Self-sufficiency and Domestic Production of Blood Products in Scotland and for Northern Ireland: Presentation Note

Contents

1. Introduction

1. This presentation note relates to domestic production of blood products and self-sufficiency in Scotland and Northern Ireland, focusing on the period to around 1990. In particular, it explores the role of the Protein Fractionation Centre (PFC) in UK-wide fractionation; the nature of Anglo-Scottish relations with respect to self-sufficiency; the supply of NHS blood products to Northern Ireland; and PFC's capacity and production of factor concentrates. It also examines research and development of viral inactivation methods at PFC, and their impact on Scotland's ability to achieve and maintain self-sufficiency.

2. The Inquiry will be hearing evidence from two key figures in PFC's work during this period: Dr Peter Foster (Head of Research and Development) and Dr Robert Perry (Quality Control Inspector from 1981 to 1984 and Director from 1984 to 2003). This presentation is not intended to pre-empt or rehearse their evidence; instead, it provides an overview of the available documentary material. Similarly, it does not address all of the topics relevant to Dr Foster and Dr Perry's evidence; for example, technical matters relating to the manufacture of blood products are not covered in any detail.

3. Many of the issues covered by this presentation were investigated by the Penrose Inquiry. The focus of this note is on contemporaneous documents and witness evidence. Where appropriate, however, reference is made to evidence submitted to or findings made by the Penrose Inquiry.

4. It is also important to note that this presentation is given in the context of the documentary and witness evidence already considered by the Inquiry. For example, the history and organisation of blood services in Scotland and Northern Ireland were addressed in a written and oral presentation.[1] Further reference is made to such evidence below.

5. The following annexes accompany this note:

[1] See **INQY0000307** and the transcript of the oral presentation on 9 November 2021.

a. Annex A: Consumption of Factor VIII and IX concentrates in Scotland.
b. Annex B: Consumption of Factor VIII and IX concentrates in Northern Ireland.
c. Annex C: Table of PFC factor concentrates to 1991.
d. Annex D: Anglo-Scottish co-operation in the late 1970s and early 1980s – views of prominent figures.
e. Annex E: The role of SAG-M in Scotland's plasma supply.

6. Unless specified otherwise, page references to documents are to Relativity, rather than internal, numbering.

2. Anglo-Scottish co-operation: PFC origins and role in UK-wide fractionation

7. A number of non-contemporaneous documents outline the early history of plasma fractionation in Scotland.[2] They record that, during World War II, the preparation of freeze-dried plasma began at the Royal Infirmary Edinburgh (RIE). The facilities – then named the Blood Products Unit (BPU) – were extended after the war and were the responsibility of the South East Scotland BTS (then headed by Dr Robert Cumming and Dr Drummond Ellis). Dr Ellis travelled to the United States during the early 1950s to study plasma fractionation methods being developed by Edwin Cohn at Harvard. This led to the creation of Scotland's first fractionated plasma product in 1952 (an immunoglobulin), and an early version of factor VIII in 1956 (known as Cohn Fraction I). The capacity of the BPU was extended in 1961, and it was re-named the PFC in 1970.

8. These non-contemporaneous documents also suggest that the BPU's creation was part of a policy for the UK to have more than one facility for fractionating plasma (the other being the Lister Institute/Blood Products Laboratory in England). A 1999 Department of Health and Social Security (DHSS) memo stated that '*[b]oth were originally set up in 1950 to meet a government commitment to self-sufficiency in plasma fractionation and manufacture of plasma products for the NHS. There was a deliberate policy to have two fractionation plants in the UK in case production at one of them had to cease at any stage*'.[3]

9. According to a document submitted by Dr Foster to the Penrose Inquiry, it was estimated at a February 1965 meeting (for which no minutes are available), that the new Scottish facility '*should be capable of processing up to 1000 litres*

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[2] See, in particular: Robert Girdwood, 'Fifty years of an organized blood transfusion service in Scotland', **PRSE0003986**; Dr Foster, 'Plasma fractionation in Scotland, *Blood*, 2008, **PRSE0001732**; and memo from Charles Lister to Lady Hayman, re: Review of UK Blood Products Manufacturing, 1 July 1999, **DHSC0042309_023**. See also Chapters 19 and 20 of the Penrose Final Report, **PRSE0007002**.

[3] Memo from Charles Lister to Lady Hayman, re: Review of UK Blood Products Manufacturing, 1 July 1999, **DHSC0042309_023.**

of plasma per week'.[4] It was also intended that the facility should remain in Edinburgh, but move from the RIE to the Liberton area.

10. A DHSS memo – which appears to be from the late 1970s – recorded that in 1965, '*faced with a growing demand for certain blood products*', the Scottish Home and Health Department (SHHD) drew up plans to build a new PFC unit '*which would operate on a continuous-flow principle to deal with 1500, and if necessary up to 3000, litres of plasma per week*'. [5] Also in 1965, the '*then Ministry of Health made a formal agreement with the SHHD*' that the PFC would fractionate plasma for the NHS using plasma from four English regions (Newcastle, Leeds, Manchester and Liverpool, then collecting 20,000 litres per annum), with Scotland recovering the cost of the extra processing. The memo recorded that the '*original request to Scotland was that they should provide annually for the NHS about 30,000 bottles of plasma protein fraction and anti-haemophilic globulin from 10,000 bottles of blood*'.

11. On 9 May 1968, the projected capacity of the Scottish facility was adjusted in a meeting between the SHHD, DHSS and the Blood Transfusion Services of England and Wales and Scotland. It was anticipated that the PFC would be commissioned in June 1972 with an initial capacity of 1,500 litres of plasma per week, with a capability to increase to a maximum of 3,000 litres per week. [6] It was agreed by Mr Watt (Scientific Director of PFC) and Dr Maycock (Director of BPL) that the PFC should be prepared to cope with the requirements of a larger part of England than originally intended.

12. On 24 October 1968 the Treasury approved in principle the scheme to build the new facility, at a cost of about £1 million, subject to the provision of detailed and costed proposals.[7] This figure proved to be an underestimate. A

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[4] Dr Foster, 'Planning of plasma fractionation in Scotland', July 2001, **PRSE0000808**.

[5] Paper on 'Protein Fractionation Centre Liberton and the Arrangements with the NBTS', undated, **DHSC0003715_171**, para 1-2. The figures for litres of plasma would appear to be more likely to be those from 1968, when they were adjusted, than 1965.

[6] Minutes of SHHD, DHSS, BTS Edinburgh and BTS Elstree Meeting, 9 May 1968, **SBTS0000470_105**.

[7] Letter from M Widdup to A.H.Mitchell (SHHD), re: Blood Transfusion Service, 24 October 1968, **DHSC0103209_160**.

later DHSS memo noted that the final cost was £1.7 million, and that the SHHD had asked that the DHSS contribute to the capital cost.[8]

13. On 1 November 1968, a meeting on the progress of BPL and PFC indicated that the latter's construction was subject to funding constraints. The original cost estimate had increased to £1.4m during the build and operating capacity was one of the main factors influencing cost. It was therefore decided that, despite a 1,500 litre capacity, PFC would initially be equipped to operate at 1,000 litres/week to reduce the estimated build cost to £1.2m.[9] It was also noted that commissioning would not be completed until at least 2-3 months later than the earlier estimate of June 1972.

14. In late 1968, the SHHD began its attempts to obtain a contribution to the capital cost of the new PFC facilities from the DHSS. On 24 December 1968, Mr A H Mitchell (SHHD) wrote to Mr R P S Hughes (DHSS), referring to a Scottish commitment to process up to 20,000 litres of plasma per annum '*produced by the Northern English Counties, for which an appropriate revenue, including an element to reflect the capital costs, would have been made*'.[10] The letter recorded that financial arrangements to process plasma on behalf of England had not yet been formally established. In light of the increasing cost, Mr Mitchell requested that the DHSS contribute to the capital cost of Liberton in return for not including any capital charge on blood products supplied by the unit to England. At this point in time, Mr Mitchell estimated that the total cost of the scheme would be £1,392,000. Based on the likely ratio of the use of the facilities, England's share of the capital was estimated to be approximately £577,000, spread over the years 1969-1973. Without the contribution, there would be a significant delay. As described further below, the DHSS eventually invested £400,000 in the PFC.[11]

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[8] Paper on 'Protein Fractionation Centre Liberton and the Arrangements with the NBTS', undated, **DHSC0003715_171**, para 3.

[9] Minutes of BPL Meeting, 1 November 1968, **WITN3530077.**

[10] Letter from A.H. Mitchell (SHHD) to R.P.S. Hughes (DHSS), re: Financing PFC, 24 December 1968, **DHSC0103209_157**, para 2.

[11] Note from J Harley 'Blood Products Laboratory: Notes on Mr Hart's Paper on 8.8.80' BPL: Notes on Mr Hart's Paper of 8.8.80,13 August 1980, **DHSC0002315_067**.

15. The SHHD's funding request prompted internal DHSS discussions, in which reference was made to England's anticipated reliance on PFC and the redevelopment of BPL. In a 31 December 1968 memo, Mr Hughes noted that a delay in building the Scottish facility would prove serious for England for two reasons. First, England was to be reliant on the Scottish laboratory for as much as one third of the country's requirements; and secondly, there would in any case be a period of time between the completion of the PFC and '*the English laboratory*' during which England would be reliant on Scotland for all its requirements.[12]

16. There is a degree of uncertainty and ambiguity around this second point, as the evidence suggests that BPL was in operation before the new PFC facilities were built. However, it appears that planning was underway in the late 1960s for a new unit at BPL. A 30 May 1968 letter from an SHHD official to the Treasury, seeking approval for the building of the Liberton site at a cost of around £1 million, referred to a timetable '*for the new unit at Elstree*' and stated that the '*building is due to start in Mach, 1969, with aim of completion by mid-1970*'.[13] It may be that this related to the following entry in Dr Maycock's description of the '*building history*' of BPL:[14]

> '1972 extension: this enlargement originated from the relatively immense need for normal immunoglobulin to prevent rubella in exposed pregnant women. Later it was decided that the plan should include means for meeting the estimated needs of factor VIII concentrate … Planning, completed in 1965, was affected by the severe constraints imposed on the site…'

17. At a 14 March 1969 meeting, the commissioning date for PFC was again pushed back: it would not be before the end of 1972 and was more likely to be early in 1973.[15] During a discussion on plasma supplies from northern

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[12] Memo from R.P.S. Hughes to Mr Reeve, re: Blood Products Unit at Edinburgh, 31 December 1968, **DHSC0103209_004**.

[13] Letter from A.H.M. Mitchell, SHHD, to M. Widdup, Treasury, 30 May 1968, **DHSC0103209_172**.

[14] Dr Maycock report to the Advisory Sub-Committee on Blood Products and Blood Group Reference Laboratories, 8 September 1978, **CBLA0000840** p.11.

[15] Minutes of the Meeting Held in the Regional Blood Transfusion Centre, 14 March 1969, **PRSE0002199**.

England, Mr Watt stated that the new Scottish facility had been designed to start at 69,000 units produced, rising to 130,000 units over time. Dr Maycock indicated that '*Elstree hoped to deal with two-third of the plasma from England and Wales and the remaining one-third would be processed at Liberton*', while noting that the plan could be adjusted as production schedules evolved.

18. On 2 December 1969, the SHHD provided the Treasury with a final cost estimate of £1,728,079 and requested approval to begin pre-tender work.[16] Mr Lawrie (SHHD) noted it was probable there would be '*a time lag between the Scottish unit's coming into production and the unit at Elstree*', with a possibility of increased hospital expenditure as clinicians not served by Elstree obtained a service elsewhere (such as purchasing from commercial sources). The cumulative effect of delays meant that Liberton was unlikely to start any production before the second half of 1973. Delay resulted from various factors, including a lengthy examination by the SHHD of all aspects of the scheme to ensure the facilities at PFC were '*no more than adequate*'.[17]

19. Treasury approval was subsequently granted '*for this novel, one-off project*', despite the lack of an assessment on revenue consequences, given the previous delays and the need to avoid the expenditure described by the SHHD.[18]

20. Construction at Liberton began in 1971 and Mr Watt, who had been appointed Director of the BPU in 1967, became the Director of the recently re-named PFC.[19] As described further below, building work continued until 1974.

21. On 20 March 1973, the Expert Group on the Treatment of Haemophilia discussed current trends in haemophilia treatment and the development of facilities to process blood products. The Group, which had been assembled

[16] Letter from WP Lawrie to JA Patterson (Treasury Chambers) re: Blood Products Uni, Edinburgh, 2 December 1969, **DHSC0103209_139**.

[17] Letter from WP Lawrie to JA Patterson (Treasury Chambers) re: Blood Products Uni, Edinburgh, 2 December 1969, **DHSC0103209_139**.

[18] Letter from J A Patterson to W P Lawrie (SHHD) re: Treasury approval for final cost limit, December 1969, **DHSC0103209_140**.

[19] Robert Girdwood, 'Fifty years of an organized blood transfusion service in Scotland', **PRSE0003986**; Dr Foster, 'Plasma fractionation in Scotland, *Blood*, 2008, **PRSE0001732**.

by the DHSS, emphasised the importance of close collaboration between UK nations in relation to production of blood products, emphasising that:

a. It was essential that the production and distribution of the therapeutic agents concerned should be considered as a UK exercise.
b. Close co-operation between England (in this context including products produced in England for use in Wales and Northern Ireland) and Scotland would be required in order to co-ordinate and optimise blood collection and transport, the fractionation processes, distribution of the therapeutic agents, and utilisation of other blood fraction by-products.[20]

22. Following the meeting of the Expert Group, on 20 June 1973, the first meeting of a Joint Steering Committee on Blood Products Production was held to coordinate UK planning. Targets for AHG[21] production were discussed and it was reiterated that, in principle, the UK should be treated as a whole in aiming for self-sufficiency, with a target date of 1975. Full-scale production at BPL had been achieved, and it was said to be '*urgent for PFC to know what volume of plasma they would be asked to fractionate for England*'. DHSS representatives alerted the SHHD to the fact that England might require the PFC to fractionate more time-expired plasma on its behalf than had been arranged in 1968. The SHHD asked to be informed as soon as possible if this were to occur, so that any necessary modifications to the PFC could be undertaken while the contractor remained on site.[22] Accordingly, while the newly built PFC was not yet in operation, Anglo-Scottish planning proceeded on the basis that it would play a key role in UK-wide production of blood products.

23. On 1 May 1974, the UK's approach to self-sufficiency was discussed in a Blood Product Production Meeting. Attendees agreed that the SHHD and

[20] Minutes of Expert Group on the Treatment of Haemophilia Meeting, 20 March 1973, **PRSE0004706**.
[21] I.e. anti-haemophilic globulin.
[22] Minutes from the first Joint Steering Committee on Blood Products Production meeting, 20 June 1973, **PRSE0004359**, para 19, pg.5.

DHSS were both in pursuit of a common goal, and SHHD representatives reaffirmed a readiness to assist with meeting UK-wide need.

Relocation of the PFC and UK planning

24. PFC relocated to the purpose-built facility at Liberton during the course of 1974. In his Inquiry statement, Dr Foster explains that *'PFC staff were given access to the Administration block of the new centre from April 1974. This included facilities for the Quality Department, the R&D department and Administration, including a Library*'.[23] He adds that facilities for production and engineering became available at the end of 1974. Until that point, production had continued at the RIE site, and it '*was only from January 1975 that commissioning of the new centre by PFC staff could begin*'.

25. In a 2008 article, Dr Foster explained that the design of '*the new PFC facility was centred on a computer-controlled, continuous-flow, small-volume mixing (CVSM) cold-ethanol fractionation process; a technical innovation, which promised a high throughput, with on-line monitoring and automatic control.*'[24] He added that, '*although the PFC facility was designed to accommodate plasma from the north of England as well as from Scotland, it was equipped initially for Scottish needs only*'.

26. On 24 December 1974, Mr B Gidden (DHSS) wrote to Regional Administrators in England and Wales about the need to increase plasma supplies to meet demand for AHG concentrate, noting that BPL's output was limited by the amount of plasma supplied by Regional Transfusion Centres (RTCs). The letter added that blood product production should be coordinated with Scotland, and that some of England's increased output of plasma could be processed at the PFC in Liberton.[25]

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[23] Dr Peter Foster Witness Statement to IBI, 7 March 2022, **WITN6914001** pp.23-24.
[24] Dr Foster, 'Plasma fractionation in Scotland, *Blood*, 2008, **PRSE0001732**
[25] Letter by B Gidden (DHSS) to Regional Administrators, re: PFC inclusion in Blood Products Production, 24 November 1974, **CBLA0000239.**

27. On 11 August 1975, the SHHD queried when the DHSS would provide PFC with English plasma for fractionation.[26] A 7 November 1975 DHSS reply stated that the AHG programme in England and Wales (for producing factor VIII blood products) was underway but that an increase in plasma supply was not anticipated '*for some months yet*'. Mr M Draper (DHSS) noted that BPL could process all supplies in England and Wales for at least another year but that the situation would be kept under review.[27]

28. By 1976, with PFC in routine operation, Ministers stressed the need for collaboration in manufacturing blood products between Scotland and England. On 11 March 1976, for example, at a meeting between DHSS, SHHD, BPL and PFC representatives, it was noted that Dr Owen (Minister of State for Health) had reaffirmed an intention to achieve NHS self-sufficiency by the middle of 1977, and that '*he was anxious that there should be maximum co-operation between the production units in England and Scotland both in achieving the target figure and reversing any preference which some users might have for one or more commercial products*'.[28]

29. This issue was discussed further on 13 January 1977, at a Haemophilia Centre Directors' Meeting. Reference was made to the UK requiring 40-50 million units of factor VIII per year as a minimum reasonable need. Elstree's maximum capacity, with its existing facilities, was said to be 14-15 million units. Dr McDonald (Royal Infirmary, Glasgow) stated that Liberton had the capacity to make 60 million units a year, but that it would require £25,000 for additional equipment and running costs, including staff payments to enable a 24-hour shift work system.[29] Dr Richard Lane (Director, BPL) later asserted

[26] Letter from TH McLean to MW Draper, re: When PFC will process English Plasma, 11 August 1975, **SCGV0000074_010**.

[27] Letter from M W Draper (DHSS) to T H McLean (SHHD), re: BPL capacity to process plasma for another year, 7 November 1975, **SCGV0000074_007**.

[28] Minutes of meeting held at DHSS to consider Factor VIII production, 11th March 1976, **CBLA0000343**.

[29] Minutes of the Haemophilia Centre Directors of the United Kingdom Minutes, 13 January 1977, **PRSE0002268**, pg. 12-13.

that the SHHD figure '*was nonsense, but was not apparently challenged*'.[30] Nevertheless, the meeting minutes record that agreement in principle had been reached between the DHSS and SHHD:

> 'Plans had been made to divert plasma from south of the Border to Liberton when Mr. Watt was ready to receive it. It was planned that the Factor VIII made from this plasma would return to Centres south of the Border. Agreement in principle had already been reached between the DHSS in London and the Scottish Home and Health Department'.[31]

30. Dr Lane later asserted that, to his knowledge, nothing ever came of these plans.[32] There is, however, evidence that a small amount of English plasma was supplied to Scotland, likely as a result of the agreement in principle between the DHSS and SHHD. On 11 April 1977, Mr Watt reported to the Scottish National Blood Transfusion Service (SNBTS) that he held 10,000 litres of plasma from England, but that he did not have any arrangement in place for processing it.[33] This increased to 20,000 litres by the time of a July 1977 SNBTS, PFC and SHHD meeting, during which '*Directors agreed that a system acceptable both to BTS England and Wales and to SNBTS would have to be evolved and that this should be borne in mind by those presently negotiating the supply of plasma from England to PFC*'.[34]

31. This English plasma was still held in store by the time of the next Scottish Directors' meeting in January 1978.[35] It was agreed at that meeting that no large-scale processing of plasma from England and Wales should begin until a detailed plan had been agreed, but that PFC would fractionate a limited

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[30] 5th Draft Proof of Evidence of Richard Spencer Lane for HIV Haemophilia Litigation, 10 December 1990, **CBLA0000005_002**, para 137, pg.55-56.
[31] Minutes of the Haemophilia Centre Directors of the United Kingdom Minutes, 13 January 1977, **PRSE0002268**, pg. 12-13.
[32] 5th Draft Proof of Evidence of Richard Spencer Lane for HIV Haemophilia Litigation, 10 December 1990, **CBLA0000005_002**, para 137, pg.55-56.
[33] Letter from Mr Watt to Miss Corrie at the SNBTS, 11 April 1977, **PRSE0001205**.
[34] Minutes of 12 July 1977 Directors' meeting, **PRSE0004548**.
[35] Minutes of the 17 January 1978 directors' meeting, **PRSE0004707**.

amount of English plasma for around two weeks. This would be intended to establish yield and costs and would be carried out on the basis of an extended working day, pending agreement on shift-working. The meeting also '*generally agreed that Scotland should source its own supply of fractions before undertaking work for NBTS*'. As described further below, the evidence suggests that a system for the large-scale processing of plasma from England and Wales into concentrates was never ultimately established.

Divergence from UK production

32. From 1977, with no established system to process English and Welsh plasma in Scotland, a shift in tone on the PFC's role in UK-wide fractionation began to appear. The evidence suggests that, after years of dialogue and a continued lack of formal agreement, England revised its approach and began focussing on BPL. For example, in a 22 July 1977 letter to Dr Maycock, Mr Dutton (Principal Secretary, DHSS) noted that, despite budgeting arrangements having been made in June 1974 to include expenditure for the processing of plasma by PFC on the DHSS's behalf, with no fractionation of English plasma in Scotland to date, this money was instead being used for funding the expansion of BPL production.[36]

33. In his response, Dr Maycock suggested that arrangements should be made for the PFC to fractionate time-expired plasma and cryoprecipitate supernatant that was in excess of BPL's capacity.[37] Amongst other products, this plasma would be used to produce plasma protein fraction (PPF, an alternative to albumin). He also stated, '*[i]n spite of past requests*', BPL had '*not yet been able to examine samples of plasma protein fraction*' prepared at the PFC, which was said to be '*essential before an agreement is concluded*'. Dr Maycock does not appear to have ruled out the possibility of the PFC fractionating fresh frozen plasma (FFP) from England and Wales, but the letter seems to suggest that he did not consider it necessary at that time.

[36] Memo from T E Dutton to Dr Maycock, re: Use of PFC Liberton, 22 July 1977, **SCGV0000001_164**.
[37] Letter from Dr Maycock to Mr Dutton, 26 July 1977, **DHSC0003715_194**.

Having summarised recent supplies of FFP to BPL, he wrote: '*The planned capacity of BPL is 1,200 L per week. When this figure is reached, arrangements for fractionating further volumes of fresh plasma will then have to be brought into use*'. Dr Maycock then included the following sentence, around which manuscript brackets have been added: '*Preliminary discussions could with advantage take place when arrangements for time-expired plasma are considered'*.

34. This shift in tone and approach appears to have coincided with the appointment of Dr Lane as BPL Director. On 22 August 1977, it was reported at a joint DHSS and SHHD meeting that Dr Lane, who was due to succeed Dr Maycock, intended to '*concentrate on the production of Factor VIII at the BPL*'. Dr Lane was said to consider that, that as both the BPL and PFL (the Protein Fractionation Laboratory) were funded by the DHSS, '*it would be wrong, in his view, to send plasma from Regional Transfusion Centres in England to the PFC, if this had the effect of leaving spare capacity at Elstree and meant service charges having to be paid. In his view this would have the effect of duplicating costs. He envisaged that only time expired plasma would be sent to the PFC and was unwilling to enter into any long term agreement to have regular quantities of plasma fractionated in Edinburgh*'.[38] The minutes record some disquiet about '*any fundamental departure at this stage from what had already been agreed about the fractionation by the PFC of plasma from England*'. It was agreed that Directors should set out a '*statement of intent*' on English plasma to be fractionated in England for the following 2-3 years. The minutes also refer to the difficulties which had been encountered in seeking to introduce shift working at the PFC.

35. The feasibility of sending English plasma to Scotland was subsequently evaluated. The difficulties predominantly revolved around whether shift working could be introduced to increase operational capacity at the PFC. On 24 October 1977, for example, the possibility of plasma being sent from England to Scotland for fractionation was discussed at a UK Haemophilia

[38] Joint DHSS/SHHD meeting on Mutual Problems, 22 August 1977, **SBTS0000283_006**.

Centre Directors meeting. It was noted there would be difficulties with such an arrangement. Any increase in fractionation at the PFC would require the running of 3 shifts per day. Other factors such as pay structure would also have to be discussed with the unions and the Whitley Council[39] before any progress could be made. Dr McDonald reported that while he had been invited to organise a meeting of those involved in the problem of factor VIII supply, including members of the SHHD and DHSS, '*in some quarters there was little enthusiasm for such a meeting*' and so he had not gone ahead with it.[40]

36. This changing approach seems to have continued into late 1977. In a 1 November 1977 memo, Mr Parrott (DHSS) noted that the '*original philosophy*' had been that BPL would not have capacity to fractionate all requirements for blood products as demand increased, and therefore that surplus plasma would need to be sent to PFC for processing. He explained that opinion within parts of the DHSS seemed to be '*moving away from the rather simplistic planning approach*' which had led to the DHSS providing financial and other support for the Liberton project in the late 1960s and early 1970s. Even if all the '*difficulties in shift working at Liberton could be overcome tomorrow*', '*it would not be regarded as sensible policy to put all our eggs in the Scottish basket as the planners appear to have originally intended*'. Instead, Mr Parrott suggested that there be flexible co-operation between England and Scotland as partners, '*each of which has the capacity to be self-sufficient in the essentials, where each could help the other in an emergency and where rationalisation of certain aspects of production would be encouraged*'. He commented that '*a fully integrated UK approach to the fractionation of blood plasma is not a practical proposition*', while noting that it would not be easy for the DHSS to disentangle itself from the '*implied moral (and actual financial) commitment*' that had been given by their predecessors in connection with the

[39] Whitley Councils were bodies containing employer and trade union representatives, through which pay and working conditions were discussed.
[40] Minutes of the 8th United Kingdom Haemophilia Centre Directors Meeting, 24th October 1977, **PRSE0001002**, pg. 9-11.

building of Liberton. He considered that the DHSS needed to concentrate on building the capacity of Elstree.[41] This change appears to have been reflected in the allocation of funding, with money previously allocated for PFC fractionation charges for 1978-79 instead earmarked for the BPL.[42]

37. With a growing change in philosophy as to the role of PFC, discussions about recouping the DHSS contribution to PFC's capital costs began. On 11 July 1979, Mr Harley (DHSS) wrote to Mr P J Wormald (DHSS) and stated that, if Scotland were at fault for the DHSS not getting value from the capital investment, the DHSS should ask for its money back.[43]

38. On 2 June 1980, Mr Wormald wrote to Mr Angus Macpherson (SHHD) and explained that the DHSS had not been pressing for answers regarding PFC's capacity as a result of factors such as the Medicines Inspectorate's report (explained below), but that it was anxious to see a return on its investment or have the money back '*suitably inflated*'.[44]

39. On 13 August 1980, Mr Harley indicated in an internal DHSS memo that he was looking into the issue of the investment, which was said to amount to £400,000.[45] On 20 August 1980, Mr Harley wrote to Mr Macpherson, stating that if planning on the new BPL had to begin without an answer on PFC's capacity, it would be assumed that Liberton could make no contribution and the DHSS would ask for its investment to be repaid.[46] A 27 November 1980

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[41] Memo from A L Parrott to Mrs Maunsell, re: PFC Edinburgh, 1 November 1977, **DHSC0003715_176**.

[42] Handwritten Memo from Mr Dutton to Mr Parrott and second Memo from Yuille, re: PFC shift-working and allocation of funding for PFC, 12 May 1977, **SCGV0000001_007**.

[43] Memo from PJ Wormald to Mr. Harley, re: PFC Edinburgh, 11 July 1979, re: DHSS investment in PFC, **SCGV0000001_117**, para 2.

[44] Memo from P J Wormald to Mr Hart et al, re: Enclosing letter to Mr Macpherson on Future Supply of Blood Products, 3 June 1980, **DHSC0002313_044**, para 6, pg.3.

[45] Note from J Harley 'Blood Products Laboratory: Notes on Mr Hart's Paper on 8.8.80' BPL: Notes on Mr Hart's Paper of 8.8.80,13 August 1980, **DHSC0002315_067**, para 2(a), pg.1.

[46] Letter from Mr Harley to A M Macpherson (SHHD), re: Taking PFC Capacity into account in England and allocation of DHSS funding to PFC, 20 August 1980, **SCGV0000127_044**, para 8, pg.2.

DHSS file note calculated that the £400,000 was worth £1,425,970 at 1980 inflated prices.[47]

Further consideration of UK production

40. The links between the PFC and BPL – including comparisons of their manufacturing processes – continued to be explored in the early 1980s. On 20 March 1981, the Joint Management Committee for the CBLA expressed its concern that the PFC had '*not yet started its proposed trial of the 3 shift system*', and stated it was '*vital*' to assess the effectiveness of a shift-working trial at PFC to enable consideration of the role of continuous small volume mixing technology in the re-developed BPL.[48]

41. On 24 November 1981, the NBTS Scientific Technical Committee recorded that a shift-working experiment had been carried out at PFC. [49]

42. On 15 December 1981, Mr Wesley (Production Manager, BPL) produced a report on this experiment, described as a feasibility exercise to test the continuous small volume mixing fractionation system under continuous operation.[50] The report recorded that the PFC's CVSM fractionation system had been brought into use in 1976, but that it had been confined to the production of albumin. Moreover, 24-hour shift-working had been prevented to date due to a shortage of plasma and administrative issues. For the trial, this was overcome by using time-expired plasma from BPL and through an agreement between the Common Services Agency (CSA) and the unions

[47] File note by S Godfrey, re: Allocation of 400k to capital cost of Liberton, 27 November 1980, **SCGV0000001_077**.

[48] Minutes of the 11th Joint Management Committee for the Central Blood Laboratories Meeting, 20 March 1981, **CBLA0001315**.

[49] Minutes of the NBTS Scientific and Technical Committee for the Central Blood Laboratories, 24 November 1981, **CBLA0001506**.

[50] Report on 'Feasibility Exercise Performed at Protein Fractionation Centre' by Mr Wesley, 15 December 1981, **CBLA0001528**.

representing PFC staff. Continuous operation of the CVSM system took place over 10 working days, divided into two weeks of five days each.

43. The report concluded that, with sufficient plasma and fractionation staff, the system could have operated for longer; and that there was '*no reason to believe that the BPL could not also be operated on a 24 hour system indefinitely, provided a suitable formula can be found for staff employment*'. It should be noted that the additional blood products produced during the exercise did not include Factor VIII or IX. The report recorded: '*During the Feasibility Exercise, Factor VIII production was limited to the normal quantity. No evidence is available therefore from the Exercise to suggest what increase could be made to factor VIII production by the fractionation of large volume of fresh plasma*'.[51]

44. On 18 December 1981, Mr Hibbert reported at a Policy Steering Group meeting that he had observed the shift-work experiment and considered that the '*PFC was capable of improvement. Its layout was not ideal and its output might be increased if the present system were changed*'.[52] He also noted that the PFC appeared to be less cost effective than BPL, but that the experiment had shown the equipment could function on a continuous basis (although he did not expect that this would overcome the shortcomings of the existing system). He stated that PFC '*hoped eventually to service the Northern English Regions*'.

45. Dr Lane expressed reservations about the experiment at the meeting, noting that '*there appeared to be several inconsistencies in the information provided and that the study had examined only one aspect of the production process*'. In terms of the PFC's place in UK-wide fractionation, the Group agreed to consider more fully the role it could play in its present form, as well as the

[51] Report on 'Feasibility Exercise Performed at Protein Fractionation Centre' by Mr Wesley, 15 December 1981, **CBLA0001528**.

[52] Minutes of the 4th Policy Steering Group for the Re-development of the BPL Meeting, 18 December 1981, **CBLA0001517**.

possibility of upgrading and expanding the facility using earmarked money for the redeveloped BPL. Mr Harley noted '*it would be difficult to assess quickly the cost-benefit of redeveloping PFC in harness with BPL, but agreed to put this to SHHD*'. Lastly, the Group deemed it essential to obtain a firm commitment from the SHHD on the amount of plasma from England which PFC could fractionate. Mr Harley was asked to press the SHHD for this information as a matter of urgency.[53]

46. Professor Cash (National Medical Director of the SNBTS from 1979) later suggested that the shift-working trial provided evidence that Scotland had '*very substantial spare capacity*' to assist with fractionation of plasma from England and Wales.[54] On another occasion, he stated that, based on the trial, the PFC would have been able to produce albumin for all of England, though it would have been necessary to complete additional work to finish it.[55]

47. By contrast, Dr Lane later considered that the results of the shift experiment at the PFC were '*inconclusive*', on the basis that it took place over a short period of time and that factor VIII was not produced. His view was that the trial was unrepresentative of what would occur in practice.[56] Furthermore, Dr Lane suggested that it was not sustainable for the PFC to operate on a 24-hour basis without further investment in facilities, plant and equipment.[57]

48. As requested by the Policy Steering Group, on 21 December 1981 Mr Harley wrote to the SHHD and pressed for information as to how much English plasma the PFC could fractionate using its existing facilities. He noted that '*the need for information about the contribution we can expect from the PFC is*

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[53] Minutes of the 4th Policy Steering Group for the Re-development of the BPL Meeting, 18 December 1981, **CBLA0001517**, pg. 2- 4.

[54] Letter from John Cash to Mr J Hamill (SHHD), re: HIV Litigation and PFC grave error of judgement to focus only on Scotland, 11 January 1990, **SBTS0000187_047.**

[55] Edited Notes of Interview with Professor John Cash, 30 May 1990, **SBTS0000053_055**, pg. 8

[56] Draft Proof of Evidence of Richard Spencer Lane for HIV Haemophilia Litigation, 10 December 1990, **CBLA0000005_002**, para 335, pg.141-142.

[57] 5th Draft Proof of Evidence of Richard Spencer Lane for HIV Haemophilia Litigation, 10 December 1990, **CBLA0000005_002,** para 292, pg.121-122.

delaying progress in planning the new BPL, since further work depends on a decision about its capacity'. The Policy Steering Group wished to ascertain whether, instead of redeveloping BPL to meet all UK needs for factor VIII and albumin, except those met by the existing PFC, it '*would be more cost-beneficial to invest part of the available money in expanding the PFC*'.[58]

49. On 11 January 1982, the need for investment in the PFC was articulated by Mr Macpherson in a letter to Mr Harley. Mr Macpherson stated that, while the 24 hour shift-working trial had concluded satisfactorily, '*PFC, Liberton could process substantial quantities of English plasma only if further ancillary facilities can be provided, and that more land will be needed for the building required*'. Additional expenditure of around £6-7 million would be necessary, with an appropriate portion of the capital cost of the additional facilities to be funded by the DHSS. It was estimated that the necessary building work could be completed in approximately 2 and half years. In addition, staff at the PFC could not be expected to work in shifts regularly until the DHSS had reached an agreement through the Whitley Council.[59]

50. On 13 January 1982, Mr Harley informed Mr Macpherson that he would provide an update on whether the proposition to develop the PFC to meet English and Welsh needs would be pursued after the next Steering Group meeting.[60]

51. On 1 March 1982, the Policy Steering Group convened once more and agreed that, as the PFC would not be able to fractionate any substantial quantity of English plasma without the introduction of a 3-shift working system, plans for the redevelopment of BPL should not proceed on the assumption that PFC would process plasma for England and Wales. Instead,

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[58] Letter from Mr Harley to M Macpherson (SHHD), re: Requesting information on PFC capacity to assist England and whether funding should be provided to PFC, 21 December 1981, **SCGV0000002_032**.

[59] Letter from A. M. Macpherson (SHHD) to J. Harley (DHSS), re: PFC processing English plasma, capacity and expenditure, 11 January 1982, **CBLA0001532** pg. 2; Draft Proof of Evidence of Richard Spencer Lane for HIV Haemophilia Litigation, 10 December 1990, **CBLA0000005_002**, para 340, pg.144.

[60] Letter from Mr Harley to A M Macpherson (SHHD), re: Policy Steering Group to meet and advise on the PFC role, 13 January 1982, **SCGV0000002_026**.

'Mr Harley was asked to seek JMC[61] approval for planning to proceed on the assumption that BPL would process all plasma for England and Wales. The estimated production capacity of the new laboratory could be revised if necessary at a later date if there were a substantial change in Liberton's position'.[62]

52. On 4 March 1982, Professor Cash wrote to Mr Macpherson and stated that PFC's ability to assist England appeared *'to hinge on the conclusion of a shift-working agreement with its staff'*. He noted that he had asked the DHSS's Personnel Division, in conjunction with the SHHD, to consider the likelihood of such an agreement being reached.[63]

53. Also on 4 March 1982, Mr Harley informed Mr Macpherson that the Steering Group had decided to recommend to the Joint Management Committee that it proceed on the assumption that BPL would process all plasma from England and Wales, and that the PFC would process plasma for Scotland and Northern Ireland.[64] An extract from the minutes of a meeting on 27 April 1982 records that the Committee endorsed this conclusion. It also recommended that discussions be initiated between the DHSS and SHHD with a view to reciprocal supply arrangements in times of shortage.[65]

54. DHSS officials anticipated that the SHHD would be concerned about this approach. In a 23 July 1982 internal DHSS minute, Mr Harley commented that the SHHD would be worried about the prospect of having to find substantial funds to update the PFC, and that it would be '*even more worried if we ask*

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[61] I.e. the Joint Management Committee.

[62] Minutes of 5th Policy Steering Group for the redevelopment of the BPL Meeting, 1 March 1982, **DHSC0002215_087,** para 6, pg.2

[63] Letter from John Cash (DHSS) to AM Macpherson (SHHD), re: Shift working agreement, 4 March 1982, **DHSC0001621**.

[64] Letter from Mr Harley to AM Macpherson (SHHD), re: PFC to focus on Scotland and BPL on England and Wales, 4 March 1982, **SCGV0000002_024**.

[65] Minutes of Joint Management Committee meeting, April 1982, **DHSC0002217_010**.

them to repay our original investment, which is now equivalent to nearly £2m'.[66]

55. A draft DHSS ministerial submission – which would appear to be from September 1982 - stated that it would be more cost efficient to build a BPL '*capable of achieving self-sufficiency*' rather than building a smaller BPL and investing money in PFC. The following breakdown of estimated costs was provided:

    a. Building a smaller BPL (£18.6 million) and investing in the PFC (£4 million) would total £22.6 million
    b. A full redevelopment of the BPL would cost £21.03 million.[67]

56. The draft recorded that, in the view of DHSS officials, it remained '*highly doubtful whether a shift-working agreement can be negotiated with staff at PFC without serious repercussions on pay of other groups in the NHS and the Industrial Civil Service*.'

57. On 15 September 1982, Mr J Walker (SHHD) wrote to Mr J P Cashman (DHSS) regarding this draft submission. He began by commenting: '*I note, not without some sense of relief, that you have ruled out PFC, Liberton, as a source of supply for England and Wales*'. He went on to clarify that the £6-7 million investment suggested for PFC would not be entirely attributable to increased fractionation of English plasma. About half of this sum was required regardless, to bring the facility up to Medicines Inspectorate standards.[68] Mr Walker also highlighted that the PFC was designed to work on a continuous flow system and was capable of a high throughput, but that this relied on shift-working which had only operated during a limited trial period due to the lack of negotiated shift-working arrangements. He added that he was *'a little*

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[66] Letter from Mr Harley to Mr Cashman, re: Funding PFC upgrade, 23 July 1982, **SCGV0000002_012**.

[67] Ministerial submission on 'BPL Redevelopment', undated, **DHSC0002309_108**. See a reference to the submission in a 22 September 1982 DHSS minute: **DHSC0002309_017**. The final version of the submission is available at **CBLA0001606**.

[68] A handwritten comment on the letter noted that over half of the figure would be required as a direct result of processing plasma from England.

unhappy' with the suggestion that the concept of shift-working would be '*too difficult for the NHS*': '*We here take the view in the light of the known attitude of the main Scottish union official involved that an acceptable agreement can be negotiated, though not without difficulty*'.[69]

58. In her oral evidence to the Inquiry, Dr Diana Walford noted that the estimate of £6-7 million '*put a stop to any further discussions*' with Scotland.[70] She described this as a '*sort of bitter blow*' and a realisation that England could not '*easily*' or '*reasonably*' utilise the PFC.[71] Dr Walford also stated that the SHHD had confirmed a development in the PFC '*was going to take about two and a half years*'.[72]

59. In his Inquiry witness statement, Dr Foster suggests that the comparative speed at which the PFC could have been re-developed, in contrast to a full redevelopment of the BPL, was not given proper consideration:

> '(xi) Despite the marginal differences in these cost estimates, the time taken to complete the different options does not seem to have been taken into consideration, despite the option to utilise PFC and to build a much smaller BPL obviously being much quicker to achieve than constructing a much larger BPL.
>
> (xii) Construction of the new BPL took about 5 years to complete, at a capital cost of £59m… almost 3x greater than the cost estimate on which this option was chosen'.[73]

60. On 15 October 1982, Mr Walker wrote to the Private Secretary to Mr MacKay (Scottish Health Minister), noting that '*[i]t has always been clear that the*

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[69] Letter from J Walker (SHHD) to John P Cashman (DHSS), re: shift working arrangements and PFC's role in processing English plasma, 15 September 1982, **DHSC0002333_018**.
[70] Dr Diana Walford oral evidence, 20 July 2021, p.105, lines 11-16.
[71] Dr Diana Walford oral evidence , 20 July 2021, p.104, lines 2-8
[72] Dr Diana Walford oral evidence, 20 July 2021, p.105, lines 14-16.
[73] Dr Peter Foster Witness Statement to IBI, 7 March 2022, **WITN6914001**, pg.166.

DHSS and English NHS interests concerned would prefer… to redevelop the BPL on a basis which would make England and Wales fully self-sufficient in this field'. Mr Walker stated that the option of processing English plasma at PFC had been rejected on the grounds that it would be more expensive and that '*it remains highly doubtful whether a shift-working agreement can be negotiated with staff at PFC without serious repercussions on the pay of other groups in the NHS and the Industrial Civil Service (continuous shift-working at PFC would be a prerequisite for handing the volume of material needed to meet parts of England's requirements)*'.[74] As for the SHHD's views on whether this problem could be resolved, Mr Walker wrote:

> 'Although we take a more optimistic view than DHSS of the shift-working issue (a successful shift-work experiment was carried out at PFC late in 1981) there is still much work to be done before a scheme acceptable to all interested parties can be developed. The indications were that the trade union mainly concerned (ASTMS) might be persuaded to reach an acceptable agreement on shift-working, albeit following hard bargaining over hours of work, staffing levels and so on, but the current pay dispute has introduced an element of militancy which makes understandable the DHSS reluctance to back an option which relies on union co-operation. Although Mr Gordon Craig, Scottish Divisional Officer of ASTMS, urged the desirability of developing the PFC and creating additional jobs when Ministers met the STUC on 15 January 1982, his union has never committed itself to the changed working practices required for this purpose'.[75]

61. Mr Walker considered that the possibility of handling English material at the PFC had been '*sufficiently considered*', and that the SHHD should accept the DHSS's conclusion that the '*balance of advantage for them lies in developing*

[74] Memo from Mr Walker to Mr MacKay, re: Decision not to send English plasma to PFC, 15 October 1982, **SCGV0000147_114**.
[75] Memo from Mr Walker to Mr MacKay, re: Decision not to send English plasma to PFC, 15 October 1982, **SCGV0000147_114**.

the BPL to cover English requirements'. He proposed that '*action in Scotland should now concentrate on identifying the improvements needed at the PFC to enable Scottish and Northern Ireland plasma to be processed in conditions which fully satisfy the increasingly stringent requirements of the Medicines Inspectorate*'.

62. On 22 September 1982, Mr Godfrey recorded a discussion with Mr J Shaw (DHSS) on the possibility of reclaiming the DHSS investment into the PFC in light of the decision not to use it.[76] Mr Shaw had explained that the £400,000 had to be written off on the '*knock for knock*' understanding since there had been so many interdepartmental transfers of this sort.[77] It therefore appears that the possibility of the DHSS recouping its £400,000 investment from the SHHD was abandoned during the course of 1982.

63. The Scottish Office's formal agreement to the separate roles to be played by BPL and PFC was recorded in late 1982. On 11 November 1982, Mr J Wastle (SHHD) wrote to Mr Godfrey to confirm that Mr Mackay had '*accepted*' that BPL '*should be re-developed to meet English processing requirements*' and that the PFC should '*concentrate on fractionating Scottish and Northern Irish plasma*'.[78]

64. In his oral evidence to Penrose, Dr Foster commented as follows on this outcome: *'the decision ultimately was to build the large plant for the whole of England and Wales and not to send plasma to Scotland, and that was justified on some costings that I think, looking at now, could be seen to be quite wrong*'.[79]

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[76] Handwritten Note by Mr Godfrey, re: Reclaiming DHSS £400k investment in PFC, 22 September 1982, **SCGV0000002_011**.

[77] Handwritten Note by Mr Godfrey, re: Reclaiming DHSS £400k investment in PFC, 22 September 1982, **SCGV0000002_011**.

[78] Letter from JO Wastle (SHHD) to S Godfrey (DHSS), re: PFC to focus on Scottish and Northern Irish plasma, 11 November 1982, **DHSC0001638**.

[79] Transcript of Peter Foster Oral Evidence to the Penrose Inquiry, 10 May 2011, **PRSE0006022**, pg. 80-81.

65. Annex D contains further detail on the views of a number of prominent figures on Anglo-Scottish co-operation during this period.

3. PFC assumes responsibility for Northern Ireland fractionation[80]

66. Whilst PFC did not ultimately fractionate plasma on behalf of English regions, it did assume responsibility for the fractionation of Northern Irish plasma.

67. Between 1972 and 1998, Northern Ireland was governed by direct rule from Westminster.[81] This included responsibility for blood collection and other health matters.

68. In 1973, following a major restructuring, healthcare in Northern Ireland was administered by four health and social boards representing the East, North, South and West, servicing a population of approximately 1.5m.[82] Northern Ireland's blood transfusion centre – part of the Northern Ireland Blood Transfusion Service (NIBTS) – was based in Belfast. Colonel Field was director of the NIBTS and its transfusion centre from 1968 to 1980; he was replaced in June 1980 by Dr Morris McClelland.[83]

69. Northern Ireland's haemophilia centre was based at the Royal Victoria Hospital, Belfast, and was designated a Reference Centre in September 1981 by the Northern Ireland Office.[84] Dr Elizabeth Mayne joined the Royal Victoria Hospital in 1968, initially as a Senior Registrar in haematology, before becoming a Consultant Clinical Haematologist with a special interest in bleeding and clotting disorders.[85] She was Director of the Belfast Haemophilia Centre from 1978 to 1999. The Belfast area and its four hospitals, including

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[80] It is important to note that the Inquiry has to date considered a range of evidence relating to Northern Ireland, including from Dr Elizabeth Mayne and Dr Morris McClelland, and through the presentation on the Belfast Haemophilia Centre. This section refers to some of that evidence and should be read alongside it.
[81] Report titled 'Four decades of public health: Northern Ireland's health boards 1973 - 2009'. **WITN3449008**. See also the Inquiry presentation note on the history of blood services in the UK: **INQY0000307**.
[82] Report titled 'Four decades of public health: Northern Ireland's health boards 1973 - 2009'. **WITN3449008,** pg.9;11.
[83] Written statements of Dr Morris McClelland, **WITN0892001** and **WITN0892006**. See also the transcript of Dr McClelland's oral evidence to the Inquiry on 1 February 2022.
[84] Minutes of the twelfth meeting of the UK Haemophilia Centre Directors, 9 October 1981, **CBLA0001464**.
[85] Written Statement of Dr Elizabeth Mayne, 20 May 2019, **WITN0736001.**

the Royal Victoria Hospital, were part of the Eastern Health and Social Services Board (EHSSB).[86]

70. Dr Mayne's evidence is that the NIBTS '*did not have the capability to manufacture concentrate*', though it did provide '*local volunteer derived, single donation cryoprecipitate*'.[87] Similarly, Dr McClelland stated that the '*establishment of a plasma product manufacturing facility requires enormous investment in terms of expertise, facilities etc. of a level that would not have been feasible to service a population of 1.5 million.*'[88] As a result, haemophilia patients in Northern Ireland who were treated with concentrate received either NHS products manufactured elsewhere in the UK, or imported commercial products.

71. As noted in the Inquiry presentation note on the Belfast Haemophilia Centre, the Centre was included in the UKHCDO Oxford supra-region until 1981.[89] A June 1981 DHSS memo recorded that Northern Ireland did not pay for fractionation services – i.e. blood products – provided by BPL.[90] In her Inquiry evidence, Dr Mayne stated that prior to 1982, Northern Ireland received limited quantities of concentrate from Elstree and Oxford, '*although this was largely on the basis of the good relationship I had with Dr Lane and Drs Bidwell and Grant respectively*'.[91]

72. From 1980, consideration began to be given to PFC fractionating plasma not only on behalf of England, but also on behalf of Northern Ireland. Dr McClelland's evidence is that, following his June 1980 appointment as NIBTS Director, he began investigating the possibility of Northern Ireland supplying

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[86] Report titled 'Four decades of public health: Northern Ireland's health boards 1973 - 2009'. **WITN3449008,** pg.13.
[87] Written Statement of Dr Elizabeth Mayne, 21 February 2020, **WITN0736006**.
[88] Dr Morris McClelland's Second Written Statement, para 11, **WITN0892006**.
[89] **INQY0000246**; see also p.6 of the 26 February 1980 Reference Centre Director meeting minutes, **HCDO0000405**.
[90] Letter from S. Godfrey to Dr. R. S. Lane, re: Supply of Blood Products to Northern Ireland, 10 June 1981, **BPLL0004342**.
[91] Written Statement of Dr Elizabeth Mayne, 4 March 2021, **WITN0736009**, pg.65.

FFP to BPL, as well as the time-expired plasma it was already sending.[92] He stated that, soon after, he '*became aware of capacity issues with BPL together with the apparent spare capacity at PFC*'. There were also '*obvious practical attractions*' in using surface rather than air transport to supply plasma to PFC in Scotland (via road and ferry) rather than BPL in England.

73. On 1 December 1980, the SHHD, DHSS, DHSS (NI) and Welsh Office met to discuss UK self-sufficiency in blood and blood products. The discussion addressed the need to increase plasma supply in order to meet growing demand. It was agreed that the PFC '*could play a role in helping to meet total UK need*', and it was suggested that it could fractionate plasma from Northern Ireland as well as four northern regions in England. Dr Acton (DHSS, NI) agreed to liaise with his department regarding the logistics of sending plasma to Edinburgh.[93]

74. Alongside discussions regarding the PFC's role in UK-wide fractionation, BPL was preparing to introduce a pro-rata distribution system of blood products from April 1981. The Advisory Committee on the NBTS in February 1981 confirmed that this system would result in Regional Health Authorities (RHAs) receiving blood products in proportion to the quantity and quality of plasma supplied to BPL. The Committee noted that Northern Ireland, which received over 1,000 vials of factor VIII a year from BPL, would not be entitled to any under the pro-rata system, as it did not supply FFP to BPL.[94] It was recorded that NIBTS planned to increase production of cryoprecipitate to compensate for the loss of these supplies, as well as exploring the advantages and disadvantages of transporting FFP to either BPL or PFC.[95] BPL's introduction of a pro-rata distribution system appears to have been an important factor in Northern Ireland's transition to being supplied with blood products from Scotland.

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[92] Written statement of Dr Morris McClelland, **WITN0892001**, pg.5.
[93] Minutes of SHHD, DHSS (NI) and Welsh Office to discuss UK self-sufficiency in blood and blood products Meeting, 1 December 1980, **DHSC0000064**.
[94] Northern Ireland supplied only time-expired plasma: see Dr Morris McLelland's evidence and **DHSC0000064**.
[95] Paper by DHSS 'Pro-Rata Distribution of Blood Products', February 1981, **CBLA0001294**.

75. Preliminary discussions on the possibility of PFC processing Northern Irish plasma began in February 1981. In a 12 February 1981 letter to Professor Cash, Mr Watt explained that Dr Morris McClelland and Mr Maxwell (Chief Technician, Belfast RTC) had recently visited the PFC. The meeting included:

    a. A general discussion on the scale, feasibility and logistics of supplying plasma and receiving product in return;
    b. A tour of PFC and its resources;
    c. A detailed discussion about achieving adequate storage of plasma in Northern Ireland and transporting it to Edinburgh.[96]

76. Mr Watt considered that, for a first meeting, it had been deemed '*fairly successful*'. The logistics of any arrangement were explored in considerable detail. With regard to transportation, a PFC refrigerated truck visiting both Carluke and Belfast was considered to be the '*most practicable*' option. PFC expected to receive less than 600kg of plasma per month from Northern Ireland, of which half would be time-expired plasma. Dr (Morris) McClelland also wished to obtain all plasma fractions from PFC in proportion to plasma input: '*In effect… he would be wishing to regard the Belfast operation as an equal partner both in the burden of providing plasma to the PFC and in the recovery of product*'. A possible timetable for PFC accepting Northern Irish plasma was recorded, though a limiting factor was the method of assay used for hepatitis B in Northern Ireland. It was suggested that plasma should not be sent to Scotland until a move to radioimmunoassay (RIA) had been completed. Dr McClelland felt that this could be achieved before September 1981.[97]

[96] Letter from John G. Watt to Dr. John D. Cash re: Northern Ireland Blood Transfusion Service, 12 February 1981, **NIBS0001677**.
[97] Letter from John G. Watt to Dr. John D. Cash re: Northern Ireland Blood Transfusion Service, 12 February 1981, **NIBS0001677**.

77. On 6 March 1981, Mr Macpherson summarised a telephone call from Mr Harley, which included why an agreement between Northern Ireland and Scotland had been delayed by a period of 6 months. The note suggested that the main difficulty in handling plasma from Northern Ireland was that the test applied for hepatitis differed to that used in Scotland.[98] Similarly, in an 11 March 1981 letter to Dr McClelland, Professor Cash wrote that '*the most immediate and pressing problem is to get the NIBTS transferred to HBs-Ag RIA testing of all donations*'.[99] Professor Cash also wrote that the SNBTS Directors '*would prefer to see an evolution of the relationship with the NIBTS in which you were integrated, as far as possible, into our organisation as an equal partner…*'. Dr McClelland addressed this letter, and the steps the NIBTS were taking at the time to enable FFP to be sent to the PFC, in his oral evidence to the Inquiry.[100]

78. On 23 February 1981, it was confirmed in the second meeting of the Advisory Committee on the NBTS that the BPL pro-rata scheme would apply to Northern Ireland, but that the NIBTS intended to send plasma to PFC.[101] Discussions between the DHSS (NI) and SHHD were ongoing, and a number of practical and technical problems remained. In the interim, BPL would '*continue to fractionate plasma from Northern Ireland and the system of pro rata distribution of certain products… will be applied in the same way as to other Transfusion Centres*'.[102]

79. Further to this meeting, in an internal 24 February 1981 SHHD minute, Dr Bell (SHHD) recorded his suggestion that the DHSS (NI) contact the SHHD regarding any proposed formal policy for PFC to process Northern Irish

[98] Note from A. M. Macpherson to Dr. McIntyre et al. re: Blood Transfusion Service Liaison with DHSS, 6 March 1981, **SCGV0000104_149**.
[99] 11 March 1981 letter from Professor Cash to Dr McClelland, **NIBS0001680**.
[100] See from p.45 of the transcript of Dr McLelland's 1 February 2022 evidence.
[101] Minutes of the 2nd Advisory Committee on the NBTS Meeting, 23 February 1981, **CBLA0001287**.
[102] Paper on 'Supply of Blood Products to Northern Ireland' by DHSS, 1981, **CBLA0001387.** As noted above, Northern Ireland did not send FFP to BPL. Products fractionated by BPL for Northern Ireland would not, therefore, have included factor concentrates.

plasma.[103] Dr Bell noted that the pro-rata system of supply from BPL would result in nil supply to Northern Ireland, and that '*[a]pparently*' DHSS (NI) and DHSS officials had agreed to this. The Northern Ireland representative at the 23 February 1981 meeting, Dr Lawson (DHSS, NI), had stated that '*only about 10% of their Factor VIII comes from BPL, so that additional commercial purchases to that extent are feasible for an interim period*'.

80. On 14 April 1981, Mr J Finnie (SHHD) recorded in an internal minute that, although there was a '*a dialogue between Scotland and Northern Ireland at the working level*', there had been '*no formal contact with our opposite numbers regarding the basic question of whether or not we would be prepared to undertake the work*'.[104] This would involve discussion of cost, '*both capital and revenue*'.

81. After this period of informal discussion, Dr Bell confirmed on 11 June 1981 that a formal approach from DHSS (NI) to the SHHD had been made.[105] The SHHD had no objection to the arrangement in principle, and detailed negotiations would take place between the Eastern Health and Social Services Board and the CSA. The SHHD position was also reflected in a 12 June 1981 letter from Mr Macpherson to the CSA.[106]

82. On 22 June 1981, at a further meeting of the Advisory Committee on the NBTS, Dr Bell informed the Committee of the formal approach made by Northern Ireland.[107] It had been agreed that BPL would continue to supply Northern Ireland during the changeover.

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[103] Memorandum from A. E. Bell to Dr. McIntyre et al. re: Northern Ireland BTS, 24 February 1981, **SCGV0000104_150**.
[104] Memo from J.H.F. Finnie to Dr Bell re: Plasma from Northern Ireland, 14 April 1981, **SCGV0000104_140**. The 9 April 1981 letter and enclosure referred to in Mr Finnie's minute would appear to be the documents at **SCGV0000104_141** and **SCGV0000104_142**.
[105] Letter from A.E. Bell (SHHD) to Dr. J.D. Cash (National Medical Director, SNBTS) re: Supply of Blood Products to Northern Ireland, 11 June 1981, **SCGV0000104_128**.
[106] Letter from A.M. Macpherson to J.R.Y Mutch, re: PFC Supply of Blood Products to Northern Ireland, 12 June 1981, **SCGV0000104_129**.
[107] Minutes of the 3rd Advisory Committee on the NBTS Meeting, 22 June 1981, **CBLA0001388**.

83. In September 1981, Professor Cash prepared a preliminary report regarding SNBTS fractionation of Northern Irish plasma.[108] His conclusions included the following:

a. Estimates provided by Northern Ireland of plasma supply fell '*significantly short*' of existing SNBTS regional averages;
b. The Belfast quality assurance programme was not satisfactory;
c. The existing refrigeration facilities for plasma in Northern Ireland were not adequate and required modification;
d. The HBs-Ag testing was not adequate and would need to meet the level of sensitivity recommended in the Third Report of the Advisory Group on Testing for the Presence of Hepatitis B Surface Antigen and its Antibody (1981);
e. These factors should not delay the onset of the proposed programme, with the exception of improved HBs-Ag testing;
f. There was '*no doubt*' that the SNBTS could undertake fractionation of NIBTS plasma up to a total of 12,000kg/year (note that this included a variety of blood products, rather than only Factor VIII and Factor IX);
g. Six months after the beginning of the programme, and based on its proposed plasma supply, the NIBTS could expect to receive 4,000 vials of factor VIII and factor IX (DEFIX) as required during the first year.

84. In a 23 February 1982 minute summarising progress on arrangements with Northern Ireland, Mr Finnie noted that, as a part of BPL's assessment of workload following the 1979 Medicines Inspectorate report[109], it had been suggested by the DHSS to the Northern Ireland Office that processing of Northern Irish plasma should be diverted to PFC.[110]

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[108] Report on 'SNBTS - Fractionation of Northern Ireland Blood Transfusion Service (Preliminary Report)' by John D Cash, September 1981, **SCGV0000104_117**.
[109] See the December 1979 DHSS document, 'Blood Products Laboratory, Elstree, Medicines Inspectorate Report', **DHSC0002305_010**.
[110] Letter from J H F Finnie, SNBTS) to Mr Davies re: Processing of Blood Plasma from Northern Ireland, 23 February 1982, **SCGV0000104_108**.

85. On 24 March 1982, Dr McIntyre (SHHD) proposed a meeting to discuss a number of matters, including progress in the arrangements to process plasma from Northern Ireland. He noted that it was at least possible that this might require a modified system of shift-working.[111]

86. In a 7 April 1982 minute, Mr Sivell (SHHD) stated that, despite the apparent exclusion of PFC from English plans, the acquisition of blood from Northern Ireland and the PFC proposal to change to shift-working by August 1982 required fairly urgent action '*on the Whitley front*'.[112]

87. The precise dates on which plasma from Northern Ireland began to be processed in Scotland, and PFC blood products supplied in return, are unclear. On 26 August 1982, a meeting to discuss the supply of blood products from Scotland to Northern Ireland was held.[113] Dr Morris McClelland stated in his oral evidence to the Inquiry that he did not believe that Northern Ireland had begun supplying FFP to the PFC by the time of this meeting, adding: '*I think that would have commenced shortly … perhaps a couple of months later. I'm not 100 per cent sure of that*'.[114] The minutes of an NBTS Advisory Committee meeting on 15 September 1982 noted that batches of Northern Irish plasma had been '*satisfactorily processed*' at the PFC, though financial arrangements had not yet been finalised.[115]

88. Dr McClelland's evidence is that it took around 18 months for the agreement that PFC would fractionate Northern Ireland's plasma as a result of a '*mixture of issues*'.[116] These included administrative and operational reasons, including the introduction of RIA testing for hepatitis B, the need to carry out building work and the purchase and commissioning of additional equipment.

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[111] Letter from A D McIntyre to Mr Walker et al re: SNBTS Matters including Arrangements to Process Northern Ireland Plasma, 24 March 1982, **SCGV0000104_103**.
[112] Memo from M P Sivell to Mr Sinclair re: Future Expansion of PFC, 7 April 1982, **SCGV0000104_101**.
[113] Note of a 26 August 1982 meeting, **SCGV0000104_090**.
[114] See the transcript of Dr McLelland's oral evidence on 1 February 2022, pg.56-57.
[115] Minutes of Advisory Committee on the National Blood Transfusion Service, 15 September 1982, **CBLA0001621**.
[116] See the transcript of Dr McLelland's oral evidence on 1 February 2022, pg.57-58.

89. The effect of the transition from BPL to PFC products would appear to be reflected in the Belfast Haemophilia Centre annual return data, set out in Annex B. The returns do not specify the provenance of NHS product, but record that 122,049 iu of NHS factor VIII were used in 1981; 12,960 iu were used in 1982 (described as having been '*only available for November-December 1982*'); and 159,090 iu in 1983.[117]

90. Professor Cash later commented that PFC began fractionation of plasma for Northern Ireland in 1982 in response to '*intense and direct pressure from the Department*'.[118] It is not entirely clear whether this is a reference to the SHHD or DHSS, though the former is perhaps more likely given its direct relationship with the SNBTS. Dr Foster's Inquiry witness statement includes the following: '*To the best of my knowledge there was no opposition to this proposal, which was welcomed by the staff and management of PFC as it enabled them to make a greater contribution to health care. To the best of my knowledge plasma from Northern Ireland was treated no differently to plasma from Scotland once it had been validated as suitable for the production of FVIII concentrate*'.[119]

91. As shown in Annex B, the arrangement with PFC appears to have contributed to a very significant increase in the amount of NHS product used at the Belfast Haemophilia Centre (although substantial quantities of commercial concentrates continued to be used). The quantity of NHS Factor VIII recorded in the Centre's annual returns increased from 122,049 iu in 1981 to 159,090 iu in 1983, 595,520 iu in 1984 and 2,008,760 iu by 1985. Moreover, commercial concentrate use decreased from 2,101,450 iu (1981), 2,177,292 (1982) 1,374,373 (1983), 1,366,632 (1984) to 605,274 iu in 1985.

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[117] See Belfast Annual Returns as follows: **HCDO0001493**, **HCDO0001596** and **HCDO0001692**.
[118] Report on 'Efficiency Savings,1985, SNBTS Review for Management Committee, 1985, SBTS0000617_072, pg.7.
[119] Written Statement of Dr Foster, **WITN6914001**, pg.156.

Financial arrangements

92. A delay in agreeing the financial arrangements between Northern Ireland and Scotland appears to have caused some tensions. On 7 November 1983, Mr J W Morrison (Treasurer, CSA) wrote to Mr Wastle and made reference to an indication from the SNBTS that '*the Protein Fractionation Centre is being adversely affected by the lack of income from Northern Ireland from the plasma being processed from that country*'.[120]

93. It appears that this issue was eventually resolved during the course of 1984. On 29 August 1984, during a meeting of the Blood Transfusion Service Sub-Committee, it was noted that the SHHD had proposed in late 1983 that the charges for 1982/83 and 1983/84 should reflect a proportional share of the PFC's total running costs, based on the amount of plasma supplied by Northern Ireland, with a similar approach in 1984/85.[121] The Eastern Health and Social Services Board had yet to confirm its agreement to this approach. However, by the time of the Sub-Committee's meeting on 21 November 1984, it was confirmed that the EHSSB had made a payment to account for the processing of Northern Irish plasma.[122]

94. A report prepared by Professor Cash recorded that this payment did not go directly to the PFC, and was instead transferred to the Treasury under a mechanism known as appropriation in aid. The lack of direct funding for processing Northern Irish plasma to the PFC was a contentious issue for Professor Cash. He wrote:

> 'We began the fractionation of plasma for Northern Ireland in 1982… operationally it has proved to be an outstanding success. However, the financial burden to the SNBTS has been considerable, because the

[120] Letter from J. W. Morrison to J. O. Westle Esq, re: PFC and Northern Ireland relationship, 7 November 1983, **SCGV0000104_067**.
[121] Scottish Health Service Common Services Agency – Meeting of the Blood Transfusion Service Sub-Committee, 29 August 1984, **SBTS0000139_005**.
[122] Blood Transfusion Service Sub-Committee meeting minutes, 21 November 1984, **MACK0001815**.

Northern Ireland contract has been and continues to be wholly subsidised by development monies received from Northern Ireland for the work done… No provision has ever been made in the SNBTS development allocations for this operational development and subsequent expansion'.[123]

95. Professor Cash also raised concerns about Northern Ireland's plans to increase plasma supply to the PFC in 1985/1986, which would '*once again have to be undertaken at the expense of the SNBTS's revenue development monies and further efficacy savings*'.[124]

96. These concerns seem to have led Professor Cash to take steps to limit the supply of blood products to Northern Ireland. In a 24 March 1986 letter to Mr Murray at the SHHD, he wrote that he had '*instructed Dr Perry to arrest all plans to increase supplies of plasma fractions to Belfast*'.[125] In a letter to Dr Perry that same day, Professor Cash requested that '*all possible steps*' be taken to contain the supplies of PFC products to Belfast for 1986/87 at the 1985/86 level.[126]

97. Professor Cash's views do not appear to have been shared by the SHHD. Mr Macniven (SHHD) wrote to Professor Cash on 5 June 1986, recording the SHHD's position that it was '*in the public interest to fractionate Northern Ireland blood in Scotland*', and noting that the NIBTS paid for the services provided by the PFC. He stated that, provided the NIBTS demand forecast was reasonably accurate each year, financial allocations to the PFC would cover the cost of producing blood products for Northern Ireland.[127] In his response, Professor Cash noted that he was satisfied with these arrangements and committed to fractionating plasma from Northern Ireland

[123] Report on Northern Ireland/Plasma Fractionation, Dr J Cash, 28 October 1985, **SCGV0000104_051**.
[124] Report on Northern Ireland/Plasma Fractionation, Dr J Cash, 28 October 1985, **SCGV0000104_051**.
[125] Letter from Dr J Cash, SNBTS, to A J Murray, 4 March 1986, **SCGV0000104_038**.
[126] Letter from Dr Cash, SNBTS, to Dr R J Perry, SNBTS, 24 March 1986, **SCGV0000104_039**.
[127] Letter from D. Macniven, Scottish Home and Health Department, to Dr. J. D. Cash, Scottish Blood Transfusion Service, re: Northern Ireland Contract, dated 13 June 1986, **SCGV0000104_016**.

from within existing allocations for the financial year (noting that he would make separate funding bids in subsequent years, should there be further increases in demand).[128]

98. Developments in Scotland's supply of factor concentrates to Northern Ireland, in particular with respect to virally inactivated products, are addressed further below.

[128] Letter from John D. Cash, Scottish National Blood Transfusion Service, to Duncan McNiven, Scottish Home and Health Department, dated 23 June 1986, **SCGV0000104_015**.

4. Demand estimates for Factor VIII and Factor IX in Scotland

99. Anglo-Scottish co-operation in the early 1970s, as set out above, included attempts to estimate demand for factor concentrates on a UK-wide basis. Accurate forecasts were considered to be essential to achieving self-sufficiency.

100. At the 20 March 1973 meeting of the Expert Advisory Group on the Treatment of Haemophilia, attended by Dr Macdonald on behalf of the SHHD, it was '*generally agreed that 400,000 donations would be required to treat UK sufferers from haemophilia of all degrees of severity, and more if strenuous efforts were made to clear surgical waiting lists and if home treatment or eventually prophylactic treatment became accepted ways of dealing with the problems of haemophiliacs*'.[129] The '*anticipated annual uptake*' of AHG concentrate was 20 million units.

101. In June 1973, Mr Watt undertook his own appraisal, estimating demand both for Scotland individually and the UK as a whole. He noted that the '*official estimate of the need for fresh frozen plasma for AHG preparation*' was 10 donations/1,000 population. Mr Watt considered that this figure was '*probably 30% too low*'; it did not account for increased use in domestic therapy or likely yield limitations. He suggested that the Scottish need for FFP would be 15,000 donations/million (rather than the 10,000/million then available), which he believed was '*well within the capacity*' of Scottish RTS '*without recourse to plasmapheresis*'. Mr Watt calculated the equivalent demand for AHG in England[130] to be 48 million units, giving a total UK requirement of 53 million units. Mr Watt argued that the current English facilities would not be able to process sufficient quantities of plasma, and that the best approach would be to develop PFC Liberton, and that this '*would appear to be the most economic*

[129] Minutes of Expert Group on the Treatment of Haemophilia Meeting, 20 March 1973, **PRSE0004706**.
[130] In light of Mr Watt's approach to population figures, references to England in Mr Watt's report were presumably intended to cover Wales and Northern Ireland.

and most rapid means of achieving adequate fractionation capacity in the UK'.[131]

102. The Joint Steering Committee on Blood Products Production, set up in 1973 to co-ordinate UK plasma fractionation, met on 20 June 1973.[132] In estimating demand on a UK basis, the Committee decided that '*the first target should be*' an estimate by Rosemary Biggs (of the Oxford Haemophilia Centre), with a *'lower* estimate' of *'plasma from 400,000 donations with 700,000 donations as the ultimate target*'. The '*initial aim*' was to provide AHG concentrate from 250,000 donations by 1975 (of which 10% should be a high potency product, and the remainder intermediate potency). It was noted that South East Scotland, where there was '*no restriction in use*', was '*already well on the way to using plasma from 50,000 donations per year*' for factor VIII concentrate, which contrasted with a figure of 34,000 donations in one of the papers prepared for the meeting.

103. According to a later DHSS memo, this was the Joint Steering Committee's only meeting, though SHHD and DHSS officials did meet again to discuss these issues.[133]

104. In a 14 November 1973 letter to the DHSS, Miss M K Macdonald (SHHD) recorded that subsequent meetings of the Joint Steering Committee had been postponed, and that there appeared to be a '*significant divergence of view*' between England and Scotland on the required levels of production of blood products.[134] She added:

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[131] Draft Report on 'Plasma fractionation in the United Kingdom - A Personal Appraisal' by John G Watt, 12 June 1973, **PRSE0003153.**

[132] Minutes from the first Joint Steering Committee on Blood Products Production meeting, 20 June 1973, **PRSE0004359.**

[133] Paper on 'Protein Fractionation Centre Liberton and the Arrangements with the NBTS', undated, **DHSC0003715_171**, para 4.

[134] Letter from Miss Macdonald (SHHD) to Mr Gidden (DHSS) re: Joint Steering Committee on Blood Products Production, 14 November 1973, **SCGV0000074_033.**

'The Blood Transfusion Service in Scotland has consistently planned to provide substantially greater quantities of blood products per head of population than the service in England. The quantities proposed in Scotland have initially seemed fairly liberal, but have been supported by reasoned argument and where events have overtaken us, as in the case of Factor VIII, have proved to be about right. The implications of these levels of production have been known to our Regional Directors for some time and they are confident that there will be a sufficient supply of plasma available to meet them'.[135]

105. Miss Macdonald commented that the situation had been '*changed fundamentally within the past year by the commencement of importing of blood products, beginning with Factor VIII*' and outlined two alternative approaches: for the BTS to '*attempt to meet the reasonable demands of clinicians*'; or to '*accept that we must depend upon a significant level of imports, over which we will have no direct control, because purchases will be made at hospital level*'.

106. Three interdepartmental meetings were held from December 1973 to June 1974 between the DHSS and SHHD in an effort to resolve their differences in approach.[136] The meetings focused on estimating demand for and production of PPF. Nonetheless, the minutes include a number of comments of potential relevance to the production of factor concentrates. For example, at the second meeting, Dr Macdonald explained that the SHHD's estimate of requirements for PPF '*had been made in terms of what clinicians would use assuming that there was no supply problem and not of what could be supplied by the blood transfusion service*'. [137] During a discussion on increasing plasma supply in England at the same meeting, Dr Maycock '*pointed out that twice as*

[135] Letter from Miss Macdonald (SHHD) to Mr Gidden (DHSS) re: Joint Steering Committee on Blood Products Production, 14 November 1973, **SCGV0000074_033.**

[136] Letter from L H Brandes to Mr Bourton,re: UK Production Meetings, 22 May 1974, **DHSC0003741_015**. The first interdepartmental meeting was in December 1973 (**DHSC0103209_087**); the second in May 1974 (**DHSC0103209_066**); the third was in June 1974 (**DHSC0103209_062**).

[137] Meeting of DHSS to discuss Blood Products Production Note, 1 May 1974, **DHSC0103209_066**.

much per head of the population was spent in Scotland as in England on blood transfusion'.

107. Similarly, the (draft) minutes of the third meeting referred to a paper on a joint DHSS/SHHD production policy, said to be '*generally accepted*', and which included the following passage (under the heading '*Realities of the situation*'):[138]

> 'In Scotland, as compared with England and Wales, expenditure on the blood transfusion service per head of the population is twice as great and the rate of blood donations one-third greater; the use by clinicians of concentrated red cells is twice as great and the percentage of blood returned unused by hospitals is a third greater…'

108. In order to '*avoid criticism that the two Departments differ in their estimates of need for PPF*', the paper suggested a five-year aggregate PPF production target for Great Britain. The target was considered to be achievable on the basis of BPL's and PFC's existing capacity. By contrast, meeting the SHHD target on a UK-basis would involve both a significant increase in plasma supply, as well as '*the provision of further laboratory facilities either by extending PFC Liberton or a new BPL at Elstree or elsewhere*'.

109. Alongside these meetings, a group led by Dr Biggs was undertaking UK-wide estimates of factor VIII consumption. In a report based on usage in 1969-1972, presented to Haemophilia Centre Directors on 31 January 1974, Dr Biggs estimated that the total amount of factor VIII required annually in the UK was likely to be between 38,327,800 and 53 million units.[139] This estimate was for '*all types of bleeding (spontaneous, at operation and for dentistry)'*. It included 'on demand' treatment and the upper figure assumed '*the general*

[138] Meeting of DHSS to Discuss Blood Products Production, 4 June 1974, **DHSC0103209_062**; Draft policy entitled 'Blood Products: Joing DHSS/SHHD Production Policy', undated, **DHSC0003741_016**

[139] Minutes of a Joint Haemophilia and Blood Transfusion Director Meeting, 31 January 1974, **CBLA0000187** and Report on 'Factor VIII concentrates made in the United Kingdom and the Treatment of Haemophilia Based on Studies made during 1969-1972' by Dr Biggs et al. undated, **PRSE0002350**.

application of the present best yield of factor VIII'. It also included home treatment, which was not expected to lead to an increase in use.

110. Within Scotland, there continued to be recognition of the challenge involved in reliably estimating future demand. Discussion at an 8 May 1975 meeting of SNBTS and Haemophilia Directors '*underlined the difficulty at arriving at any precise total requirement for the future in terms of Factor VIII*'.[140] Major-General Jeffrey agreed to prepare a questionnaire for Haemophilia Directors to complete, giving information about the number of haemophiliacs, the severity of their haemophilia and '*other related data*'.

111. In 1976, the journal *Clinics in Haematology* published a paper by Major-General Jeffrey – '*Problems of Supply and Demand*' – addressing a range of blood products.[141] The paper commented that there was, at that time, '*a transition stage in the supply of blood products which influences estimates of demands over the coming years*'. As for factor VIII requirements, the haemophilia population of Scotland was about 400. In 1973-1974, around 6,000 units of factor VIII per patient per year had been used, spread across cryoprecipitate, AHF and intermediate concentrate (with AHF described as a '*crude forerunner*' of intermediate factor). Patients treated in England in 1971 had received an average of 8,500 units. For planning purposes, a figure of 10,000 units of factor VIII per patient per year was suggested as a reasonable estimate '*for the next few years at least*', while noting that a '*much clearer picture will emerge when standardised factor VIII is in routine use*'. It was suggested that home treatment should not increase requirements and that early treatment might in fact lower the amount required, but that prophylactic treatment would involve much more material. In a document submitted to the Penrose Inquiry, Dr Foster described this estimate as equating to a total of 4 million units of factor VIII per annum for Scotland, equivalent to 0.75 units per

[140] Meeting of SNBTS Directors and Haemophilia Directors, 8 May 1975, **CBLA0000275**.
[141] Journal Article on 'Problems of Supply and Demand' by H.C.Jeffrey, 1976, **RCPE0000314_002.**

head of population per annum.[142] As for factor IX, Major-General Jeffrey wrote that existing use of a preparation fractionated from citrated plasma suggested a need for around 2,000 doses per year.

112. On 18 September 1976, the British Medical Journal published a study on haemophilia A and the blood transfusion service by Professor Cash (at that time Director of the South East Scotland RTC) and Mary Spencely (Lecturer at the University of Edinburgh).[143] It contained an analysis of blood products and donations used in managing patients with haemophilia A in South East Scotland in 1961-75. The article described sharp increases, including for the introduction of on-demand treatment, which was available to all patients by 1973. From that point, there had been no further increases in demand, suggesting '*that a saturation level may have been reached*'. It was noted that, despite demand increasing by seven and a half times during 1961-1975, total donations increased only by a third over that period, which '*indicated a substantial change towards more efficient use of blood donations*'. No commercial factor VIII had been used. Having noted that extrapolation to national figures and to other regions had to be approached '*with some caution*', it was suggested that the blood transfusion services '*should consider a production target of an average of 15 000 units of factor VIII/patient/year with a total UK annual requirement of around 50 million units*'. These as well as regional calculations were '*based on the assumption that 70% of the concentrate used is cryoprecipitate*'. Any '*movement towards completely replacing cryoprecipitate by AHF, unless counterbalanced by reducing the dose of factor VIII at treatment*', would require a '*substantial increase in donations*' to 20,000 donations/million population/year.

113. The purpose of haemophilia treatment was one of the elements involved in estimating demand. For example, in a letter dated 28 February 1977 to Dr

[142] Report on 'Scottish National Blood Transfusion Service Self-Sufficiency and the Supply of Blood Products in Scotland' by Dr Foster, February 2011, **PRSE0001083** p.23.
[143] Paper by John Cash and Mary Spencely 'Haemophilia A and the Blood Transfusion Service: A Scottish Study', 18 September 1976, **PRSE0003425**.

Easton at the Yorkhill Children's Hospital, Mr Watt stated that the number of units required for factor VIII and factor IX could only be calculated by the number of units required '*to maintain the patient in a reasonable state of health*'. He suggested that there was '*general* agreement' that this could be defined as health that would '*allow the patient to maintain a normal sedentary existence*'.[144]

114. In December 1977, the Working Group on Trends in Demand for Blood Products reported its findings.[145] The Group had been appointed by the DHSS, in consultation with the SHHD and Welsh Office, in January 1977. Professor Cash was one of its members. The report recorded that the '*broad aim of the Health Departments … is to achieve NHS self-sufficiency in therapeutic blood products, and to discontinue the present practice whereby the commercial manufacturers of blood products supply part of the needs of the Service, particularly factor VIII concentrate, albumin solutions and certain immunoglobulins*'.

115. The Group estimated that, to '*meet the needs of haemophiliacs in the foreseeable future the amount of Factor VIII produced will have to be about 1000 iu per 1000 population per annum*'. If sufficient blood were to be collected to meet a target for albumin, '*approximately 1300 iu of Factor VIII would also be available per 1000 population, an amount sufficient for all likely needs, especially if it is possible to improve yields of Factor VIII*'. It was believed that '*the long term aim should be the complete transfer of cryoprecipitate to a fractionated freeze dried concentrate*'. As for factor IX, if the requirements for albumin were met, the Group believed that '*there could also be sufficient Factor IX to meet anticipated requirements of this component but additional fractionation may be needed*'. The report added that '*[a]dditional fractionation capacity is also needed, even allowing for some possible expansion of the Liberton plant's output. The present UK capability is*

[144] Letter from John G Watt to Dr Easton, re: Demand calculations, 28 February 1977, **PRSE0000659**.
[145] Report of the Working Group on Trends in the Demand for Blood Products, 10 October 1977, **DHSC0001318**

less than half what we regard as essential. Additional major investment is, therefore, also needed for this.'

116. Demand for blood products was re-visited at the 11 December 1979 SNBTS Directors' meeting, held at the PFC.[146] Professor Cash confirmed during the meeting that Directors should assume a target of 1,800 units of factor VIII per 1,000 population per annum. In his Penrose evidence, Dr Foster described this as a target of 1.8 units per head of population per annum.[147]

117. In January 1981, ahead of an SNBTS, SHHD and Haemophilia Directors' meeting, Professor Cash produced a report which looked in detail at demand estimates for factor VIII and factor IX.[148] He commented that estimating future developments in demand was a '*particularly difficult problem at the present time*', primarily because home treatment was still evolving, the appropriate method of treating patients with inhibitors was unresolved, and haemophilia patients were living longer (and so requiring the surgical interventions that came with age). Having consulted colleagues internationally as well as in the UK, Professor Cash proposed a target of 2.75 units per head of population per annum (rising to 3.75 units by 1996). Elsewhere in the report, he described this as a target of 2.75 million per million population per annum for the next 5 years (i.e. until 1986), '*with an increment thereafter of 100,000 i.u. p.a*'.

118. Professor Cash's report was discussed at a 30 January 1981 meeting of SNBTS and Haemophilia Directors, attended by the SHHD, and the following was recorded with respect to factor VIII requirements:[149]

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[146] Minutes of SNBTS Directors Meeting, 11 December 1979, **SBTS0000089_120**.
[147] Report on 'Scottish National Blood Transfusion Service Self-Sufficiency and the Supply of Blood Products in Scotland' by P R Foster, February 2011, **PRSE0001083.**
[148] Paper by John Cash 'Notes for Scottish Health Service Haemophilia Centre/Transfusion Service Directors' Meeting', January 1981, **CBLA0001252**.
[149] Meeting of SNBTS and Haemophilia Directors, 30 January 1981, **PRSE0000144**.

a. Of the different haemophilia centres for which annual consumption figures were available, Oxford's figure of 20,000 units was typical for the UK as a whole, but the Newcastle figure of 50,000 units (a region with greater home treatment) was considered more realistic for (Scottish) planning.
b. Professor Cash's figure of 2.75m iu per million population per year was '*a suitable basis for further consideration*'.

119. These production targets were also considered at a 4 March 1981 meeting of the Haemophilia and Blood Transfusion Working group.[150]

120. Professor Cash revisited demand estimates in a February 1982 paper: '*A proposal to increase the production of factor VIII concentrate in order to achieve self-sufficiency in Scotland for the next decade*'. He recorded that, '*[l]ess than 5 years ago*', a DHSS committee had advised that the '*basic needs*' of the UK's haemophilia A population could be met by producing 1 million iu of factor VIII per million population per year. The SNBTS had considered that this figure was '*more closely related to what was believed to be possible with regard to plasma procurement and the fractionation facilities of the NBTS, rather than a true estimate of what was required*'. The earlier figure had also been calculated by reference to 'basic needs' and had not taken into account the extensive introduction of home treatment or prophylaxis. Professor Cash referred to studies '*carried out in the last 6 months in Scotland*' as having revealed that a figure of 2.75m iu per million population per year would be more appropriate, described as a '*dramatic increase*'.[151] He noted that factor VIII use in Scotland for the year ending 31 March 1981 was around 1.5m iu per million population, and was thought likely to have risen to 1.7m for the year ending 31 March 1982.

[150] Meeting of Haemophilia and Blood Transfusion Working Group, 4 March 1981, **SBTS0000382_008.**
[151] Report of 'A proposal to increase the production of Factor VIII Concentrate in order to achieve self-sufficiency In Scotland for the Next Decade' by John Cash, 1 February 1982, **SBTS0000613_003**.

121. Professor Cash later commented on these demand estimates (in a July 1988 report, considered further below). He stated that it was agreed at the 30 January 1981 meeting that his proposed targets '*were acceptable and should form the basis for SNBTS forward planning*'. The targets were subsequently '*reviewed annually*' and on all occasions the SNBTS had been '*advised not to modify them*'.[152] Professor Cash added that he had been told, following the 30 January 1981 meeting, that '*these targets were not formally accepted by SHHD*'. He also reported that, in November 1981, the SHHD '*indicated that it did not wish to comment on self-sufficiency in blood and blood products*', and that he had '*consistently had the impression that SHHD considered these forecast targets to be unrealistically high*'.

122. In a 10 February 1989 letter, Jim Donald (General Manager, CSA) commented that the amount of PFC factor VIII issued since 1979 had followed Professor Cash's 1981 estimate '*remarkably closely*'.[153] Mr Donald recorded the CSA's view that the SHHD had '*never actually subscribed*' to '*the 1996 demand forecast of 2.7m*' iu per million population[154], and that the CSA's bids in 1985, 1986 and 1987 had not led to the '*required extra resource to procure more plasma*' and process it for factor VIII production.

123. In a letter written in the context of the HIV litigation, Professor Cash suggested that a significant part of the funding required to achieve self-sufficiency in Scotland was found '*through efficiency savings against our baseline funding*', and that '*[l]ittle to no support came from SHHD*'[155].

124. Similarly, in a 1990 discussion paper for SNBTS Directors, Professor Cash suggested that the SHHD did not take a formal policy position on

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[152] Report of 'Comments on the Current Difficulties in the Supply of Factor VIII for the SHS by the SNBTS and Proposals for the Reassertion of Self-Sufficiency' by John Cash, July 1988, **SBTS0000626_139**.
[153] Letter from J. T. Donald to Hance Fullerton (Grampian Health Board Aberdeen) re Transfer of Factor VIII from Northern Ireland, 10 February 1989, with enclosed graph **SBTS0000280_018 and SBTS0000280_019.**
[154] Note that Mr Donald's letter referred to demand of 2.7m iu per million population by 1996, and his enclosed graph put the figure at 2.75m, but Professor Cash's January 1981 estimate suggested the figure would rise to 3.75m units by 1996.
[155] Letter from Prof. John D. Cash to A. W. Leslie, re: HIV Haemophilia Litigation, 8 January 1990, **SBTS0000689_028**.

self-sufficiency until 5 July 1989.[156] Instead, self-sufficiency was made the SNBTS's '*operational policy by the SNBTS Directors, in isolation, in 1980. We achieved our objective in 1984 without any targeted additional resources, particularly staff resources*'. He added:

> 'Directors will be aware that on several occasions SHHD have declined to comment on proposed product targets. There can be no doubt this sustained negative managerial approach has ultimately and overwhelmingly depressed the drive and enthusiasm of many senior SNBTS managers. There must be some form of 'Main Board' for this self-sufficiency exercise and it is far from clear whether SHHD wishes or is able to fulfil this function. We need clear decisions on this matter in order to develop appropriate strategies'.[157]

[156] Paper on 'Self-Sufficiency in Blood and Blood Products - Discussion Paper for SNBTS Directors' by John Cash, undated, **PRSE0004541**.

[157] Paper on 'Self-Sufficiency in Blood and Blood Products - Discussion Paper for SNBTS Directors' by John Cash, undated, **PRSE0004541**.

5. Self-Sufficiency in Scotland and Northern Ireland: A chronology of PFC capacity and production

I. Routine operation of the PFC and working toward self-sufficiency (1973 to 1984)

Factor VIII

1973-1979

125. In December 1973, shortly before the move to the Liberton site, Mr Watt prepared a report on the development of factor VIII concentrates.[158] He described attempts over the previous year to improve the potency of PFC's product. The aim was to replace an early factor VIII concentrate (referred to as 'Fraction I AF', and sometimes described as Cohn Fraction I elsewhere), with a higher purity product. Mr Watt recorded that a '*product of intermediate type*' had been developed at a 100 litre scale. In the '*present accommodation*', and with other commitments, about 150 doses per month could be prepared, rising to about 250 doses/month if scale-up were successful. Mr Watt suggested that it would be '*prudent to emphasise the production of large stocks*' of this intermediate material before committing large resources to the development of a high potency product.

126. A quarterly report for the production of PFC products, ending on 27 September 1974, recorded that this was the last report in which AHF/Cohn Fraction I would appear.[159]

127. In a 6 January 1975 letter to Area Health Boards, Major-General Jeffrey outlined a brief history of changes to the PFC and their effect on the supply of

[158] Report on 'Development of factor VIII concentrates' by Mr Watt, December 1973, **PRSE0000678**.
[159] PFC quarterly report for quarter ending 27 September 1974, **PRSE0001471**.

blood products.[160] He recorded that a pilot plant for fractionating plasma had been established at the RIE in 1968, using a '*new small volume continuous fractionation process*', which was *'computer-controlled*' and had been invented by Mr Watt. The building of the new Liberton site had been authorised in 1969 and was in the process of being commissioned. The letter noted that it was not possible to overlap production at the RIE and Liberton, as the computer had been moved to the latter. There would therefore be a period, while the new plant was brought into production, when the supply of blood products would be reduced. However, it was not expected that this would include factor concentrates:

> '*The supply of intermediate factor VIII should not decrease markedly from that existing at present as in the terminal stages of the operation of the pilot plant a bulk stock was prepared which is now being processed into the final product, but no extension of supplies of this factor will be possible until the early summer of 1975.*'

128. An April 1975 summary report, prepared by Dr Foster, provides an insight into PFC's research and development activities at that time.[161] As well as continuing to develop '*a basic continuous fractionation unit with semi-automatic computer control*', research was ongoing into factor VIII recovery, which was expected to lead '*to a substantial increase*' in recovery of factor VIII from FFP.

129. Alongside the development of the PFC's new facilities, securing an adequate plasma supply was a key part of attempts to achieve self-sufficiency. It appears that, in this respect, Scotland's approach to the collection and use of blood donations gave it an advantage over England from the early 1970s: in particular, its use of red cell concentrates, rather than

[160] Letter from Major General Jeffrey (National Medical Director, SNBTS) to All Chief Administrative Medical Officers, 6 January 1975, **SCGV0000127_062**.
[161] Report on 'PFC Research and Development Department - A Summary Report' by P.R. Foster, April 1975, **PRSE0002008**.

whole blood, in certain transfusions. By separating and using concentrated red cells, plasma which would otherwise be transfused in whole blood could be made available for fractionation. In effect, plasma supply to PFC could increase from the same volume of blood donated in Scotland.

130. The use of red cell concentrate rather than whole blood was described in a 1973 booklet, issued by the DHSS, SHHD and Welsh Office for the NBTS and SNBTS.[162] It was noted that administering whole blood where concentrated red cells were more suitable was '*not good transfusion practice*'.

131. The contrast between Scotland and England can be seen, for example, in the minutes of the 1 May 1974 SHHD/DHSS meeting on blood products production. It was noted that the SHHD expected to achieve a *'60% use of red cells, because regions in Scotland were smaller and the task of persuading clinicians was easier than in England*'. It was said that Scottish transfusion directors had *'put in a lot of hard* work' and there had been a symposium in Edinburgh on the subject. Major-General Jeffrey stated that plasmapheresis (an alternative way of increasing plasma supply) carried some risks and was only used in Scotland for some donors.[163] Dr Maycock appeared to wish to emulate Scotland's approach, stating that he would not like to start large-scale plasmapheresis and that '*the only economical way of increasing supplies of plasma was by stepping up the use of concentrated red cells*'.[164]

132. In his 1976 paper, '*Problems of Supply and Demand*', Major-General Jeffrey recorded that around 3,000 transfusions of red cell concentrates were recorded in Scotland in 1973-1974, '*representing 35 per cent of transfusions in which red cells were included*'.[165] It was expected that this ratio would '*gradually rise with a proportionate decrease in the use of blood*'. As of December 1974, less than 10% of blood donations in England and Wales

[162] 'Notes on Transfusion', issued by the DHSS, SHHD and Welsh Office, 1973, **HCDO0000861**.
[163] Minute of Blood Product Production Meeting, 1 May 1974, **DHSC0103209_066**.
[164] Minute of Blood Product Production Meeting, 1 May 1974, **DHSC0103209_066**.
[165] Journal Article on 'Problems of Supply and Demand' by H.C.Jeffrey, 1976, **RCPE0000314_002.**

were used in the form of concentrated red cells, compared with 30-40% of donations in Scotland.[166]

133. At an 11 June 1975 meeting of SNBTS Directors, it was noted that targets of a 40% minimum use of concentrated red cells by 30 September 1975, and 50% by 31 March 1976, had in some cases already been reached or exceeded. When considering long term plasma requirements, Directors were '*of the opinion that plasmapheresis should not be introduced as a method of obtaining normal plasma at present*'.[167]

134. Despite being given further consideration at points – for example, in a February 1982 report from Professor Cash[168] – there is little evidence to suggest that the routine use of plasmapheresis gained significant support in Scotland in the 1970s and 1980s. In a report submitted to Penrose, Dr Foster stated that funding for the routine collection of normal plasma by plasmapheresis was not available to the SNBTS until 1990.[169]

135. It appears that, in the mid-1970s, ensuring that sufficient quantities of plasma were sent to the PFC was of particular importance in enabling a move from cryoprecipitate to concentrates. A paper prepared by Major-General Jeffrey for the 11 June 1975 SNBTS Directors' meeting recorded that the '*main concern*' was the '*supply of FFP for Factor VIII so that a stockpile can be built up before a changeover from cryoprecipitate to intermediate factor can be planned*.'[170] To facilitate increased plasma supply, the meeting agreed that the five Scottish regions would set their supply targets for 1975 to 1978 in accordance with guidelines prepared by Professor Cash, which suggested

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[166] Letter by B Gidden (DHSS) to Regional Administrators, re: PFC inclusion in Blood Products Production, 24 November 1974, CBLA0000239.

[167] Minutes of SNBTS Directors Meeting, 11 June 1975, **PRSE0003812**, pg. 4.

[168] Dr J Cash, 'A proposal to increase the production of Factor VIII concentrate in order to achieve self-sufficiency in Scotland for the next decade', 1 February 1982, **SBTS0000613_003**, pg. 6

[169] Report on 'Scottish National Blood Transfusion Service Self-Sufficiency and the Supply of Blood Products in Scotland' by P R Foster, February 2011, **PRSE0001083 p.34**.

[170] SNBTS paper on 'Regional Intake and Utilisation of Blood 1974-75 and the Supply of Plasma to PFC, 11 June 1975, **SBTS0000098_031**, para 7.

that regional targets should be based on a basic maintenance figure of 12,000 donations per million population per annum.[171] The annual targets ranged from 2,400 donations in Inverness to 34,800 donations in Glasgow.

136. A detailed discussion of supply and demand for PFC factor VIII took place at a 14 November 1975 meeting of SNTBS and Haemophilia Directors.[172] The minutes refer to an earlier agreement to '*look again at the possibility*' of releasing factor VIII to haemophilia centres before a '*stock target of 1,000,000 units had been reached*'. Major-General Jeffrey had agreed with Mr Watt that reserves could be held at RTCs rather than the PFC, but there had been a delay in distribution. Despite 1,115,000 units having been issued by the end of September 1975, some Haemophilia Directors were concerned about security of supply. The meeting was '*assured that supplies would be secured if the present average level of plasma intake at the PFC continued*'. Nonetheless some concern was expressed about the amount of plasma being supplied to PFC. In particular, there had been '*an enormous increase in the West in the demand for cryoprecipitate and this had meant that little fresh frozen plasma was going to the PFC.*' At this stage, '*the real problem ... was the limited quantities of fresh plasma available rather than the production potential of the PFC*'.

137. It was suggested at the meeting that, during the potentially lengthy shift from cryoprecipitate to concentrates, commercial products be considered. There was agreement to keep the SHHD's policy under review, but Major-General Jeffrey '*expressed himself as against the purchase of commercial material unless for a particular patient; he was against its use as a routine treatment*'. He also expected the '*present difficulty*' in supply to be short-lived, and to last for about 6 months to a year.[173]

[171] Annex on Fresh Plasma Processing for Factor VIII, 1975, **SCGV0000065_117**.
[172] Minutes of SNBTS Directors and Haemophilia Directors Meeting, 14 November 1975, **PRSE0002823**.
[173] Minutes of SNBTS Directors and Haemophilia Directors Meeting, 14 November 1975, **PRSE0002823**.

138. Similar points were made at a 17 December 1975 SNBTS Directors' meeting, held at the PFC.[174] As well as recording the amount of factor VIII concentrate recently issued to RTCs, it was noted that '*a small stock held at PFC would be available to Directors in emergencies*'. Major-General Jeffrey asked Directors '*seriously to consider reducing their preparation of cryoprecipitate. It was agreed that, in the West at least, the ability to do so depended on the acceptability to clinicians of intermediate Factor VIII*'. It was agreed that a study into the comparative yields of cryoprecipitate and concentrate would be undertaken.

139. At an 11 March 1976 meeting between representatives of BPL and the SNBTS, concerning factor VIII production, it was noted that for both England and Wales and Scotland, the '*main factor*' was the '*availability of fresh plasma*'. The production target for Scotland was around 4.5 million iu (equating to 10,000-12,000 units/year for each of Scotland's 420 haemophilia A patients).[175] The minutes record that the PFC had been processing sufficient amounts of plasma to meet this target for several weeks, using stockpiled plasma held in cold storage, but that the supply of FFP coming in was dropping. This was mainly due to a drop in supply from the West of Scotland, which was '*partially the result of a greater demand*' for cryoprecipitate. It was also said to be '*just possible*' that this drop was '*encouraged ever so slightly and perhaps unconsciously by the transfusion centre whose staff get some satisfaction out of making this product*'. Overall, it was thought that the yearly factor VIII target could '*easily be met given sufficient FFP*' – there was '*ample manufacturing capacity*' at the PFC.[176]

140. Concerns around plasma supply, as well as the effect of home therapy on demand, were reiterated in a 23 August 1976 letter from Mr Watt to Major-General Jeffrey. Mr Watt expressed his fear that the '*current plasma*

[174] Draft policy entitled 'Blood Products: Joint DHSS/SHHD Production Policy', undated, **PRSE0002061.**
[175] Note of Factor VIII Production Directors Meeting, 11 March 1976, **SCGV0000114_023**.
[176] Note of Factor VIII Production Directors Meeting, 11 March 1976, **SCGV0000114_023**.

supply situation' was such that '*almost every unit dose of intermediate concentrate is committed to a home therapy programme long before it is issued*'. He explained that the supply of plasma to PFC came largely from Edinburgh, accounting for 53% of the total plasma intake, with roughly 15% each provided from Dundee, Glasgow and Inverness. He advised that the intake of fresh plasma should support the production of about 1.8 million units of AHF per year, which approached '*50% of the national requirement*'. It was Mr Watt's impression that the national plasma intake had increased, but that the increased issue of intermediate factor VIII had '*not produced the expected reduction in the demand*' for cryoprecipitate.[177]

141. Annex A, based on data from Scottish Haemophilia Centre annual returns, shows that 1,265,993 units of cryoprecipitate were used in Scotland in 1976, compared to 1,314,747 units of NHS factor VIII concentrate and 174,744 units of commercial concentrate.

142. A summary of Scotland's attempts to achieve self-sufficiency, as of the mid-1970s, can be found in the SNBTS annual report for 1975-1976.[178] In an introductory section, the report commented that '*[o]f all the blood products available, the only one which has aroused an emotive response in the UK (Scotland is less vociferous) is the supply of Factor VIII and its use in the treatment of haemophilia*'. It was noted that cryoprecipitate remained the '*mainstay in treatment at present*' and that the use of PFC's intermediate concentrate was '*particularly suitable for home therapy*'. The report recorded that issues of cryoprecipitate in 1975-76 had increased by 13% over the previous year. This represented, '*at the average yield claimed by centres, 2.38 million units of FVIII*'. The amount of intermediate concentrate which had been issued represented 0.82 million units. This gave a total of 3.2 million units. It was noted that the effects of issuing concentrate were '*slowly appearing*', and that the amount of cryoprecipitate being issued had decreased in the first

[177] Letter from John Watt to Major-General Jeffrey re: Factor VIII Concentrate Inverness, 23 August 1976, **SBTS0000303_101**, pg.1
[178] SNBTS Annual Report 1 April 1975 to 31 March 1976, 1976, **PRSE0002133**.

quarter of 1976-77. This had not yet been reflected in any material increase in FFP received by the PFC, '*whose production capacity for fractionating Factor VIII is limited solely by the FFP intake*'. The report's targets for 1977-78 included: '*at least 90% of cryoprecipitate is replaced by concentrated factor VIII*.'

143. The report added the following comment, suggesting that self-sufficiency in blood products for haemophilia A patients was understood not to be limited to concentrates:

> 'As regards self-sufficiency, Factor VIII is available to treat adequately the known haemophilia population in Scotland. The form in which it is available does not as yet meet the major demand for home therapy. Present policy is to issue intermediate factor to centres, with only a very small national reserve at the PFC; Directors of haemophilia and regional transfusion centres are expected to maintain their own reserves and patients should be introduced to home therapy only when an adequate reserve – three months' anticipated use – is available for each individual in case the PFC meets manufacturing difficulties.'

144. As for PFC's operation, the report recorded that commissioning was '*virtually complete*' and production figures were '*rising for all products where plasma supply is adequate. Full production to meet Scottish needs is now in sight (provided appropriate plasma is forthcoming from regional centres).*' As for the relationship between staffing and operational capacity, the report added:

> 'The PFC was planned to fractionate plasma for part of England's needs and staff have been recruited and trained on the accepted principle that, in due course, small evening and night shifts be instituted. The time for this has now come, but unacceptable trade union proposals have prevented this. The PFC can cope with Scottish

needs on a day staff only basis, but the absence of the shifts decreases cost-effectiveness and precludes acceptance of plasma from furth of Scotland.'

145. Some of the obstacles preventing an increase in PFC's production, in particular the shift-working issue, were addressed in an October 1977 paper, prepared by the SHHD for the Civil Service Department in London.[179] The paper set out the background to the construction of the Liberton facilities and the relationship between production in Scotland and the rest of the UK. Given the investment in PFC to enable it to operate a continuous flow process on a 24-hour basis, its single-shift system was described as '*a quite unacceptable waste of resources*'. The reasons why a multi-shift system had not been introduced were described. These included that, because the PFC was '*classed as an NHS laboratory, the introduction of such a system is seen as having wide-ranging implications within the Health Service, and the unions involved are unwilling to negotiate such a system for staff who are regarded as being on normal Whitley gradings without raising the wider question of a shift system to cover these grades as a whole*'. The paper described a proposed system for PFC employees, designed by the CSA, which the SHHD wished to discuss further. Negotiations on the introduction of a shift system during the first half of 1976 with the relevant trade unions were said to have made little progress.[180]

146. While the PFC building was designed to have enough capacity to process some English as well as Scottish plasma, PFC's production capacity may have been held back by equipment as well as staffing. In his Inquiry witness statement, Dr Foster comments that the design capacity of the PFC incorporated processing for England and Scotland but that equipment and staffing was only provided for meeting Scotland's needs at that time. '*This*

[179] Letter from David Stevenson (SHHD) to A U Eason (Civil Service Department, Whitehall), re: PFC Extra Duty Working, 28 October 1977, **DHSC0003715_177** and Report on 'Protein Fractionation Centre, Edinburgh', 1977, **DHSC0003715_178.**
[180] Report on PFC, undated, **DHSC0003715_178**, pg.3, para 10.

included 6 continuous-flow modules', despite the design allowing for up to 15 continuous-flow modules to be operated.[181]

1980-1982

147. By 1980, the amount of factor concentrate issued by the PFC had increased significantly. As shown in Annex A, the total quantity of PFC Factor VIII concentrate used by Scottish Haemophilia Centres increased from 1,747,197 iu (1979) to 3,866,851 iu (1980).

148. On 1 December 1980, at a meeting involving the SHHD, DHSS, DHSS (NI) and the Welsh Office, it was recorded that '*Scotland was almost self-sufficient (e.g. 5½ million ius of Factor VIII were currently produced and one million ius purchased commercially)*'.[182] This statement was qualified by reference to a need to consider Northern Ireland's requirements. It was also suggested that, in the short term, the PFC could fractionate an extra 500 litres of FFP per week to produce factor VIII and albumin. In the longer term, '*it was considered that PFC could cope with up to 1500 litres per week, and perhaps more provided funds were made available and provided agreement could be reached on shift working. SHHD intended to give the go ahead early in the new year to an experimental 3-4 week shift run to assess how the PFC would cope with the system*'.

149. Around this time, changes were being made to PFC's distribution arrangements. In his Inquiry witness statement, Dr Perry records his understanding that a pro-rata system for allocating PFC products was established in the late 1970s. He understood this to be intended partly to '*provide an equitable system for PFC product distribution to RTCs*', but also to incentivise RTCs to increase their plasma supply to the PFC, including by encouraging the use of packed (i.e. concentrated) red cells instead of whole

[181] Dr Foster Witness Statement to IBI, **WITN6914001**, p.151.
[182] Minutes of SHHD, DHSS, DHSS (NI) and Welsh Office Meeting, 1 December 1980, **DHSC0000064**.

blood. '*This system was therefore based on RTC performance rather than national clinical need*'.[183]

150. The PFC's approach to distributing factor VIII as of February 1980 was described in a letter from Mr Watt (concerning Dr Ludlam's attempts to secure greater quantities of factor VIII for the Edinburgh Haemophilia Centre):

> 'The present situation regarding the distribution of Factor VIII to regional centres from the Protein Fractionation Centre is that as each pool comes to be ready for issue, we place 10% in the national stockpile to be available for emergency purposes and the remainder is distributed to regional centres in a proportion which has been agreed by Directors. This is roughly according to the distribution of population in the various regions but with a slight bias in favour of Inverness where the geography of the region makes a more widespread utilisation of home therapy a rather necessary fact of life.
>
> This arrangement is not entirely equable [sic] since, of course, Haemophiliacs are not distributed equally in the regions and the input of fresh frozen plasma to the PFC is far from equable in rate. However, that is how matters stand'.[184]

151. This system was adjusted later in the year. In a 19 December 1980 letter to Professor Cash, Mr Watt explained that, from 1 January 1981, factor VIII would be allocated monthly as follows: the first 15% would be placed in a national (i.e. Scottish) reserve; a specific amount would be set aside for Inverness; and proportionate amounts would be allocated to the four other regions. Should a region require more factor VIII one month, this would be '*seen as a deficit against the following month(s) unless the extra issue is necessary to meet unexpected emergency demand which would be a*

[183] Dr Perry Witness Statement to IBI, **WITN6920001**, pg.53, para 159.
[184] Letter from John Watt to Dr Frank E Boulton, re: Distribution of Factor VIII, 5 February 1980, **PRSE0004005**.

legitimate call on the National Reserve".[185] Mr Watt suggested this arrangement '*should correct the serious disparities which have developed in relation to Aberdeen and build the National Reserve in advance of the shift experiment*.'

152. The growth in PFC's production of factor concentrates in the early 1980s appears to have been due partly to increased plasma supply, and partly to improvements in manufacturing techniques. Some of these techniques had been outlined in a January 1976 PFC project proposal.[186] A continuous thawing method was described in a September 1978 letter from Dr Foster and a PFC colleague to the Lancet.[187] Dr Foster's Inquiry statement explains that procedures implemented between 1976 and 1981, including continuous thawing, increased factor VIII yields by about 50% by 1981.[188] Further detail on PFC's plasma thawing method can be found in a 1982 article by Dr Foster and others in Vox Sang.[189]

153. Around this time, changes to the PFC's facilities were also being implemented as a result of inspections by the Medicines Inspectorate. It appears that these began in 1979, with a first report in January 1980, followed by further visits and an updated report in October 1981. This report found that, while there had been some improvements, there remained a number of areas in which progress was still not adequate, including: inadequate space in some production and storage areas; unsatisfactory processing conditions; unsatisfactory work flow patterns, which could lead to product mix-up; and unacceptable staff movements through production areas, which could lead to contamination of components and product. Concerns relating to documentation were also highlighted. Overall, the report concluded: '*The*

[185] Letter from John Watt to Dr Cash, re: Distribution of Factor VIII in Scotland, 19 December 1980, **PRSE0002207**.
[186] Report on 'The Isolation of FVIII Project Proposal' by S Middleton et al., January 1976, **PRSE0002225**.
[187] Article on 'Thaw-Siphon Technique for Factor VIII Cryoprecipitate' by Peter Foster and Barry White, 9 September 1978, **PRSE0001426**.
[188] Dr Foster Witness Statement to IBI, **WITN6914001**, p.21.
[189] Article on the 'Control of Large-Scale Plasma Thawing for Recovery of Cryoprecipitate Factor VIII' by Dr Foster et al., 1982, **PRSE0003156**.

present buildings and facilities continue to fail to reach minimum standards of GMP [i.e. Good Manufacturing practice]*, and a licence would not be recommended for an industrial equivalent unless agreed upgradings were instituted as a matter of urgency*'.[190]

154. The following phases of development were subsequently agreed with the Inspectorate:

a. Phase I: Provision of additional laboratory space and pilot plant facility.
b. Phase II: Upgrading of specific production areas and creation of new areas with local filtration.
c. Phase III: Provision of a production area extension to incorporate specialist warehousing and limited additional production facilities.
d. Phase IV: To facilitate the integration of functions of phase III with the existing production facilities.[191]

155. In a January 1981 paper, prepared for a meeting of SNBTS and Haemophilia Centre Directors, Professor Cash reiterated that '*the aim of the SNBTS is to eliminate the necessity for the purchase of Factor VIII concentrates from commercial concerns*'.[192] The document set out figures from 1975 to 1980, showing an increase in the amount of FFP processed for factor VIII concentrate and a significant increase in the amount of intermediate factor VIII issued by the PFC (from 110,000 units in 1975 to 1,990,000 units in 1980). Overall, the figures for cryoprecipitate had decreased, though with variation between years. The figures also showed that the SNBTS's aim had not yet been achieved: 850,000 units of commercial concentrate had been purchased in 1979 and 1 million in 1980.

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[190] Medicines Inspectorate Report on the Current Status at the Protein Fractionation Centre, Edinburgh as of October 1 1981. Inspectors - D Haythornthwaite and K J Ayling, **PRSE0004516.**
[191] Report on 'Phase II(a) and Beyond' by Robert J Perry and Professor Cash, April 1984, **PRSE0001300,** pg.3.
[192] Notes for Scottish Health Service Haemophilia Centre - Transfusion Service Directors' Meeting, January 1981, **CBLA0001252**.

156. Annex A shows that use of cryoprecipitate in Scotland had reduced significantly by this time, from 1,558,560 units in 1980 to 983,460 units in 1981. However, commercial concentrate use remained in the region of 700,000 iu to 958,000 iu.

157. At a 4 March 1981 meeting of the Haemophilia and Blood Transfusion Working Group, concern was expressed '*at the level of commercial material being purchased and it was agreed that the aim must be for the NHS in Scotland to be self-sufficient. This could be achieved with good planning, and steps had been taken to improve the input of plasma*'. Professor Cash suggested that self-sufficiency included '*the provision of a reserve stock capable of meeting unexpected demands such as a temporary failure at PFC*'. Professor Cash's figure of 2.75 million iu of factor VIII per million population per year was agreed as a reasonable target.[193]

158. The importance of a reserve stock of factor VIII was revisited in late 1981 at a meeting of the SNBTS Directors: it was agreed that '*the concept of self-sufficiency implied uninterrupted supply and that, generally, the national stock should consist of 12 months' usage of products, labelled and ready for issue*'.[194] The Directors noted that the SNBTS factor VIII production target of 2.75 million units per million population per year contrasted with an NBTS target of 2 million.

159. It appears that, by August 1981, plasma supply was reaching the limit of PFC's operational capacity. In a 20 August 1981 memo to Mr Watt, Alan Dickson (Manufacturing Manager) referred to an estimated 25% growth in supply of FFP in six months. If this growth was sustained, the capacity of the '*Usifroid*' (a freeze drier) would be exceeded '*fairly soon*'. He suggested that

[193] Minutes of Haemophilia and Blood Transfusion Working Group, 4 March 1981, **SBTS0000382_008**.
[194] Minutes of SNBTS Directors Meeting, 8 December 1981, **PRSE0003364**, pg.3.

the PFC would '*not be able to maintain throughput*' without both of its freeze-drying machines '*functional at all times*'.[195]

160. These limitations continued into early 1982. In a 17 February 1982 letter to Professor Cash, Mr Watt described a '*slowly gathering difficulty because of freeze-drier limitation*'. The drier capacity for FFP was limited to 720 kg per week and PFC was receiving 700kg per week. For a number of reasons, including lots which had been missed during the shift-working trial, the stock of plasma held at PFC had increased. Steps were being taken to increase capacity, including a new shelf in the drier and the correction of a fault, which were expected to increase plasma process capacity to '*about 2000kg per full two week period*' (i.e. about 1,000 kg per week).[196] Mr Watt proposed that stocks in the South East and West of Scotland RTCs be kept lower while the PFC '*built up the national stock*'. He commented: '*over the period of perhaps 15 months to come it will be necessary to keep very close attention to all factor VIII reserves, regional and national because, to build up such a stockpile and try to minimise purchase, we shall need to work as close to the safe margin as possible.*'

161. The supply of plasma to PFC increased again as a result of Scotland's arrangements with Northern Ireland. An April 1982 minute recorded Mr Watt's expectation that Northern Irish plasma would arrive in August, and that it would necessitate the introduction of a two-shift system.[197]

162. Concerns over PFC's ability to meet demand for factor VIII and maintain a stockpile of product continued through the remainder of 1983. On 30 September 1982, Mr Watt wrote to Dr Hopkins (Glasgow and West of Scotland RTC) regarding the re-allocation of material to the national stock, referring to the '*perilous state of Factor VIII supply*". He pointed to factors

[195] Memo from Alan Dickson (Manufacturing Manager of PFC) to John Watt, Re: Fresh Plasma Receipt, 20 August 1981, **SBTS0000472_113.**
[196] Letter from John Watt to Dr J.D. Cash, re: Supply of Factor VIII, 17 February 1982, **PRSE0002316**.
[197] Memo from M P Sivell to Mr Sinclair re: Future Expansion of PFC, 7 April 1982, **SCGV0000104_101**.

including a lower than expected yield which resulted in overstated PFC calculations, as well as the loss of a lot of 750 vials.[198]

163. Similarly, in a 4 November 1982 letter to Professor Cash, Mr Watt explained that the PFC would be able to meet '*foreseeable supply at the existing level but with no margin*'. He noted that PFC had been '*saved from a period of acute shortage entirely by the generous 'gift' of 2 000 doses to the national stock from the West of Scotland*'. Mr Watt referred to the arrival of a '*new freeze-drier*', which would allow some plasma stock to be cleared '*before the flood of SAG(M) plasma begins to arrive*'.[199] He had hoped that this increased capacity would '*reflect the beginning of a stockpile so we could weather the lean times ahead*'.[200]

164. Annex A shows that, at the time of this correspondence, Scottish Haemophilia Centres continued to use commercial concentrates: over 500,000 units of commercial factor VIII were administered in 1982.

Freeze-dried cryoprecipitate

165. Alongside these developments in the production of factor VIII, some exploration of freeze-dried cryoprecipitate as an alternative to concentrate took place in the early 1980s in Scotland. This product, which could be prepared in pool sizes of between 10 and 30 donations, has been explored in other evidence obtained by the Inquiry: see, in particular, the statement and oral evidence of Dr Gamal Gabra of the Glasgow and West of Scotland RTC.[201] The following is a brief summary of relevant documents in the context of PFC's development of factor concentrates.

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[198] Letter from John G Watt to Dr D Hopkins, re: Shortfall in Factor VIII supply, 30 September 1982, **PRSE0000408**.

[199] The role of SAG-M in Scotland is described in Annex E.

[200] Letter from John G Watt to Dr John Cash, re: Pro-rata supply of Factor VIII, 4 November 1982, **PRSE0000496**.

[201] Written Statement of Dr Gamal Gabra, 16 December 2021, **WITN5495001**. See also the transcript of Dr Gabra's oral evidence to the Inquiry on 3 February 2022.

a. Proposals to develop freeze-dried cryoprecipitate appear to have originated from the Glasgow and West of Scotland RTC, and Mr Watt was strongly opposed to them from the start. In a December 1980 letter to the RTC's Director, Dr Mitchell, he described the preparation of the product as 'a *step back in history'*.[202]

b. At a 4 March 1981 meeting of the Haemophilia and Blood Transfusion Working Group, Professor Cash outlined proposals for a multi-centre study of freeze-dried cryoprecipitate.[203] He suggested that there were '*two factors in favour of cryoprecipitate (a) the increased yield and (b) the increased pool size, although there was a school of thought in the UK that the larger pool may increase the risk of hepatitis*'. Dr Foster is reported to have said that the PFC did not have the resources to take part, and it was noted that a trial was already underway in the West of Scotland. While Dr Ludlam expressed an interest in participating, it was decided that the trial would be confined to the West of Scotland.

c. Mr Watt continued to express his opposition to the development of freeze-dried cryoprecipitate, and in particular to any suggestion that it be prepared at the PFC. In a 5 April 1982 letter to Professor Cash, he described the product as '*a contradiction to the GMP guidelines*'.[204] He suggested that producing it at the PFC would not be possible until after work resulting from inspections by the Medicines Inspectorate had been carried out, and even then '*only if special space provision is included*'. Mr Watt also questioned whether freeze-dried cryoprecipitate was in fact a safer and higher yield product than PFC concentrate. If it was to be produced, it should continue to be in the West of Scotland; *'[i]n the meantime PFC should continue to develop safer products for haemophilia treatment to make sure that a better-oriented GMP approach is possible*'.

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[202] Letter from Mr Watt to Dr Mitchell, re: Freeze-dried cryoprecipitate development in Scotland, 9 December 1980, **PRSE0000840**.
[203] Minutes of Haemophilia and Blood Transfusion Working Group Meeting, 4 March 1981, **SBTS0000382_008**.
[204] Letter from Mr Watt to Professor Cash, re: Freeze dried cryoprecipitate, 5 April 1982, **SBTS0000269_005**.

d. Mr Watt returned to some of these points in a 25 October 1982 letter to Professor Cash.[205] He added that, while it would be '*some time before PFC can issue a properly pasteurised product … at least we now know how to get at such a material and major effort is being expended in getting it to a practical stage*'. Mr Watt suggested that producing freeze-dried cryoprecipitate would be '*dangerous*', in that it would result in '*several breaches of the policy of GMP*' and would make '*logical operation of PFC difficult*'; and that it would be expensive, because it would require a separate area and equipment.

e. Further production of freeze-dried cryoprecipitate appears to have been abandoned soon thereafter. At a 21 January 1983 meeting of SNBTS and Haemophilia Directors, Professor Cash described the West of Scotland clinical trial as successful but explained that, '*[n]otwithstanding this work, it had been decided to abandon production of FDC meantime, having regard to the closure of the plasma freeze drying plant at Law and the cost of meeting the standards demanded by the Medicines Inspectorate*'.[206] Further, the '*prospective availability of a hepatitis risk reduced factor VIII concentrate*' was said to '*cast uncertainty over the future of FDC at the present time*'.

1983-1984

166. By 1983, the position on stocks of PFC factor VIII appears to have improved. In an 18 March 1983 letter to Professor Cash, Mr Watt proposed a review of changes to PFC's distribution system. He recorded that the '*plan of last year was that we should abandon 'pro rata' in the absolute sense and revert to a pattern of distribution established in October 1981 so that a stockpile should accrue at PFC against expected lean times associated with renovation*'. With the exception of South-East Scotland, all regions had '*established a reasonable stock of Factor VIII*'. The quantity of '*material in*

[205] Letter from Mr Watt to Professor Cash, re: View on freeze dried cryoprecipitate, 25 October 1982, **SBTS0000269_003**.
[206] Minutes of SNBTS Director Meeting, 21 January 1983, **PRSE0001736,** pg.3.

process' had risen from 6,000kg to 18,500kg of plasma during 1982. The national stock of factor VIII held at PFC was not labelled or packaged but '*could be brought to issue very quickly if needed*'. For 1983-84, Mr Watt proposed that the PFC '*start the year by issuing Factor VIII in the proportions of plasma received at PFC in October-December 1982*'.[207]

167. By the time of a 24 May 1983 meeting of the SNBTS Co-ordinating Group, plasma supply had continued to grow and the PFC was having difficulty processing it all.[208] The minutes record that '*the PFC had received a record input of 61,000 Kg of plasma in the year to 31 March, 1983*'. Mr Watt had suggested periodic spells of shift working to clear the stockpile, as with '*the existing staff levels and technology only 50,000 Kg could be processed*'. Professor Cash referred to attempts to arrange temporary shift working, and the meeting acknowledged *'the difficulties which would confront those attempting to negotiate a permanent shift agreement for PFC and appreciated that it may be necessary to have an interim arrangement'*.

168. Notwithstanding this increase in plasma supply, supply issues appear to have existed in the South East and Edinburgh region in early 1983. These were discussed at a meeting of SNBTS Directors on 21 January 1983, with Dr Ludlam expressing '*some misgiving that Edinburgh perhaps did not receive as much PFC Factor VIII concentrate as it should pro-rata*'. Professor Cash emphasised that the pro-rata system '*was not intended to be applied inflexibly and that products could be transferred between regions in the event of a local shortage*'.[209]

169. The supply position in Edinburgh and the South-East led Dr Ludlam to enter into an agreement, in early 1983, for the exchange of commercial concentrates for PFC products with the Belfast Haemophilia Centre.[210] In a

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[207] Letter from John G Watt to John D Cash, re: Pro-rata and SNBTS Stockpile, 18 March 1983, **PRSE0004811**.
[208] Minutes of SNBTS Co-Ordinating Group Meeting, 24 May 1983, **PRSE0003620.**
[209] Minutes of SNBTS Director Meeting, 21 January 1983, **PRSE0001736**, pg.3.
[210] Letter from Dr Ludlam, Edinburgh Royal Infirmary to Dr. D. McClelland Edinburgh and South East Scotland BTS, 11 January 1984, **LOTH0000005_085.**

later letter to Dr Brian McClelland on the subject, Dr Ludlam wrote that the agreement was entered into because at that time, SNBTS factor VIII was '*in very short supply*'. He explained that the '*first part of the exchange arrived shortly after the negotiations and at the time SNBTS material markedly improved*'.

170. This arrangement appears to have been concluded by late 1983 or early 1984. In a 30 December 1983 letter to Dr Ludlam, Dr Brian McClelland noted that Edinburgh and the South-East was '*continuing to receive substantial quantities of PFC Factor VIII from Belfast*'. Dr McClelland noted that the region's stock level of PFC factor VIII was low, but that the SNBTS had '*at present very healthy*' stock levels. He queried whether the exchanges with Belfast remained necessary.[211] In response, on 11 January 1984, Dr Ludlam described the background to the agreement and stated: '*The material that has arrived recently just completes the exchange. As I understand it we are now quits with Belfast*'.[212]

171. This arrangement seems to have been implemented by Dr Ludlam and Dr Mayne without Professor Cash's knowledge. In a 5 January 1984 letter to Dr Mayne, he wrote:

> 'Through colleagues here at our Protein Fractionation Centre I have discovered that there has been a fairly substantial movement of commercial Factor VIII, purchased in Edinburgh (we think) and shipped to you in exchange for the PFC material you have received via Dr M McClelland.

[211] Letter from Dr. D. McClelland, Edinburgh and South East Scotland BTS, to Dr. Christopher Ludlam, Royal Infirmary Edinburgh, 30 December 1983, **LOTH0000005_071**.
[212] Letter from Dr Ludlam, Edinburgh Royal Infirmary to Dr. D. McClelland Edinburgh and South East Scotland BTS, 11 January 1983, **LOTH0000005_085.**

Am I right? If so, could you illuminate? On the face of it this development looks a little worrying - AIDS etc. - and I'm anxious to help as much as possible'.[213]

172. To date, the Inquiry has been unable to identify additional contemporaneous evidence which would cast further light on this arrangement between Edinburgh and Belfast. More documentation is available in respect of a similar exchange in the late 1980s, described further below.

173. A number of reports suggest that – by at least some measures – Scotland had achieved self-sufficiency in Factor VIII concentrates by late 1983 or early 1984. One report asserted that it was earlier than that. In a 4 July 1983 letter to Professor Cash, announcing his resignation as PFC's Scientific Director, Mr Watt wrote that Scotland had become '*the first country in the world to be truly self-sufficient in plasma fractions*'.[214]

174. In an 18 November 1983 internal PFC memo, Dr Perry highlighted a concern that Factor VIII stocks were such that there was a risk of product becoming out-of-date.[215] He noted that the PFC held a stockpile of around 7 million units, compared to 5 million units the previous year, commenting that '*presumably this increase in stockpile represents our present excess annual output over and above the present demand*'. In his oral evidence to Penrose, Dr Perry stated that it was his view at the time that there was more than enough product to '*meet effectively the unconstrained needs of the haemophilia population in Scotland*'.[216]

175. Various other sources suggested, around this time, that Scotland had achieved self-sufficiency in factor VIII concentrate, or had nearly done so. For example, a September 1983 press release by the Scottish Office press

[213] Letter from John D. Cash, SNBTS, to Dr. E Mayne, Royal Victoria Hospital, 5 January 1984, **NIBS0001714**.
[214] Letter from Mr Watt to Dr Cash, re: Resignation and PFC, 4 July 1983, **PRSE0004211.**
[215] Memo from Dr Perry to Mr Watt et al. re, Factor VIII supply and demand, 18 November 1983, **PRSE0001576**.
[216] Penrose Inquiry Transcript of Dr Robert Perry, 13 May 2011, **PRSE0006025**, page 22.

asserted: '*Scotland is self-sufficient in whole blood and* ***virtually so*** *in blood products*' (emphasis added).[217] In January 1984, at a meeting with the CBLA, Professor Cash referred to '*indications*' that self-sufficiency in Scotland had '*virtually been achieved*', and that, '*in the near future, Factor VIII could be produced by the PFC in excess of clinical demand*'. He '*wondered whether arrangements could be made for the Scottish surplus, when achieved, to be used to augment the English/Welsh supply*', a proposal which was welcomed by Mr Smart of the CBLA.[218]

176. According to a note of the 9 February 1984 NIBSC meeting on AIDS, prepared by the pharmaceutical company Alpha, Professor Cash stated that '*Scotland is now totally self-sufficient*' in factor VIII.[219] A January 1988 response to a Parliamentary Question, prepared by the SHHD for Michael Forsyth (Parliamentary Under-Secretary of State, with responsibility for Health), noted that Scotland had been self-sufficient in '*blood and all normally required blood products since the end of 1983*'.[220] Similarly, the 1987 SNBTS Public Expenditure Survey stated that Scotland achieved self-sufficiency in blood and blood products in early 1984.[221]

177. Despite self-sufficiency apparently having been achieved, it appears that some commercial concentrate continued to be purchased or used in 1983 and early 1984. In his January 1984 report for a Scottish Haemophilia Centre and Transfusion Service Directors' meeting, Professor Cash wrote that '*[c]linical colleagues may wish to note that there is increasing evidence (which will be fully analysed in mid-April 1984) that the SNBTS production of factor VIII concentrates may be exceeding clinical demand.*' He added: '*Subject to the satisfactory clinical acceptability of the SNBTS product range, the current production level of SHS* [i.e. Scottish Health Service] *material is such that*

[217] Press Notice by SHHD entitled 'Information Leaflet on AIDS Issued', 1 September 1983, **PRSE0002778**.
[218] Minutes of CSA to CBLA Meeting, 20 January 1984, **PRSE0002588**.
[219] Letter from M. Carr (Alpha) to B. Blomstrom et al. re: Members of the Operations Committee, regarding a meeting on AIDS held on 9 February 1984, 21 February 1984, **CGRA0000610**, pg.2.
[220] Written Answer by Mr Michael Forsyth to a Parliamentary Question from Mr Tony Worthington, 25 January 1988, **SCGV0000035_061**.
[221] SNBTS Public Expenditure Survey, 1987, **PRSE0003941**, pg. 3.

there no longer appears to be a need for commercial purchase of human Factor VIII concentrates'. Professor Cash invited his clinical colleagues to comment on why commercial concentrates continued to be bought, while stating that it was probable that these purchases occurred prior to Scotland achieving self-sufficiency.[222]

178. Professor Cash's paper was discussed in some detail at the meeting itself, on 2 February 1984.[223]

a. Attendees '*agreed that it was desirable to stick to the target production figure of 2.75 million iu per annum/million total population, and that the existing stocks required to be held for sudden demands which could be made in the service, and to bridge the period the PFC would be converting to a heat treated product*'. If surplus factor VIII '*became a reality other parts of the UK could be asked if they wished to make use of the product in preference to purchasing from other sources*'.
b. The meeting also discussed the production of and use of cryoprecipitate, particularly in light of '*the new danger of AIDS*'. It was agreed that '*a certain minimal amount of cryo was required and Dr Cash pointed out that TDs* [i.e. Transfusion Directors] *could produce it in emergencies*'.
c. Professor Cash asked attendees to consider whether, given the production level of Scottish factor VIII, '*it was necessary to purchase commercially unless exceptionally a superior product was available*'. Dr Ludlam said that he required '*a small stock of high purity commercial material for a very few patients*'.
d. Dr Bell (of the SHHD), '*emphasised that the aim of the SNBTS and of national policy was for Scotland to be self sufficient, and although the Department would not wish to intervene in what clinicians prescribed, it*

[222] 'Notes for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1984, January 1984, **PRSE0004741**.
[223] Minutes of SNBTS and Haemophilia Director Meeting, 2 February 1984, **PRSE0001556.**

was not sensible to purchase imported material when suitable NHS product was available'.

179. The figures in Annex A suggest that, by 1984, the use of commercial factor VIII in Scotland was at a very low level. Commercial concentrate use increased until 1980, before decreasing year on year to 1984. In 1983, 387,850 units were used, dropping to 46,810 units in 1984. By 1985, Scottish Haemophilia Centres recorded no use of commercial concentrates.

180. Annex B shows that Northern Ireland's use of commercial factor VIII dropped following the 1982 agreement with Scotland, but remained significant in 1983 and 1984. The Belfast Centre used 2,177,292 units of commercial product in 1982, 1,374,373 units in 1983 and a similar amount in 1984. Use of commercial material decreased in 1985, but remained relatively significant at 605,274 units.

181. The view that Scotland had achieved self-sufficiency in 1984 appears to have been shared by the Edinburgh and South-East Scotland RTC. In a 15 May 1984 letter to Dr Ludlam, Dr B McClelland wrote: '*It looks as though we are now entering a situation where Factor VIII supplies should be stable and adequate*'.[224]

182. Similarly, Dr Morris McClelland wrote as follows with respect to the supply of PFC Factor VIII in a 21 May 1984 letter to Dr Mayne:

> 'This has been produced in considerable excess of demand in Scotland during the past year or two with the result that the present pro-rata arrangement for supplies (in proportion to input of fresh frozen plasma from Transfusion Centres) is to be abandoned at least for the present.

[224] Letter from Dr McClelland to Dr Ludlam, re: Requirements for Factor VIII and Factor IX, 15 May 1984, **PRSE0000585**.

> On a pro-rata basis, we [Northern Ireland] would now be entitled to receive Factor VIII at a rate of about 1.8 million units per year. (The increase has resulted partly from increased plasma supply and partly from increased yields during fractionation) With this new, more flexible arrangement we could certainly obtain more than this - at least 2.5 million units per year.
>
> I am aware from conversations with you that you are not at present planning to use this amount but may find this information useful for future planning'.[225]

183. The quantity of factor VIII produced by the PFC in 1984 was such that surplus product was offered to England and Wales, as well as Northern Ireland. Professor Cash addressed this point in a May 1984 paper: *'Proposal for the decanting of excess factor VIII concentrate to Northern Ireland and England and Wales*'. He wrote that the '*combined forces*' of '*the desire for self-sufficiency and the calculations which have been made to turn this into a reality*' – likely referring to estimates of demand informing plasma supply targets – '*have shaped, in a major way, many developments within the SNBTS over the last 8 years and have resulted in substantial investment and remarkable increases in staff productivity at the RTCs'.* Professor Cash pointed to improvements in the amount of plasma obtained by RTCs from blood donations and significant increases in fractionation yields at the PFC through technical modifications.[226]

184. Partly as a result of increases in production, the Scottish Health Service had become '*over supplied with a product which has a limited shelf-life and thus if not used will have to be discarded*'. Professor Cash further recorded:

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[225] Letter from W. M. McClelland, to Dr Elizabeth Mayne, re: Supply of Blood Products from Scotland, 21 May 1984, **NIBS0001718.**

[226] Report on 'Update on SNBTS Factor VIII Production: Proposal for the decanting of excess factor VIII concentrate to Northern Ireland and England and Wales, May 1984, **SCGV0000118_056.**

a. SNBTS Directors had agreed that the '*current operational requirements to maintain a stable factor VIII supply position*' required a '*national minimum stock of a size to take into account a full 12 month supply*', to be divided 50/50 between PFC and RTCs. A 12-month supply was viewed as desirable '*to insure against any future vagaries in production and clinical demand*', and its size would be reviewed annually.
b. SNBTS Directors had '*advised the Haemophilia Directors that in view of the present supply/demand position and in the interests of economy cryoprecipitate use for the management of haemophilia A should be abandoned. This has formally been accepted by the Haemophilia Directors*'.
c. Northern Ireland was '*currently unable to generate sufficient fresh plasma*' to meet its factor VIII needs. At the time of the report, the pro-rata agreement resulted in the delivery of 1.1 million iu per year to Northern Ireland, likely to rise to 1.5 million in 1984/85. Northern Ireland's '*current calculated requirement*' was for 2 million per year.

185. Professor Cash made a number of proposals:

a. That arrangements be made to dispose of factor VIII concentrate which was surplus to Scottish needs.
b. That the '*first priority in the disposal exercise*' be Northern Ireland.
c. That the '*residual surplus be offered to the CBLA*'.
d. That consideration be given to a charge for this product, both for Northern Ireland and the CBLA.
e. That the disposal or surplus factor VIII be reviewed in November/December 1984.

186. These proposals were discussed and accepted at a BTS Sub-Committee meeting on 23 May 1984.[227] It was noted that there was '*a degree of urgency*

[227] Minutes of Blood Transfusion Service Sub-Committee Meeting, 23 May 1984, **PRSE0003159**

in relation to' their implementation, *'as there was a possibility that the product could outdate*' unless arrangements were made by the end of July.

187. Some evidence is available of surplus Scottish factor VIII being offered to England and Wales around this time. For example, in October 1984, Dr Perry – who had become Acting Director of PFC – wrote to Dr Lane to offer approximately 2,000 vials of factor VIII (equating to 460,000 iu) which had failed to meet certain product specifications.[228] Although these products would previously have been issued in Scotland if there had been a shortfall in NHS supply, in light of its '*present supply situation*' and '*tentative evidence*' in relation to the AIDS infectivity of commercial products, Dr Perry offered the stock to BPL.[229] Dr Lane rejected this proposal, stating that he did not feel that it was '*in order to step outside normal regulatory practices, even in our current complicated situation with AIDS*'.[230]

188. Whether and when Scotland achieved self-sufficiency in blood products depends to some extent on how the term is defined. In a document submitted to Penrose, Dr Foster concluded that, at any time between 1975 and 1988, '*the SNBTS had available sufficient Factor VIII to meet average UK clinical practice, if cryoprecipitate was considered to be suitable to supplement Factor VIII concentrate*'.[231] If cryoprecipitate were excluded, then with the '*exception of the two year period 1978/79 – 1979/80, the availability of Factor VIII concentrate from the SNBTS was sufficient to meet average UK clinical use throughout this period*'. Elsewhere in the same document, he stated:

a. If cryoprecipitate is accepted as having been suitable for the treatment of haemophilia A '*when there was a shortfall of Factor VIII concentrate, then sufficient factor VIII was supplied by the SNBTS to provide*

[228] These were '*slight elevations in isoagglutinin levels*' or solubility times of between 20 and 30 mins.
[229] Letter from R.J. Perry to Dr Lane, re: Surplus Factor VIII, 1 October 1984, **CBLA0001900**.
[230] Letter from Dr Lane to R J Perry, re: Surplus Factor VIII, 1 November 1984, **CBLA0001912.**
[231] Report on 'Scottish National Blood Transfusion Service Self-Sufficiency and the Supply of Blood Products in Scotland' by P R Foster, February 2011, **PRSE0001083**, pg.60.

treatment at the average UK level throughout the period from 1975/76 to 1989/90, except for 1982/83 when only 90% of the UK level was supplied … although reserve stock was available.'

b. If cryoprecipitate is considered to have been unsuitable as an alternative to concentrate '*when there was a shortfall in the amount of Factor VIII concentrate from the SNBTS, then supply from the SNBTS did not fully match the level used in the UK until 1983/84. Despite this apparent shortfall in supply of Factor VIII concentrate, production of Factor VIII concentrate at PFC exceeded that amount of concentrate used throughout … 1979 to 1985, except for 1980 when the amount of concentrate used clinically doubled in one year*'.

c. A '*considerable amount*' of factor VIII which had been issued from PFC to RTCs was unused. Dr Foster added that '*[m]ost*' commercial Factor VIII purchased in Scotland in the early 1980s was obtained by haemophilia centres in Glasgow and was '*comparable in quantity to the unused stocks of SNBTS Factor VIII concentrate that had accumulated at the Glasgow Regional Transfusion Centre*'.

d. Thereafter, supplies of SNBTS factor VIII were '*sufficiently strong*' to avoid commercial concentrate being purchased in Scotland until 1988/89.[232]

189. On the evidence currently available to the Inquiry, Scotland's progress towards self-sufficiency in factor VIII concentrate by 1984 appears to have been possible for a number of reasons. These include:

a. PFC's manufacturing capacity following its relocation to Liberton in 1974, related to an expectation that Scotland would process part of England's plasma.

b. Increased plasma supply from Scottish RTCs, which resulted from factors including: significant and growing use of red cell concentrates

[232] Report on 'Scottish National Blood Transfusion Service Self-Sufficiency and the Supply of Blood Products in Scotland' by P R Foster, February 2011, **PRSE0001083**, pg.71.

rather than whole blood; RTCs being incentivised to send more plasma by the introduction of a pro-rata system for blood products; and a broader shift from the use of cryoprecipitate to concentrates (meaning less plasma was retained at RTCs to produce cryoprecipitate).

c. Improvements in manufacturing processes, in particular those leading to greater yields of factor VIII.
d. Higher demand estimates and production targets than in England and Wales.

Factor IX

190. The early history of products used to treat haemophilia B patients in Scotland was described in an article in a 1973 edition of Vox Sang.[233] It was noted that, until 1967, only FFP was available to treat these patients. That year, the PFC (then known as the BPU), began producing a concentrate to treat deficiencies of factors II, VII, IX and X: PPSB.[234] The article described a method of producing an alternative form of concentrate which could be used for the treatment of haemophilia B, and which had been undergoing trials since 1970. This concentrate became known as DEFIX, and appears to have been used routinely for the treatment of haemophilia B patients in Scotland from 1971.[235]

191. In a 6 January 1975 letter to Area Health Boards, Major-General Jeffrey described a transitional period following the PFC's relocation to Liberton.[236] He noted that there *'should be adequate stocks of other blood products (fibrinogen and factor IX concentrate) to meet clinical needs*.'

[233] Middleton, Bennett and Smith (of the PFC), '*A therapeutic concentrate of coagulation factors II, IX and X from citrated, factor VIII-depleted plasma*', Vox Sang, 1973 **PRSE0003648**.
[234] I.e.: prothrombin, proconvertin, Stuart factor and antihaemophilic B factor.
[235] Article on 'Studies on the Thrombogenicity of Scottish Factor IX Concentrates in Dogs' by Professor Cash et al, 30 January 1975, **PRSE0003960**.
[236] Letter from Major General Jeffrey (National Medical Director, SNBTS) to All Chief Administrative Medical Officers, 6 January 1975, **SCGV0000127_062**.

192. An April 1975 summary report, prepared by Dr Foster, recorded that PFC's research and development activities at that time included research into a factor IX concentrate with '*reduced HBAg activity*' and a '*four-factor concentrate containing factor IX*'.[237]

193. The SNBTS annual report for 1975-1976 stated that '*Factors II, IX and X, fractionated from plasma obtained from blood …. is used in the treatment of Christmas disease (haemophilia B) or experimentally in neonatal coagulation problems*'. [238] 3,279 doses had been issued in 1975-76, '*about twice that used in the previous year*'. It was suggested that a previous target of 2,000 doses be revised to 5,000. This would require 2,500 litres of fresh frozen plasma, '*but as Factor VIII can be fractionated from the same material, it should present no problem*'. Production could be '*raised to the limit of FFP intake and self-sufficiency can be achieved by appropriate effort on the part of the PFC*'.

194. In a January 1981 paper, prepared for a meeting of SNBTS and Haemophilia Centre Directors, the PFC factor IX product to treat haemophilia B patients was noted to be DEFIX.[239] Professor Cash recorded that '*because of the much smaller number of haemophilia B patients than A, the supply of these products is always more than adequate, with one exception*'. The 'exception' may refer to 1979, when the supply of DEFIX decreased relative to the previous year. Otherwise, the supply of DEFIX had increased from 500,000 units in 1975 to 1 million units in 1980.

195. In January 1983, Professor Cash noted that the supply position '*with regard to DEFIX remains strong and the issues from PFC to RTCs reasonably stable*'.[240] Similarly, at a 21 January 1983 meeting of SNBTS and Haemophilia Directors, it was noted that the '*supply position of DEFIX over the last 5 years*

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[237] Report on 'PFC Research and Development Department - A Summary Report' by P.R. Foster, April 1975, **PRSE0002008**.
[238] SNBTS Annual Report 1 April 1975 to 31 March 1976, 1976, **PRSE0002133**.
[239] Notes for Scottish Health Service Haemophilia Centre - Transfusion Service Directors' Meeting, January 1981, **CBLA0001252**.
[240] Report on 'Notes for Scottish Health Service Haemophilia Centre - Transfusion Service Directors' Meeting, January 1983, **PRSE0001991**, pg.5-6.

had remained strong and the demand reasonably stable'[241] Clinical studies of Supernine – a higher purity alternative to DEFIX – were said to have produced '*excellent results*'.

196. In a January 1984 paper, Professor Cash noted that the PFC had faced '*serious supply difficulties*' in relation to DEFIX in the summer of 1983. Reports that the product might be of value for haemophilia A patients with inhibitors had led to a '*sudden and unexpected increase in clinical demand*'. He suggested that, following adjustments to production schedules, '*this acute problem has been overcome*'. It was also hoped that treating inhibitor patients with DEFIX would '*reduce the need to purchase high cost, commercial activated factor IX concentrates'*.[242]

197. Professor Cash also referred to PFC's development of Supernine. He explained that this product '*was developed some years ago on the grounds that its increased purity would lead to a modest reduction in viral contamination*'. Results from initial clinical studies indicated that the product was acceptable, and Dr Ludlam '*expressed a desire to see Supernine replace DEFIX for the routine management of Christmas Disease patients*'. It was hoped that Supernine would be introduced for routine use in 1984/85. This was '*seen as an interim development pending the arrival of a heat treated product*'.

198. In February 1985, Professor Cash reported that the increase in demand for DEFIX had continued in 1984. He noted that there had been '*a significant and inevitably uncontrolled increase in the use of DEFIX for the management of Haemophilia A patients with inhibitors. All evidence points to the fact these patients are currently consuming approximately 50% of issued product*'. This increase in demand and an unexpected loss of product following a batch recall associated with hepatitis B surface antigen contamination had '*given*

[241] Minutes of SNBTS Director Meeting, 21 January 1983, **PRSE0001736**
[242] 'Notes for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1984, January 1984, **PRSE0004741**, pg. 10.

rise in part to significant supply difficulties in the last 12 months'. Despite ongoing efforts by PFC staff to overcome the supply challenges, as a consequence, batch dedication for DEFIX could not be introduced until substantial stocks had been achieved.[243]

199. The contrast between the difficulties in achieving self-sufficiency in factor VIII in Scotland and the relative ease with which it was achieved for factor IX is reflected in Annex A. No commercial factor IX was used in Scottish Haemophilia Centres between 1976 and 1979, and relatively small amounts were used in 1980 and 1981. A significant amount of commercial product was administered in 1985, for reasons which are explored below.

200. Annex B shows that commercial factor IX was used in Northern Ireland between 1976 and 1978. No use of commercial material was recorded between 1979 and 1989 (which covers the period from 1982, when PFC began fractionating Northern Irish plasma).

II. Viral inactivation and its impact on self-sufficiency

201. This section of the presentation note does not intend to address the evidence relating to viral inactivation comprehensively, in particular in relation to technical manufacturing processes. Instead, it provides an outline of key developments and their impact on self-sufficiency in Scotland and Northern Ireland.

Developments up to 1985

Factor VIII

[243] Report on 'Noted for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: March 1985, February 1985, **PRSE0003450**, pg.11.

202. Alongside efforts to achieve self-sufficiency, research and development into the viral inactivation of factor concentrates took place at the PFC from the early 1980s. As explored below, the initial aim of this research was to inactivate the agents responsible for hepatitis transmission, including those responsible for the transmission of non-A non-B hepatitis (NANB hepatitis). Rather than dry heat treatment, the PFC focused its early efforts on the feasibility of heat treatment via pasteurisation (sometimes known as 'wet heat treatment'). The emergence of AIDS, and in particular the discovery in autumn 1984 that patients who had been treated with Scottish concentrate had tested positive for HLTV-III, eventually changed the PFC's approach. These developments, as well as attempts to inactivate NANB hepatitis, would have a significant effect on Scotland's ability to maintain self-sufficiency.

203. In late 1980, the SNBTS and PFC became aware of reports of an important development in viral inactivation: the German company Behring claimed to have pasteurised factor VIII successfully. Reports of this apparent breakthrough were made at an October 1980 conference in Bonn, Germany. The conference was attended by Professor Cash, who wrote the following in a 27 October 1980 letter to Mr Watt:

> 'During the meeting in Bonn I learnt, for the first time, that Beringwerke are getting rather excited – following chimpanzee studies – that their preparations of factor VIII, made from HBsAg positive plasma (starting at 90 ng/ml), appear to be safe. The reason given is that they are heat treating the product for 10 hours at 60°C in the presence of glycine and sucrose. Apparently the glycine and sucrose protect the VIII from denaturation.
>
> Sounds unbelievable: thought you might be interested.'[244]

[244] Letter from Professor Cash to Mr Watt, re: Behringwerke heat treatment of Factor VIII, 27 October 1980, **PRSE0003704.**

204. In September 1981, Dr Alex MacLeod (a PFC research scientist) began preliminary experiments which aimed to replicate Behring's findings.[245]

205. In December 1981, Professor Cash established the SNBTS Factor VIII Concentrate Study Group (Factor VIII Study Group) to explore '*new developments in the widest possible sense with regard to the production of factor VIII concentrates and thereby create the opportunity for cross fertilisation and co-ordinated research within the SNBTS*'.[246]

206. The Group's first meeting took place on 2 January 1982. The minutes record a very brief reference to viral inactivation methods, including pasteurisation.[247] It was agreed that various sub-groups should be set up, including a Safety Action Group.

207. Dr MacLeod summarised the results of his preliminary experiments in pasteurising factor VIII in a 10 February 1982 report.[248] He concluded that '*it would seem that the ability to pasteurise a FVIII concentrate is linked to the production of a high purity product*'.

208. The Safety Action Group – made up of Drs Pepper, Sommerville and Cuthbertson – held preliminary meetings on 9-10 February 1982, and prepared a first report dated 16 March 1982.[249] It summarised possible avenues for research and, as with Dr MacLeod, suggested that '*it is clear that low fibrinogen (= high purity) is a desirable product for both heat inactivation or y-irradiation processes*.'

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[245] Penrose Final Report, **PRSE0007002**, pg.964, paras 23.40 and 23.41. See also Dr Foster's witness statement: **WITN6914001**.
[246] Letter from Professor Cash to Dr Prowse, 17 December 1981, **PRSE0001684**.
[247] Minutes of Factor VIII Study Group Meeting, 28 January 1982, **PRSE0001020**.
[248] Report on 'Preliminary Studies on the Heat Treatment of PFC FVIII Concentrate' by Dr MacLeoud, 10 February 1982, **PRSE0001549**.
[249] The Safety Action Group first meeting: SNBTS FVIII Study Group, First Report of the Safety Action Group, 9-10 February 1982, **PRSE0003227**.

209. This report was discussed at a meeting of the wider Factor VIII Study Group on 30 March 1982.[250] Dr Pepper suggested that the '*proposals to achieve a hepatitis reduced VIII product would take time and considerable investment. It was thought this could not be achieved in less than 2 years and it was possible that in the interim other current developments throughout the world might render this study less viable*'. Nonetheless, it was agreed that the work should continue.

210. Dr Pepper provided a further update, in particular with respect to animal experiments, at the 3 June 1982 meeting of the Factor VIII Study Group.[251] At a 23 June 1982 meeting, the Safety Action Group considered a protocol for testing factor VIII infectivity in tamarin monkeys using a '*putative human non-A, non-B hepatitis virus*'.[252] The work was divided into three stages, and it was estimated that the '*total period of time required may be up to 2 years, but is unlikely to be less than one year*.'

211. In early August 1982, Dr Foster attended the International Society of Haematology/International Society of Blood Transfusion Congress in Budapest. He subsequently produced a report which included a section on viral inactivation of factor VIII and IX concentrates.[253] With respect to factor VIII, Dr Foster recorded that '*[t]wo new products were introduced at the Congress, one from Biotest and one from Hyland*'. The Hyland method was '*said to involve pasteurisation*'. Dr Foster noted that there was no presentation from Behring, but that literature was available giving details of its experiments. Reference was made to a study involving factor VIII, in which the '*concentrate in the freeze dried state was heated for 10 hours at 100°C without loss of activity*'. Dr Foster commented that the '*work of Rubinstein using labile factors in their freeze dried state is very interesting but freeze drying is also likely to protect the virus and infectivity data is essential*'. He considered that the

[250] Minutes of Factor VIII Study Group Meeting, 30 March 1982, **PRSE0000752**.
[251] Minutes of Factor VIII Study Group Meeting, 3 June 1982, **PRSE0001489**.
[252] Minutes of Factor VIII Safety Action Group Meeting, 23 June 1982, **PRSE0001142**.
[253] Report on 'ISH/ISBT Congress Budapest 1982' by P.R. Foster, August 1982, **PRSE0003247**.

Hyland product was '*perhaps the most interesting. If the yield indicated (200 iu/l) is confirmed this is probably higher than the present method of manufacture for Hemofil and therefore represents a definite break-through in FVIII stabilisation. Will this ever be published?*'.

212. When the PFC Factor VIII Study Group met on 14 October 1982, it discussed viral inactivation in some detail. Of the different possibilities, heat treatment had become '*the first option of the group*' (rather than methods such as irradiation or treatments with detergents). It was agreed that Dr MacLeod would '*continue studies of heat process using high purity products*'.[254] In a 19 October 1982 letter to Dr Jim Smith (BPL/PFC), Dr Foster commented that '*[e]veryone is getting very hot about pasteurisation, especially since Budapest. The little work that we have done suggests that higher purity material is needed…*'.[255] Dr Foster provided a further update in a 1 December 1982 letter to Dr Smith.[256]

213. In a 6 January 1983 letter to Dr Forbes (Royal Infirmary Glasgow), Professor Cash explained that the PFC hoped to have a new, higher purity factor VIII concentrate available for trial by late spring 1983, which would be followed by a heat-treated version.[257]

214. The timeline in Professor Cash's letter was reflected in an 11 January 1983 internal PFC memo, prepared by Dr Foster, on heat-treated factor VIII.[258] Dr Foster noted that a number of commercial manufacturers would be making heat-treated factor VIII available to clinicians '*in the very near future*'. This '*could well have major implications for the NHS users and suppliers of concentrate*', and so there was '*some urgency*' in demonstrating that the NHS could produce such concentrates. PFC's research and development was

[254] Minutes of Factor VIII Study Group Meeting, 14 October 1982, **PRSE0002206**.
[255] Letter from Dr Foster to Dr Smith, re: Requesting advice on Factor VIII and viral inactivation methods, 19 October 1982, **PRSE0003756**.
[256] Letter from Dr Foster to Dr Smith, re: Results of Heat Treatment of DEFIX, 1 December 1982, **CBLA0002476**.
[257] Letter from Professor Cash to Dr Forbes, re: New SNBTS Factor VIII Concentrates, 6 January 1983, **PRSE0002880**.
[258] Memo from Dr Foster to Mr Watt et al., re: Heat Treated Factor VIII, 11 January 1983, **PRSE0001554**.

described as '*advancing well*', and Professor Cash had provided a target of producing a small quantity of heat-material for clinical testing within three months. Dr Foster provided a detailed update on the technical issues the PFC had encountered in a 20 January 1983 letter to Dr Smith.[259]

215. An outline of PFC's progress with heat-treated materials was provided at a 21 January 1983 meeting of SNBTS and Haemophilia Directors.[260] As well as referring to the arrival of heat-treated factor VIII from commercial producers, reference was made to an apparent tension between heat treatment and self-sufficiency:

> 'Mr Watt explained the problems which had to be overcome in preserving acceptable yields and providing a product which was not too expensive, considerations that were of less importance with the commercial product. Directors were made aware of the fierce competition facing the PFC from commercial concerns and were asked to bear in mind the stated policy for the Scottish Health Service to be self-supporting in blood products.'

216. Soon thereafter, references to possible AIDS risks entered into PFC's consideration of virally inactivated blood products. In a document prepared for an 8 March 1983 presentation at the RIE Haematology Department – '*Methods for preparing non-infective blood products*' – Dr Foster outlined problems with some of the proposed solutions to the 'hepatitis problem'.[261] The last of these was: '*OTHER INFECTIOUS AGENTS (CMV, AIDS)*'.

217. Developments in PFC's heat treatment of factor VIII, as well as AIDS, were discussed at a 22 March 1983 meeting of the Haemophilia and Blood

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[259] Letter from Professor Cash to Dr Smith, re: Factor VIII heat treatment studies, 20 January 1983, **CBLA0002478.**
[260] Minutes of SNBTS and Haemophilia Directors Meeting, 21 January 1983, **PRSE0001736**.
[261] Report on 'Methods for Preparing Non-Infective Blood Products' by P.R. Foster, 8 March 1983, **PRSE0001201** pg.3.

Transfusion Working Group.[262] Mr Watt explained that PFC was not trying to heat treat its existing product, and that '*Dr Foster in cooperation with colleagues in the USA was working on a completely new Factor VIII product of higher quality with low fibrinogen content*'. A small amount of this product had been produced, and some of it had been heat-treated at 60°C for 10 hours. A small quantity was available for clinical trials, and Dr Forbes and Dr Ludlam expressed willingness to take part in such trials. Mr Watt considered that it would take around a year to reach full production; some changes in the design of PFC's equipment would be necessary for the heat treatment process. AIDS appears to have been discussed separately to heat treatment. The minutes record that '*AIDS was an emotive issue in the USA and Canada, and was causing a move away from factor VIII concentrates to the use of cryoprecipitate, with resultant supply problems*'.

218. However, a link between AIDS and PFC's heat treatment strategy was soon made explicit. In a 3 May 1983 internal PFC memo, Dr Foster outlined the possibility that PFC's approach would need to change.[263] He recorded that, '*[u]ntil very recently the objective of our heat treatment programme was to cope with the hepatitis problem in haemophiliacs*'. This strategy was based on only mild and moderate haemophiliacs benefiting from a treated product, because severe haemophiliacs had '*already been heavily exposed to untreated products*'. It was estimated that the mild/moderate patients could use up to 30% of the total (treated) factor VIII. A full-scale plant to handle 30% production of heat-treated factor VIII had therefore been planned for 1984/85 at the earliest. Meanwhile, mild and moderate haemophiliacs could '*continue to receive single donor cryo*'.

219. If AIDS were transmitted by concentrates, these calculations would change. Dr Foster wrote: '*The possibility that another more serious infectious agent (AIDS) is now involved suggests that we may need to review this strategy*'. In

[262] Meeting of Haemophilia and Blood Transfusion Working Group Meeting, 22 March 1983, **PRSE0000728**.
[263] Memo from Dr Foster to Mr Watt, re: Heat Treatment of Factor VIII - A Strategy, 3 May 1983, **PRSE0001111**

this '*new scenario*', severe haemophiliacs were most at risk, and there was '*already evidence of a panic recourse to cryoprecipitate*'. He added that in '*the absence of any hard data, heat treatment (of everything) looks at the moment to be the most likely possibility that we have to face up to*'. Dr Foster commented that timing '*may become crucial*', for the following reasons:

a. The '*publicised view that FVIII is infectious and that there may be a long incubation period (i.e. 3 years). We may argue that this has not been proven but hard data (one way or the other) could take years to achieve. Meanwhile decisions will probably be taken according to a 'worst case' hypothesis*'.
b. There were some '*who would find a move back to cryo attractive and if this gathers momentum (it would only need 1 suspected case from NHS FVIII) we could see our FFP disappear overnight*'.

220. Dr Foster considered that there '*may therefore be a case for accelerating our heat treatment programme*', noting that it might be possible to '*introduce an intermediate stage, still using the pasteurisation cabinets*'.

221. It appears that a change in approach was agreed within PFC. In a 5 May 1983 letter to Professor Cash, Mr Watt summarised progress in PFC's existing heat-treatment programme.[264] He explained that pasteurising at a higher temperature for a shorter period – 70°C for under one hour rather than 60°C for 10 hours – had been shown to be '*much more effective*'. The heating process carried '*a penalty*', in that as much as 20% of the factor VIII activity could be lost, but heating at 70°C did not incur an appreciably greater loss than lower temperatures. He added that in view of '*recent news exposure of (?) infectivity of Factor VIII concentrates we have made a re-assessment of heat-treated concentrate based on a careful step-by-step appraisal of a series of pilot-scale lots*.'

[264] Letter from Mr Watt to Professor Cash, re: Heat Treatment of Factor VIII, 5 May 1983, **PRSE0000998.**

222. Mr Watt summarised this proposed change as follows:

> 'In most areas of the development I believe we now possess sufficient data to allow, by adopting a few calculated risks, this programme to be speeded up substantially. It would mean expansion of the make-shift process now in use and would involve expenditure now instead of 1984-85 as well as some additional expenditure which would not advance the longer-term production process. By doing this we could expand production of the (H)F VIII quickly to process at least the level of present production, which is limited by the ability to process the resultant cryo-poor plasma. My colleagues are engaged in a cost for the expedited programme in case public opinion rather than science may dictate the best course of action.'

223. Professor Cash responded on 1 June 1983.[265] He commented that he regarded the paragraph of Mr Watt's letter reproduced above to be '*the most important, and am particularly pleased that you and your colleagues are currently engaged in a costing exercise designed to expedite the heat treatment programme. As you say, public opinion may eventually press us heavily*'. Professor Cash stated that there were '*no funds available in 1983-84*' for Mr Watt's proposals, but that the SHHD might wish to reconsider '*in the light of the current pressures (AIDS etc.)*'.

224. There then followed a series of letters and funding bids in which the CSA sought additional funding from the SHHD, initially linked to costs which were required to meet recommendations arising from the Medicines Inspectorate report on PFC. The outcome was that a sum of £90,000 – not linked to the Medicines Inspectorate report – was eventually approved, though not until mid-August 1984. The relevant documents are summarised in the Penrose Report.[266] Penrose considered whether the time it took to authorise funding

[265] Letter from Professor Cash to Mr Watt, re: Heat Treatment of Factor VIII, 1 June 1983, **PRSE0002624.**
[266] Penrose Final Report, **PRSE0007002,** para 23.123. See also paras 23.125 to 23.127.

relayed PFC's heat treatment programme, and recorded the evidence of Drs Perry and Foster, as well as Professor Cash, that it did not (on the basis that clinical trials were the key factor, rather than funding).

225. Meanwhile, the Safety Action Group held a further meeting on 15 June 1983.[267] The minutes of its meeting begin with the following summary: '*Considerable progress has been made at P.F.C. in producing heat treated FVIII and clinical trials should start towards the end of the summer in Glasgow and Edinburgh. No infectious model for non-A, non-B has been produced yet. The putative 'AIDS' virus must be considered a potential hazard in FVIII concentrates*'. A preliminary pasteurisation protocol was suggested, involving heating at 60°C for 10 hours followed by 70°C for 30 minutes, with anticipated losses in factor VIII activity of 20-30%. Reference was made to developments among commercial manufacturers, including Hyland's process which was believed to include a '*3 day dry heat step at 70°C*', though '*the additives (if any)*' were unknown. The minutes record discussion of alternative viral inactivation methods to heat treatment, including irradiation or organic solvents.

226. As for the impact of AIDS: '*Although not proven to be a virus, this apparently infectious agent has been found in haemophiliacs in the U.K. it would seem wise to try somehow to encompass AIDS inactivation along with HBV and NANB inactivation schemes.*' The Group considered that this reinforced the choice of heat or irradiation methods and commented: '*Taking a pessimistic view, some viruses are known with heat resistance up to 80°C, so 70°C may not be sufficient.*'

227. Mr Watt summarised the difference between the approach taken by the PFC and some other manufacturers in a 1 August 1983 letter to Professor Johnson at New York University, in which he sought details of a method to produce '*high yield and very high purity*' factor VIII. The letter explained: '*we*

[267] Minutes of Factor VIII Safety Sub-Committee Meeting, 15 June 1983, **PRSE0003460.**

believe that our [factor VIII activity] *loss level is much lower than that of other manufacturers despite the fact that our virucidal stage is applied to the liquid preparation rather than dried final product and for that reason is more likely to be effective*'.[268]

228. Dr Foster provided an update in a 23 August 1983 letter to Dr Smith, noting that PFC intended to make a (relatively slight) adjustment to its factor VIII heating regime.[269]

229. Dr Foster provided a more detailed update on PFC's work in a 20 December 1983 report for the Factor VIII Study Group: '*Progress report on studies to improve yields and quality of factor VIII concentrate*'. He reported that '*[e]xtensive studies have been carried out on the stability of FVIII:C and a range of model viruses to heating in solution in the presence of sorbitol and glycine*'. '*Improved heating*' conditions had been identified and were summarised in an appendix; '*[e]ven more severe heating*' resulted in '*substantial loss of FVIII activity*' and the improved conditions were '*probably the best that can be achieved without an unacceptable loss of yield*'. Work was ongoing to address issues arising from scaling up production.

230. Dr Foster also indicated that PFC had begun experiments on dry heating as an alternative to pasteurisation: '*Other manufacturers are heating their products in the freeze dried state (Hyland, Armour). Experiments using this technique are being carried out using vaccinia and mumps to allow a comparison with heating in solution. Initial results suggest that the viral kill is less than that achieved by heating in sugar solutions at 60°C for 10 hours*'.[270]

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[268] Letter from Mr Watt to Professor Johnson (Department of Medicine, New York University Medical Centre), re: NY prefix for Factor VIII, 1 August 1983, **PRSE0002190**.The letter explains that the 'NY' prefix in PFC products was used because of a relationship with Professor Johnson at New York University.
[269] Letter from Dr Foster to Dr Smith, re: Update on Factor VIII work, 23 August 1983, **PRSE0000508.**
[270] Report on 'Progress Report on Studies to Improve Yield and Quality of FVIII Concentrate' by Dr Foster, 20 December 1983, **PRSE0001119**.

231. In his evidence to Penrose, Professor Cash stated that the first experimental dry heating of PFC product took place in November 1983.[271] On 5 January 1984, Dr Smith provided Dr Foster with details of BPL's approach to dry heating its factor VIII.[272]

232. In his January 1984 report for a meeting of SNBTS and Haemophilia Directors, Professor Cash highlighted '*the potential risk associated with respect to transmitting non-A/non-B hepatitis following the infusion of BPL intermediate concentrate*'.[273] The report summarised PFC's progress in heat treating factor VIII. It was anticipated that batches of product, pasteurised at 60°C for 10 hours, would be available for preliminary clinical studies by April 1984. Professor Cash added:

> 'At the present time it is not possible to give an accurate estimate on the likely timing of a phase introduction of heat treated VIII concentrates for routine use in the SHS. However, current planning indicates that limited but significant amounts of this material could be available for clinical use by September 1984 and full scale production introduced by April 1985 (both subject to available funding). In the meantime it would be of advantage to the SNBTS if Haemophilia Directors were able to indicate where they see the priorities lie and where it is possible to provide a measure of quantitation (the annual amount of heat treated product for the priority patients). To this end there is also an urgent need to ascertain whether this type of concentrate is efficacious in the management of appropriate patients with Von Willebrand's Syndrome, and particular assistance is requested'.

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[271] Witness Statement of Professor John Cash on Viral Inactivation to Penrose Inquiry, **PRSE0002836,** pg.16.
[272] Memo and minute extract of Strategy, Method and Results of dry heat on NANBH study, 5 January 1984, **PRSE0003743.**
[273] 'Notes for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1984, January 1984, **PRSE0004741**.

233. The minutes of the meeting which followed this report record some discussion of heat-treated factor VIII, though it is not clear whether Directors agreed a timetable or priorities for introducing heat-treated products.[274]

234. Initial trials of PFC's pasteurised factor VIII – referred to with the prefix 'ZHT' – took place in early 1984. In January 1984, Dr Ludlam reported an adverse reaction in a batch he had tested on a severe haemophilia patient.[275] By contrast, Dr Forbes reported no adverse reactions in March 1984.[276] In a 27 April 1984 letter to Professor Cash, Dr Perry wrote that the PFC's first batch of heat-treated factor VIII – amounting to 30 vials of 100 iu – was '*ready for issue*'. The PFC's expectation was to make at least 100 vials of 200 iu per month available, starting in May.[277]

235. Professor Cash outlined distribution arrangements for this heat-treated factor VIII in a 26 June 1984 letter to Dr Perry.[278] For the first few months, all distribution would take place through the local RTC in response to specific requests, rather than being issued from RTC stocks. At this stage, the concentrate continued to be used for studies. Professor Cash wrote that the '*product can only be issued on a named patient basis for the agreed clinical evaluation studies*'.

236. In his Inquiry witness statement, Dr Foster stated that 11 pilot batches of ZHT were prepared between February 1983 and September 1984.[279]

237. It therefore appears that, until late 1984, PFC continued to focus on producing a pasteurised factor VIII. A 1984 report by Professor Cash on the activities of the Factor VIII Study Group recorded that '*[w]et heat treatment*

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[274] Minutes of SNBTS and Haemophilia Director Meeting, 2 February 1984, **PRSE0001556**
[275] Letter from Dr Ludlam to Professor Cash, re: Heat Treated Factor VIII Batch NY761, 11 January 1984, **SBTS0000319_010**. For Professor Cash's and Dr Foster's responses to Dr Ludlam, see **PRSE0001801** and **PRSE0003903**.
[276] Letter from Dr Forbes to Profesor Cash, re: Affected patients, 14 March 1984 **SBTS0000321_019.**
[277] Letter from Dr Perry to Professor Cash, re: Heat Treated Factor VIII, 27 April 1984, **PRSE0004453.**
[278] Letter from Professor Cash to Dr Perry, re: SHS Heat Treated Factor VIII Studies, 26 June 1984, **PRSE0002949.**
[279] Written Statement of Dr Foster, **WITN6914001.**

was considered to be the most appropriate immediate target area. This decision has been implemented and Directors are aware of subsequent progress.'[280]

October 1984: change in approach

238. A major shift in the PFC's approach to viral inactivation occurred in October 1984 following the discovery that a cohort of patients in Edinburgh treated with PFC factor VIII had developed antibodies to HTLV III. The timing of, and immediate response to, the discovery on the part of the SNBTS has been addressed in evidence already heard by the Inquiry (notably that of Professor Ludlam and Dr Brian McClelland) and is not addressed in detail here. An early chronology of events, beginning on 26 October 1984, is available in a 20 November 1984 memo from Dr McClelland to Dr Perry and Professor Cash.[281]

239. In his Inquiry statement, Dr Foster describes learning of the Edinburgh patients on Monday 29 October 1984.[282] He says that he arranged with Dr MacLeod to test samples of PFC factor VIII to determine whether the addition of additives could extend the time that it could withstand dry heat treatment at 68°C. Dr Perry describes being told the following day that PFC's existing factor VIII could withstanding heating at this temperature for up to three hours.

240. On 1-2 November 1984, a plasma fractionation conference was held in Gronigen, the Netherlands. It was attended by Drs Foster, Perry and McIntosh on behalf of the PFC. In his Inquiry statement, Dr Foster describes learning during the conference of a report that dry heat-treatment had inactivated HTLV-III in factor VIII, with fewer than 10 of out 100,000 particles of HTLV-III per ml remaining after heating at 68°C for one hour, and none remaining after

[280] Report on 'Activities of the SNBTS HQ Factor VIII Study Group' by Dr Cash, 1984, **PRSE0000327**.
[281] Letter from Dr McClelland to Dr Perry, cc: Professor Cash, re: Events leading up to the recall of Factor VIII Batch 023110090, 20 November 1984, **PRSE0000828**.
[282] Written Statement of Dr Foster, **WITN6914001**.

heating at 68°C for 24 hours. These results were summarised in Dr Foster's contemporaneous notes of the conference.[283]

241. On 6 November 1984, having returned to the UK, Dr Foster wrote to Professor Cash regarding the inactivation of HTLV-III, commenting: '*There was some encouraging information from the Gronigen Meeting however (see notes appended)*.'[284] In his witness statement, Dr Foster suggests that the decision to dry heat PFC factor VIII at 68°C for two hours had been taken by the time of this letter.

242. The change in PFC's approach was recorded in the minutes of a 13 November 1984 meeting of PFC heads of department: '*Dr Perry advised the meeting that as a result of the amount of information being publicised through the press on the subject of AIDS, there was an immediate requirement for PFC to render all FVIII free from HTLV III virus*.'[285] Dr Perry explained that experiments were being set up to heat the factor VIII '*at a higher temperature to kill the HTLV III virus without compromising the quality of this product*', and it was noted that Dr Foster had '*already subjected some material to this heating process*'.

243. By 20 November 1984, two small batches of PFC factor VIII had been dry-heated and were undergoing review ahead of clinical observations. The batches were expected to be available on 26 or 27 November 1984. General release of the heat-treated product in early January 1985 was described as the objective.[286]

244. Dr Perry provided a more detailed update in a letter to Professor Cash on 22 November 1984. Alongside the provision of vials to Drs Ludlam and Forbes for 'clinical trial' on 26/27 November, the PFC would immediately

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[283] Notes from the Meeting on Plasma Fractionation held in Groningen 1 - 2 November 1984 by P.R. Foster, 1984, **MACK0001821_001.**
[284] Letter from Dr Foster to Professor Cash, re: Inactivation of HTLV III, 6 November 1984, **PRSE0000807**.
[285] Minutes of Heads of Department and Section Managers Meeting, 13 November 1984, **PRSE0004148**.
[286] Minutes of AIDS: Decisions Taken at Co-Ordinating Group Meeting, 20 November 1984, **PRSE0002053**.

heat-treat 6 batches of material at 68°C for 2 hours to expedite the issue of heated products to RTCs. Subject to quality control and information from Drs Ludlam and Forbes, this material would be issued to RTCs in the week beginning 10 December. Dr Perry also confirmed that PFC planned to embark on a programme of heat treating all existing PFC stocks of factor VIII, as well as recalling and replacing all RTC, blood bank and home treatment stocks with heat-treated product. He wrote that heated factor VIII '*should be available continuously at RTCs after 10-15 December*.' As a further measure, PFC intended to implement a policy of whole batch issue to RTCs to minimise patient exposure to risks of HTLV-III and hepatitis.[287]

245. Dr Perry provided a summary of the change in the PFC's approach to heat treatment at a 28 November 1984 special meeting of SNBTS and Haemophilia Directors.[288]

246. On 6 December 1984, Dr Perry wrote to RTC Directors to inform them of arrangements for distributing heat-treated factor VIII.[289] Around one month's supply would be dispatched on 10 or 11 December. Following this, plans were '*in hand to supply quantities of heated product to each RTC equivalent to twice the min/max stock level to take account of the need to replace domestic and blood bank stocks*.' It was anticipated that this phase would be complete before Christmas. In the New Year, PFC would arrange for non-heated product to be collected from RTCs, and Dr Perry asked that Directors '*make arrangements for this material to be recalled as widely as possible in preparation for this replacement programme*'. Regional batch dedication had not been achieved for the initial deliveries, but Dr Perry stated that it would be subsequently.

247. On 17 December 1984 Professor Cash wrote to all Scottish Haemophilia Directors to inform them that, '*within the next day or so*', they would be

[287] Letter from Dr Perry to Professor Cash re Heat treatment of Factor VIII, 22 November 1984, **PRSE0002485**.
[288] Meeting of Haemophilia Directors and SNBTS representatives, 29 November 1984, **PRSE0002066.**
[289] Letter from Dr Perry to Transfusion Directors, re: Heat Treated Factor VIII, 6 December 1984, **PRSE0002675**

receiving the SNBTS's '*first generation heat treated factor VIII*', which would be '*the start of a complete changeover from the non heat treated product*'.[290] He asked them, where possible, to gather information on clinical efficacy, evidence of sero-conversion and the development of inhibitors.

248. Dr Perry summarised PFC's progress in dry heating factor VIII, as well as its future plans, in an 8 January 1985 letter to Dr Duncan Thomas of the NIBSC.[291] The letter included the following:

a. All factor VIII issued from PFC had been subjected to heat treatment since mid-December 1984.
b. PFC would be '*recalling all existing regional stocks of non heat-treated FVIII for heat treatment and reissue*'.
c. Dry heating conditions to date had been 68°C for 2 hours '*on the basis that this was the best time/temperature profile which could be established for the existing product…*'.
d. Plans were '*well advanced for the manufacture of a new product which is subjected to more extreme conditions of temperature and time*'.

249. In his Inquiry witness statement, Dr Foster comments that '*[o]ne benefit of selecting dry heat conditions that could be applied to the existing PFC Factor VIII concentrate was that over 12 months supply was available, enabling heat treatment to be applied immediately and providing a stock of heated treated Factor VIII to fill the national supply chain*'. [292]

[290] Letter from Professor Cash to Scottish Haemophilia Directors, re: SNBTS Heat Treated Factor VIII, 17 December 1984, **PRSE0000266.**
[291] Letter from Dr Perry to Dr Ducan Thomas (National Institute for Biological Standards and Control), re: Heat Treated Factor VIII, 8 January 1985, **PRSE0002706**.
[292] Written Statement of Dr Foster, **WITN6914001**

Factor IX

250. The evidence suggests that investigations into the heat-treatment of PFC's factor IX concentrate took place from the early 1980s, but that the first heat-treated product was introduced later than the factor VIII equivalent.

251. Dr Foster provided an update on PFC's early attempts to heat DEFIX in a 1 December 1982 letter to Dr Smith.[293]

252. At a 21 January 1983 meeting of SNBTS and Haemophilia Directors, it was noted that studies on the heat-treatment of factor IX were ongoing – using Supernine rather than DEFIX – but that the rate of progress would be slower than with factor VIII because of the need for animal studies to confirm that the product was not thrombogenic.[294]

253. In a January 1984 paper, Professor Cash provided a more detailed update on PFC's attempts to heat-treat factor IX.[295] He described a number of obstacles and suggested that it was unlikely that a product would be available for preliminary clinical studies for around two years:

> 'Work on this product [heat-treated factor IX] continues at PFC. Colleagues will wish to note that the technology involved raises problems of a much complex nature than the sister development associated with factor VIII. In the first place there will be a requirement, prior to clinical studies, for extensive animal studies, in order to ensure that the heat treatment does not potentiate the inherent thrombogenicity of these concentrates. These are also other technical considerations: whether to heat Supernine or DEFIX. The former is currently a low yielding product and it may not be desirable to suffer

[293] Letter from Dr Foster to Dr Smith, re: Results of Heat Treatment of DEFIX, 1 December 1982, **CBLA0002476**.
[294] Minutes of SNBTS and Haemophilia Directors Meeting, 21 January 1983, **PRSE0001736**.
[295] 'Notes for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1984, January 1984, **PRSE0004741**, pg. 10.

further losses associated with heat treatment as the final 'market' for a safer factor IX concentrate may be much larger than is currently envisaged (now involving, in addition to Christmas Disease, patients requiring oral anticoagulant reversal, severe liver disease and perhaps some noenates [sic]).

It is not envisaged that a heat treated factor IX concentrate will be available from PFC for preliminary clinical studies until approximately 24 months' time.'

254. Brief reference was made to factor IX and Professor Cash's paper at the 2 February 1984 meeting of SNBTS and Haemophilia Directors.[296] It was noted that some (non-heated) DEFIX was '*still required and its availability would be retained, but subject to the provision of data which satisfies the Licensing Authority it was hoped to introduce Supernine for routine use throughout the SHS in 1984/85*'. The meeting further recorded that these '*arrangements were seen as an interim development pending the development of a heat treated product*', as set out in Professor Cash's paper.

255. By the end of 1984, PFC had not yet produced a heat-treated Factor IX product.

Developments from 1985

Factor VIII

256. PFC's work on heat treatment continued in 1985.

257. Annex A suggests that Scotland maintained self-sufficiency in factor VIII products as this was taking place: no use of commercial concentrate was recorded in 1985. On 5 February 1985, John Mackay (Secretary of State for Scotland) stated in response to a Parliamentary Question that Scotland was

[296] Minutes of SNBTS and Haemophilia Director Meeting, 2 February 1984, **PRSE0001556**.

self-sufficient '*in all normally required blood products*' and that since 1 January 1985 SNBTS products had been heat-treated.[297]

258. Nonetheless, a number of issues arose, including:

a. The impact on yield of dry heating factor VIII beyond 68°C for 2 hours, and thereby the impact on self-sufficiency.

b. The development of a virally inactivated factor VIII which did not transmit NANB hepatitis.

259. Dr Foster outlined developments in PFC's heat-treatment programme in a February 1985 report for the Factor VIII Study Group. Having summarised why the Group had previously supported pasteurisation rather than dry heat treatment – including the relative effects of the methods on NANB hepatitis – he wrote: '*Although heating in solution would seem to be still the preferred option recent information concerning HTLV-III has led to the introduction of a dried-heating procedure for the existing product*'.[298]

260. Further detail was provided in another February 1985 paper for the Study Group.[299] Various developments in viral inactivation were outlined, including internationally, and a summary of PFC's own work included the following:

> 'Considerable action has taken place on the heating of FVIII, both wet and dry. The latter is not entirely satisfactory for elimination of hepatitis B (probably = 2 logs), whilst the effect on NANB is still uncertain in the absence of a titred infectious source. Dry heat appears to be satisfactory for the inactivation of AIDS virus (HTLV III) since this agent has been shown to be far more heat sensitive than HBV. Wet heating has the greatest potential for killing viruses. However, it is in abeyance

[297] Extract from Hansard (Volume 72-54), House of Commons, re: Self-sufficiency of blood products in Scotland, 5 February 1985, **PRSE0003841**.
[298] Report on 'Progress Report for Factor VIII Study Group' by P R Foster, February 1985, **PRSE0000927**.
[299] Update Paper for Factor VIII Study Group on 7 February 1985 on 'Virucidal action since last meeting one year ago', 1985, **PRSE0004681**.

at the moment for two reasons: firstly, the scale-up of the zinc high purity project has been shelved due to other developments in FVIII manufacture and secondly, because of pressure on PFC to complete dry-heat treatment of all existing batches of FVIII.'

261. Also in February 1985, Professor Cash outlined the PFC's progress on viral inactivation and related issues in a paper for a meeting of SNBTS and Haemophilia Directors.[300] He noted that there had been '*some understandable criticisms*[301] *of the way we moved to make available unlimited quantities of heat treated factor VIII concentrate in late December 1984*'. Professor Cash considered the criticism to be justified but recorded his support for PFC staff and his belief that the SNBTS had acted responsibly and in the best interests of patients. As for developments in heat treatment of factor VIII:

a. Professor Cash summarised the background to PFC's existing heat-treated product. It was anticipated that it would '*remain the standard routine SNBTS issue until the autumn of 1985*'.
b. A second generation version of this product – heated at 68°C for 24 hours – was being developed. As with the first, it involved dry heat treatment of PFC's '*routine intermediate product*', though it required the addition of stabilisers prior to heat treatment. PFC had '*already determined optimal conditions*' and it was anticipated that preliminary clinical evaluations would be completed by the end of May 1985. The introduction of the product would be discussed with Haemophilia Directors, and Professor Cash proposed that it be evaluated '*within the context of the 'virgin' haemophiliacs/LFTs*'. Overall yield losses were in the region of 15-20%.
c. In addition, work on a high purity product continued. A heat treatment regime had not yet been decided but wet heat treatment was currently

[300] Report on 'Noted for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: March 1985, February 1985, **PRSE0003450**
[301] The nature of these criticisms is not entirely clear. It may be that Professor Cash was referring to a 19 December 1984 letter from Professor Hann of the Glasgow Children's Hospital, outlining Professor Hann's '*ethical and professional doubts at the way in which this major change has been instituted*'.

favoured. It was hoped that limited quantities would be available for preliminary clinical studies by late autumn 1985. Efforts would be '*directed with this product to achieve AIDS and viral hepatitis 'safety*".

262. Professor Cash also outlined initial progress in evaluating a system of batch dedication, which he considered to be a major and important development.

263. Another paper for the March 1985 SNBTS and Haemophilia Directors meetings – prepared on behalf of the PFC – provided an update on self-sufficiency. Taking into account decreased yield due to heat treatment, it was reported that Scotland was satisfying demand for factor VIII and that it held a national stock level of approximately 12 months of supply, assuming stable demand and that plasma quality was maintained.[302] The paper added that, as a result of decreasing yield due to heating and increasing demand, Scotland and Northern Ireland no longer had surplus product and it was unlikely that further material would be provided to England and Wales in the foreseeable future. The paper also provided a detailed update on the development of PFC's 24 hour heated product.

264. These developments were reviewed at the 7 March 1985 meeting of SNBTS and Haemophilia Directors, when Dr Perry '*informed members that a new intermediate Factor VIII concentrate, dry heat treated at 68°C for 24 hours, was ready for clinical evaluation*'.[303] The question of compensation and clinical trials was also discussed. It was '*generally agreed that the current situation was unsatisfactory and Dr Cash explained the difficulties that the SNBTS had perceived in attempting to resolve the problems through the CSA. Dr Ludlam requested that some action should be taken urgently*'.

[302] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1985, 1985, **PRSE0004101**, pg.3.
[303] Minutes of SNBTS and Haemophilia Director Meeting, 7 March 1985, **SBTS0000829**.

265. Batches of PFC's second generation heat-treated factor VIII were sent to the Edinburgh and South-East Scotland RTC soon thereafter.[304] However, on 19 March 1985, Dr Ludlam indicated his reluctance to participate in the clinical evaluation of this product without an assurance that a '*reasonable system for compensating patients*' was in place in case of adverse reactions. Without such an assurance, Dr Ludlam would have to seek approval from his local ethics committee.

266. In a 22 March 1985 letter to Dr Ludlam, Professor Cash stated that he was '*most distressed and surprised*' to learn of Dr Ludlam's position and asked that he reconsider it. Professor Cash outlined his attempts to resolve the issue of compensation arrangements, and stated that the SNBTS was '*utterly relying*' on Dr Ludlam's co-operation for its 1985-1986 production schedules. He also referred to an important aspect of the PFC's and SNBTS's approach to the introduction of different generations of heat-treated products: exhausting existing stocks before the introduction of a new product. The letter recorded: '*we envisage that by June/July 1985 the supplies of the first-generation product (68°C for 2 hours Dry Heat) will be exhausted – production was stopped in February 1985*'.

267. In response, Dr Ludlam explained that he had sought ethical approval for previous trials and indicated that he was willing to participate in the trial of this product before the compensation issue was resolved: '*As soon as I receive details of the present factor VIII product that requires testing I shall be delighted to arrange this. So far as the future is concerned I shall be looking for a concrete guarantee from the Department* [i.e. the SHHD] *for my patients*'.[305] In a further letter on 29 April 1985, Dr Ludlam stated that he had sought ethical approval for the trial and that arrangements were being made for four patients to participate in it '*in the very near future*'.

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[304] Letter from Dr Perry to Dr Bolton, re: Clinical Evaluation of Heat Treated FVIII (18/24 hours), 13 March 1985, **PRSE0001791**.

[305] Letter from Dr Ludlam to Dr Cash, re: Heat Treated Factor VIII, 4 April 1985, **PRSE0001907**. For Dr Boulton's comments to Professor Cash on this letter, see **PRSE0004240**.

268. At a 15 May 1985 meeting of SNBTS and Haemophilia Directors, Dr Perry reported that he '*expected the 68°C (dry heat) for 2 hours material would be exhausted in July/August and it would be replaced by the 68°C (dry heat) for 24 hours material which is thought to be a superior product and may also reduce the transmission of Non A/Non B hepatitis.*'[306] It was '*agreed that PFC would not issue 68°C for 24 hours material until stocks of the 2 hours material had been exhausted*'. Dr Perry explained that the '*decrease in yield of Factor VIII using a 24 hours dry heated method would be between 15 and 20%*'. An update was also provided on compensation arrangements for clinical trials.

269. The effect of heat treatment on Scotland's reserves of factor VIII was confirmed by Professor Cash who, in June 1985, wrote to Dr Lane informing him that PFC would not offer surplus factor VIII to BPL that year. Professor Cash explained that *'increased clinical use coupled with the fall in yield associated with heat treatment will inevitably result in our plasma supply balancing the product need*'.[307]

270. In a 15 July 1985 letter to Dr Lane, Dr Perry suggested there was little expectation that the 24-hour heated product would be safe from NANB hepatitis: '*we are primarily concerned with half-life and recovery since it is unlikely that we will achieve freedom from NANB*'.[308]

271. In a 26 August 1985 letter to RTDs, Dr Perry explained that PFC had '*nearly exhausted*' its stocks of the original heat-treated factor VIII and that it would be '*issuing new generation material in the near future*'.[309] Directors could '*expect to receive consignments within the next two months of the 'new' product at a level to maintain the system of batch dedication*'.

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[306] Minutes of Haemophilia and Blood Transfusion Working Group Meeting, 15 May 1985, **PRSE0003930**.
[307] Letter from John Cash to Dr Lane, 20 June 1985, **SBTS0000001_013**.
[308] Letter from Dr Perry to Dr Lane, re: Heat Treated Factor VIII, 15 July 1985, **CBLA0002217**.
[309] Letter from Dr Perry to Scottish Transfusion and Northern Ireland Blood Transfusion Directors, re: New Generation of Heat Treated Factor VIII (68 degrees/2 hours), 26 August 1985, **PRSE0004675**.

272. From January to September 1985, while the second generation product was being developed, PFC's 68°C for 2 hours heat-treated factor VIII was distributed in Scotland and Northern Ireland.[310] The 24 hour product was issued and used from September/October 1985. As at the date of a 10 January 1986 report by Dr Perry, there had been no reports of a HLTV-III seroconversion '*following the use of either of these products although equally it is recognised that the current heat treatment regime is unlikely to produce a non-infective product with respect to NANB or Hepatitis B*'. That said, recent unconfirmed reports had suggested that HTLV-III might be '*less susceptible to heat inactivation*' than '*originally thought*'. In response, PFC had '*recently recalled all residual stocks of 68°C/2 hr material*'.

Batch dedication

273. In addition to developments in viral inactivation, a batch dedication scheme, intended to limit the number of donors to whom patients were exposed, came into operation at the PFC in early 1985.[311]

274. The scheme was initially envisaged by Dr Brian McClelland as being based on a cycle of approximately six months, with each patient receiving a single batch for a period of no less than six months before moving onto a new batch.[312] On 22 January 1985, however, Dr Perry suggested a system based on a 3 month cycle, involving 3 cohorts of patients, to provide '*more immediate manoeuvrability and minimise the need to disrupt or increase the number of patients in an individual cohort if we run into problems later in the year*'.[313]

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[310] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**, pg.4.

[311] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**, pg.5.

[312] Letter from Dr McClelland to Dr Perry, re: Batch Dedication of Factor VIII and IX, 31 December 1984, **PRSE0001427**.

[313] Letter from Dr Perry to Dr Boulton, re: Comments in regard to a system of batch dedication to be implemented within the SNBTS, 22 January 1985, **SBTS0000324_073**.

275. Professor Cash had suggested a similar batch arrangement as early as 29 November 1983, noting that he had '*long dreamt that this might eventually be introduced (even gradually) - to reduce the number of donor exposures*'.[314] Professor Cash had also raised the matter of batch issues of product to individual patients at a meeting of SNBTS and Haemophilia Directors on 2 February 1984, noting concerns that '*individual patients were often exposed to a large number of batches in any one year*'. He recognised that an arrangement '*would not be easy*' but considered it '*could be achieved with close co-operation with clinical colleagues*'.[315]

276. In a paper prepared for the same meeting, Professor Cash wrote that, while '*a limitation of batch exposure, on the basis of minimising the risk of transmissions of non-A/non-B hepatitis may be largely theoretical it could be of relevance in the context of reducing the exposure to B virus and AIDS*'.[316] He suggested that, in light of the significant reserves of intermediate factor VIII, '*the time is opportune to direct efforts towards reducing the number of batch exposures per patient per year*'. Dr Perry suggests in his Inquiry witness statement that no further action was taken on this proposal until late 1984.[317]

277. In a report for a Scottish Haemophilia and SNBTS Directors meeting in March 1985, it was noted with regard to the batch dedication system that:

> 'The ability to prospectively dedicate whole batches of product to individual patients or groups of patients depends, for success, on substantial reserves of products. Such reserves are now available and it is now possible to implement a system of limited batch exposure.

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[314] Letter from Professor Cash to Mr Watt, re: Supplies of PFC Factor VIII and batch dedication, 29 November 1983, **PRSE0001537**.
[315] Minutes of SNBTS and Haemophilia Director Meeting, 2 February 1984, **PRSE0001556**.
[316] 'Notes for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1984, January 1984, **PRSE0004741**, pg.6-7.
[317] Dr Perry Witness Statement to IBI, **WITN6920001,** pg.59, para 176.

> Briefly, such a system would operate by dividing patients into groups (on a regional basis) with each group receiving product from a designated batch held at the RTC. RTCs would also carry reserve batches for replacement of 'active' batches when these became exhausted. Groups of patients would be assembled such that product batches would last between 3 and 6 months (depending on batch size).
>
> …
>
> Present estimates indicate that such a system can be in place by the end of March 1985… this will provide a smooth National transition from old product [factor VIII heated at 68°C for 2 hours] to new [factor VIII heated at 68°C for 24 hours]. Initial estimates suggest that such a system might reduce the annual batch exposure by a factor of five (or more in some cases)'.[318]

278. At the meeting itself, on 7 March 1985, Professor Cash '*said that although there were substantial national supplies there was still a need to build up further stocks at the PFC.*'[319] Pilot schemes in Edinburgh and Glasgow had indicated that batch dedication was '*feasible, though not without problems*'. It was considered '*likely that only a limited system of batch dedication could be applied to N. Ireland and to the smaller Scottish centres*'.

279. By the time of the 15 May 1985 meeting of SNBTS and Haemophilia Directors, it was '*agreed that the batch dedication system was operating well at the various RTCs and would continue to be monitored*'.[320]

280. In his 10 January 1986 report, Dr Perry commented that the system had '*operated successfully*', and that it would '*continue until a safe non-infective product*' was being issued routinely.[321] It was agreed, at a 5 March 1986

[318] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1985, 1985, **PRSE0004101**, pg.5.
[319] Minutes of SNBTS and Haemophilia Director Meeting, 7 March 1985, **SBTS0000829**
[320] Minutes of Haemophilia and Blood Transfusion Working Group Meeting, 15 May 1985, **PRSE0003930**
[321] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**

meeting of SNBTS and Haemophilia Directors, that the system was continuing to operate effectively and should be retained for a further 12 months.[322]

Further developments in heat treatment

281. In the course of 1985, as well as the heat treatment of its intermediate factor VIII at 68°C for 24 hours, PFC attempted to produce a high purity product which could be heat-treated under conditions giving comparable levels of viral inactivation to the BPL product 8Y. The aim of the programme was to achieve '*a new FVIII product which is high yielding, high purity and non-infective*'.[323]

282. Penrose detailed a number of experiments, undertaken in late 1985, in pursuit of this aim.[324] One of these, in October 1985, found that the high purity product failed to withstand dry heat treatment to 80°C but that it could tolerate a new freeze-drying process, whilst PFC's intermediate purity product could withstand both. Part of this experiment was described in a 22 October 1985 memo from Dr Foster to Dr McIntosh.[325]

283. In light of these findings, the PFC began to focus on the importance of drying conditions rather than product purity during the heat treatment process. On 13 November 1985, Dr Foster wrote to Dr Smith to ask for details of 8Y's freeze-drying conditions, noting that the PFC had '*some preliminary data that suggests that drying conditions may be particularly critical for the subsequent sensitivity of both protein and virus components to heating*'.[326] Dr Smith set these out in his response on 11 December 1985[327]; according to Dr Foster in his evidence to Penrose, this '*confirmed that the new freeze dry cycle devised*

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[322] Minutes of Directors of SNBTS and Haemophilia Director Meeting, 5 March 1986, **PRSE0001081**.
[323] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**, pg.4-5.
[324] Penrose Final Report, **PRSE0007002**, pg. 1048-1050, para 24.70-24.76.
[325] Memo from Dr Foster to R.McIntosh, re: Heat Treatment of Factor VIII, 22 October 1985, **PRSE0000404**
[326] Letter from Dr Foster to Dr Smith, re: Freeze drying conditions for FVIII concentrate, 13 November 1985, **PRSE0000668**.
[327] Letter from Dr Smith to Dr Foster, re: Freeze drying conditions for FVIII concentrate, 11 December 1985, **PRSE0003521**.

at the PFC was similar in design to that being used to freeze dry 8Y, consistent with this being the key aspect of the 8Y, rather than the degree of purification'.[328]

284. Dr Foster summarised the options available to PFC for its next generation of heat-treated factor VIII in an 18 December 1985 memo to Dr Perry.[329] He set out six possibilities, half of which involved PFC's high purity product (referred to as the 'NYU project'), with the other half using existing intermediate concentrate. He proposed giving top priority to two of the NYU options, but to continue on the third NYU option and one involving an intermediate concentrate '*so that we can either change tack on the NYU project if progress is slow or produce a modification of our existing product if pressure on heat inactivation demands it*'.

285. It appears that these options were discussed at an internal PFC meeting on 23 December 1985. In his Inquiry statement, Dr Foster states that, '*[h]aving discovered what we believed to be the importance of freeze drying to BPL's 8Y, we agreed that modifying our current product to be able to tolerate dry heating at 80°C would be the fastest route to achieving a greater margin of safety against HIV*'.[330]

286. Dr Perry's Inquiry statement records his recollection that there was '*no formal record prepared of this internal PFC meeting*'.[331] As for the decision taken at the meeting, he states:

> 'The prevailing view from this meeting was that virus safety and product yield were more important than product purity per se, and it was agreed to recommend to Professor Cash and subsequent Haemophilia Directors that resources should be focused on

[328] Penrose Final Report, **PRSE0007002**, pg.1050-1051, para 24.77.
[329] Memo from Dr Foster to Dr Perry, re: Factor VIII Progress and Options, 18 December 1985, **PRSE0004009**.
[330] Dr Peter Foster Witness Statement to IBI, 7 March 2022, **WITN6914001** p.90.
[331] Dr Robert Perry Witness Statement to IBI, 16 February 2022, **WITN6920001,** p.124.

modifications to the existing FVIII product and its heat treatment to 80°C/72hrs. This became known as the Z8 programme. When this objective had been achieved a return to the high purity NYU process development was envisaged.'

287. In his January 1986 report for a meeting of SNBTS and Haemophilia Directors, Dr Foster noted that preliminary data suggested that BPL's new product 8Y, heated at 80°C for 72 hours, appeared to be non-infective for HTLV III, hepatitis B and NANB hepatitis.[332] His description of PFC's work seemed to suggest a continued focus on a virally inactivated high purity factor VIII: '*While it is unlikely that the current PFC product could be successfully treated under these conditions, a major development programme has been underway for 12 months with a view to the production of a high purity FVIII product which can be formulated and heated treated, under conditions which give comparable levels of viral inactivation. Such treatment may not require such vigorous heating conditions*'.

288. In the same report, Dr Foster outlined some of the impact of heat treatment on Scotland's self-sufficiency in factor VIII. He recorded that demand for factor VIII was approaching PFC's output capacity earlier than previously anticipated, as a result of yield losses of between 25-30% due to heat treatment and increases in demand. As much as 9 to 12 months of national supply stock remained, but Haemophilia Directors were invited to comment on the possibility that demand would exceed production output in 1986 -1987. Dr Foster reported that efforts were being made to increase supply via improved manufacturing technology, improved plasma quality and increased plasma supply to PFC. It was calculated that 30,000 kg of additional plasma would be required in 1987/88.[333]

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[332] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**, pg.4.

[333] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457**.

289. A change in PFC's approach to heat-treatment was clarified in an addendum to Dr Foster's 10 January 1986 report (which may have been prepared prior to the 23 December 1985 meeting).[334] The report noted, based on a personal communication from Dr Smith, that dry heating at 80°C for 72 hours '*may well be effective in ensuring non-infectivity of products*'. It had been '*generally believed that heat treatment of this severity can only be achieved with high-purity products*', but recent PFC research had shown that this was '*not the case and that severe heating can be tolerated even at low purity if key process steps are carefully controlled prior to heat treatment.*' This would '*enable a non-infective product to be achieved using intermediate-purity material without compromising the development of the very high purity product.*' It was thought likely that a non-infective intermediate purity product would be available for evaluation in April 1986.

290. Notwithstanding a lack of contemporaneous records, Penrose suggested that it was highly likely that Professor Cash approved a change of direction at the PFC to develop an intermediate purity factor VIII product which was severely dry-heated – which came to be called Z8 – at some stage in early 1986.[335]

291. The PFC's revised focus was communicated by Professor Cash at a meeting of SNBTS and Haemophilia Directors on 5 March 1986:

> '… difficulties have arisen in relation to the heat treatment of the new high purity product and it has been decided to introduce an intermediate stage: a product which is only 2-3 times purer than the existing intermediate FVIII but can be dry heated at 80°C for 72 hours. It is hoped that this intermediate product will be available for clinical evaluation in April and for routine clinical issue within 3 months'.[336]

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[334] Addendum to Development of New Products 1986/87 for Factor VIII (Intermediate Purity Non-Infective), undated, **PRSE0002156**
[335] Penrose Final Report, **PRSE0007002**, pg.1054, para 24.89
[336] Minutes of Directors of SNBTS and Haemophilia Director Meeting, 5 March 1986, **PRSE0001081**.

292. The meeting also discussed pressures on PFC's ability to produce sufficient quantities of factor VIII concentrate to meet demand.

293. The name Z8 appears to have been suggested by Dr Foster in a 5 March 1986 memo, in which he commented that the '*multiplicity of PFC products under consideration*' could cause confusion outside PFC.[337]

294. The note of a meeting on 17 March 1986 suggests collaboration between PFC and BPL in the development of their heat-treated products.[338]

295. PFC's development of Z8 continued during the remainder of 1986. Penrose recorded that the first viral inactivation experiments were performed on Z8 at 80°C on 25 April 1986, and that the first pilot scale production of Z8 at 80°C for 72 hours was carried out on 23 June 1986.[339] Dr Foster's Inquiry statement provides further detail on this process, including technical obstacles encountered by the PFC.[340]

296. Around this time, Dr Ludlam was making enquiries about the availability of BPL's 8Y in Scotland for certain patients, pending the production of Scotland's next generation heat-treated factor VIII. This issue has been explored in other evidence heard by the Inquiry and is not considered in detail here, save to note the following:

a. In a 27 June 1986 letter to Professor Cash, Dr Boulton reported his understanding that, a few weeks earlier, Dr Ludlam had asked whether 8Y '*could be made available in the event of a 'virgin' haemophiliac being presented. He tells me that he would be happy to treat such*

[337] Memo from Dr Foster to Dr Perry and Dr McIntosh, re: New Factor VIII Products, 5 March 1986, **PRSE0004156**
[338] Note of PFC Meeting, 17 March 1986, **PRSE0003764**
[339] Penrose Final Report, **PRSE0007002**, pg.1058, para 24.104 to 24.107.
[340] Dr Peter Foster Witness Statement to IBI, 7 March 2022, **WITN6914001** pp.91-93.

patients with a product prepared by the SNBTS that has been subjected to an 'equivalent heat-treatment regime'.[341]

b. In another letter that same day, Dr Boulton passed on '*a couple of verbal comments about blood products*' from Dr Ludlam to Dr Perry.[342] One of these was that a '*young haemophiliac who previously had minimal therapy with factor VIII*' had been treated with PFC's existing heat-treated product about a month earlier, and was showing signs of NANB hepatitis. Dr Ludlam was described as '*a bit ruthful with his own staff about this because he feels that this patient should have received VIIIY or an equivalent product*.'

297. In a 2 July 1986 response to Dr Boulton's letter, Dr Perry suggested that Z8 would be introduced shortly, and that there might be a modification to the PFC/SNBTS policy of exhausting stocks before introducing a new product.[343] He wrote that the PFC was '*poised to introduce yet another FVIII product which will be heat treated at 80°/72 hrs and should therefore be comparable to 8Y and better than anything available commercially*.' As for the PFC's stock policy, he added: '*I've no doubt that as soon as this becomes available, virgin patients will be able to gain access to this product before stocks of the existing product are exhausted. However, this has not been formally agreed and we should yet declare this as a policy*.'

298. In a further 7 July 1986 letter to Dr Boulton, Dr Perry indicated that the PFC was continuing to develop a high purity, non-infective factor VIII alongside Z8, and that Z8 would not begin to be introduced until September 1986.[344] The high purity concentrate – described as the '*phase IV product*' – was '*planned for production in January '87 and therefore it is hoped that supply will be in September '87 – after we've used up stocks of Phase III product*'. While there

[341] Letter from Dr Boulton to Dr Cash, re Trials of Factor VIII Products, 27 June 1986, **PRSE0002000**
[342] Letter from Dr Boulton to Dr Perry, re: Patient treated with heat-treated DEFIX has no evidence of NANB Hepatitis, 27 June 1986, **PRSE0003845**
[343] Letter from Dr Perry to Dr Boulton, re: Introduction of heat treated factor VIII at PFC comparable to BPL's 8Y, 2 July 1986, **PRSE0003030**
[344] Letter from Dr Perry to Dr Boulton, re: Factor VIII Trials, 7 July 1986, **PRSE0003814**.

would be no PFC product '*virucidally comparable to 8Y*' until September 1986, it was Dr Perry's intention '*to supply the Phase III product* [i.e. Z8] *to 'virgins' since we hope to demonstrate by that time that it is virucidally equivalent thus removing the need to go South.*' For the July to September 1986 period, Dr Perry suggested that supplies of 8Y '*for special cases*' could probably be obtained. Steps appear to have been taken subsequently to obtain some 8Y in Scotland. Around 1 August 1986, Dr Smith sent 50 vials of 8Y to PFC to '*protect Category I patients before your Z8 is ready*'.[345]

299. On 30 July 1986, a PFC steering group agreed that '*no further old-style FVIII (NY) will be made for the time being*' (i.e. heated at 68°C for 24 hours) and that Z8 large scale production would commence on 4 August 1986.[346] A report from the following month recorded that this decision was made in order to reduce the existing stockpile of NY material in preparation for the introduction of Z8.[347]

300. PFC's production of Z8 initially seemed to proceed smoothly. On 7 August 1986, Dr Perry informed Dr Boulton that PFC had '*successfully manufactured 2 batches*' of the product and that, '*assuming all is well on the QA* [i.e. Quality Assurance] *front, we are well on target to make product available for clinical trial end of August/beginning of September.*'[348]

301. However, later that month, difficulties in the manufacturing process arose. In a 29 August 1986 letter to Dr Boulton, Dr Perry explained that the PFC had '*recently encountered an eleventh hour problem with freeze drying which we are now addressing with some considerable urgency*'.[349] The result was that the PFC would '*not be able to meet the target dates of early September for*

[345] Letter from J K Smith (Chief Project Scientist) to Dr R Perry (Director, Protein Fractionation Centre) re: Trial Protocol and 50 vials of 8Y 3312, 1 August 1986, **PRSE0002616**.
[346] Minutes of New FVIII Product Manufacture Steering Group Meeting, 30 July 1986, **PRSE0000813**.
[347] Supply and Demand 1987/88 Production Distribution 1987/88 Report, dated 7 April 1987, **PRSE0001909**.
[348] Letter from Dr Perry to Dr Boulton, re: PFC Heat Treated Factor VIII (80/72 hours), 7 August 1986, **PRSE0002611**
[349] Letter from Dr Perry to Dr Boulton, re: Trials of Phase III Factor VIII, 29 August 1986, **PRSE0002591.** Dr Perry was responding to a 22 August 1986 letter from Dr Boulton (**PRSE0000362**).

clinical trials', though Dr Perry was '*confident that the delay*' would be '*measured in weeks rather than months*'.

302. Another issue affecting Z8's introduction was the question of compensation arrangements for those involved in clinical trials, which was discussed briefly at a 20 August 1986 meeting of the SNBTS sub-committee.[350]

303. A detailed update on Z8 production was provided at a 14 October 1986 meeting of the Coagulation Factor Study Group. Dr Foster reported losses of 30-70% of factor VIII activity when full scale production was attempted, with solubility times of 35-40 minutes. A number of manufacturing modifications were being considered. The minutes record that it '*was thought that it was unnecessary to heat at 80°C/72 hours and studies on product heated at 75°C/72 hours had yielded approximately 300iu FVIII/L plasma (current yield was 200iu)*'.[351] Professor Cash agreed to seek the agreement of Haemophilia Directors to undertake a small study of the product heated at 75°C for 72 hours.[352] It was also reported that, as a result of a number of factors including the '*diversion of effort to Z8*', there had been no progress in the development of PFC's phase IV, high purity product.

304. In a 15 October 1986 letter to Dr Perry, Professor Cash confirmed his view that it was appropriate to commence production of the Z8 product treated at 75°C for 72 hours, while continuing to develop the 80°C version.[353]

305. The following month, in a 13 November 1986 letter to Dr Boulton, Professor Cash explained that the PFC intended to '*begin routine production, hopefully in the very near future*' of Z8 heated at 75°C for 72 hours.[354] He understood that the product would be available for trial purposes soon, and asked Dr Boulton to liaise with Drs Ludlam, Forbes and Mayne regarding half-life and

[350] Minutes of Blood Transfusion Service Sub-Committee Meeting, 20 August 1986, **PRSE0000410**
[351] Minutes of Coagulation Factor Study Group Meeting, 14 October 1986, **PRSE0000294**.
[352] Letter from Professor Cash to Dr Perry, re: Temperature of treating Z8, 15 October 1986, **SBTS0000332_014**.
[353] Letter from Professor Cash to Dr Perry, re: Temperature of treating Z8, 15 October 1986, **SBTS0000332_014.**
[354] Letter from Dr Cash to Dr Boulton, re: PFC Factor VIII Concentrate (Z8), 13 November 1986, **PRSE0002335.**

recovery studies. At a 1 December 1986 meeting, held to review SNBTS trials of PFC products, Dr Perry reported that the 75°C for 72 hours product was '*now available for half-life and recovery studies in Edinburgh, Glasgow and Northern Ireland prior to its introduction into routine use*'.[355]

306. A PFC document recorded that a batch of 75°C Z8 was '*placed at issue*' – i.e. certified as fit for clinical use – on 2 December 1986, with the batch's first vials sent to Dr Boulton in late December 1986.[356] Correspondence also took place during December 1986 regarding arrangements for sending trial material to the Glasgow and West of Scotland RTC.[357]

307. Around this time, the absence of compensation arrangements for clinical trials was raised again. Dr Boulton outlined Dr Ludlam's concerns about this issue in a 5 December 1986 letter to Professor Cash, recording that he had a '*strong feeling that he* [Dr Ludlam] *will be unwilling to agree to such trials unless there is a specific commitment by the SHHD that any patients who suffer adverse effects as a result of the infusion will be given appropriate compensation*.'[358] Dr Ludlam put his concerns directly to Professor Cash in an 11 December 1986 letter, noting that he had '*raised this a long time ago with SHHD and there has been no response*'.[359]

308. This issue remained unresolved in early 1987. Dr Ludlam raised it again in a 5 January 1987 letter to Professor Cash, in which he wrote: '*with great regret, I am unwilling to test further blood products on patients until I receive written assurance that appropriate compensation will be available*.'[360] A series of further letters followed, including to the SHHD, and the matter was

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[355] Note of Clinical Trial Review Meeting, 1 December 1985, **PRSE0003763.**
[356] SNBTS PFC Factor VIII Batch Issue History for Batch 0310-60110, 1987, **PRSE0001468**. For evidence of the meaning of the phrase 'placed at issue', see the Penrose Final Report para 24.133 and footnote 264.
[357] Letter from Dr Boulton to Dr Perry, re: Z8 update, 1 December 1986,**PRSE0003688;** letter from R J Crawford to Dr Perry, re: Clinical Trial of New Factor VIII Product Z8, 12 December 1986, **PRSE0000054**; and letter from Dr Perry to Dr Boulton, re: Clinical Trial of Z8, 23 December 1986, **PRSE0001565.**
[358] Letter from Dr Boulton to Dr Cash, re: Z8 Patient Trials, 5 December 1986, **PRSE0003951.**
[359] Letter from Dr Ludlam to Dr Cash, re: Clinical Assessment of Z8, 11 December 1986, **PRSE0000696.**
[360] Letter from Dr Ludlam to Dr Cash, re: Assessment of New NHS Blood Products, 5 January 1987, **PRSE0003282.**

considered within the SHHD and the Treasury.[361] Other clinicians shared Dr Ludlam's concerns: see, for example, a letter from Drs Dawson and Bennett of the Aberdeen Haemophilia Centre to Processor Cash in mid-January 1987.[362]

309. In a 6 February 1987 letter, Alexander Murray (SHHD) informed Professor Cash that compensation arrangements '*for the clinical trials of heat-treated Factor VIII*' had been agreed.[363] The issue was discussed in detail at the 9 February 1987 meeting of SNBTS and Haemophilia Directors (attended by SHHD representatives), when it was confirmed that the arrangements would '*only apply to the initial trials of the new factor VIII*'.[364] The scheme did not apply to '*administration for therapeutic purposes*'. It was also noted that further batches of factor VIII manufactured since January 1987 had been dry heated at 80°C for 72 hours.

310. Dr Ludlam continued to be involved in correspondence regarding the scope of the compensation arrangements in February 1987.[365] Notwithstanding these queries, it appears that clinical trials of Z8 began around late February. At a meeting of PFC heads of department on 17 February 1987, it was recorded that '*the Glasgow Centre had received 75°C for trial and Dr Ludlam had undertaken to carry out 75°C trials in minor bleeding patients not non-bleeding patients*'.[366] It was also noted that Dr Ludlam would be '*delighted to receive the 80°C product. Dr Cuthbertson undertook to send this material to him immediately*'.

311. As with the introduction of factor VIII heated at 68°C for 24 hours, as Z8 became available for routine distribution, the PFC/SNBTS policy of exhausting

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[361] See, for example, the documents at **PRSE0001927, PRSE0001209, PRSE0002134, PRSE0000222, PRSE0001577, PRSE0003888, PRSE0001726.**
[362] Letter from Bruce Bennett and Audrey A. Dawson (Aberdeen Royal Infirmary) to Dr Cash,, re: SHHD compensation for Z8, 13 January 1987, **PRSE0003233**
[363] Letter from A J Murray (SHHD) to Dr Cash, re: Department view on compensation for PFC heat treated Factor VIII reactions, 6 February 1987, **PRSE0000760.**
[364] Minutes of SNBTS Director and Haemophilia Directors Meeting, 9 February 1987, **PRSE0002769.**
[365] See, for example, the documents at **PRSE0003852 and PRSE0004360**.
[366] Minutes of PFC Heads of Department and Section Managers, 17 February 1987, **PRSE0004736.**

existing supplies before introducing a new product was maintained, though with an exception for certain patients. Dr Perry addressed this point and a number of matters in a report prepared for an SNBTS annual supply and demand meeting on 7 April 1987.[367] He also recorded that, at present rates of demand, it was estimated that Z8 would become available for all patients by July 1987.

312. At the meeting itself, it was noted that '*all the NY product had now been issued and Z8 introduced in its place*'.[368] The following proposals were agreed:

a. Batch dedication would be maintained.
b. Residual stocks of NY and Z8 heated at 75°C would be '*fed into the batch dedication system as normal*'.
c. Additional batch dedication lanes would be created at each RTC for 80°C Z8, to make it available '*for special patient cohorts prior to consumption of existing stocks of old material*'.

313. It was also noted that Directors were '*free to negotiate with Dr Perry*' for the replacement of the existing NY product for Z8.

314. In a 10 April 1987 letter to Dr Perry, Professor Cash confirmed that he was satisfied that the PFC could now issue Z8 for routine clinical use.[369]

315. According to Penrose, Z8 was then gradually introduced through the batch dedication scheme in May to July 1987.[370] During this period, Dr Ludlam continued to correspond with the SHHD and others about the scope of

[367] Report on 'Supply and Demand 1987/88 Production Distribution 1987/88', 7 April 1987, **PRSE0001909.**
[368] Minutes of SNBTS Annual Supply and Demand Meeting, 7 April 1987, **SBTS0000248_021**, pg.4.
[369] Letter from Professor Cash to Dr Perry, re: Z8 Phase I Studies, 10 April 1987, **PRSE0003917.**
[370] Penrose Final Report, **PRSE0007002**, pg.1071, para 24.158.

compensation arrangements. The issue was eventually resolved in November 1987.[371]

316. As shown in Annex A, between 1985 and 1987, no commercial factor VIII was used in Scottish Haemophilia Centres. NHS factor VIII used in Scotland increased from 6,889,163 iu (1985) to 8,019,560 iu (1987). Note that the latter figure does not include data from Aberdeen, and is likely to be an underestimate, as the Inquiry has been unable to locate the Centre's 1987 return.

317. By contrast, Annex B shows that commercial Factor VIII continued to be used in Northern Ireland during this period. While the amount dropped significantly relative to 1984, the Belfast Centre used 605,274 iu in 1985, 745,413 iu in 1986 and 986,750 iu in 1987.

318. Despite self-sufficiency in factor VIII apparently having been maintained in Scotland during this period, there were concerns about the future. In 1987, an SNBTS public expenditure report confirmed that Scotland remained self-sufficient in blood and blood products but that '*the arrival of AIDS, the continued escalation in demand for existing and new products continues to threaten this position*'. The primary problem was said to be '*the availability of finance*', and it was suggested that '*continued limitations in the release of adequate funds as witnessed over the past 5 years may ensure the need for the SHS* [Scottish Health Service] *once again to rely on the commercial sector: a high cost and less safe (for the patients) option*'.[372] The report noted a weakening in Scotland's previously strong position on self-sufficiency, referring to the introduction of products such as high purity and heat-treated

[371] Letter from D Macniven (SHHD) to Professor Cash, re: Clinical Trials Compensation, 9 November 1987, **PRSE0000118** and letter from Dr Ludlam to Professor Cash, re: Clinical Trials Compensation, 19 November 1987, **LOTH0000010_043.**
[372] SNBTS Public Expenditure Survey, 1987, **PRSE0003941**, pg. 2; 6.

factor VIII, the impact of AIDS and a fall in yield, resulting in a possible requirement for increased plasma input.[373]

Factor IX

319. Professor Cash outlined the PFC's progress in producing a heat-treated factor IX in a paper for a March 1985 meeting of SNBTS and Haemophilia Directors.[374] He noted that '*[d]espite considerable efforts over the last 2 years it has only very recently been possible to make arrangements for animal model (thrombogenicity) testing*.' It was anticipated that a heat-treated concentrate – which appeared likely to be a heated DEFIX – would be available for preliminary clinical evaluation by late spring 1985.

320. Another paper for the March 1985 meeting – prepared on behalf of the PFC – provided the following update on heat treatment of factor IX:[375]

> 'A heat treatment programme for FIX has been underway for some time at PFC and while the problems of product solubility and FIX decay subsequent to heat treatment are much less than those of FVIII, there remain more complex problems associated with an increased possibility of thrombogenicity following heat treatment. A detailed animal study has been initiated (in collaboration with BPL) and subject to a satisfactory outcome of this study it is hoped that a heated FIX product (DEFIX) will be available by the end of 1985 for preliminary clinical studies.
>
> There are no plans at the present time to reintroduce Supernine as an alternative to DEFIX'.

[373] SNBTS Public Expenditure Survey, 1987, **PRSE0003941**, pg. 2; 6.
[374] Report on 'Noted for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: March 1985, February 1985, **PRSE0003450.**
[375] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1985, **PRSE0004101.**

321. At the 7 March 1985 meeting of SNBTS and Haemophilia Directors, Dr Perry said that there had been '*a substantial increase in the use of* [unheated] *DEFIX and PFC currently had only 2/3 months supply, which was insufficient for a programme of batch dedication. The target was a 12 months supply.*'[376] As for heat treatment, Dr Ludlam '*enquired about the prospects of SNBTS heat treated factor IX and whether it might be advisable to buy commercial concentrate for certain patients*.' Dr Perry explained in response that the PFC's plans for Factor IX '*did not include a crash programme of heat treatment but aimed for a high purity product*.' It was said that there had been a lack of facilities for animal thrombogenicity testing, but it was '*hoped that clinical evaluations for heat treated factor IX would soon be completed*.'

322. An update was provided at the 15 May 1985 meeting of SNBTS and Haemophilia Directors.[377] Dr Perry explained that '*the heat treatment of Factor IX was a high priority project*' and that animal tests were underway. PFC expected clinical evaluation studies to begin in 2-3 months' time.

323. In his Inquiry statement, Dr Perry suggested that PFC stopped supplying unheated factor IX in May 1985 and placed stocks of this product in quarantine, but that it did not recall unheated product which had been issued.[378] He added: '*To the best of my knowledge, the quarantined product was not used on any occasion for patient treatment between May and October 1985*.'

324. By the time of a 16 August 1985 meeting of PFC heads of department, Dr Perry reported that PFC's heat-treated factor IX '*had now been issued for routine use at Edinburgh Centre and further issues would be made to remaining Centres in September/October 1985*.'[379]

[376] Minutes of SNBTS and Haemophilia Director Meeting, 7 March 1985, **SBTS0000829**.
[377] Minutes of Haemophilia and Blood Transfusion Working Group Meeting, 15 May 1985, **PRSE0003930.**
[378] Dr Robert Perry Witness Statement to IBI, 16 February 2022, **WITN6920001**, from para 508.
[379] Minutes of PFC Heads of Department and Section Managers, 16 August 1985, **PRSE0002252.**

325. In a January 1986 report, Dr Perry recorded that PFC's heat-treated factor IX – heated at 80°C for 72 hours – was '*now at routine issue*'.[380] As to whether it was likely to be non-infective, he wrote: '*Extrapolation of the clinical data derived from the BPL FVIII (80°C/72 hrs) product would suggest that PFC FIX is likely to be non-infective*.' Extensive animal studies indicated that the product carried '*no additional risk of thrombogenicity*'.

326. In January 1987, Professor Cash reported that in 1985/1986, PFC declined to issue a dry heat-treated factor IX (80°C for 72 hours) for clinical use until its safety in terms of thrombogenicity had been validated by animal model studies. As a result, '*in this period substantial commercial purchases were made*'. Professor Cash noted that by the time the PFC was in a position to issue a validated product, there had been a remarkable escalation in clinical demand, likely due to the '*management of haemophilia A patients with inhibitors*'. As a result, PFC had severe difficulties maintaining supplies and significant difficulties remained.[381]

327. Other evidence suggests that there was pressure on PFC's capacity to meet demand for heat-treated factor IX around this time. In a March 1987 report, Dr Perry wrote that increased production of this product in 1986/87 had '*coincided with a commensurate increase in demand*'.[382] It had become apparent that the increased usage was not associated with non-haemophilia patients. He added: '*FIX is <u>not</u> in abundant supply therefore it is proposed that usage in 1987/88 is restricted to Haemophilia patients*'.

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[380] PFC Report for SHS Haemophilia and SNBTS Directors Meeting in March 1986 by R J Perry, 10 January 1986, **PRSE0003457.**

[381] Report on 'Noted for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: February 1987, January 1987, **PRSE0004419**, pg.6-7.

[382] Report on 'Supply and Demand 1987/88 Production Distribution 1987/88', 7 April 1987, **PRSE0001909.**

III. Challenges to maintaining self-sufficiency in Scotland and the exchange of material between Scotland and Northern Ireland (1988 to 1991)

Factor VIII

328. Concerns around Scotland's ability to maintain self-sufficiency in factor VIII were reflected in a 19 April 1988 report from Dr Perry.[383] He recorded that there existed a '*clear upward trend in the use of FVIII during 1988. This trend is substantial overall but perhaps most significant during the last quarter of 1987/88*.' Issues in 1988 were said to '*represent a major and unplanned escalation in demand*.' Coupled with manufacturing/technical difficulties at PFC, these had '*resulted in supply difficulties towards the end of 1987/88*.' Dr Perry added: '*Whilst these technical problems associated with the introduction of the new Z8 product have now been substantially resolved, their effect combined with increased demand has led to a major depletion of National product stocks*.' The report also outlined PFC's development of high purity factor VIII concentrates.

329. Professor Cash reported at a 15 June 1988 meeting that Scotland was no longer self-sufficient in factor VIII and albumin. A letter was to be written to Scottish Health Boards indicating they would need to purchase around 2.5 to 3 million iu of factor VIII in 1988/9 and, if demand stayed the same, 3 million iu in 1989/90.[384] A June 1988 letter from the SHHD to the CSA referred to some of the factors which were impacting self-sufficiency, including a *'recent rapid rise in the demand for Factor VIII'* and a decline in donations in some parts of Scotland (though it was suggested that the drop in donations had been checked as a result of a publicity campaign).[385]

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[383] Paper on 'Haemophilia Directors Meeting May 1988 (Scotland only)' by Dr Perry, 19 April 1988, **PRSE0000215.**

[384] BTS: miscellaneous issues note of meeting, 15 June 1988, **SBTS0000178_011**.

[385] Letter from William (SHHD) to Donald Macquaker (Chairman of CSA), re: BTS product licences for Factor VIII and Z8, and self-sufficiency in Scotland, 14 June 1988, **PRSE0000711**.

330. A SHHD note of a meeting with Glasgow Haemophilia Directors in August 1988 recorded that '*[s]elf-sufficiency for Factor VIII has been lost, after being achieved 4 or 5 years ago.*' As a result, Glasgow had arranged to purchase 100,000 units of commercial product a month at a monthly cost of £23,000. It was believed that Edinburgh had entered into a similar arrangement.[386]

331. An increased reliance on commercial concentrates from 1988 is reflected in the Scottish Haemophilia Centre return data in Annex A. Use of commercial factor VIII increased from zero in 1987 to 748,930 iu in 1988. Meanwhile, consumption of PFC factor VIII decreased from 8,019,560 iu in 1987 to 7,524,566 iu in 1988.

332. Professor Cash addressed some of these issues in an August 1988 paper (which appears to have been prepared for a November 1988 meeting with the SHHD): '*Comments on the current difficulties in the supply of factor VIII for the SHS by the SNBTS and proposals for the reassertion of self-sufficiency.*'[387] Having set out a number of problems with the operation of PFC, Professor Cash summarised developments in the supply and demand of factor VIII in Scotland as follows:

> 'Colleagues will recall that in 1983/84 the combined effect of the increased PFC yields and RTC plasma collections were apparent – substantial stocks of factor VIII were put in place and significant quantities of finished product were dispatched to BPL. This success story was destabilised with the onset of heat treatment and over the subsequent years the rising (as predicted) clinical demand was met by a combination of continued production and use of national stocks…

[386] Letter from Dr Forrester (SHHD) to Dr Scott et al. re: Factor VIII use and requirements, 26 August, 1988, **SCGV0000110_026**.
[387] 'Comments on the Current Difficulties in the Supply of Factor VIII for the SHS by the SNBTS and Proposals for the Reassertion of Self-Sufficiency' by Dr Cash, July 1988, **SBTS0000626_139.**

By March 1988 the stocks had been exhausted and the anticipated improvements in production yields not materialised – this interplay of factors is the root cause of current difficulties. They were foreseen in 1985 and efforts to head off the impending crisis by introducing a factor (increase in plasma to PFC), which was the only one that would guarantee success, did not materialise.'

Re-allocation from Northern Ireland

333. In response to this emerging reliance on commercial concentrates, an agreement was reached to re-allocate some PFC factor VIII from Northern Ireland to Scotland. This appears to have come about following discussion of Scotland's loss of self-sufficiency at a September 1988 meeting of Haemophilia Reference Centre.[388] Dr Ludlam stated that there would be '*a shortfall of 2 million units in the current year*'. He described this as being due to '*a fall in donations and problems with stock control*', and suggested the problem was likely to last for two years. In response, Dr Mayne suggested that the relationship between Scotland and Northern Ireland could be revisited to consider '*whether or not a more realistic arrangement could be made between the two countries*'.

334. This led to an agreement to re-allocate a significant quantity of Z8 from Northern Ireland to Scotland the following year. A June 1989 report for a meeting of SNBTS and Haemophilia Directors recorded that '*1 million IU of Z8 which was made for Northern Ireland were supplied to the Scottish Health Service in January to March 1989. In compensation for this supply, Scottish Health Boards purchased an equivalent amount of commercial Factor VIII for use in Northern Ireland*,'[389]

[388] Minutes of the Thirtieth Meeting of the Haemophilia Reference Centre Directors' meeting, 5 September 1988, **HCDO0000431**.
[389] Report titled 'Notes For Scottish Health Service Haemophilia Centre - Transfusion Service - Directors Meeting', Dr R.Stewart, 23 June 1989, **PRSE0004030**.

335. Dr Mayne explained the rationale for suggesting this arrangement in a 23 November 1988 letter to Professor Cash. She wrote that she had proposed it in '*view of the widespread discussions regarding alterations to immunological tolerance in multi-transfused patients*.' She noted that there were children and other patients in Scotland who had previously only been treated with NHS factor products and had not received any commercial concentrate. By contrast, in Northern Ireland, '*all patients except children were exposed to commercial factor VIII*' up until 1985. Dr Mayne had therefore suggested the exchange '*to enable all patients who had never received other than NHS factor VIII to continue to do so*.' She explained that she would be '*happy to let them have my allocation of NHS factor VIII, barring the needs for the children here and one or two patients who were in the same category as those in Scotland, namely never exposed to commercial material*.' She noted that during '*the past few years I have used Profilate for replacement therapy during surgery, etc, and was happy to make some arrangements which would be beneficial to the majority of patients in both situations, i.e. Northern Ireland and Scotland*.' The letter stated that this exchange was intended to be a temporary measure designed to protect the greatest number of patients who had not previously been treated with commercial products.[390]

336. On 1 December 1988, Dr Mayne issued an instruction to allow part of the Northern Ireland allocation of NHS product to be released to Scottish Centres. She advised Dr Perry that 300,000 iu of commercial concentrate had been purchased and that the equivalent amount of NHS factor VIII concentrate, previously allocated to Northern Ireland from the PFC, could be released to the Lothian Health Board.[391]

337. It appears that Dr Mayne may not have had the authority necessary to issue this instruction. In a 13 December 1988 letter, Dr McKenna, the

[390] Letter from Dr. E. Mayne to Professor Cash re: SNBTS and Northern Ireland exchange of FVIII, 23 November 1988, **NIBS0001767**.
[391] Letter from Dr. E. Mayne, Northern Ireland Haemophilia Reference Centre, to Dr R Perry, SNBTS, 1 December 1988, **SBTS0000384_066**.

Northern Ireland Chief Medical Officer, informed Dr Mayne that she did not have the authority to issue the instruction in her 1 December 1988 letter. He explained that '*[s]ervices provided by one Department for another have to be formally agreed and indeed officials of this Department would normally keep the Minister informed of arrangements of this kind*.' Nonetheless, Dr McKenna considered that the '*proposals in this case were sound*' and indicated that they would be formalised shortly.[392]

338. In a 15 December 1988 letter, Duncan Macniven of the SHHD recorded that the DHSS (NI) had approved the arrangement, as well as summarising its aim and how it would work in practice.[393]

339. As shown in Annex B, use of NHS factor VIII in Northern Ireland decreased from 2,022,958 iu in 1987 to 998,700 iu in 1988. This would appear to be as a result of this re-allocation arrangement.

Regaining self-sufficiency

340. In a 10 February 1989 letter to the Grampian Health Board, Mr Donald (of the CSA) summarised Scotland's attempts to achieve self-sufficiency in factor VIII on the basis of Professor Cash's 1981 demand estimates.[394] He recorded that, from 1986 onwards, demand had '*accelerated very steeply and the anticipated demand for the year ending 1989 some 12m i.u.'s is clearly far beyond the present productive capacity of the SNBTS*.' He also noted that manufacturing the Z8 product had had '*a dramatic effect on the overall yield of Factor VIII*.' Mr Donald stated that the SNBTS was '*clearly not funded in such a way as to allow for the purchase of commercial Factor VIII*', and so could not purchase commercial products on behalf of the Health Board. He further

[392] Letter from J. McKenna, Chief Medical Officer to Dr Elizabeth Mayne, re: Authority for exchange, 13 December 1988, **NIBS0001770**.
[393] Letter from D Macniven (SHHD) to J T Donald (CSA), re: Northern Ireland exchange with Scotland, 15 December 1988, **SCGV0000105_018**.
[394] Letter from J. T. Donald to Hance Fullerton (Grampian Health Board Aberdeen) re Transfer of Factor VIII from Northern Ireland, 10 February 1989, **SBTS0000280_018**.

referred to the arrangement with Northern Ireland: '*we as a Country are most fortunate in the current situation where the Northern Ireland Centre has agreed to transfer 1m of their 1.8m units to Scotland*.'

341. In a June 1989 paper for a July meeting of SNBTS and Haemophilia Directors, Dr Stewart reported that the decline in usage of factor VIII concentrates which had occurred in 1986 had been reversed, and usage was '*back to the level seen in 1984*'.[395] As yield had been reduced by the introduction of heat treatment, and there had been no increase in plasma procurement, '*the maintenance of supply in the years 1986-1988 was at the expense of the National Stock.*' In order to replenish the national stock to 2 million units, the amount of Z8 issued by the PFC had been cut back to around 7 million units. The report noted that the PFC had produced a small scale batch of high purity factor VIII, but difficulties had been encountered in large scale production.

342. At the 21 July 1989 meeting, it was noted that factor VIII would continue to be issued at 8 million units per year but that '*this would slow the rebuilding of the national reserve stock which had been depleted*.'[396] There was '*some prospect of increased production*' but this was said to be '*dependent on funding*'. A new, high purity product (S8) was discussed. Haemophilia Directors '*expressed their hope that this product…would be in production shortly, as the present Z8 product had a very low purity*.'

343. A number of production issues arose at PFC during 1989. Alongside ongoing difficulties around working patterns, these appear to have placed significant strain on PFC's ability to meet demand for factor VIII. The issues were described in a 19 December 1989 letter, in which Dr McIntosh informed the CSA of a series of '*production set-backs… that have greatly reduced stock levels of finished FVIII ready for issue. Some of these - like the long*

[395] 'Notes For Scottish Health Service Haemophilia Centre - Transfusion Service - Directors Meeting' by Dr R.Stewart, 23 June 1989, **PRSE0004030.**
[396] Note of SNBTS and Haemophilia Directors Meeting, 21 July 1989, **PRSE0004188.**

shut-down for repairs and maintenance - were foreseen and planned for, some were donor related, and others were due to breakdowns in the processing itself. Stock levels are now undesirably low, at less than 750,000 units.'

344. Dr McIntosh noted that the PFC was keen to maintain agreed issue levels of 860,000 units per month and that, following the completion of production lots passing quality checks, it was estimated that PFC would accumulate a stock level of 1.2m iu by March 1990. This stock would be made up of Z8, rather than the high purity product S8, until levels had increased. Dr McIntosh commented that '*though we do expect to survive without a crisis this financial year, we cannot regard ourselves as being completely out of the woods by any means*'. To meet the challenge ahead, Dr McIntosh considered that the PFC needed to address '*its artificially restricted capacity*' via the introduction of longer shift patterns:

> 'Out of 168 hours available per week we only currently work 30 hours in our key bottleneck processing areas. This is not only inefficient in terms of capital utilisation but also quite crippling in terms of capacity at a time of high and rising demand. Worst of all, it is also quite inappropriate in terms of good manufacturing practice in an area designed for continuous processing. Quality, cost and availability all demand that we increase the length of our normal working week with all speed. The PFC management team are already working on detailed proposals for us and I hope that we can move forward into more intensive production in key areas during the first quarter of 1990. This would allow proper production trials for S8, a comfortable Z8 stock build up, and in due course an increase in our level of issues. For this we will, I believe, require a variation order from SHHD - enabling us to work on shifts in a flexible and responsive way'.[397]

[397] Letter from David B McIntosh to J T Donald (CSA), re: PFC Factor VIII stock and shift-working, 19 December 1989, **PRSE0001425**.

345. A January 1990 SNBTS report recorded that PFC (as opposed to RTC) stocks of Z8 had fallen to 1.25 million iu. Targets of 2 million iu by March 1990 and 5 million iu by March 1991 had been set to increase the national stock.[398] In March 1990, Dr McIntosh confirmed that the PRC's '*gradual recovery to target stock levels*' was on schedule. The end of year stock of factor VIII would not be less than 1.9 million iu.[399]

346. A number of issues around the distribution and quality of Z8 were discussed at a 23 April 1990 meeting of the Factor VIII Working Party for Scotland and Northern Ireland. Concerns relating to distribution were raised by Dr Ludlam, including that some RTCs '*had a relatively large stock of Z8, while others had none*'. Dr Mayne raised the issue of Z8's poor solubility and attributed low usage of the product in Northern Ireland to it. Dr Perry *'admitted that this had been a problem with Z8 for some time*' and that solubility between vials was very variable. He outlined recent improvements, leading Dr Mayne to state that she '*expected Northern Ireland demand to increase once more*', provided the improvement could be sustained. Dr Ludlam also highlighted particular batches with slow solubility and which Haemophilia Directors were reluctant to use. These minutes suggest that, leaving aside availability, Z8 may not have been the preferred product of all haemophilia clinicians in Scotland and Northern Ireland around this time.[400]

347. Nonetheless, it appears that Scotland was returning closer to self-sufficiency in factor VIII concentrate. In a 31 May 1990 memo to Dr McIntosh, Dr Stewart wrote that the PFC's output for the year should increase to 10 million iu. Based on the demand estimate provided by Haemophilia Directors, it was expected that this amount would return Scotland '*to*

[398] Report on 'SNBTS Stock of Factor VIII Summary', 29 January 1990, **PRSE0004581**.
[399] Letter from David McIntosh to Mr J T Donald (CSA), re: Factor VIII Year End Stock, 29 March 1990, **PRSE0000787**.
[400] Minutes of Factor VIII Working Party for Scotland and Northern Ireland Meeting, 23 April 1990, **NIBS0001666**.

self-sufficiency except for patients who cannot tolerate Z8.'[401] In a further, October 1990 memo, Dr Stewart informed Dr McIntosh that no Profilate (a commercial factor VIII) had been used in Scotland in September. He added: '*Thus, allowing for the 'specialised use' of Monoclate in 'allergics and 8Y in vWD, it can be regarded that self sufficiency in normal Factor VIII was achieved in this month.*'[402]

348. Annex A shows that Scottish Haemophilia Centres mainly used Scottish Factor VIII in 1988-1990, but that they also used significant quantities of commercial product: 748,930 iu in 1988; 907,500 iu in 1989; and 521,193 iu in 1990. In Northern Ireland, similar amounts of commercial and NHS concentrate were used in 1988, and more commercial product was used in 1989, though the trend reversed in 1990.

Factor IX

349. Supply issues for heat-treated factor IX continued in 1988. In an April 1988 report, Professor Cash alerted SNBTS and Haemophilia Directors to a '*substantial and continuing increase in the demand for factor IX concentrates.*' He asserted that '*there is no doubt that the size of this escalation has put a major pressure on the Service*', and suggested that the '*major cause of this escalation is the increasing use of these concentrates in the management of haemophilia A patients with inhibitors*'.[403] During the 5 May 1988 meeting which followed, Dr Perry stated that the use of DEFIX had multiplied 2.5 times since 1983.[404] He reported that PFC's production '*may encounter a limit of 3 million units per year, which may prove technically hard to exceed*'.

[401] Memo from Bob Stewart to D McIntosh, re: Factor VIII Supply to the SHS, 31 May 1990, **PRSE0004761**.
[402] Memo from Dr Stewart to Mr D McIntosh, re: Self Sufficiency in Factor VIII, 23 October 1990, **PRSE0002185**.
[403] Report on 'Noted for Scottish Health Service Haemophilia Centre / Transfusion Service Directors' Meeting: May 1988, April 1988, **PRSE0002391**, pg.6-7.
[404] Minutes of SNBTS and Haemophilia Directors Meeting, 5 May 1988, **SBTS0000832.**

350. These pressures appear to have eased by the following year. In a June 1989 report, Dr Stewart suggested that there was '*no evidence of significant usage of DEFIX by specialities other than Haemophilia Directors and thus we must assume the products* [sic] *is almost wholly being used for haemophilia B patients*.'[405] He added that the '*fears of continued escalation in demand for DEFIX appear to have been misplaced*', while seeking information on anticipated trends in demand from Haemophilia Directors. Dr Stewart added that the heat-treatment of DEFIX at 80°C for 72 hours appeared to be '*well tolerated by the product*.'

351. Despite supply pressures in the late 1980s, Annex A does not record the use of commercial factor IX in Scotland in 1988-1990. Annex B shows that no commercial product was used in Northern Ireland in 1988-1989, but that a small amount was recorded in 1990.

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[405] 'Notes For Scottish Health Service Haemophilia Centre - Transfusion Service - Directors Meeting' by Dr R.Stewart, 23 June 1989, **PRSE0004030.**