Presentation on the size of pools of plasma used in domestic production of blood products in Scotland

Introduction

1. This presentation will explore the size of plasma pools used in producing blood products, and in particular Factor VIII, in Scotland in the 1970s and early to mid-1980s. This period saw a transition from cryoprecipitate to factor concentrates as the most prevalent form of treatment for patients with haemophilia and other bleeding disorders. The focus is on fractionation at the Protein Fractionation Centre (PFC).

The transition from cryoprecipitate to PFC factor concentrates in Scotland

2. The transition from cryoprecipitate to factor concentrates has been considered in other evidence and presentations at the Inquiry, and that detail is not repeated here. The issue for this presentation is the effect that this transition had on the way in which blood products were produced in Scotland, and in particular on the size of the pools of plasma that were fractionated to allow for such production.

3. One issue that arose was the question of whether domestic production in Scotland should be centralised in a large-scale, specialised plant, or whether smaller-scale production at regional centres should be preferred. An early indication of the position of John Watt, Scientific Director of the Scottish National Blood Services (SNBTS), is found in a letter that he sent to the editor of the British Medical Journal in February 1972. This was a response to a

report of Dr Dormandy's success in manufacturing prothrombin complex on a small scale. The letter was co-signed by Dr Jim Smith, then the Chief Scientist at the PFC.

4. Mr Watt and Dr Smith congratulated Dr Dormandy and her colleagues, but warned that '*the method is inherently unsuitable for large pool exploitation and the economies of multiple small pool processing, because of the high cost of control, can be justified only in situations where no alternative exists*'. Mr Watt and Dr Smith concluded that, in light of the national need in Scotland for preparation of all coagulation factors, this would be best met by '*central, comprehensive fractionation*' within UK facilities which were rapidly expanding and acquiring capacity to satisfy the need for plasma products.[1]

5. An echo of this debate of whether central or local production should be preferred is found in the later discussion over the role (or lack of role) for freeze-dried cryoprecipitate. As this is a matter that is likely to be addressed in oral evidence the Inquiry will hear in due course, is it not considered further in this presentation.

6. In broad terms, the approach of the Scottish authorities in the 1970s and 1980s was to prioritise the use of PFC as a single centre for domestic production of blood products. SNBTS Directors and Haemophilia Directors met on 8 May 1975 and it was confirmed that the Scottish Home and Health Department wished to increase the production of PFC factor concentrates. The comparative costs of treatment of a severe haemophilia patient per year were provided, ranging from £400 using cryoprecipitate, £1,000 using PFC factor concentrates and £1,800 for commercial concentrates. Directors ultimately agreed '*that the aim should be eventually to replace cryoprecipitate completely by concentrate… It was suggested that cryoprecipitate could be obsolete in 5 years*'.[2] Limited explanation is provided for this decision in the

[1] Letter from Mr Watt to Dr Maycock, re: Enclosing paper on Clotting Factor Concentrates, 9 February 1972, **CBLA0007394**.
[2] Minutes of SNBTS and Haemophilia Directors Meeting, 8 May 1975, **CBLA0000275**.

minutes, but it is notable that Directors agreed that '*the home treatment programme should be given first priority*'.[3]

7. Although the preference for concentrates over cryoprecipitate appears to have been driven by clinical preference,[4] practical factors may also have played a role. Dr Foster in his report to the Penrose Inquiry on self-sufficiency noted that concentrates could be amenable to large volume manufacture compliant with the Good Pharmaceutical Manufacturing Practice (GMP), whereas cryoprecipitate could not.[5] GMP guidelines were accepted and evolving standards which were enforced by the Medicines Inspectorate to ensure organisational compliance.[6]

8. Dr Gamal Gabra (Consultant Haematologist at Glasgow and West of Scotland Blood Transfusion Centre between 1980 to 1989) told this Inquiry that the lack of infrastructure '*was certainly a crucial factor*' in not producing greater quantities of cryoprecipitate to meet the demands for blood products. Dr Gabra considered that significant development of facilities would have been required to depend on cryoprecipitate rather than factor concentrates to meet GMP standards:

> 'Space was not adequate and required development to meet GMP standards necessitating the creation of newer up-to-date facilities in Scotland in order to produce both small pool cryoprecipitate as well as a fractionation facility to produce the local Factor VIII concentrate.'.[7]

9. The transition to concentrates saw increasing demand being met in part from commercial sources. On 4 March 1981, following concerns at the level of commercial concentrates being purchased in Scotland, the Scottish Haemophilia and Blood Transfusion Working Group met and agreed that '*the*

[3] Minutes of SNBTS and Haemophilia Directors Meeting, 8 May 1975, **CBLA0000275**.
[4] See the discussion in the Chronological Presentations for England and Wales, and for Scotland and Northern Ireland.
[5] 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.11.
[6] Statement of Dr Cuthbertson, Dr Perry and Dr Foster to Penrose re: Conditions at PFC, Liberton during the 1980s, **PRSE0001919.**
[7] Written Statement of Gamal Gabra, 16 December 2021, **WITN5495001**, pg.29, §111.

aim must be for the NHS in Scotland to be self-sufficient'.[8] Self-sufficiency in blood products was, by that time, a long standing goal of the SNBTS.[9]

10. According to the Penrose Report, the perceived greater risk of commercial concentrates due to their larger pool size was a further factor in the drive toward self-sufficiency in Scotland:

> 'The use of domestic Scottish products was believed to carry less risk because the pool size was smaller and the prevalence of infection in the donor population was thought to be lower than in the USA. The differences were not sufficient to eliminate risk in Scotland, however, and in time it came to be understood that the general position remained the same as elsewhere: the move to concentrates increased the risk of transmission of viral infection'.[10]

11. The transition to concentrates took longer than the five years that had been anticipated at the meeting in 1975. In 1982, RTC's in Scotland were still preparing cryoprecipitate. However, according to Scottish Haemophilia Centre annual returns the use of cryoprecipitate had decreased significantly since the mid-1970s (from 1,265,993 iu in 1976 to 681,880 iu in 1982). Meanwhile production of PFC Factor VIII had almost quadrupled from 1,314,747 iu in 1976 to 4,754,658 iu in 1982.[11]

The increase in pool sizes for factor concentrate production at the PFC (1973 to 1983)

12. From the data presented below it is evident that pool sizes increased at the PFC. It is possible, from the documents, to identify a number of factors that contributed to this process. What follows is not an exhaustive list, and is based on what can be read on the face of the relevant documents. Other analyses, which may go beyond what is expressly written in these and other

[8] Minutes of Scottish Haemophilia and Blood Transfusion Working Group, 4 March 1981, **SBTS0000382_008,** pg.2.
[9] SNBTS Annual Report for 1 April 1975 to 31 March 1976, 1976, **PRSE0002133, ep.2, §4**.
[10] Penrose Inquiry Final Report, 2015, **PRSE0007002**, pg.33, [2.64].
[11] Annex A of the Chronological Presentation on the Domestic Supply of Blood Products in Scotland and for Northern Ireland. **INQY0000344**.

documents, may be presented by others for the Chair's consideration in due course.

13. First, pool sizes were determined at least in part by the levels of Factor VIII required to satisfy estimated demand. UK-wide demand estimates for Factor VIII were prepared from 1973 and it was calculated that Scotland required production at levels of 50,000 donations per annum.[12] On 16 March 1973, Mr Watt wrote to Dr Macdonald and confirmed that the PFC were embarking on a high purity fraction entitled '*Supereight*'. The planned production capacity for the product was one pool of 200 litres per week. Mr Watt intended to pool material at this volume to issue product in accordance with estimated demand:

> 'This was deliberately chosen to meet a projected need to process 50,000 donations of plasma p.a. [per annum] to meet Scottish needs for this product... It has been intended that the 200 litre batch size would continue through the commission period and that the frequency of one per week would satisfy Scottish need'.[13]

14. Second, increasing pool sizes was deemed advantageous to improve yield and reduce losses of Factor VIII. In a review undertaken by Dr Foster and Ida Dickson (PFC) in January 1980 of Factor VIII recovery at the PFC between April 1975 and August 1979, it was noted that losses in Factor VIII could be reduced by both the introduction of continuous thawing and by increased plasma pool size. The report concluded that:

> '[T]he mean plasma volume per lot... for continuous thawing has been about 190 litres, giving Q.C. [Quality Control] losses of... 11%... for a 40ml fill. This loss would be reduced to about 4% if the plasma pool size could be increased to give at least 500 vials of concentrate per lot. This will probably be possible once the design of the continuous plasma thawing system has been completed'.[14]

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[12] Paper RTD(73)20 on the 'Provision of Plasma for AHG Concentrate', 1973, **CBLA0000155**.
[13] Letter from Mr Watt to Dr Macdonald, re: Pool sizes at the PFC, 16 March 1973, **SBTS0000309_023**.
[14] Report on 'A Review of Factor-VIII Recovery at PFC from April 1975 to August 1979' by Dr Foster and Ida Dickson, January 1980, **SBTS0003269_230**, e.pg.17.

15. Third, in the face of rising demand for Factor VIII and in order to meet Scottish trends, developments to enhance PFC capacity involved increasing pool size. In a memorandum dated 29 December 1980, Dr Foster explored the capacity at the PFC to identify any limitations, with production levels now estimated at 66,000 kilograms (kg) of Fresh Frozen Plasma (FFP) per year. Dr Foster noted that a new-scale thawing tank would be ready for use by the beginning of 1981 which would increase capacity for Factor VIII production. The maximum pool size for crushing and thawing was estimated to increase to around 700 to 800 litres of plasma per day within standard working hours (8.30am - 5.00pm). However, Dr Foster concluded that the key limiting factor on both plasma pool size and frequency of processing was the freeze drying capability at the PFC. Two freeze dryers were available for use. The Leybold Heraeus was limited to a plasma pool of 300kg while the Usifroid was limited to 500kg. He recommended, as a partial solution, the adoption of smaller Factor VIII vials to increase the pool size in the Usifroid to 700kg. Additional freeze dryers would be required in the long term to process all Scottish plasma and a proportion from England.[15]

16. Dr Perry (Quality Control Inspector from 1981 to 1984 and Director of PFC from 1984 to 2003) wrote in his statement to the Inquiry that PFC pool sizes:[16]

> '[W]ere designed and established to be aligned with anticipated process yields and the maximum capacity of freeze driers used for the final stage of processing. At the time in question, PFC had two production scale freeze driers of different capacities for this purpose.'

17. There are various pieces of evidence that refer to pool sizes in this period.

18. In 1984, Dr Foster and Mrs Dickson produced a review of Factor VIII recovery at PFC from April 1980 to September 1983. Included in this were tables showing Factor VIII batches that were, at the time of writing, still '*in process*' (i.e. those that had been held back from despatch for various reasons) and those that had failed quality assurance tests. The tables include a column

[15] Memo from Dr Foster to Mr Watt et al., re: Plant Capacity for Factor VIII production, 29 December 1980, **PRSE0002177**.
[16] Dr Perry Witness Statement to IBI, **WITN6920001**, pg.103-104 [307].

showing the plasma volume of the relevant batch in litres. The table is not, of course, a full record of all plasma batches, but it does provide the following information:

a. One batch is listed for 1978/1979. This was fractionated from a pool of 114 litres of plasma.
b. Three batches are listed for 1979/1980. The plasma pools are recorded as being 167 litres, 170 litres and 300 litres.
c. Five batches are listed for 1980/1981. The plasma pools are recorded as being 235 vials, 144 litres, 252 litres, 268 litres and 290 litres.
d. Ten batches are listed for 1981/1982. The plasma pools are listed as 255 vials, 484 vials, 260 litres, 265 litres, 276 litres, 290 litres, 450 litres, 479 litres, 535 litres, 540 litres.
e. Seven batches are listed for 1982/1983. Three of the batches listed were fractionated from plasma pools of just under 300 litres, and four were between 495 and 555 litres.
f. One batch is listed for 1983/1984, with the size of plasma pool given as 555 litres.

19. Other sources include the following:

a. In a letter from November 1990, Professor Cash (National Medical Director of the SNBTS) wrote that the pool sizes for Factor VIII actually used at the PFC were 200kg to 300kg between 1978 and 1980.[17]
b. According to a minute from Dr Foster dated 11 February 1982, the smallest pool compatible with production at the PFC at that time was 100kg.[18] To utilise maximum freeze drying capacity, the smallest production pool was 250kg.[19]
c. According to Dr Perry in his written statement to the Inquiry, pool sizes increased during the early 1980s and varied between 300kg to 550kg,

[17] Letter from Professor Cash to Anthony Deas, re: Haemophilia HIV Litigation and Pool sizes at PFC, **SBTS0000041_126**.
[18] Dr Foster drew a distinction in the minute between 100kg pools for production, and 10kg pools that were used in the research and development laboratory.
[19] Memo from Dr Foster to Mr Watt, re: SNBTS Plasmapheresis study and smallest production pools, 11 February 1982, **SBTS0000312_046**.

equating to approximately 1,200 donations and 2,200 donations respectively.[20] He considered the pool sizes in the table produced by Dr Foster and Mrs Dickson to be typical of those used in the period 1980 to 1984.[21]

d. Dr Perry's evidence is consistent with the pool sizes listed in the October 1981 to June 1983 report of the SNBTS Factor VIII Study Group, which discussed the existing practice in Scotland. This document recorded pool sizes of either 320kg or 550kg in a study of nine batches that were fractionated in September and October 1982. It is relevant to note that both sizes were regularly used at that time, seemingly dependent on which of the vial freeze dryers at the PFC was being used (see above).[22]

20. Dr Perry's evidence to this Inquiry is that PFC batch size was expressed and recorded in kg/litres as these were the parameters used for manufacture and that figures can be converted by applying a conversion factor of 4-5 donations per kg. For example 320kg would equate to between approximately 1,280 and 1,600 donations and 550kg would equate to between approximately 2,200 and 2,750 donations.[23] In the Presentation on Pool Sizes for England and Wales a figure of 5.5 donations per kilogramme or litre of plasma is adopted, for reasons given there. Using that figure, and applying it to the table contained in Dr Foster and Mrs Dickson's 1984 review produced the following result.

[20] Dr Perry Witness Statement to IBI, **WITN6920001**, pg.94 [274]. In giving these approximations, Dr Perry is assuming 4 donations per kilogramme. As is discussed below and in the presentation on pool sizes in England and Wales, this is an approximation and other figures could be used. In the presentation on England and Wales, 5.5 donations per kilogramme or litre is adopted. This would give a range of approximately 1,650 to 3,000 donations.
[21] Dr Perry Witness Statement to IBI, **WITN6920001**, pg.105 [308].
[22] Report on 'Quality of Fresh Frozen Plasma, Current Practice in Scotland, Comments and Recommendations' by Dr Gabra for SNBTS Factor VIII Study Group, 1 June 1983, **PRSE0000912**, e.pg.57-58.
[23] Dr Perry Witness Statement to IBI, **WITN6920001**, pg.103 [306].

Year	Plasma pool size in litres[24]	Estimated donations[25]
1978/79	114	627
1979/80	167 to 300	919 to 1,650
1980/81	144 to 290	792 to 1,595
1981/82	260 to 540	1,430 to 2,970
1982/83	283 to 555	1557 to 3,053
1983/84	555	3,053

Pool sizes at the PFC from 1983/1984

21. The Inquiry legal team have found limited evidence of pool sizes at PFC in the period after 1983 to 1984. It is apparent from several documents that reduction of pool size was not adopted as a response to the risk of AIDS, with priority instead given to the exclusion of high risk donors, heat treatment and batch dedication.[26] [27] [28] [29] [30] [31] [32] [33] These measures are not considered

[24] The data presented in this graph adopts the highest and lowest figures presented in both Table 3 and Table 4 of: Report on 'A Review of Factor VIII recovery at PFC from April 1980 to September 1983' by Dr Foster and Ida Dickson, April 1984, **SBTS0000238_009**, pg.8-9. See 'plasma (l)' column indicating pool size.

[25] Donations have been estimated based on 5.5 donations per 1 litre/kg as per the Pool Size Presentation for England and Wales. This is relatively consistent with Dr Perry's estimate of 4-5 donations per 1 litre/kg. See Dr Perry Witness Statement to IBI, **WITN6920001**, pg.103 [306].

[26] Report on 'Initial Report for Scottish Regional Transfusion Directors' Meeting on 8 December 1983, WHO Meeting on AIDS - Geneva 22-25 November 1983' by Dr McClelland, 5 December 1983, **PRSE0003634**.

[27] Minutes of the Infections Hazards of Blood Products at National Institute for Biological Standards and Control Meeting, 9 February 1984, **PRSE0003071**, pg.6-7 and pg.10

[28] Letter from Professor Cash to Dr Perry, re: Haemophilia FVIII Batch Dedication, 7 December 1984, **PRSE0003102**.

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

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

further in this presentation, though they have been or will be explored in other evidence before the Inquiry.

22. The limited evidence available suggests that there was some increase in pool sizes at PFC in the mid-1980s. As the Inquiry has heard, in late 1984, 16 patients from Edinburgh – the so-called '*Edinburgh Cohort*' – were identified as having been infected with HTLV-III through the use of PFC products.[34] In a memorandum dated 31 January 1985, Dr Perry wrote that 4,000 donors had contributed to what he described as the *'pool of FVIII'* that was implicated in the infections.[35]

23. In the midst of the response to the news of the Edinburgh Cohort, Professor Cash wrote to Dr Perry on 7 December 1984 to give his view that:

> 'Any moves directed towards restricting donor pool size (designated plasma pool for each donor) must be discussed by all Directors before implementation. It's an exciting option but I suspect will have colossal cost and operational implications. There is much to be done before we need consider this option'.[36]

24. In an article on the control of large-scale plasma thawing from 1985, Dr Foster and Alan Dickson (PFC) recorded that pool sizes for continuous thawing at the time of writing were between 600kg and 1,000kg, depending upon the size of freeze dryer available.[37] Adopting the same 5.5 donations/kilogramme conversion figure, this equates to 3,300 to 5,500 donations.

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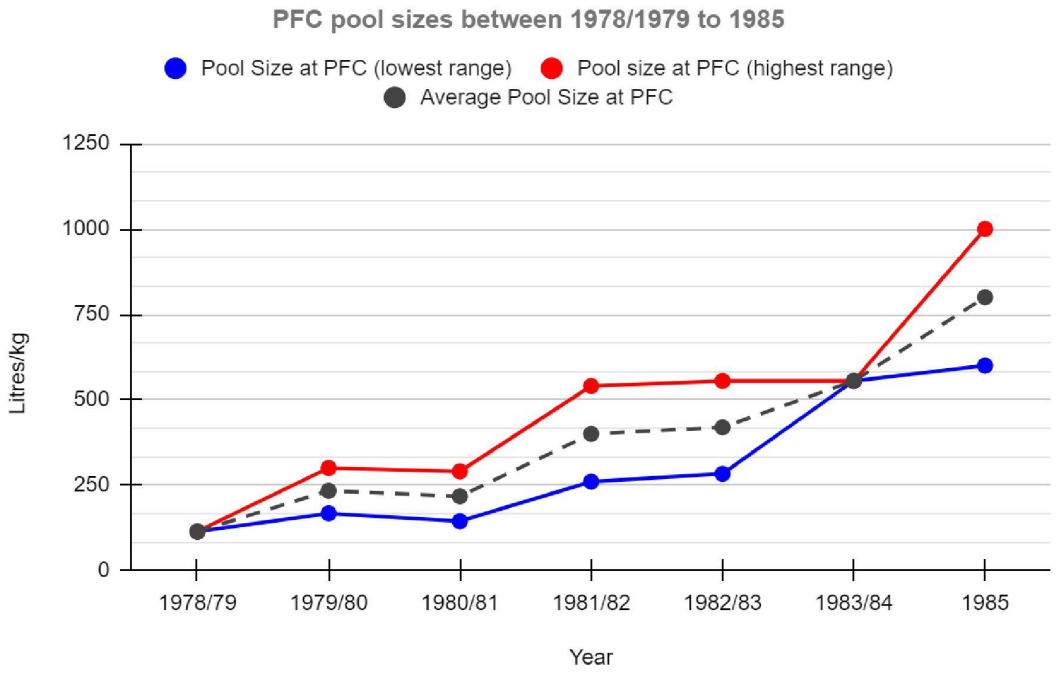
[31] Letter from Dr Perry to Dr Boulton, re: Comments in regard to a system of batch dedication to be implemented within the SNBTS, 22 January 1985, **SBTS0000324_073**.
[32] Report on 'SNBTS Heat Treated Factor VIII - Preliminary Clinical Evaluation Studies' by Professor Cash, February 1985, **PRSE0004052.**
[33] Report on Notes for SHS Haemophilia Centre and Transfusion Service Director's Meeting: March 1985', February 1984, **PRSE0003450,** pg.8.
[34] 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**; Letter from Dr McClelland to Professor Cash, re: Seroconversion in Edinburgh Cohort, 15 November 1984, **LOTH0000005_052**.
[35] Memo from Dr Perry to All Staff re: AIDS in Scotland, 31 January 1985, **PRSE0000965**.
[36] Letter from Professor Cash to Dr Perry, re: Haemophilia FVIII Batch Dedication, 7 December 1984, **PRSE0003102**.
[37] Report on 'Developments in Haematology and Immunology - Control of Large-Scale Plasma Thawing' by Dr Foster and Mr A.J. Dickson, 1985, **PRSE0000232**; Report on 'Progress Report for Factor VIII Study Group' by Dr Foster, February 1985, **PRSE0000927**, pg.4 [1.2.2].

25. It is relevant to note that from 1 January 1985, all Factor VIII produced at PFC was subject to heat treatment.[38]

Overview of pool sizes at the PFC

26. The graph below illustrates pool sizes at the PFC between 1978/1979 to 1985. As the pool sizes were variable for each year, the lowest and highest figure identified has been presented, along with an average figure. The findings demonstrate that pool sizes at the PFC gradually increased over time, from as low as 114 litres in 1978/79, to as high as 1,000kg by 1985. It should be noted, however, that the data set on which this graph is based is small, particularly in the 1970s. It is possible that larger pools were also being fractionated at that time, but were not recorded in the sources identified above. This possibility is strengthened by the reference, as early as 1973, for a plan for a pool of 200 litres (a figure that is not included in the graph below as it the Inquiry legal team have not identified evidence showing that this pool size was in fact used).



[38] Extract from Hansard (Volume 72-54), House of Commons, re: Self-sufficiency of blood products in Scotland, 5 February 1985, **PRSE0003841**.

Year	Pool Size at PFC (lowest range in litres/kg)	Estimated donations[39] (lowest range)	Pool size at PFC (highest range in litres/kg)	Estimated donations (highest range)
1978/79[40]	114	627	300[41]	1,650
1979/80	167	919	300	1,650
1980/81	144	792	290	1,595
1981/82	260	1,430	540	2,970
1982/83[42]	283	1557	555	3,053
1983/84	555	3,053	555	3,053
1985[43]	600	3,300	1000	5,500

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[39] Donations have been estimated based on 5.5 donations per 1 litre/kg as per the Pool Size Presentation. This is relatively consistent with Dr Perry's estimate of 4-5 donations per 1 litre/kg. See Dr Perry Witness Statement to IBI, **WITN6920001**, pg.103 [306].

[40] This data, with the exception of 1985 and the highest range for 1978/79, is derived from Table 3 and Table 4 of: Report on 'A Review of Factor VIII recovery at PFC from April 1980 to September 1983' by Dr Foster and Mrs Ida Dickson, April 1984, **SBTS0000238_009**, pg.8-9. See 'plasma (l)' column indicating pool size.

[41] The highest estimate of PFC pool size in 1978/79 is as per Professor Cash's figures provided in relation to the HIV litigation. Professor Cash stated that pools of between 200-300kg were used in 1978 to 1980 at the PFC, **SBTS0000041_126**.

[42] This data does not include a range of between 320 to 550 litres for 1982 (data identified in **PRSE0000912,** pg.57-58) as all other data between 1978 and 1984 is in relation to the financial year. It was not therefore possible to amalgamate this range with the existing data set. It is important to note that the range of 320 to 550 litres for 1982 is generally consistent with the data range used for 1981/82 to 1982/83.

[43] 1985 is the only year where data is presented on a yearly basis, rather than the financial year. As we have identified no wider data for 1985, this data has been included to demonstrate the increase in pool sizes at the PFC. This data derives from a report on 'Developments in Haematology and Immunology - Control of Large-Scale Plasma Thawing' by Dr Foster and Mr A.J. Dickson, 1985, **PRSE0000232**; Report on 'Progress Report for Factor VIII Study Group' by Dr Foster, February 1985, **PRSE0000927**, pg.4 [1.2.2]