

BPL had introduced screening for Hepatitis B in plasma received when the test was available. By the late 1970s manufacturers of coagulation factor concentrates were looking into ways of rendering blood products safe from NANBH. Various approaches were used, including heating, chemical treatment, ultraviolet light and immunoabsorption. It had been known since the 1950s that wet-heating (pasteurising) albumin solution at 60°C for 10 hours rendered it non-infectious for hepatitis. BPL and some commercial companies (notably Behringwerke in Germany) started work on heat treatment in the UK in the early 1980s, and trials were conducted which involved some patients in the UK. However the yield from this process was extremely low and was therefore not seen as practical for application in the UK.

By May 1983, a number of commercial manufacturers of Factor VIII were hoping to introduce Factor VIII concentrates which had undergone an additional heat-treatment step (using different regimens) which was designed to reduce viral infectivity. The FDA approved on 24 May 1983 a new heat treatment to reduce infectious agents in Factor VIII. However commercial concentrates were later shown to still be transmitting NANBH.

Factor VIII did not withstand heating well, and the challenge was to develop a production process which would not result in a significant loss of the yield (and thus require increased amounts of plasma from the RTCs) or to the inactivation of the product. In addition, there was a potential for heating to promote the development of unwanted antigens. This generally meant making purer preparations of Factor VIII with added stabilisers. In addition, because there were no markers available for NANBH until 1989 (and no tests until 1991) the effectiveness of the heating process could only be tested through close monitoring of the patients after receiving the product. The decision over which regimen to use was therefore governed by observations of the amount of heat a product could withstand to inactivate viruses before its effectiveness deteriorated.

Up to mid-1984, BPL investigated both pastuerisation and dry heating, in collaboration with the Plasma Fractionation Centre in Scotland. At this point, consensus was reached that HTLVIII (later HIV) was the causative agent for AIDS and in October 1984 the US Center for Disease Control stated that the virus could be inactivated by heat treatment. This increased the pressure on the manufacturers, including BPL, to develop methods of viral inactivation, and as a consequence BPL progressed their existing programmes.

In November 1984, BPL announced that Factor VIII manufactured there would be heat treated by April 1985. Since commercially available heat-treated products were not licensed in the UK, the Committee on Safety of Medicines suggested that existing commercial product licence-holders be asked to make an early application for variations in their licences to allow introduction of heat-treated products. In the meantime, practitioners continued to have discretion to prescribe unlicensed

heat-treated Factor VIII concentrates on a named patient basis only. The choice of treatment was of course a matter for the judgement of the clinician responsible for the patient.

At the meeting of Haemophilia Reference Centre Directors on 10 December 1984, it was agreed that children should be treated with cryoprecipitate or if necessary with heat treated Factor VIII. New haemophiliac patients should be treated with heat treated Factor VIII. Most agreed that untreated BPL Factor VIII could continue to be used until heat treated Factor VIII was available from BPL. There were some Directors who were not willing to do this, and declared that all patients would have "safe" heat treated Factor VIII. By March 1985, a number of product licenses had been granted for imported heat-treated Factor VIII.

Dry heat treatment of Factor VIII was achieved and implemented on schedule by BPL. Very limited quantities of BPL standard intermediate purity Factor VIII (HT1, heated at 60°C for 72h) were available for clinical trials from May 1984. This combination was selected since it had been used for other blood products and was felt at the time to be the severest without degrading the properties of the concentrate. Although it was subsequently considered to be effective in destroying the virus causing AIDS, it was not thought to inactivate NANBH and therefore further products were developed.

First issues of HT2 (heated at 70°C for 24h since this was felt to be the optimum combination without loss of yield) were issued in February 1985 and by 2 May 1985 all heat-treated Factor VIII issued by BPL was heated to least at this temperature.

During 1984 there were indications that more severe heating may be necessary to inactivate NANBH and in December 1984 BPL developed a new product. Trial issues of this (HT3, heated at 80°C for 72h) were issued in February 1985. BPL made the decision on this combination because the product could withstand it, and they wanted to heat it at the highest temperature possible in order to inactivate NANBH. Factor IX, heat-treated to the same temperature, was not issued until 2 October 1985 (after clinical trials in July 1985), since BPL had to ensure that heating the product did not make it thrombogenic. Factor VIII was later heated to higher temperatures, but the product started to suffer at this stage so it was not pursued.

BPL was also developing a new, high purity product (also heat treated to 80°C for 72h), designated 8Y, which was capable of maintaining satisfactory yield from fresh frozen plasma. A percentage of Factor 8Y was used in clinical trials in selected patients in July 1985 to determine safety and efficacy of product prior to making application for a product licence. It was introduced in the summer of 1985, replacing the earlier products (although there was an overlap of a few months with unheated Factor VIII, which ceased issue in July 1985), and is still used today. To date BPL Factor VIII (HT3) and VIIIY have proved safe and have not transmitted hepatitis or HIV.

In August 1985, output of heat-treated Factor VIII was increased to the maximum level possible in the current BPL plant. Until the new BPL plant came into production, there continued to be a need to obtain additional supplies of Factor VIII

from commercial sources, which was by then also heat treated. There was thus no longer any need to use non heat-treated Factor VIII concentrate.

Medicines Division insisted that from January 1986 all licensed commercially manufactured Factor VIII released in the UK was both heat treated and made from individually donor-screened plasma. The heat treatment used by BPL was for a longer time and at a higher temperature than that used in commercial processes. The BPL product had a good record of safety in clinical trial and was shown to be safe when made from screened and unscreened plasma. However for operational reasons unconnected with the safety of Factor VIII, all plasma processed at BPL since 2 June 1986 was derived from individually screened donations.

Effective heat-treatment against hepatitis was not available before February 1985, except through the West German method from about 1980 onwards which would have required huge supplies of blood donations to make the necessary Factor VIII and which was not scientifically established to transmit hepatitis until 1987. Even at that stage the amounts available were limited and we consider that the date on which heat-treated Factor VIII was made available in E&W – namely April 1985 – was the earliest that could have reasonably been achieved.

Redevelopment of BPL

The importance of Factor VIII and albumin in dictating the ultimate size of the production capacity at BPL was discussed by the NBTS in March 1979. It was estimated that if the current rate of increase in usage continued, and if BPL production was not expanded, the cost of Factor VIII concentrate to the NHS might reach between £14m and £24m by 1982. With expenditure of this order likely to be incurred, there appeared to be every incentive on economic grounds for speedy investment aimed at optimising Factor VIII production at BPL.

In July 1979 BPL received an adverse report from the Medicines Inspectorate. Several risks of microbial contamination to the products were identified, for example from clothing work by the technicians, peeling plaster and leaking equipment. However the report did not state that the products were unsafe, and recommended a set of actions which should take place immediately, and others for the longer-term.

Medicines Division considered the report and their conclusion was that “if this were a commercial operation we would have no hesitation in recommending that manufacture should cease until the facility was upgraded to a minimum acceptable level”. They called for a number of immediate upgrades to product procedures and control and for key staff to be appointed. They felt that the present facility was unsuitable for the manufacture of sterile products and incapable of being upgraded. While the existing building could be used in a different capacity, a new factory-type manufacturing facility was required. They said that the shortcomings were so serious that continued production could only be tolerated because of the essential nature of the products and only if immediate improvements were introduced.

In response to the inspectors' report, it was not considered realistic to hold production of Factor VIII and albumin at existing levels until new process areas were

commissioned. Without growth at BPL in the interim period, by 1984 the projected demand for Factor VIII was expected to be such that BPL's contributions would have become insignificant and unlikely to feature in the mainstream programme of home therapy for haemophilia. Patients would be established by habit on commercial products and pack presentation. It was argued that there must be limited growth at BPL to assist the laboratory in a more gradual transition to a new large production unit. Particularly important during the interim was the increase of the supply of plasma from the RTCs to meet the demands of a new plant.

In considering the Medicines Divisions recommendations, BPL proposed two options: (1) measures to upgrade BPL for 3 or 4 years; and (2) the longer term development of a completely new laboratory.

Ministers agreed a short-term upgrading programme for BPL at a cost of £1.3 million, which was expected to double the production capacity for Factor VIII from 15m iu pa to 30m iu pa.

The possibility of collaborating with private industry in the long-term redevelopment of BPL was investigated but Ministers decided against such an arrangement in view of BPL's dependence on volunteer donors. Ministers also decided in 1982 that a new fractionation facility should be funded and built on the existing site at Elstree at a cost of £21.1m (at November 1981 prices).

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The project was to be "fast-tracked" using a management contractor. This allowed the building to be constructed at the same time as the detailed design for services and equipment progressed. It also enabled the Central Blood Laboratories Authority (CBLA)³ to reflect changes in the technology of fractionation rather than have these excluded by the design having been frozen at a much earlier stage. For example provision was made to enable BPL to use genetic engineering methods when the necessary technology could be scaled up to produce in bulk. This flexibility was intended to prevent the BPL investment becoming too rapidly obsolete. If the scheme had proceeded on conventional lines, design changes to reflect new technology and efforts to accelerate its completion could well have cost the Government more than it subsequently did.

This rebuilding would result in increased production and was intended to make the UK self-sufficient in blood products. Construction was started in May 1983, and a target date for completion was set for January 1986.

A Press Release was issued on 23 March 1984 heralding the building of a new production unit at BPL at a cost of £24m. The scheme was thought likely to pay for itself within five or six years of reaching full production. Efficient operation of the unit required three times as much plasma as is currently processed, and RTCS were engaged in discussions about how to achieve this.

In order to be able to heat treat the material, large ovens had to be specified and built within BPL's existing premises. During the first quarter of 1985 all production of the non heat-treated Factor VIII ceased while rapid preparations were made to introduce the safer heat-treated product.

By 1985, the existing BPL plant could only process 150 tonnes of plasma per year, yielding some 40% of the Factor VIII required. It was thus this manufacturing capacity which limited output at this point, not the ability of regions to supply plasma. Regions at this stage were already supplying BPL with 250 tonnes of plasma per year. The extra plasma was stockpiled deep frozen and was used at the start of production after the plant was redeveloped. The new plant was planned to process 435 tonnes of fresh frozen plasma, in line with the targets set in 1981. By October 1985, Regions had submitted firm plans for producing 400 tonnes, and a commitment in principle for most of the balance. By then, the 1981 plasma targets were regarded as the necessary minimum to achieve self-sufficiency, in part because the heat treatment of Factor VIII produced a loss of efficacy of up to 20%.

By 1987, the project cost had escalated significantly from the first estimate of £21m in 1982 to around £57m. However it had been fully funded by the Government to safeguard the earliest possible completion date. The new laboratory was officially opened on 29 April 1987. It was not expected to be fully productive from the day it came into operation; rather, it was intended to reach full levels of production within 12 months of opening, subject to sufficient plasma being sent for processing.

The main feature of the first quarter of 1988 was the successful commissioning of the new laboratory for the production of both Factor VIII and albumin. Production levels were close to those needed to make England and Wales self-sufficient at then current levels of consumption. The consequent difficulties of maintaining a sufficient plasma supply and ensuring equitable product distribution were being addressed. Production was approaching the 450 tonnes of plasma pa level. The stockpile of plasma was sufficient to supplement current levels of plasma supply and maintain product output at the 450 tonne level for over 3 years.

However two factors weighed against this secure position: (1) an increased Factor VIII requirement was predicted and (2) the yield of Factor VIII per litre of plasma had been less than anticipated. The Department set up a Committee to consider these issues and review the plasma supply targets. Blood products had until now been allocated to regions in proportion to the amount of plasma they supplied to BPL. Such a system would no longer work sensibly once supplies increased to the extent that some Regions would have more product than they could use. Some form of cross-charging for plasma and product between BPL and Regions seemed the best way to ensure equitable distribution. A separate committee was examining the mechanics and ground rules of such a system.

By February 1990, a system of cross charging was in place where BPL "bought" plasma from the NBTS ie reimbursed the Regions for the cost of providing plasma. With money previously allocated directly to BPL, regions were intended to buy the product they needed from BPL. This system was introduced to encourage Regions to collect maximum amounts of plasma. The system ran into difficulties because users were obtaining product from commercial sources and as a result there was an increasing stockpile of (short shelf-life) NHS Factor 8Y. In some cases the problem arose because the system was misunderstood, but Haemophilia Directors were also being influenced by commercial companies to favour their products, largely because of claimed therapeutic advantages particularly for the HIV-infected haemophiliacs.

The Department had no intention to restrict the clinical freedom of haemophilia directors. However, they made Regions aware that very expensive foreign Factor VIII may be being purchased while product already paid for by the NHS went unused.

Conclusion

The information gathered during this review has been at times contradictory and incomplete, but the following conclusions can be inferred.

The Government pursued the goal of self-sufficiency in Factor VIII during the 1970s and most of the 1980s, in line with WHO and EC recommendations. The primary aim of this goal was to reduce the reliance on expensive imported concentrate, although there is some evidence that in the late 1970s this was also linked to the risks of contracted hepatitis from imported concentrate.

In 1975 the Government allocated £0.5m, about half of which was recurring, to the NHS in order to increase plasma production. At the time this was thought sufficient to achieve self-sufficiency in Factor VIII by 1977. There is no evidence that there was subsequently insufficient funding for this, particularly when one considers the amount spent on the redevelopment of BPL.

However, the rapid growth in demand for Factor VIII due to home treatment in particular meant that the amount of Factor VIII produced was not enough to achieve self-sufficiency. This was despite the rise in production of NHS Factor VIII and the resulting increase in plasma collected by the Regional Transfusion Centres to support this. Therefore it was necessary to continue to import Factor VIII concentrate from abroad. This position continued until about 1990, when BPL were obliged to compete in the market place to supply clinicians.

Although it is reasonable to suppose that the Government would have known of the risks of contracting hepatitis from blood products, this does not seem to have been the driving force behind development of policy, particularly in the 1970s. By 1983, it was thought that there were no differences in the levels of virus contained in the unheated BPL and commercial products.

Moreover, the prevailing medical opinion in the 1970s and the early 1980s seems to have been that NANBH was not particularly serious and when set against the consequences of not having treatment for haemophilia (particularly cerebral haemorrhage) it was thought to be a risk worth taking.

Although commercial companies were experimenting with heat-treated Factor VIII as early as 1980, this could not be produced in sufficient quantities for the UK market. BPL developed their own product which was subsequently shown never to transmit NANBH and AIDS (unlike some of the commercial products which were available) and this was introduced as soon as possible.

The redevelopment of BPL was decided upon following the adverse report by the Medicines Inspectorate in 1979, and the realisation that the existing laboratory did not have the capacity to provide enough material for self-sufficiency.