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

Introduction

Purpose of the report

This report is a chronology of events relating to the decision by England and Wales to become self-sufficient in blood products. It has regard to the relevant medical and scientific opinion and practice prevailing at the relevant times. A detailed chronology is attached at Annex A.

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. 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 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

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. This report concentrates on blood products for the treatment of Haemophilia A, since it is the more common 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 virus inactivated Factor IX, BPL has been able to meet all the demands made on it for Factor IX concentrate.

[1] The BPL at Elstree operates under the NHS Act 1977 to develop and manufacture for the NHS in England and Wales therapeutic products derived from human blood. The Plasma Fractionation Centre (PFC) at Liberton in Scotland produces blood products for Scotland and Northern Ireland.

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. 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.

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. In England production of NHS Factor VIII concentrate took place at the Plasma Fractionation Laboratory in Oxford, and the Blood Products Laboratory in Elstree.

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, whereas before they may have been reluctant to attend hospital for minor bleeds, they could now self-inject. Major operations on haemophiliac patients became easier. These factors, together with the advent of prophylaxis (the prevention of bleeds), particularly for children, and the longer life expectancy of haemophiliacs led to an increased usage.

Developing knowledge of Non A Non B Hepatitis (NANBH)

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 known as Hepatitis C).

On 3 August 1974, Dr Prince and others identified in the Lancet another strain of hepatitis – known initially as Non A Non B hepatitis (NANBH). On 2 August 1975, in the Lancet, Dr Craske linked an outbreak of NANBH between April and June 1974 to intravenous injections of Factor VIII commercial concentrate in the previous six months.

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 indistingishuable from Hepatatis A and B. Of a total of 138 cases where transfusion history was known, 103 have 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 will contract the virus.

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 carry 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.

On 4 July 1981 the BMJ ran an article on post-transfusion hepatitis, which 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 appears 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.

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 are used. Recipients of blood transfusions and parenteral drug abusers were, they said, at the highest risk.

The discovery of HIV in 1984 led to a drive to develop a safe concentrate. By 1986, the method used by BPL to produce and heat treat their new Factor VIIIY and Factor IXY was thought to inactivate not only HTLV-III (now HIV) but also NANBH agents. There was some evidence that the BPL products may have been superior in this regard to some commercial products.

As late as 1985, an article in the Lancet (Hay et al) postulated that progressive liver disease 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.

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.

However, at the Hepatitis C Litiigation 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.

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.

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.

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 developed until 1989.

Levels of virus in the products

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. Up to 1989/90, it was not possible to do so with any certainty, as the virus had not then been isolated.

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 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. When NANBH was first recognised, many British workers seemed to regard it as a purely American problem. At the meeting of UK Haemophilia Centre Directors on 9 October 1981, it was reporrted 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, 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

Although clinicians who prescribed clotting factors in the 1970s and early 1980s may have been aware of the viral risks attached to the use of Factor VIII, 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 an

interview with a patient who continued to use the concentrate despite knowing the risks. Although 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 commercia 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. As a result, 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 was referring to Hepatitis B **[check this – Binder 10 – could I at least say not specifically referring to NANBH]**.

[DN: I gather that there was another World in Action programme in 1975 – visiting Haemophilia Society on 16/12 to view the transcript. Apparently Lord Owen claimed in the 1975 programme that he pursued self-sufficiency because of the viral risks in imported products]

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, new opportunities in the treatment of haemophilia and associated disabilities had been developed which made further clinical demands for Factor VIII. 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 anum). 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

[2] Although it was called the National Blood Transfusion Service, blood was collected by 14 Regional Transfusion centres (RTCs).

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. The Department felt that it was for 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.

While acknowledging that the Factor VIII market is very volatile, and there have been shortages over the years, in part related to the stringent inspections to which the FDA subjected the US plants, it would appear that most of the time BPL has been able to produce sufficient quantity to satisfy clinicians needs for their product.

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 1981 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 to 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

There was therefore a large growth in plasma supplied during this period. The national target for 1982 was 131,648 kg.

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:

Financial year	Max target (t)	Min target (t)	Actual (t)
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 90 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:

Year ending March	Cost (approx)
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

Year	Total Miu factor VIII used (includes cryoprecipitate)	NHS Miu factor VIII	Comm. Miu factor VIII
1969	6.945	1.025	0
1970	8.189	0.884	0
1971	11.823	3.071	0
1972	11.039	1.939	0.095
1973	15.829	2.481	0.875
1974	20.548	2.732	2.681
1975	24.886	3.085	5.152
1976	33.716	6.915	11.069
1977	43.193	12.949 (increase reflects David Owen spend at BPL)	15.017
1978	45.050	14.600	19.273
1979	50.716	15.092	26.178
1980	57.271	14.364	34.749
1981	65.700	22.472 (increase reflects spend at BPL)	35.5
1982	73.732	22.892	45.644
1983	71.008	30.018	26.217
1984	79.910	40.192	34.003
1985	77.344	23.097 (decrease reflects introduction of HT3 at BPL)	50.902
1986	88.491	31.483	53.754
1987	87.857	25.982	59.186

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

Source: BPL annual reports for these years.
HT3 = terminal heat-treatment of the freeze-dried product at 80°C for 72 hours

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

By the late 1970s manufacturers of coagulation factor concentrates were looking into ways of rendering blood products safe from hepatitis. Various approaches were used, including heating, chemical treatment, ultraviolet light and immunoabsorption. It had been known for some time that heating albumin solution at 60*C for 10 hours rendered it non-infectious for hepatitis. BPL and some commercial companies (notably in Germany and the USA) started work on heat treatment in the UK in the early 1980s, and trials were conducted which involved some patients in the UK. Pasteurisation was not developed, since this was shown to transmit NANBH.

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 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. The heat process was thought to reduce contamination with viruses, including those that caused NANBH.

However, 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. This generally meant making purer preparations of Factor VIII with added stabilisers. In addition, because there were no markers available for NANBH until 1989 the effectiveness of the heating process could only be tested through close monitoring of the patients after receiving the product.

BPL undertook preliminary studies to assess the yield of Factor VIII intermediate concentrate after dry-heat. They showed that it was possible to maintain greater than 95% of Factor VIII activity in the finished product after heating at 60*C for 30 hours. However, this was shown not to be effective at removing the viruses. **[DN: need to check this with Terry Snape on 13 December. Not sure of the sequence of events at BPL in relation to heat treatment]**

The advent of AIDS increased the pressure on the manufacturers and 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 had 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. 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. 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 Factor VIII issued by BPL was heated at 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, since BPL had to ensure that heating the product did not make it thromobogenic.

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, 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.

[DN: where did BPL gain the knowledge to go up to 80*? BPL/Terry Snape would know]

[DN Table 1 on page 11 of additional information from SNBTS gives key events in the development of hepatitis safe Factor VIII concentrate by SNBTS. Could use as a template]

[DN Need to cover whether we introduced viral inactivation as quickly as we could have. In 1985 BPL introduced heat treatment of blood products which removed Hep C and HIV.]

[DN: need to ensure that information in this section is consistent with the Scottish report]

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.

However home produced heat-treated product was made available slightly earlier in Scotland. That heat-treatment was carried on as an experimental method with no certainty that it would be successful, but in the event it was. Other methods of heat-treatment which had been considered effective against hepatitis were not so.

There is the possibility that the introduction of heat-treated product could have been brought forward by a few months (perhaps three or four) and there is some evidence that non heat-treated product continued to be used for a few weeks after heat-treated product became readily available.

Redevelopment of BPL

BPL was built in the 1960s and by 1980 required modernisation and expansion if it was to meet the aim of self-sufficiency in blood products.

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. 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".

Medicines Division considered the report and recommended that production of none of the products should be increased under existing manufacturing conditions. 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 are 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 laboaratory.

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).

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

[3] The CBLA came into being on 1 December 1982. It was a special heath authority established to manage BPL in accordance with Government policy. **[DN: could expand – see Press Release contained in minute from J harley 19 March in Binder 14]**

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%.

[Need to check 1981/82 decision to become self-sufficient. Was this related to an elimination of the health risks attached to the use of imported commercial products derived from blood provided by blood donors. Take in earlier under self-sufficiency].

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 is 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.

Conclusions

[DN: to be drafted by 23 December]

Annex A

Chronology of events

[DN: need to check text to ensure all key dates are included and that events are covered in text. Needs to be edited further].

Definitions: HT1 = 60°C for 72 hours; HT2 = 70°C for 24 hours; HT3 = 80°C for 72 hours

Date	Event
1972	Donor screening for hepatitis Bs antigen established
1973	Biggs (BJH, 1974): seminal paper on hepatitis in haemophiliacs, showing about 80% of hepatitis due to hepatitis virus(es) other than hepatitis A and B
20 Mar 1973	1st meeting of the DHSS Expert Group on the Treatment of Haemophilia
22 Jan 1974	David Owen announces commitment to UK self-sufficiency in factor VIII and authorises special finance for that purpose
25 Feb 1975	David Owen announces allocation of £500,000 to increase production of factor VIII within the NHS
02 Aug 1975	Craske (Lancet): significance of donor pool size for hepatitis infection risk by factor VIII
23 Apr 1979	Medicines Inspectorate Inspection at BPL (23rd to 27th April)
12 Sep 1980	Zuckerman paper: "Transmission of Heptatitis viruses by plasma and blood clotting factors. The risk of Commercial donors"
May 1984	*** Trial issues of HT1 factor VIII
10 Dec 1984	HCD's meeting at BPL: heated product preferred for all patients, subject to availability; otherwise preferentially for treatment of HIV-antibody negative patients. BPL confirmed all factor VIII would be heated by April 1985. Heating would carry a 15-20% yield penalty.
Feb 1985	*** First issues of heated (HT2) factor VIII
Feb 1985	*** Trial issues of heated (HT3) factor VIII
28 Mar 1985	*** Only heated (HT2 or HT3) factor VIII issued from PFL (Oxford) after this date
02 May 1985	*** Only heated (HT2 or HT3) factor VIII issued from BPL (Elstree) after this date
13 May 1985	*** No unheated factor IX issued from PFL (Oxford) after this date
08 Jul 1985	*** First issues of heated (HT3) factor IX
18 Sep 1985	*** All factor VIII issued after this date was heated using HT3 conditions
02 Oct 1985	*** All factor IX issued after this date was heated using HT3 conditions
02 Oct 1985	*** No unheated factor IX issued from BPL (Elstree) after this date