Self-Sufficiency in Blood Products in England and Wales

A Chronology from 1973 to 1991

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List of Abbreviations

AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
BPL	Blood Products Laboratory (now known as Bio Products Laboratory)
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
GP	General practitioner
HCD	Haemophilia Centre Directors
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
NANBH	Non A Non B Hepatitis
NBTS	National Blood Transfusion Service
NHS	National Health Service
PTH	Post-transfusion hepatitis
PFL	Plasma Fractionation Laboratory
RHA	Regional health authorities
RIBA	Recombinant immunoblot assay
RTC	Regional transfusion centres
RTD	Regional transfusion directors

UK	United Kingdom
US	United States
WHO	World Health Organisation

Executive Summary

Self-Sufficiency in Blood Products in England and Wales

The Government pursued the goal of self-sufficiency in factor VIII during the 1970s and most of the 1980s, in line with World Health Organisation and Council of Europe recommendations. The primary aim of this goal was to reduce reliance on expensive imported concentrate, although there is some evidence that there were also concerns over the possible threat to the volunteered-based donor system in England and Wales should commercial firms decide to establish paid donor panels in the UK. In the late 1970s and early 1980s, these concerns were accompanied by fears of the risk of both hepatitis and in the early 1980s the additional potential risk of Human Immunodeficiency Virus (HIV) infection.

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 amount was predicted to allow England and Wales to become self-sufficient in factor VIII by 1977. However, the demand for factor VIII in England and Wales increased dramatically in the late 1970s with changes to the dosage regimen for the home treatment of haemophilia. The demand was also expected to increase further as a result of longer life expectancy of patients with haemophilia, increased provision of home therapy, and the use of factor VIII in bleeding prophylaxis. Therefore, despite the increase in plasma collection and factor VIII production, the UK still relied on imported factor VIII concentrates.

With the development of tests for hepatitis A and B in the 1970s, it became clear that other types of viral hepatitis, denoted non A non B hepatitis (NANBH), could be transmitted by blood. Before 1989, potential blood donors could only be screened for NANBH using surrogate tests; however, these were perceived to be crude and inappropriate for use in the UK. With the cloning of a portion of the hepatitis C virus (HCV) in 1989, the C100-3 antibody test for HCV became available. This was associated with a large number of false positive and negative results and, once again, was not approved for use in the UK. It was only in 1991 that a number of validated second-generation assays became widely available and routinely used to screen potential blood donors for HCV infection. It became clear that HCV was the cause of the majority of cases previously labelled as Non A Non B hepatitis (NANBH).

In the early 1980s, growing concerns over the safety of commercial concentrates imported from the US reinforced the need for self-sufficiency, and the development of both an appropriate screening assay for HCV and an effective viral inactivation treatment at Blood

Products Laboratory (BPL). In the meantime, the Haemophilia Society appealed to the Government not to ban American blood supplies and advised their members not to stop treatment in response to concerns over potential risks. However, there is no evidence to suggest that the HCV outbreak could have been avoided had England and Wales been completely self-sufficient in blood products during this period. Domestically sourced blood products carried this risk, albeit a smaller risk, of HCV transmission, and therefore it is likely that, over time, the majority of haemophiliac patients in England and Wales would have contracted the hepatitis C virus.

The prevailing medical opinion in the 1970s and the early 1980s was that NANBH was mild and often asymptomatic. Research into NANBH was hindered by the lack of a definitive serological assay, the reluctance of clinicians to perform liver biopsies in patients with a very high risk of bleeding, and the fact that, in the majority of patients, the chronic sequelae of NANBH only became apparent after more than a decade. Even in the mid-1980s however, when it became apparent that NANBH was associated with long-term chronic sequelae, including liver failure, cirrhosis, and hepatocellular carcinoma, the consensus of medical opinion was that clinicians should continue using the concentrates. Patients, their physicians, and the Haemophilia Society all maintained that the improvement in quality of life and dangers of bleeding outweighed the potential risks of treatment.

Attempts to develop viral inactivation processes to treat blood products began in the early 1980s. Available techniques resulted in a substantial loss in yield and were not capable of producing sufficient quantities of concentrates for the UK market. In 1982–1983, further products were introduced; however, their viral safety had not been firmly established and, in fact, they were later shown to still transmit NANBH. In 1985, BPL developed a new, high purity product, designated 8Y, which was capable of maintaining satisfactory yield from fresh frozen plasma, had remarkable *in vitro* heat stability in the absence of conventional stabilisers, and had a good record of safety in clinical trials. To date, 8Y has proved safe and has not been reported to transmit hepatitis or HIV.

The decision to redevelop BPL followed an adverse Medicines Inspectorate report in 1979. Furthermore, the existing laboratory did not have the capacity to produce enough material for self-sufficiency. The redevelopment project comprised both the upgrading of the current facilities at BPL over a period of 3–4 years and the development of a new laboratory with increased capacity. £1.3m was assigned to the short-term development at BPL and £21m to the building of a new fractionation facility. In the early 1980s, the total cost of redevelopment escalated; however, the project remained fully funded owing to the Government's commitment to self-sufficiency.

Efficient operation of the unit required 3 times as much plasma as it was currently processing, and regional transfusion centres (RTCs) were held responsible to meet this increased demand. Over the following years, RTCs struggled to provide the necessary amounts of plasma to BPL. By 1993 however, England and Wales produced 75% of the total requirement for factor VIII, but was therefore still reliant on a certain amount of commercial factor VIII. This situation reflected a preference of some physicians to use commercial products over the BPL product. However, the Department was keen not to restrict the prescribing choice of clinicians. Furthermore, absolute self-sufficiency was deemed associated with its own risks, leading to a reliance on a sole supplier of blood products, which was predicted to 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.

About 3000 patients with haemophilia treated with blood products in the 1970s and early 1980s were infected with HCV and many with HIV. Available evidence suggests that during this period not only was the Government actively pursuing the policy of self-sufficiency, but that NANBH was perceived as a mild, and often asymptomatic disease, and the advantages of treatment with factor VIII concentrates were perceived to far outweigh its potential risks. This view was held by patients, their physicians, and the Haemophilia Society. From the early 1980s, BPL attempted to devise an effective viral inactivation procedure. Progress was hindered by the heat sensitivity of factor VIII and lack of an appropriate animal model to investigate the efficacy of heat-treated products. However, by the time it became apparent that NANBH was more serious than initially thought, all domestic and imported concentrates were already routinely heat-treated and therefore conferred little risk of infection with NANBH or HIV.

Introduction

Purpose of the report

About 3000 patients with haemophilia treated with blood products in the 1970s and early 1980s were infected with hepatitis C (HCV), and 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 1991(when a validated screening test for HCV was introduced in the UK). 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 (NANBH), later known as HCV
- 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 the Blood Products Laboratory (BPL)[1] to produce the volumes of products required

Treatment for bleeding episodes in haemophilia

Haemophilia is a rare hereditary bleeding disorder resulting from a clotting factor deficiency, clotting factor VIII (haemophilia A) or factor IX (haemophilia B). This deficiency prevents normal fibrin formation, an essential component of the blood clotting process, and this predisposes affected individuals to serious and prolonged bleeding episodes. The severity of the bleeding tendency is determined by the residual clotting factor activity. In mild haemophilia (5–40% factor VIII), bleeding rarely occurs except following

1 The BPL at Elstree was set up in 1954 (originally as part of the Lister Institute of Preventative Medicine) to develop and manufacture for the NHS in England and Wales therapeutic products derived from human blood. BPL is now known as Bio Products Laboratory. The Protein Fractionation Centre (PFC) at Liberton in Scotland produces blood products for Scotland and Northern Ireland.

trauma. In severe haemophilia (<1% factor VIII), on the other hand, the majority of bleeds occur spontaneously in the larger joints and muscles, and symptoms, such as bruising, nose bleeds, prolonged bleeds after minor injuries, typically appear at an early age (8 to 12 months) [1].

Until only recently, haemophilia was associated with considerable morbidity and a low life expectancy; before 1960, patients with severe haemophilia had a life expectancy of only 25 years [2, 3]. Initially, there was no treatment for haemophilia apart from transfusion of whole blood and later fresh frozen plasma. However, in the large majority of cases, the volume of whole blood or plasma that could be safely transfused was not sufficient to control bleeding [1]. In 1964, Pool et al. reported a simple and reliable method of purifying clotting factor VIII as a cryoprecipitate from human plasma [4], and this became the preferred form of treatment for haemophilia A up to about 1972/73 [5]. Even as late as 1976 however, 50% of the total factor VIII consumption was in the form of cryoprecipitate [6]. In the 1960s, blood products rich in factor IX also became available for the treatment of haemophilia B [7, 8]. Furthermore, in 1968, supernatant plasma obtained from the satellite bag after cryoprecipitate could also be used as a source of factor IX [9].

By the early 1970s, freeze-dried concentrates of factors VIII and IX became available. Unlike cryoprecipitate, which was produced from single donor units [10], these plasma concentrates were produced from large (up to 10,000 donors) pools of donor plasma [11]. In the UK, NHS factor VIII concentrate was being produced as early as 1969, and its production rose steadily, almost doubling between 1976 and 1977, but then changing little in subsequent years. The production of commercial concentrate imported from the US, on the other hand, began in the early 1970s and rose steadily such that, in 1980, it represented 60% of the total factor VIII consumption [6]. The mixed system of paid and unpaid donors had allowed the US to produce concentrates in abundance for domestic use and to therefore become the world's major exporter of concentrates abroad [12].

The introduction of factor VIII concentrate revolutionised the treatment of patients with haemophilia and dramatically improved the outlook for the severely affected haemophiliac [1]. It has been estimated that, when deaths related to viral infection are excluded from the analysis of mortality in patients with haemophilia, the life expectancy of these patients almost equals that of the general male population [13]. Factor VIII activity was both much greater in the concentrates and much more predictable than in cryoprecipitate. Since it could be stored in a domestic fridge, many patients were able to treat themselves at home and were therefore able to self-inject immediately at the onset of a haemorrhage, without depending on a visit to a hospital or general practitioner (GP). Major operations on patients with haemophilia became easier. These factors, together with the subsequent advent of prophylaxis (the prevention of bleeds), particularly in children, and the longer life expectancy of patients with haemophilia led to an increased usage of these blood products [14].

This report concentrates on blood products for the treatment of haemophilia A, since this is the more common form of haemophilia and historically there have been 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 [15]. Furthermore, although the UK was striving to achieve self-sufficiency in all therapeutic blood products [16], the risk of viral infection from albumin and immunoglobulin is thought to be minimal [17]. Albumin preparations have been routinely heated-treated for many decades, thus achieving inactivation of any viruses present [18]. Immunoglobulin preparations, on the other hand which undergo a different manufacturing process, had, at that stage only been reported to transmit NANBH in a small number of patients, and all of these cases were the result of aberration in the manufacturing process. However there were further incidents in 1993 [17, 19, 20].

Developing knowledge of NANBH – later known as HCV

With the development of tests for hepatitis A and B in the 1970s, it became clear that other hepatitis-like viruses could be transmitted by blood, and these were termed NANBH [e.g. 20, 21, 22, 23] (isolated and fully identified as HCV in 1989 [24]). This new strain of hepatitis was first predicted in 1974 by Prince et al. [23]. With the isolation and full identification of HCV in 1989, it became clear that the vast majority of cases of NANBH were in fact due to HCV.

In 1975, Mannucci et al. reported that 45% of patients with NANBH had raised transaminase levels, and that the observed liver function abnormalities tended to increase with age. Accordingly, they suggested that, in patients with haemophilia, repeated and prolonged contact with the agent(s) responsible for post-transfusion hepatitis (PTH) may cause chronic liver damage not associated with overt disease [25].

In 1980, in a paper on the epidemiology of factor VIII and IX associated hepatitis in the UK, Craske stated that NANBH was an acute illness which was usually mild and clinically indistinguishable from hepatitis A and B. Of a total of 138 cases in which the transfusion history was known, 103 had been associated with first transfusion of factor VIII or IX concentrate [26]. This paper also refers to previously published evidence for the existence of at least two types of factor VIII associated NANBH post-transfusion hepatitis; one arising from transfusion of US sourced commercial products and the other from transfusion of NHS factor VIII and European products. The association of different serotypes with different brands of factor VIII is probably related to the different fractionation processes used in the US and Europe [27]. This finding is supported by the observation that some patients experience multiple attacks of acute hepatitis [21]. In the early 1980s therefore, there was a high risk that patients would contract the virus from the use of factor VIII or IX concentrates in both the US and the UK [26].

Craske also noted that, in response to increased demand for factor VIII, commercial factor VIII was being imported from Europe and the US to supplement NHS supplies. This was reported to have been associated with an increase in the incidence of hepatitis (diagnosed by the clinical appearance of jaundice) from 2.3% in 1973 to 5.2% in 1974 [26][2]. This point was reiterated by Professor Zuckerman from the World Health Organisation (WHO) in 1980. Speaking on the ITV programme, World in Action: The Blood Business, Professor Zuckerman stated that the incidence of hepatitis amongst patients with haemophilia was increasing, and that he suspected that the reason for this hinged on the fact that imported products, which were made from the blood of paid donors, carried a higher risk of infection with hepatitis. He also said that NANBH was associated with chronic and continuing liver damage and that, therefore, this was a potentially serious situation [28].

In December 1980, Craske submitted a report to the Department summarising the findings of a study into the epidemiology and chronic sequelae of factor VIII and IX associated hepatitis in the UK. It stated that, despite multiple transfusions and large numbers of grossly abnormal liver function tests, very few patients showed any evidence of chronic liver disease [29].

On 4 July 1981, an article on PTH in the BMJ stated that surveys in patients with haemophilia had reported changes in the liver architecture consistent with chronic persistent and chronic active hepatitis, and of cirrhosis. The authors also stated that "in some cases early death from liver disease might prove to be the price paid by patients with haemophilia for the improved quality of life afforded by the easy availability of clotting-factor concentrates" [30]. In 1982 and 1983, further studies were published that indicated NANBH was more serious than previously thought [31, 32, 33]. Realdi et al., for example, evaluated the long-term outcome of NANBH in patients who had developed the disease following open-heart surgery. Histological chronic sequelae were documented in 62% of patients (chronic persistent hepatitis in one patient; chronic lobular hepatitis in two patients; chronic active hepatitis in 10 patients, of whom five also developed superimposed cirrhosis). In the majority of cases, progression to these chronic states was symptomless [31].

In 1985, the American Public Health Association reported that chronic NANBH may be both symptomatic or asymptomatic, and may progress to cirrhosis, but more often improves clinically after 2–3 years. They also stated that, despite intensive efforts, serological tests suitable for a diagnosis had not been developed [34, 35] and that NANBH was more common when paid blood donors were used [35]. Recipients of blood transfusions and parenteral drug abusers were thought be at the greatest risk [35].

2 Only a small number of patients with NANBH can be identified by a clinical diagnosis of jaundice. Fletcher et al. and Kernoff et al. took elevated transaminase levels as indicative of NANBH infection, thereby explaining the higher incidence rates reported by these researchers. NANBH is used here where later HCV testing had not been done.

Around the same time, prospective studies involving previously untreated haemophiliac patients demonstrated an almost 100% incidence of NANBH following first infusion of unsterilised large donor pool clotting factor concentrate [36, 37]. The extent of the impact of NANBH on liver function in haemophiliac patients was not explored in detail, since there was an obvious reluctance to perform liver biopsies in this patient population owing to the risk of bleeding complications from the procedure [38]. However, in 1985, Hay et al. reported the findings of a study of patients with haemophilia treated with clotting concentrates. They postulated that progressive liver disease in these patients was an understated problem after observing that serial liver biopsies revealed chronic active hepatitis or cirrhosis in 21% of patients, and that there was evidence that these conditions had progressed from chronic persistent NANBH infection. On the basis of studies by Aledort et al. [38] and Hay et al. [39], it has been estimated that 20% of patients with abnormal transaminase levels will develop cirrhosis within 10 years of infection [20]. Hay et al. therefore concluded that it seemed apparent that liver disease would become an increasing clinical problem for patients with haemophilia in the future [39].

In 1992, Seeff et al. reported the findings of a study of 568 patients with transfusion-related NANBH (identified in prospective studies conduced in the US between 1967 and 1980). They found no difference in overall mortality between patients with post-transfusion NANBH and healthy controls, but did find a small, but statistically significant increase in the mortality related to liver disease. However, the majority of patients with clinical liver disease were also reported to have a history of alcohol abuse [40]. Not only is alcohol abuse one of the most common causes of chronic liver disease in Western Europe and North America, but it is known to increase the risk of cirrhosis, hepatocellular carcinoma, and possibly death from liver disease in patients with NANBH or HCV infection [41].

Similarly, Telfer et al. (1994) reported that HCV infection was associated with serious liver disease in patients with haemophilia, but that, so far, this problem had been restricted to minority of those at risk [42]. However, HCV has been reported to be a slowly evolving disease over years, even decades [43], and in Japan, the interval from blood transfusion to diagnosis of cirrhosis has been reported to be as much as 20–25 years [44]. Furthermore, it is well accepted that a follow-up period of less than 10 years would not allow assessment of the full consequences of the disease [45]. Therefore, despite the fact that it became evident in the 1970s that haemophilia patients receiving clotting concentrates were at risk of acquiring NANBH infection, the potential seriousness of the condition would not have been fully appreciated until the mid to late 1980s. This indeed appears to have been the case, the extent of the impact on liver function only being elucidated as the use of liver biopsies and testing of transaminase levels became more widespread [e.g. 36, 37, 39, 42] and reports of late-onset cirrhosis, liver failure, and hepatocellular carcinoma proliferated [45].

A Scottish review in 2000 detailing the understanding of the risks of HCV infection before the heat-treatment of blood products included interviews with Haemophilia Centre Directors (HCD). They stated that, until the late 1980s, NANBH was viewed as a mild, non-progressive condition and that, from reading the scientific literature in the late 1970s and 1980s, it was apparent there was no real consensus at the time on the progression of any disease caused by the NANBH virus [11].

Levels of NANBH virus in the products

Blood products in the late 1970s were known to transmit viral infections, in particular hepatitis B and NANBH, and this has been well documented [36, 37, 46, 47, 48, 49]. On 2 August 1975, for example, Craske et al. 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 [50]. Throughout the 1970s and 1980s, researchers discussed liver function abnormalities in patients with haemophilia and postulated that these abnormalities might be related to treatment with blood products, particularly factors VIII and IX [8, 26, 36, 37, 51, 52]. 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 first widely used) [26].

A number of practices, common in the US in the production of commercial concentrates, have been identified, that increase the risk of viral transmission. Firstly, the risks of viral transmission are thought to be increased if the plasma is obtained by plasmapheresis of paid donors [30]. These concerns were voiced in an editorial in 1981, which stated that paid blood donors were more likely to transmit hepatitis than unpaid donors [53]. Secondly, the larger the size of the donor pool, the greater the risk of viral contamination [11, 30, 54]. 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 is infected with HCV, there is a risk to the whole batch made from that pool, and to all recipients of that batch of products [11]. However, since the US fractionators produced the first high purity factor VIII products, many of the haemophilia clinical specialists in the UK justifiably wished to use these products [15].

In a study by Collins and Bassendine of patients undergoing cardiac surgery in the UK, and therefore receiving blood transfusion, the risk of NANBH transmission was found to be 0.4% per unit of single-donor blood transfused [55]. However, the authors only tested liver function tests (LFTs) once at 6 months and, since patients with NANBH often have intermittently abnormal LFTs, this single test is not likely to capture all of the patients who had acquired NANBH [56]. In a study in France in 1986, Aymard et al. reported a risk of NANBH transmission of 1.48% in cardiac surgery patients following transfusion [57]. On the basis of these studies, the risk of contacting NANBH in the UK between 1982 and 1984 from single-donor blood components has been estimated to be between 0.6% and 1%

per unit of blood component transfused [56]. In an earlier study in the US, the risk of NANBH transmission was found to be much higher, at 3.1% per single-donor blood unit transfused [58].

However, in studies published in 1983 (notably Fletcher et al. [36]), patients who had not previously been exposed to concentrates were reported to have a high risk of developing NANBH after their first exposure to concentrates that had not been subjected to viral inactivation, irrespective of whether these concentrates were produced commercially (i.e. in the US) or domestically by BPL. This was confirmed by Kernoff et al. in 1985, who showed that all concentrates, whether from paid or volunteer donors, carried a risk of hepatitis transmission of nearly 100% when transfused into patients who had never been transfused before or only infrequently transfused [37]. Furthermore, in a study of Australian haemophiliacs, markers of viral hepatitis were common despite the use of blood products obtained from entirely volunteer blood donors and the frequent use of single donor packs of cryoprecipitate [59]. There is therefore no evidence to suggest that the NANBH outbreak in the late 1970s and early 1980s could have been avoided had England and Wales been completely self-sufficient in blood products during this period. Domestically sourced blood products carried a risk, albeit a smaller risk, of NANBH transmission, and therefore it is likely that, over time, the majority of haemophiliac patients would have come into contact with contaminated product. In 1990, Garson et al. tested 18 factor VIII concentrate samples, 13 from European or American paid-donor pools and 5 manufactured within the UK from volunteer-based pools. Only one unheated concentrate, an NHS intermediate-purity product produced from fewer than 3000 donations, was found to be negative for HCV-RNA [60]

Products began to be heat treated in the 1980s and by 1985 BPL issued a heat treated product through a method proven to lead to inactivation of the viruses (see the later section on heat treatment for details and references). However, in a 1990 letter to Vox Sang, Williams et al. reported HIV seroconversion in four sexually immature haemophiliac boys following the use of a dry heated commercial factor VIII heated at 60°C for 30h (a lower temperature than NHS factor VIII). One of the boys sero-converted between September 1985 and September 1986. This led the company concerned to voluntarily withdraw the product from the British market in 1986 [61]. A study conducted by Skidmore et al. in 1990, on the other hand, indicated that none of the recipients of factor VIII heated at 80°C for 72 hrs (conditions used for NHS factor VIII) tested positive for anti-HCV [62]. These findings are confirmed by the result of a study by Garson et al.; plasma concentrates heated at 60°C for 30h were found to still contain HCV, whereas those heated at 80°C for 72 hrs tested negative for HCV RNA [60].

Tests for the HCV antibody were not introduced until 1991 [63, 64, 65], after the isolation of the virus in 1989 [24]. At this time, the knowledge that adequate methods of inactivating

pooled plasma products were already available were thought to negate the need to introduce routine screening before it could be demonstrated that such screening would be cost-effective and lead to an increase in the safety of transfusion [66]. As early as 1981, surrogate tests for HCV (or NANBH as it was then known) were available [53]. These tests were based on the observation that about 40% of cases of PTH could be prevented through the rejection of blood donations with serum ALT levels >45 IU [58]. Although there was strong association between donor ALT levels and PTH, this association was not absolute, with more than 60% of patients receiving blood with serum ALT levels >45 IU not developing HCV and 5% of those receiving blood with serum ALT levels <45 IU doing so. Therefore, there were concerns over restricting the pool of donors on the basis of a test that was not seen to necessarily signify HCV infection [53]. Despite this, surrogate testing (both screening for ALT levels and tests for the presence of antibodies to hepatitis B core antigen) was implemented in the US in 1986/1987 [67, 68]. In the UK, the crudeness of these surrogate tests was argued to negate the feasibility of their use in donor blood screening [47, 69].

In 1989, following the cloning of a complementary DNA representing a portion of the viral genome, Kuo et al. published data on the first HCV screening assay [65]. However, this test, the C100-3 antibody test, was found to be unreliable owing to the delay (median 22 weeks) in seroconversion after exposure, the lack of specificity for infection with HCV, and its association with a large number of indeterminate and false negative and false positive results [69]. If this test were to have been implemented, it was thought that the occurrence of false positives would result in blood donors being given inaccurate information on their chances of having acquired HCV infection, whereas the occurrence of false negatives would result in donors who were infectious still continuing to donate to the plasma pool. At a HCV and the Blood Transfusion Service symposium in February 1990 (London), there was consensus that the C100-3 was not sensitive or specific enough to warrant its use in donor screening, and that a confirmatory test was therefore required [70].

In 1991, the UK Advisory Committee on Transfusion Transmitted Diseases reported that there were three second-generation anti-HCV screening assays available (Ortho [66], Abbott, and UBI) and two supplementary assays (recombinant immunoblot assay [RIBA] from Ortho and Organon). Considerable published and unpublished data, available at the time, indicated that most RIBA positive sera were strongly reactive in all of the three screening assays suggesting confirmed HCV infection [64] The second-generation tests were reported to have resolved many of the issues associated with the first-generation test, and were therefore recommended for use in the screening of blood donors [63]. The observed poor correlation between C100-3 antibody positivity and that obtained using second-generation tests [64, 71, 72, 73, 74, 75] justifies the reluctance to introduce routine screening of blood donations before the introduction of the improved second-generation tests [63].

Risks of using the concentrates vs. no treatment

It is likely that clinicians who prescribed clotting factors to their patients in the 1970s and early 1980s would have been aware of the viral risks attached to the use of factor VIII concentrates [11, 33]. It was stated in literature around this time that "these complications do not justify withdrawal or limitation of the very effective and life-changing use of concentrates" [e.g. 51, 52]. As mentioned earlier, before about 1983, HCV was perceived as a mild and often asymptomatic disease. It was also thought to be a minor cause of mortality in patients with haemophilia. Rizza and Spooner published data in 1983 which stated that, between 1976 and 1980, cerebral haemorrhage was the most common cause of death for patients with haemophilia in the UK (29%) and that there were only two deaths as a result of hepatitis (2%) [6]. Therefore, the prevailing view was that, as always, patients with haemophilia, their parents, and doctors, were required to balance the improvements in quality of life and the dangers of bleeding against the risks of treatment [76]. Although in 1975 Dr Craske recommended a return to the use of cryoprecipitate for routine treatment (which was not without its own risks[50, 77]), by then the majority of patients were self-injecting at home and cryoprecipitate could not be used in this way [78].

In 1983, concerns over the safety of commercial blood products imported from the US prompted a media debate on whether or not to continue obtaining blood products from this source. On 18 May 1983, however, the Sun reported that the Haemophilia Society had appealed to the Government not to ban American blood supplies. The Society claimed that without the US imports, which accounted for 2/5 of Britain's blood products needs, there would be a sharp rise in deaths among patients with haemophilia [79]. Similarly, in an interview with Dr Peter Kernoff, published by the Haemophilia Society, patients receiving regular treatment with concentrates were urged not to stop treatment in response to concerns over potential risks [80]. However, concerns over the safety of US factor VIII were further increased when, on 18 November 1983, the Guardian printed an article on a haemophiliac's death from AIDS after transfusion with US factor VIII for the first time [81].

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. There was a body of evidence suggesting that considerably more concentrate would be used if it were available [82]. As a result of this inadequate supply, England and Wales relied on expensive imported commercial factor VIII [83]. In fact, it is estimated that, between November 1973 and March 1975, Health Authorities spent £500,000 on the purchase of imported factor VIII concentrate from commercial firms [84].

The Department of Health therefore decided to convene an expert group to assess the possible future requirements for the treatment of patients with haemophilia and the consequent need for the supply of therapeutic agents, including human factor VIII concentrate [82]. 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 this predicted requirement [85].

The expert group met on 20 March 1973 [85]. They recommended that the NHS should become self-sufficient in the production of factor VIII as soon as possible. In order to achieve this, a substantial increase in the amount of plasma reaching BPL from the Regional Transfusion Centres (RTCs) for the preparation of factor VIII was required. This increase would be wasted, however, if BPL did not have the capacity to process the increased quantities, and therefore it was also essential that more equipment was provided to BPL for the processing of the extra plasma [86]. 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 was planned to be used to increase the output of plasma from RTCs to the equivalent of 275,000 blood donations annually for the preparation of factor VIII and 100,000 donations for cryoprecipitate [87].

The Department regarded the achievement of self-sufficiency a priority. The reliance on expensive imported commercial material was seen to be costly; an estimated £6m per annum for the predicted requirements (275,000 donations) for the production of factor VIII. Furthermore, it seemed likely that, as the demand for plasma products increased, it would become necessary for commercial firms to establish paid donor panels in the UK.

This was seen as a threat to the voluntary donor system on which the National Blood Transfusion Service (NBTS)[3] was founded [88].

On 29 April 1976, the Department issued a press release re-affirming that the aim of the UK was to become self-sufficient in the supply of blood products by mid-1977. Furthermore, it stated that, since the screening of blood donors for hepatitis was less rigorous in some countries than in the UK, the Government's policy of making the UK self-sufficient in the supply of blood products commanded wide support [89]. It strongly supported the WHO resolution passed in May 1975, which stated that each country should be able to supply sufficient quantities of its own blood and blood products to meet clinical needs [12, 89, 90]. The WHO resolution also expressed serious concern about the extensive and increasing activities of private firms attempting to establish commercial blood collection and plasmapheresis projects in developing countries, and the effects that these activities were likely to have on national blood transfusion services based on voluntary non-remunerated donations [90]. The Department also supported the Council of Europe recommendation R(80)5, which stated that member states should pursue the goal of self-sufficiency of anti-haemophilia products and blood plasma for their preparation [91]. Both the WHO resolution and the Council of Europe recommendation acknowledged the fact that both the geographical origin and type of donor population have a significant effect on the risk of transmission of infectious diseases, although neither specifically mentioned NANBH [90, 91].

At a meeting held at the Department on 20 October 1976, it was stated that it was recognised that any assessment of need for factor VIII would be complicated by the readiness with which haemophilia centres purchased concentrate from commercial sources. The need to educate clinicians in the economical use of blood components was stressed, but it was also recognised that it was essential to avoid appearing to be dictating clinical practice. It was proposed at the time that the need to purchase concentrate from commercial sources would diminish as more NHS concentrate became available [92].

The Central Committee of the NBTS met on 2 November 1976. At this meeting, members heard that the supply of plasma was increasing in line with the target, but that some clinicians believed the target should be increased to 50 million (m) international units (iu) per annum (pa). The group felt that it was difficult to accurately estimate demand, but that BPL would in likelihood reach its maximum production capacity [93]. In fact, the production target for factor VIII estimated in 1975 and set for June 1977 was attained. Two of the three fractionation centres in the UK were reported to be working at full current capacity [94].]

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

In January 1977, the Working Group on Trends in the Demand for Blood Products met "to consider the likely trends in demand for blood products over the next 5–10 years, taking into account the practicalities of supply" [95]. They reported back to the Department in December 1977. Their report states that, in order to meet the needs of patients with haemophilia in the future, an estimated 1000 iu of factor VIII per 1000 population pa and 200 g of albumin would be necessary. If the full requirement of albumin was achieved, it was estimated that 1300 iu of factor VIII per 1000 population pa would also become available. This therefore far exceeds the requirements for factor VIII originally proposed by the working group. They further recommended that the Department encourage research that would lead to a reduction of the loss of factor VIII in collection, storage, and processing, and that, in the long-term, there should be a complete transfer from the use of cryoprecipitate to fractionated freeze dried concentrate. They concluded that additional fractionation capacity was needed, estimating that the present UK capacity was less than half that necessary to meet the estimated requirements for factor VIII. It would therefore need to be doubled over the next 5–10 years. The report led the Department to conclude that the organisation of the NBTS should be reviewed, particularly in relation to better national co-ordination, forecasting, and planning [16]. Although in 1975, cost and loss of the volunteer donor system were cited as the major motivating factors for the push towards self-sufficiency [88], by the middle of 1978, concerns over the methods of plasma collection and safety of imported blood products were also reported to reinforce the need for NHS self-sufficiency in blood products [96].

In September 1979 however, the Director of BPL reported that factor VIII production had remained essentially static since April 1977, and that it was at present deficient by about 30m iu pa. This deficit was predicted to increase further in the future [97].

A January 1980 Sunday Times article stated that the Department was concerned about using imported blood products owing to the attendant risk of passing on infectious diseases, particularly hepatitis. Suppliers in the US were reported to collect much of their blood from Third World countries in which there was presumed to be a higher incidence of contaminated blood products [98].

By September 1980, the projected requirement for factor VIII consumption by the mid 1980s was 90m iu pa. However, the Department believed at the time that this figure would need to be revised in the face of recent evidence indicating that UK clinicians were coming under pressure to step up the dosage regimen for the home treatment of haemophilia. Furthermore, the demand for factor VIII was expected to increase further over the foreseeable future as a result of a number of factors, including longer life expectancy of patients with haemophilia, the increased provision of home therapy, and the trend towards the use of factor VIII in prophylaxis [99].

In an Adjournment Debate on 15 December 1980, Sir George Young stated on behalf of the Government that it 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, referring only to hepatitis B [100].

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. They also stated that the projected demand for factor VIII by 1985 was 100m iu pa, which represented more than three times the current level of plasma supply and collection. The scale of the increase necessary to meet demands was reported to be expected to have considerable financial implications on health authorities [101].

In 1983, evidence emerged that US patients with haemophilia 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 [102]. The Government wrote to the Haemophilia Society to reassure them of its commitment to self-sufficiency in blood products. The Government also acknowledged in the same letter that England and Wales continued to be dependent upon additional, commercially sourced material to make up the shortfall in the home-produced supply, and that this was imported primarily from the US. In considering whether the imports should cease, it was deemed necessary to weigh the possible risks of infection from AIDS against the obvious risks arising from inadequate supplies of factor VIII. Furthermore, it was also reported that, in March 1983, the Food and Drug Administration (FDA) had introduced new regulations for the collection of plasma, designed to exclude donors at high-risk of AIDS. All future supplies of factor VIII were to be manufactured in accordance with these new regulations; however, there was still a considerable quantity of pre-March stock, both in the UK and in the US awaiting export. The FDA decided not to ban the use of this stock, since doing so would cause a crisis in supply, in both the UK and the US [103].

In a letter dated 29 September 1988, it was stated that the UK was still not self-sufficient in blood products. Errors in estimating both the amount of fresh frozen plasma stockpiled at Elstree during the mid-1980s and the net yield for factor VIII production at BPL, led to difficulties in providing the necessary amounts of factor VIII to met current needs (about 90m iu pa). Even if the RTCs were capable of providing the necessary amounts of plasma to BPL, which they were struggling to do, it was thought unlikely that the factor VIII production would exceed 79m iu pa. This would suggest that self-sufficiency could not be expected to be achieved for another couple of years [104]. By 1990, the Departmental policy was that, while England and Wales promoted the aim of self-sufficiency in blood products, it also acknowledged that clinicians were free to prescribe whatever product they considered appropriate for the patient. It was left to BPL to promote its product and for clinicians to make the choice [105].

This policy was then developed further in 1993 when England and Wales' domestically sourced products accounted for about 75% of the factor VIII market. In a briefing document for the Health Working Group, it was stated that it was felt that there were dangers in absolute self-sufficiency. The reliance on a sole supplier of blood products was perceived to 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 in relying on a sole manufacturer. The Department aimed to achieve self-sufficiency through products sourced from unpaid donations; however, clinicians were not to be prevented from using other products, where necessary, for appropriate treatment [106].

Plasma production

In 1975, the Expert Group on the Treatment of Haemophilia estimated that 275,000 donations of blood would be required to achieve self-sufficiency in factor VIII. In order to reach this target, it was deemed necessary to both divert donations used for the preparation of cryoprecipitate and increase the number of donations used for factor VIII. In March 1975, the Department gave Regions provisional targets of increased production of plasma and invited them to submit estimates of the additional expenditure that would be incurred [107].

By the middle of 1977, there was still a deficit in factor VIII, which was being met by the continued purchase of concentrate from commercial sources. It was realised at this stage that that, in order to meet the increasing demand for factor VIII, it would be necessary for the NHS to increase considerably both the volume of fresh frozen plasma and the capacity of the processing plants [108]. Shortly before, on 11 March 1977, the combined capacity of BPL and the Plasma Fractionation Laboratory at Oxford (PFL) was 17.5m iu pa [109]. The Trends Working Group report in December 1977 accepted an estimate for factor VIII requirements of 1000 international units per 1000 population per annum. They stated that 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 donations/1000 population in the next 10 years, although they also expressed concern about a consequent excess of red cells [16].

At a meeting of the Regional Transfusion Directors (RTDs) it was stated that the majority of RTCs had reached their capacity to separate plasma both given the present state of clinical acceptance locally of plasma depleted blood and as a result of 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 for factor VIII to 24m iu pa. The Department asked BPL to prepare development plans, based on agreed production targets of 50m iu of factor VIII pa [108].

Blood products from BPL were initially distributed broadly on the basis of an assessment of regional requirements for patient treatment. This method of distribution was not considered to be an adequate incentive for RTCs to improve the quality and quantity of plasma collection. Accordingly, in early 1981, it was agreed that regions should receive BPL products in quantities proportional to the amount of plasma they had sent to BPL for processing, account being taken of the yield from each batch of plasma. This pro-rata scheme took effect from 1 April 1981 [110].

The Advisory Committee to the NBTS 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. This stated that, at present, the combined capacity of BPL and the PFL was 15m iu pa. Following the interim expansion at BPL, which would be completed in 1982, production of factor VIII would increase to 30m iu pa. Furthermore, it contained the central calculation that demand for factor VIII would increase to 100m iu pa by the mid 1980s, largely as a result of predicted changes in the pattern of treatment for patients with haemophilia [111].

In 1982 Ministers decided that, in order to enable the UK to achieve self-sufficiency in blood products, there would need to be a major expansion of BPL's capacity to process plasma. It was estimated that, in order to meet the projected need for blood products in the late 1980s as much as 435,000 kg pa of fresh frozen plasma would need to be produced by the NBTS to enable the new BPL unit to function to full capacity. This would enable England and Wales to meet the future requirements for factor VIII [112]. This plasma would also produce 200g of albumin per 1000 population [16]. RTCs were advised of the proposed plasma procurement targets of 435,000 kg per annum in a letter from the Department in late 1981. The incurred costs of increasing plasma production to this level were thought to be offset by the substantial saving predicted to arise from a reduced need for commercial products: At 1980/1981 prices, the cost of producing the increased amounts of plasma was £19m, and in return, the RTCs could be expected to receive products which would cost over £32m to purchase from commercial suppliers [113].

Regional targets were originally set for 1984/85, but were revised in 1984 to accommodate a phased increase by 1987/88. This was expected to allow time for the levels of production at the new plant to increase [114]. It was left to RTCs to decide how best to achieve these targets and to determine priorities from within their resource allocations [115].

The March meeting of the Advisory Committee on the NBTS received a paper that showed that the supply of fresh frozen plasma to BPL had increased dramatically between 1979 and 1981 [116]. Further plasma increases were planned, so that the new BPL plant would open on schedule. At the RTDs meeting in early October 1985, BPL presented information on

plasma supply in relation to the target figures [117]. This information is summarised in Table 1 below.

Table 1: Plasma Supply Compared With Target Figures

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

Factor VIII production and usage

Table 2 overleaf shows the amount of factor VIII produced by the NHS and commercial sources according to year. From these data, it is evident that there was an increase in the amount of both commercial and NHS factor VIII used between 1973 and 1982. Furthermore, the total requirement of factor VIII increased steadily over this time period and showed no sign of falling off.

Points to note are:

- 87% more NHS produced factor VIII (approximately 5m iu) was issued for the year 1977 ending than in 1976 [118]
- Virtually all the increase in factor VIII usage between 1980 and 1981 was accommodated by increased NHS production (from 14m to 22.5m iu pa), there being little increase in usage of commercial products (0.75m iu)[118]

In 1983, for the first time since 1974, more NHS concentrate than commercial concentrate was used (by 4m iu). However, by 1985 the position was reversed [118]. This was partly because production of non heat-treated factor VIII was stopped during the course of the first quarter of 1985 while rapid preparations were made to introduce a safer heat-treated product [Table 2, 119].

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

Table 2: Annual consumption of factor VIII in UK (including N.I.) in Million International Units (Miu)

Year	NHS Miu factor VIII	Comm. Miu factor VIII	Total factor VIII
1969	1.025	0	1.025
1970	0.884	0	0.884
1971	3.071	0	3.071
1972	1.939	0.095	2.89
1973	2.481	0.875	3.36
1974	2.732	2.681	5.41
1975	3.085	5.152	8.24
1976	6.915	11.069	18.00
1977	12.949	15.017	27.97
(increase reflects David Owen spend at BPL)			
1978	14.600	19.273	33.9
1979	15.092	26.178	41.27
1980	14.364	34.749	49.11
1981	22.472	35.5	57.00
(increase reflects spend at BPL)			
1982	22.892	45.644	68.5
1983	30.018	26.217	56.2
1984	40.192	34.003	74.2
1985	23.097	50.902	74
(decrease reflects introduction of HT3 at BPL)			
1986	31.483	53.754	85.2
1987	25.982	59.186	85

Source: BPL [118]; HT3 = terminal heat-treatment of the freeze-dried product at 80°C for 72 hours

In July 1988, a report from the Plasma Supply and Blood Products Working Group stated that the current usage of factor VIII was thought to be in the order of 90m iu pa. The original target set by the Plasma Supply Group in 1982 of 100m iu pa was therefore deemed to be as adequate a figure as any other. To achieve this target by 1992, it was estimated that RTCs would be required to supply as much as 550 tonnes of plasma pa, although this would require additional investment by Regional Health Authorities (RHAs). However, this was anticipated to be cost-effective owing to the escalation in prices of factor VIII from commercial sources [120].

Heat Treatments

BPL introduced screening for hepatitis B in donated plasma in November 1971 [121]. By the late 1970s manufacturers of coagulation factor concentrates were looking into ways of rendering blood products safe from NANBH [11]. By 1983 there were three main types of viral inactivation processes: freeze drying followed by dry heat treatment; treatment with chemicals (e.g. ß-propiolactone, ultraviolet light); and wet heat treatment (also known as pasteurising) [122]. It had been known since the 1950s that wet heating albumin solution at 60°C for 10 hours rendered it non-infectious for hepatitis [18]. BPL and some commercial companies (notably Behringwerke in Germany) started work on heat-treatment of factor VIII 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 it was therefore not seen as practical for application in the UK [123]. In a letter to all the HCDs dated 11 January 1982, Bloom & Rizza report that there were at least four commercial companies who were about to introduce preparations of factor VIII that had been processed to reduce the risk of transmitting hepatitis B and NANBH [124]. 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) specifically designed to inactivate viruses [122, 123, 125]. On 24 May 1983, FDA approved a new heat-treatment that reduced infectious agents in factor VIII concentrates [126]. However, commercial concentrates were later shown to still be transmitting NANBH [37, 127]. Colombo et al., for example, reported in 1985 that heat-treated factor VIII concentrates that failed to transmit NANBH to chimpanzees were subsequently shown to be responsible for the transmission of NANBH to 11 of 13 patients with haemophilia [128].

Up to mid-1984, BPL investigated both pasteurisation and dry heating of factor VIII and factor IX in collaboration with the Protein Fractionation Centre in Scotland [11]. At this point, consensus was reached that HTLVIII (later known as HIV) was the causative agent for AIDS [129], and in October 1984 the US Centers for Disease Control stated that the virus could be inactivated by heat-treatment [130]. This increased the pressure on the manufacturers, including BPL, to develop methods of viral inactivation, and as a consequence BPL progressed their existing programmes [15]. However, this process was hindered by a number of different factors. Firstly, factor VIII does not withstand heating well, and therefore the heat-treating process required the addition of “stabilisers”, which ensured that factor VIII biological activity was retained. However, these “stabilisers” also stabilise viruses. The conditions needed to successfully heat-treat factor VIII were therefore determined by repetitive and time consuming experimentation [123]. Secondly, since there were no markers available for NANBH until 1989 [24, 65] (and no reliable tests until 1991), the effectiveness of the heating process could only be tested through close monitoring of 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 before its effectiveness deteriorated [117]. Thirdly, the heat-treated products needed to be

tested in patients who had not previously been treated with factor VIII or large doses of cryoprecipitate [124]. Clinical trials in chimpanzees, which had originally thought to be indicative of risk of viral transmission from tested products, were shown in 1985 to be of questionable use when products that had failed to transmit NANBH in chimpanzees led to NANBH infection in human patients [128].

In a letter to the Haemophilia Society, Lord Glenarthur referred to a decision taken by BPL to heat-treat all their factor VIII product from April 1985 [131]. 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 [131, 132]. In the meantime, healthcare practitioners were allowed to continue to prescribe unlicensed heat-treated factor VIII concentrates on a named patient basis only. The choice of treatment remained a matter for the judgement of the clinician responsible for the patient [131].

At the meeting of HCDs on 10 December 1984, it was agreed that all children should be treated with cryoprecipitate or, if necessary, with heat-treated factor VIII. In addition, new patients with haemophilia should also be solely treated with heat-treated factor VIII. Most of the Directors present agreed that non heat-treated BPL factor VIII could continue to be used until heat-treated factor VIII became available from BPL. There were some Directors who were not willing to do this, and declared that all patients should be prescribed "safe" heat-treated factor VIII [133].

BPL achieved successful dry heat-treatment of factor VIII 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 [119]. This treatment was selected since it had been used successfully for other blood products and was felt at the time to be the severest option available that did not degrade the properties of the concentrate [15]. Although it was subsequently considered to be effective in destroying the virus causing AIDS, it was not thought to inactivate NANBH [11], 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 [119].

During 1984, there were indications that more severe heating may be necessary to inactivate NANBH and, in December 1984, BPL developed a new product [15]. Trial issues of this (HT3, heated at 80°C for 72h) were issued in February 1985 [119]. 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

[119, 134, 135]. Factor VIII was later also heated to higher temperatures, but the product started to suffer at this stage so it was not pursued [11].

BPL was also developing a new, high purity product (also heat-treated to 80ºC for 72h), designated 8Y [136], which was capable of maintaining satisfactory yield from fresh frozen plasma [137]. This purer factor VIII was found to have remarkable *in vitro* stability to heat in the absence of conventional stabilisers which confer their benefits on protein and virus alike [134]. Some 8Y was used in clinical trials in selected patients in July 1985 to determine safety and efficacy of the product prior to making the application for a product licence [136, 137]. In August 1985, output of heat-treated factor VIII was increased to the maximum level possible in the current BPL plant. BPL started general issue of its new 8Y heat-treated factor VIII in September 1985 [123]. The heat treatment used by BPL was for a longer time and at a higher temperature than that used in commercial processes. Furthermore, the BPL product had a good record of safety in clinical trials [15] and, to date, BPL factor VIII (HT3) and 8Y have proved safe and have not been reported to transmit hepatitis or HIV [e.g. 138, 139, 140, 141].

Until the new BPL plant was completed, there continued to be a need to obtain additional supplies of factor VIII from commercial sources. However, by then, this was also heat-treated. There was therefore no longer any need to use non-heat-treated factor VIII concentrate [142]. Since 2 June 1986 all plasma processed at BPL was derived from donations individually screened for HIV-antibody [15].

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. The Scientific and Technical Committee for the Central Laboratories estimated that, if the current rate of increase in factor VIII 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 predicted expenditure of this amount, there appeared to be every incentive on economic grounds for speedy investment aimed at optimising factor VIII production at BPL [143].

In July 1979, BPL received an adverse report from the Medicines Inspectorate[4]. Several risks of microbial contamination to the products were identified. However, the report did not state that the products were unsafe. Instead, it recommended a set of actions that should take place immediately, and others that should be implemented in the long term [144].

The 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 unsuitable for upgrading. While the existing building could be used in a different capacity, a new factory-type manufacturing facility was required [144]. They said that the shortcomings were "so serious that continued production could only be tolerated owing to the essential nature of the products and only if immediate improvements were introduced" [97].

In response to the Medicines Inspectorate's 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 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 also argued that there must be limited growth at BPL to assist the

4 The Medicines Inspectorate was established within the Medicines Division of the Department of Health and Social Security (DHSS; now known as Department of Health) in 1971 in accordance with the Medicines Acts 1968 and 1971. It was set up to inspect and ensure compliance with Standard Provisions (including GMP and GDP) by all applicants for, and holders of, manufacturer's and wholesale dealer's licences in the UK.

laboratory in a more gradual transition to a new, larger production unit. Particularly important during the interim period was the increase of the supply of plasma from the RTCs to meet the demands of a new plant [97, 144]. The redevelopment of BPL was therefore planned to involve two major stages: the upgrading of the current facilities at BPL over a period of 3–4 years; and the development of a new laboratory with an increased capacity [97].

Ministers agreed a short-term upgrading programme for BPL at a cost of £1.3m [145], which was expected to double the production capacity for factor VIII from 15m iu pa to 30m iu pa [146]. The possibility of collaborating with private industry in the long-term redevelopment of BPL was investigated; however, Ministers decided against such an arrangement in view of BPL's dependence on volunteer donors [147]. In November 1980, a parliamentary written answer from Dr G Vaughan stated that £21m had been allocated to the building of a new fractionation facility on the existing site at Elstree [147]. This rebuilding was envisaged to 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 [148]. On 23 March 1984, a press release was issued heralding the building of a new production unit at BPL. By then, the cost for the project had already increased to £24m. However, 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 it was currently processing [149], and RTCs were engaged in discussions about how to meet this demand [150].

By 1985, the existing BPL plant could only process 150 tonnes of plasma per year, yielding some 40% of the factor VIII required. Therefore, at this point, it was the limited manufacturing capacity of BPL that limited production output, not the ability of regions to supply plasma. RTCs at this stage were already supplying BPL with 250 tonnes of plasma per year. The extra plasma was stockpiled in deep freeze conditions 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, RTCs had submitted firm plans for producing 400 tonnes, and a commitment in principle for most of the remaining balance [151].

By mid-1986, the redevelopment of BPL project cost had escalated further, rising from the first estimate of £21m in 1982 to around £52m. In addition, a further £7m had been allocated to the development of a warehouse quality assurance and engineering building. Despite these escalating costs, the re-development project had been fully funded by the Government to safeguard the earliest possible completion date. At this time, four reasons were cited for the importance of early completion of the BPL redevelopment project. Firstly, since 1980, it had been clear that BPL was not capable of meeting Medicines Act requirements and had, therefore, been relying on Crown Immunity to stay in operation.

Secondly, there was a considerable potential for saving money on imported blood products and a potential income from products surplus to NHS requirements. Thirdly, there were documented problems with hepatitis and HIV contamination of imported factor VIII and, although all imported factor VIII was heat-treated, there was evidence that suggests that the BPL product remained superior to their commercial alternatives [152]. Although the new laboratory was not expected to be fully productive from the day it came into operation, it was intended to reach full levels of production within 12 months of opening, subject to sufficient plasma being sent for processing [153].

By the end of 1987, the consequent difficulties of maintaining a sufficient plasma supply and ensuring equitable product distribution were being addressed [154]. In late 1988, it was reported that a large quantity of plasma (about 120 tonnes) had not been subjected to individual donation screening for HIV-Ab which meant that the current stockpile of plasma available for processing at BPL was only 330 tonnes rather than 450 tonnes of plasma. It was therefore thought unlikely that the NBTS would be able to produce sufficient amounts of plasma to allow BPL to operate at full capacity [104].

It was therefore expected that England and Wales would not achieve self-sufficiency for a few years [104]. 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 RTCs would receive more product than they could use. Some form of cross-charging for plasma and product between BPL and RTCs seemed the best way to ensure equitable distribution [120]. A separate committee was examining the mechanics and ground rules of such a system [154].

By April 1989, a system of cross-charging was in place. BPL "bought" plasma from the NBTS i.e. reimbursed the RTCs for the cost of providing plasma. With money previously allocated directly to BPL, RTCs were then required to buy the product they needed from BPL [155, 156]. This system was introduced to encourage RTCs to collect maximum amounts of plasma. However, the system ran into difficulties because users were obtaining products from commercial sources and, as a result, there was an increasing stockpile of NHS 8Y (with reducing shelf-life). In some cases, the problem arose because the system was misunderstood; however, HCDs were also being influenced by commercial companies to favour their products, largely because of claimed therapeutic advantages particularly for the HIV-infected patients with haemophilia [156]. Furthermore, BPL, unlike its commercial rivals, was not promoting products directly to the clinicians. There was therefore a need to persuade regions, districts, and clinicians to use more BPL products [157], although the Department had no intention of restricting the clinical freedom of haemophilia directors [156]. However, they made RTCs aware that the purchase of very expensive foreign factor VIII meant that products already paid for by the NHS went unused [156]. It is now known

that it is an indisputable reality that very few counties are capable of completely satisfying their blood needs (i.e. becoming self-sufficient) without acquiring a proportion of blood from paid donors [158].

Conclusions

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 Council of Europe recommendations. The primary aim of this goal was to reduce the reliance on expensive imported concentrate, although there is some evidence that there were also concerns over the possible threat to the volunteered-based donor system in England and Wales should commercial firms decide to establish paid donor panels in this country. In the late 1970s and early 1980s, these concerns were accompanied by fears of the risk of transmission of both hepatitis and HIV infection from imported factor VIII 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 adequate to achieve self-sufficiency in factor VIII by 1977. However, the demand for factor VIII in the UK increased dramatically in the late 1970s. Clinicians were coming under pressure to step up the dosage regimen for the home treatment of haemophilia. This demand was expected to increase even further owing to a longer life expectancy of patients with haemophilia, the increased provision of home therapy, and the trend towards the use of factor VIII in bleeding prophylaxis. Therefore, despite the increase in both the plasma collected by RTCs and the amount of factor VIII produced by the NHS, it was still necessary to import factor concentrates.

With the development of tests for hepatitis A and B in the 1970s, it became clear that other types of viral hepatitis could be transmitted by blood, and these were termed NANBH. Before 1989, potential blood donors could only be screened for NANBH using surrogate tests; however, these were perceived to be crude and inappropriate for use in the UK. With the cloning of a portion of the hepatitis C virus in 1989, the C100-3 antibody test became available. This was associated with a large number of false positive and negative results and, once again, was not approved for use in the UK. It was only in 1991 that a number of validated second-generation assays became widely available and routinely used to screen potential blood donors for NANBH infection.

The prevailing medical opinion in the 1970s and the early 1980s was that NANBH was mild and often asymptomatic. Therefore, as always, patients with haemophilia, their parents, and doctors, were required to balance the improvements in quality of life and the

dangers of bleeding against the risks of treatment. Research into NANBH was hindered by the lack of a definitive serological assay for NANBH, the reluctance of clinicians to perform liver biopsies and other invasive procedures in patients with a very high risk of bleeding, and the fact that, in the majority of patients, the chronic sequelae of NANBH only became apparent after more than a decade. Even in the mid-1980s however, when it became apparent that NANBH was associated with long-term chronic sequelae, including liver failure, cirrhosis, and hepatocellular carcinoma, the consensus of medical opinion was that clinicians should continue using the concentrates. Patients, their physicians, and the Haemophilia Society all maintained that the improvement in quality of life and dangers of bleeding outweighed the potential risks of treatment. In an editorial in the British Medical Journal (BMJ), it was stated that early death from liver disease was viewed as a price that might have to be paid by a small minority of patients with haemophilia.

In 1983, growing concerns over the safety of commercial blood products imported from the US reinforced the need for both self-sufficiency in blood products and the development of an effective viral inactivation treatment at BPL. Although it was widely known that there was a risk of NANBH infection from imported concentrate, the Haemophilia Society appealed to the Government not to ban American blood supplies, claiming that, without the US imports, there would be a sharp rise in deaths among patients with haemophilia. Furthermore, they advised their members not to stop treatment in response to concerns over potential risks.

Attempts to develop viral inactivation processes to treat blood products began in the early 1980s. Initially, a number of commercial companies experimented with different heat-treating regimens; however, these techniques resulted in a substantial loss in yield and therefore were not capable of producing concentrates in sufficient quantities for the UK market. In 1982–1983, further products were introduced; however, the viral safety of these had not been firmly established and, in fact, they were later shown to still transmit NANBH. In 1985 BPL developed a new, high purity product, designated 8Y, which was capable of maintaining satisfactory yield from fresh frozen plasma, had remarkable *in vitro* stability to heat in the absence of conventional stabilisers, and had a good record of safety in clinical trials. To date, 8Y has proved safe and has not been reported to transmit hepatitis or HIV.

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. The redevelopment project comprised two main stages: the upgrading of the current facilities at BPL over a period of 3–4 years; and the development of a new laboratory with an increased capacity. Ministers agreed a short-term upgrading programme for BPL at a cost of £1.3m and £21m was allocated to the building of a new fractionation facility on the existing site at Elstree. In the

early 1980s, the total cost of BPL redevelopment escalated; however, the project remained fully funded owing to the Government's commitment to self-sufficiency, and thus the earliest possible completion date for the proposed redevelopment. Furthermore, the scheme was projected to pay for itself within 5–6 years of reaching full production.

Efficient operation of the unit required 3 times as much plasma as it was currently processing, and RTCs were held responsible to meet this increased demand. The 'error' in estimating both the amount of fresh frozen plasma stockpiled at Elstree during the mid-1980s (p 25) and the net yield for factor VIII production at BPL led to difficulties in meeting factor VIII requirements. Even if the RTCs were capable of providing the necessary amounts of plasma to BPL, which they were struggling to do, it was thought unlikely that the factor VIII production at BPL would exceed 70% of the total requirement nationally.

In the mid 1980s, when heat-treated factor VIII products were being produced both domestically and abroad, the risk of transmission of either NANBH or HIV from these products was minimal. Therefore, once again, the primary driving force for self-sufficiency became the cost saving predicted should the reliance on commercial products be reduced even further. By 1993, England and Wales produced 75% of the total requirement for factor VIII, but was still therefore reliant on a certain amount of commercial factor VIII. This situation reflected a preference of some clinicians to use commercial products over the BPL product. The continued use of commercial products therefore prevented the achievement of complete self-sufficiency; however, the Department was keen not to restrict the prescribing habits of clinicians, leaving them free to prescribe the product they considered most appropriate for the patient. At this time, it was also felt by groups representing patients with haemophilia, that there were dangers in absolute self-sufficiency. This, they claimed, would lead to a reliance on a sole supplier of blood products, which was predicted to 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 in relying on a sole manufacturer.

About 3000 patients with haemophilia who were treated with blood products in the 1970s and early 1980s were infected with HCV and many with HIV. Available evidence suggests that during this period not only was the Government actively pursuing the policy of self-sufficiency, but that NANBH was perceived as a mild, and often asymptomatic disease. The advantages of treatment with factor VIII concentrates were perceived to far outweigh its potential risks. This view was held by patients, their physicians, and the Haemophilia Society. From the early 1980s, BPL attempted to devise an effective viral inactivation procedure. However, by the time it became apparent that NANBH was more serious than initially thought, all domestic and imported concentrates were already routinely heat-treated and therefore conferred little risk of infection with NANBH or HIV.

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Annex A: Chronology of events

Date	Event
Early 1970s	Use of factor concentrates becomes more widespread.
November 1971	Screening for hepatitis B becomes available.
Early 1973	It becomes apparent that the production of factor VIII in the UK is insufficient to meet the stated needs of clinicians.
March 1973	DHSS Expert Group on the Treatment of Haemophilia recommends that the NHS should be self-sufficient in blood products as soon as possible.
03 August 1974	NANBH strain of hepatitis first predicted by Prince et al.
December 1974	The Minister of State earmarks central funds of £0.5m (half of which was to be recurring). This was to be used to increase the output of plasma from RTCs to 275,000 blood donations annually for the preparation of factor VIII and 100,00 donations for cryoprecipitate.
Beginning 1975	Expert Group on the Treatment of Haemophilia estimated that 275,000 donations of blood would be required to achieve self-sufficiency in factor VIII.
March 1975	Department gave Regions provisional targets of increased production of plasma and invited estimates of the additional expenditure that would be incurred.
May 1975	WHO resolution states that each country should be able to supply sufficient quantities of its own blood and blood products to meet clinical needs.
August 1975	Mannucci et al. report 45% of patients with NANBH had raised ALT levels; Craske et al. links an outbreak of hepatitis (some NANBH) after intravenous injections of commercial factor VIII concentrate.
April 1976	Department issues a press release re-affirming the aim of the UK to become self-sufficient in the supply of blood products by mid-1977.
June 1977	Factor VIII production target set in beginning of 1975 attained; however demand had increased.

Date	Event
December 1977	Working Group on trends in the demand for blood products confirms estimate of 1000 iu per 1000 population pa and recommends complete transfer from the use of cryoprecipitate to fractionated freeze dried concentrate.
July 1979	Medicines Inspectorate inspection report published on plasma fractionation facilities at BPL recommending a set of actions that should take place immediately, and others that should be implemented in the long term.
Early 1980	Blood products begin to be heat-treated; however, yield is very low and not shown subsequently to inactivate NANBH.
August 1980	Short-term upgrading of facilities at BPL agreed at cost of £1.3m. Expected to double production capacity from 15m iu pa to 30m iu pa.
October 1980	Craske claims that NANBH is mild and often asymptomatic, but might cause chronic liver disease not associated with overt disease.
November 1980	£21m allocated to the building of a new fractionation facility on existing site at Elstree.
1 April 1981	Regions started to received BPL products relative to amount of plasma supplied i.e. pro rata distribution.
Mid 1981	Advisory committee to NBTS estimated that demand for factor VIII would increase to 100m iu pa by mid-1980s; regional targets for plasma set.
1982/1983	Studies published that indicate that NANBH is more serious than previously thought.
1983	Studies, such as that by Fletcher et al. confirm that commercial and BPL concentrates contain equal risk of transmitting hepatitis.
1983	Rizza and Spooner paper showing cerebral haemorrhage most common cause of death for patients with haemophilia; only 2% of patients die as a result of chronic hepatitis infection.
1983	US patients with haemophilia contracted AIDS strengthening concerns over the safety of imported commercial blood products.
March 1983	FDA introduces new regulations for the collection of plasma excluding donors from high-risk groups. The use of pre-March stocks was not banned owing to concerns that this would lead to a crisis in supply.
May 1983	Construction started at BPL.

Date	Event
18 May 1983	Haemophilia Society appeal not to ban imported blood products and urge patients not to stop treatment in response to concerns over potential risks.
May 1984	Trial issues of HT1 factor VIII.
10 Dec 1984	HCD's meeting at BPL. Heated product preferred for all new 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.
1985	Studies revealed almost 100% transmission of NANBH following treatment with unsterilised large donor pool clotting factor concentrate. Hay et al. reported that progressive liver disease in patients with haemophilia was an understated problem.
February 1985	First issues of heated (HT2) factor VIII.
February 1985	Trial issues of heated (HT3) factor VIII.
July 1985	Trials of a new, high purity product, 8Y, conducted in selected patients.
September 1985	BPL starts general issue of its new 8Y heat-treated factor VIII.
02 Oct 1985	Heat-treated factor IX issued from BPL on this date.
Mid-1986	Re-development project costs escalate to around £52m; however project remains fully funded owing to Government's commitment to self-sufficiency.
September 1988	UK was still not self-sufficient in blood products owing to errors in estimating both the amount of plasma stockpiled and the net yield for factor VIII production at BPL, and could only be expected to become self-sufficient in a couple of years.
1989	NANBH virus isolated by Choo et al.
April 1989	System of cross-charging in place to encourage RTCs to produce maximal amounts of plasma.
1991	Second-generation HCV screening assays become widely used in the screening of donor blood in the UK.
1993	Domestically sourced blood products account for 75% of the UK factor VIII market. There were concerns, however, at this time, that absolute self-sufficiency was not without its own risks.

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

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