Evidence of Dr James Smith: Presentation

Contents

Introduction

1. This presentation focuses on the evidence of Dr James Kemp (Jim) Smith, a chemist who worked in the field of fractionation in Edinburgh, Oxford and Elstree. It draws on the following materials: a witness statement provided to this Inquiry by Dr Smith in 2020 [**WITN3433001**]; a draft proof of evidence produced for/by Dr Smith during the HIV haemophilia litigation [**CBLA0000016_034**]; Dr Smith's oral evidence to the Lindsay Tribunal [**LIND0000318**]; Dr Smith's written statements to the Penrose Inquiry [**PRSE0004045**] [**PRSE0004368**]; Dr Smith's oral evidence to the Penrose Inquiry [**PRSE0006059**] [**PRSE0006060**]; and a selection of contemporaneous documents.[1]

[1] Dr Smith's Inquiry statement explained that most of his historical correspondence and documents relevant to virus inactivation were removed from his office at PFL without his knowledge; he did not know by whom: **WITN3433001**, para. 5.

2. This presentation is not intended to be an exhaustive or comprehensive description of Dr Smith's work at PFC, PFL and BPL. Rather, it describes some particular aspects of his work and then addresses a number of themes which are explored in his various statements: self-sufficiency, knowledge of hepatitis and AIDs, the relationship between PFL/BPL and SNBTS/PFC, the availability of resources, pool sizes, and reversion to cryoprecipitate. The aim is to provide a flavour of Dr Smith's evidence on these topics and to highlight key elements from his statements and supporting documentation. His work on the development of 8Y is not easily summarised and is best understood by reading the relevant statements/proofs of evidence in full.

3. Dr Smith held the following qualifications[2]:

- 1958 – 1962: B.Sc. Hons. Pure Chemistry, University of Edinburgh.
- 1962 – 1965: PhD in the Department of Clinical Chemistry[3], University of Edinburgh. Thesis: "Purification and identification of placental histaminase".
- C.Chem. and (until retirement in 2015) Fellow, Royal Society of Chemistry.
- Formerly (until retirement in 2015) registered with the Royal Society of Chemistry as Qualified Person - i.e., qualified by experience and knowledge to release pharmaceutical products for issue to prescribers.

4. Dr Smith held the following positions and responsibilities:

- 1965 – 1968: Post-doctoral studies in Department of Clinical Chemistry, University of Edinburgh. Research Assistant to Dr D W Moss. Separation and investigation of iso-enzymes of diagnostic interest.
- 1968 – 1975: Senior Biochemist, then Chief Chemist, responsible at overlapping times for production management, product development and quality control of plasma protein concentrates in Protein Fractionation Centre (formerly Blood Products Unit) ("PFC") in Edinburgh (SNBTS).

[2] See the CV at **PRSE0001136**.
[3] Or in the Faculty of Medicine: see HIV Litigation draft proof of evidence **CBLA0000016_034,** para 1.

- 1975 – 1992: Scientist in charge of fractionation, responsible for product development, manufacturing and research and development, in Plasma Fractionation Laboratory, Oxford ("PFL"). Responsible to Dr Ethel Bidwell for the manufacture on a scale rising from 70kg to 200kg (plasma batch sizes), of Factor VIII and Factor IX concentrates. Also responsible for research and development of improved factor concentrates. From January 1983 Chief Project Scientist based at PFL, responsible for the improvement of safety and economy of coagulation factor concentrates and extending the range of concentrates recoverable from human plasma.[4]

- 1979 – 1982: Seconded to additional duties as head of coagulation factor production (with some research and development responsibilities) at Blood Products Laboratory, Elstree ("BPL"); attended both laboratories for part of every day. Planned and oversaw remedial action at existing BPL facility; initiation at BPL of systems of batch documentation.

- 1992 – 2015: Independent Consultant Adviser on fractionation and coagulation.

[4] HIV Litigation draft proof of evidence **CBLA0000016_034**, para 3; see also **BART0000536_001**, p1.

Dr Smith's evidence to other inquiries/litigation

5. Dr Smith's draft proof of evidence in the HIV litigation (headed Draft 3, with the date 1.11.90) was not a final statement.[5] It comprised five principal sections: the first (paras. 5 to 16) set out a brief history of PFC; the second (paras. 17 to 29) explained some of the terminology associated with fractionation; the third (paras.30 to 86) described the research work carried out by PFL and BPL into the heating of Factor VIII and IX products to inactivate viruses; the fourth (paras. 87 to 95) dealt with the restricted pool Factor VIII trials in 1983/4; and the fifth (paras. 96 to 149) contained a commentary on documents.

6. Dr Smith's oral evidence to the Lindsay Tribunal was given on 18 July 2001.[6] The Inquiry does not have a copy of the written statement which he provided to the Lindsay Tribunal. Unsurprisingly, the oral evidence covered issues of particular relevance to Ireland: the extent to which PFC could have fractionated Irish plasma and produced factor concentrates for Ireland; the extent of Dr Smith's contact with fractionators, clinicians etc. in Ireland; the work undertaken at PFL on the Gail Rock method of attempting to increase the yield of Factor VIII from plasma; and PFL's work on means of pasteurising and dry heating factor concentrates.

7. Dr Smith provided two written statements to the Penrose Inquiry:

   7.1. The first, dated 22 June 2011, addressed the Penrose Inquiry's topic B3 – viral inactivation in the period to 1985 – and comprised a section headed 'Snapshots and Landmarks', five notes authored by Dr Smith (referred to as JKS 1-5), and comments on specific paragraphs of the Penrose Inquiry's Preliminary Report.[7] The subject matter of the five notes were: "Impediments to the development of heat treatment against NANBH", "Pasteurisation of albumin is not directly transferable to Factor VIII", "The clinical trial of

[5] **CBLA0000016_034.** In his statement to the Inquiry, **WITN3433001**, paras. 12-14, Dr Smith set out his recollection of the context in which the draft was produced and observed that he had found nothing in the narrative or explanatory section which was contrary to his recollections, but that there was much there that he had not retained over 30 years and must simply take at first value.
[6] **LIND0000318.**
[7] **PRSE0004045.**

PFC's first pasteurised Factor VIII (late 1983) and its impact on the pasteurisation programme", "Why did fractionators in Scotland and England take different decisions on heat treatment of Factor VIII?" and "Clinical trials of 8Y".

7.2. The second, dated 29 August 2011, addressed the Penrose Inquiry's topic C3 – Hepatitis C and viral inactivation 1985-1987 – and comprised Dr Smith's response to questions posed by the Penrose Inquiry and a supplementary note from Dr Smith referred to as JKS Supplementary Note 6 entitled "Collaboration between PFC and PFL/BPL in the period 1981-87".[8]

8. Dr Smith gave oral evidence to the Penrose Inquiry on 1 November 2011[9] and 2 November 2011.[10]

[8] **PRSE0004368.**
[9] **PRSE0006059.**
[10] **PRSE0006060.**

Aspects of Dr Smith's work over the years

9. In the early 1970s in Scotland, Dr Smith was involved in work relating to Factor IX development. Some of this work, relating to the production of the Factor IX preparation DEFIX, has already been explored during the oral evidence of Ms Sarah Middleton on 1 October 2021[11]; see also the article co-authored by Ms Middleton, Ida Bennett and Dr Smith in Vox Sang in 1973[12].

10. Dr Smith and Ms Middleton also participated in a collaborative project with Dr Johnson and other scientists at New York University, which aimed to produce a more potent Factor IX concentrate with a reduced Hepatitis B surface antigen (HBsAg) content.[13]

11. *"There was a period during the 1970s"*, according to Dr Smith's draft proof of evidence in the HIV Litigation, that marked the beginning of co-operation between the transfusion centres and the fractionation laboratories in an effort to serve the *"common goal"* of meeting the identified requirements of Factor VIII. During this time, attempts were made to improve the quality and freshness of plasma and to increase the amount of Factor VIII recovered from plasma. Shortly after Dr Smith's arrival at PFL, it was proposed that blood should be separated within 4 hours of collection if it was to be used for the manufacture of Factor VIII. This would have led to an improvement in recovery of approximately 5%. However, the proposal was never implemented, due to RTCs being unable to consistently separate more than 10 to 20% of blood, and no significant improvement than that separated from overnight blood.[14]

12. When Dr Smith arrived at PFL in 1975 there was (according to his Inquiry witness statement) no recognisable Research and Development (R&D) department at BPL.

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[11] **INQY1000151**.
[12] *A Therapeutic Concentrate of Coagulation Factors II, IX and X from Citrated, Factor VIII-depleted Plasma"*, Vox Sang. 24: 441-456 (1973), **PRSE0003648**.
[13] *'Removal of hepatitis B surface antigen from plasma fractions'* J Lab Clin Med (1976) 88, 91-101, **PRSE0003799**; Penrose Preliminary Report, **PRSE0007003**, para 1.50. See also the discussion with Milt Mozen (Cutter) on 4 August 1975 recorded in **BAYP0003775**.
[14] Draft proof of evidence in the HIV Litigation, **CBLA0000016_034**, para 96.

Any coagulation factor development that was being undertaken was conducted at the margins of production.[15] Around 1980, Dr M J Harvey was appointed as the Head of R&D at BPL and set up labs and staff for research and development; effectively, however, all work on coagulation factors was delegated to PFL until the latter closed in 1992 and the staff were transferred to BPL. Dr Ethel Bidwell directed R&D at PFL until her retirement in 1980, with day-to-day oversight by Mr Dike, PFL Chief Technician. Dr Smith subsequently took *de facto* charge of R&D at PFL and responsibility for all coagulation factor R&D in the organisation.[16]

13. According to his Inquiry statement, in February 1981 and again in July 1981 Dr Smith presented to Dr Lane some first outline proposals to tackle virus transmission by coagulation factor concentrates[17]: see Dr Smith's proposal of 27 February 1981[18] and his memorandum of 27 July 1981.[19]

14. Dr Smith was involved in considering the merits of pursuing different products and approaches to reduce the risk of viral transmission, including freeze-dried cryoprecipitate and smaller pool sizes. On 27 April 1981, for example, Dr Smith prepared a draft paper for Dr Gunson's Working Party on Plasma Supply. This paper considered the merits of frozen cryoprecipitate, small pool freeze-dried cryoprecipitate, large pool freeze-dried cryoprecipitate and intermediate purity concentrates. Dr Smith concluded that small-pool frozen or freeze-dried cryoprecipitate *"has unique advantages for patients needing only infrequent treatment"*, but that *"the major component in our national strategy for Factor VIII production should be intermediate purity concentrate"*.[20]

15. On 29 April 1981, Dr Smith sent Dr Lane a memorandum on "Small-Pool Freeze-Dried Cryoprecipitate and Other Small-Pool Products". Dr Smith noted that plasmapheresis was a *"major source of plasma for Factor 8"* and outlined two approaches to the production of small-volume pools (i.e. 2 kg or 10 donations) and

[15] Written statement of Dr Smith, **WITN3433001**, para 83.
[16] Written statement of Dr Smith, **WITN3433001**, para 83; 84.
[17] Written Statement of Dr Smith, **WITN3433001**, para 35.
[18] Proposal for support of a research project, **CBLA0001291**.
[19] Memo from Dr Smith to Dr Harvey dated 27 July 1981 **BPLL0011141**.
[20] Dr Smith's draft for the Working Party on Plasma Supply, **CBLA0001342_001,** p5.

larger pools (i.e. 50-100 kg from 10-20 donors); he indicated that the approach described was dependent *"on the kind of intensive plasmapheresis programme operated in Belgium, and some dilution of the current concept of "accredited" pools, but would approximate more closely to a defensible process for central fractionation"*.[21]

16. In September 1981 Dr Smith, Dr Lane and Dr Harvey held discussions regarding hepatitis antigens in plasma and final products and submissions for research and development products, following which Dr Lane invited Drs Smith and Harvey to proceed with submissions in a number of areas, including hepatitis transmission, in time for the next Scientific and Technical Committee meeting.[22] At a meeting of the Scientific and Technical Committee on 24 November 1981, Dr Smith gave a short address on the inactivation of hepatitis in BPL products; his review covered *"the consequences of transmitting both B and non-A non-B hepatitis viruses, the incidence of infection among multi-transfused haemophiliacs and the special problem of infrequently transfused patients who had no immunological defence"*. He explained that:

> *"The risk of transmitting hepatitis might be diminished by more specific and sensitive screening of blood donations intended for fractionation; limiting the size of plasma pools for recovery of certain products; neutralisation or adsorption of virus with an excess of hepatitis antibody; vaccination of recipients; selective removal of viruses during fractionation, e.g. by precipitation with PEG; and by inactivation of virus e.g. with B-propiolactone or by heating in the presence of reagents preserving the biological activities of plasma proteins. A policy was suggested for the selective application of these approaches to individual coagulation factor concentrates"*.[23]

17. On 22 September 1981, in a letter to Dr Lane, Dr Snape asked whether it was too late to request for Dr Smith to be invited to the next meeting of Haemophilia Centre

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[21] Memo from Dr Smith to Dr Lane, re: Small-Pool Freeze-Dried Cryoprecipitate and other Small-Pool Products, **BPLL0007526.**
[22] **CBLA0001446**.
[23] Minutes of the meeting of the Scientific and Technical Committee for the Central Blood Laboratories on 24 November 1981, **CBLA0001506**.

Directors for his expertise on coagulation factor concentrates both from PFL and BPL, a request which Dr Lane passed on to Miss Spooner at Oxford HC. [24] A manuscript note dated 23 September 1981, prepared by Dr Smith in case he did not get an invitation to the meeting, stated that during 1981 the combined fractionation capacity of BPL and PFL ran at 150,000 kilograms per annum and that during the same year the laboratories were together producing about 20,000,000 I.U. finished product at current rates.[25] Dr Smith did attend the UKHCDO meeting of 9 October 1981[26], and had in fact attended previous meetings in October 1977, November 1979 and September 1980, representing PFL and/or BPL.[27]

18. In the 1980s, Dr Smith played a role in developing informal communication between PFL/BPL and the PFC. Having been employed in both England and Scotland, he had a distinctive understanding of how both facilities operated. Dr Smith noted that he was the main PFL/BPL link to *"our friends in PFC"* and their work, sharing anything that he thought might help their endeavours on the pasteurisation option of heat treatment to inactivate viruses in blood products. As time went on, the respective scientists were encouraged to form their own links with each other, but *"factual communication was normally between me [Dr James Smith] and Dr Peter Foster (R&D Director at PFC), or with our blessing."* Such exchanges were not scheduled on a regular basis and never sought to change the other's policies or strategies.[28]

19. In November 1982 for example, Dr Foster, at PFC, telephoned Dr Smith to discuss some work which they were doing on the heat treatment of Factor IX. Earlier, in the summer of 1982, Dr Smith recalled that *"we had begun to get word of some success in the field of heat treatment through the usual gossip at scientific meetings"*.[29]

20. It was the advent of AIDS that triggered intensive work on dry-heating, Dr Smith recalled,

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[24] **CBLA0003763.**
[25] **CBLA0001454**.
[26] **HCDO0000248_002**.
[27] At the September 1980 meeting, Dr Smith informed attendees that it was BPL's aim to double its present output of Factor VIII concentrates: **PRSE0003946** p5.
[28] Written statement of Dr Smith, **WITN3433001**, para 66.
[29] Draft proof of evidence in the HIV Litigation, **CBLA0000016_034**, para 31.

"We started pasteurisation and dry-heating only after clues from elsewhere, in or about 1982, that they might be feasible, despite being completely counterintuitive to us. It was the advent of AIDS that triggered intensive work on dry-heating, for which it was possible to equip even the existing plant. We were further encouraged by reports that, although some heated commercial products transmitted NANBH, the patients did not contract AIDS."[30]

21. Dr Smith was one of the recipients of a memo regarding AIDS from Dr Lane on 24 March 1983, which drew attention to the *"likelihood that a return to cryoprecipitate as a desirable form of treatment may become irresistible"*.[31] He attended a meeting on 18 April 1983 with Dr Lane, Dr Snape and others, at which it was noted that *"an association was now being formed between heat treated concentrates in reducing the risk from AIDS"*. Dr Smith was asked whether BPL should promote the collection of small pool material into a working programme.[32]

22. Dr Smith's statement recalled that PFC started to experiment seriously with pasteurisation in 1983. PFL did quite a bit of imitative work on Factor VIII and a little later on Factor IX, well into 1984. Dr Smith stated:

"I always considered that dry-heating was unlikely to succeed against NANBH, and that we should be ready to exploit pasteurisation whenever BPL's premises might permit it. What became 8Y was initially a project, inspired by PFC's success with zinc-heparin, to obtain a more purified FVIII intermediate to facilitate the downstream stages of a full pasteurisation process. Our pasteurisation efforts, on both FVIII and FIX, were assumed to have been only "interrupted" in Autumn 1984 by the pressing priority of providing heated products that would at least be safe from AIDS transmission."[33]

23. In 1983 Dr Smith returned to PFL full-time and gave up production responsibilities at BPL. The only full-time member of staff in R&D at PFL at the beginning of 1983 was

[30] Written statement of Dr Smith, **WITN3433001**, para 103.
[31] Memo from Dr Lane to Mr Mallory, copied to Dr Smith and others, dated 24 March 1983, **CBLA0001691**.
[32] Notes of a meeting held on 18 April 1983, **BPLL0008758**.
[33] Written statement of Dr Smith, **WITN3433001**, para 77.

Mrs Lowell Winkelman, who worked on Factor VIII and Factor IX until permission was granted to hire Dr Peter Feldman in 1983. PFL followed a policy of using industrial equipment that could easily be scaled up at BPL.[34]

24. During this period, the R&D scientists at PFL did not have permanent technical staff. Instead, the production staff, many of whom had, according to Dr Smith, *"an enquiring mind"*, were released for a day per week, as production shifts permitted, to collaborate on lab-scale work with the scientists. On average the R&D staff had technical assistance one or two days per week.[35]

25. Dr Smith's statement recalled that in 1983 there was some work on dry-heating of the existing IP Factor VIII product, '8CRV' but no immediate prospect of determining whether NANBH had been deactivated.[36] More broadly, in terms of his own responsibilities, Dr Smith explained that:

> *"In this phase of my life, I was primarily responsible for evaluating: the virus-reduction methods being proposed in UK and elsewhere; the probability of their success against this or that virus; the likely development time, using existing resources and what might be obtained in a realistic time-frame; how many avenues we could explore simultaneously, including how we might depend on PFC in particular to work in parallel with us; and how any selected method might be feasible in the context of the renovation of BPL and the construction of a new plant."*[37]

26. In 1983, according to Dr Smith's draft proof of evidence in the HIV litigation, BPL was *"very concerned about the incidence of NANBH after first use of Factor VIII and Factor IX concentrates in previously untreated patients, even though the source plasma was from unpaid UK donors"*. Through 1983, Dr Smith *"would have said with increasing conviction that AIDS had the hallmarks of a blood borne virus"*, but he added that there was virtually no experimental evidence until late 1984 (clinical

[34] Written statement of Dr Smith, **WITN3433001**, para 84.
[35] Written statement of Dr Smith, **WITN3433001**, para 85.
[36] Written statement of Dr Smith, **WITN3433001**, para 56.
[37] Written statement of Dr Smith, **WITN3433001**, para 64.

data, not until early 1985) that any physical or chemical treatment would inactivate it.[38]

27. According to Dr Smith's Inquiry witness statement, in September 1983, *"heated (60°C/72h) IP F.VIII available to all HCs, but was used (March 1984) in only 3 patients"*.[39] Further detail about the limited use of the heated concentrate was set out in the draft proof of evidence in the HIV litigation: Dr Smith recounted being asked by Professor Stewart (Middlesex Hospital) in March 1984 for a heated concentrate for a patient who was especially anxious not to get hepatitis and preparing three batches for this and two further patients of Dr Colvin (London Hospital). There were, he said, no further takers of the dry-heated 8CRV, although he was almost certain that Dr Rizza, Professor Bloom, Dr Preston and other RCDs knew that it was available on request.[40]

28. In the course of 1984, there was the development of higher purity (HP) concentrate, initially intended as part of the pasteurisation programme, and the surveillance of all PFL and BPL batches of IP product for resistance to 60°C and 70°C.[41]

29. A memo dated 3 January 1984 from Dr Smith set out a proposal for a special preparation of 8CRV dry pasteurised: the strategy was to heat conventional 8CRV concentrate for the maximum time at the maximum temperature compatible with a > 10% loss of factor VIII:C activity and the appearance of no other undesirable characteristics. The memo referenced *"Our late start in more rigorous inactivation studies"*.[42] Dr Smith produced a further memo on 16 January 1984 suggesting a strategy for the production of "hepatitis-safer" Factor IX concentrates.[43]

30. On 16 March 1984, Dr Lane wrote to Dr Aronstam at Lord Mayor Treloar College regarding the use of Oxford Factor VIII, expressing the view that this product had *"an unexpectedly higher degree of safety than we anticipated"*. There was sufficient of

[38] Draft proof of evidence of Dr Smith in the HIV Litigation, **CBLA0000016_034**, para 87.
[39] Written statement of Dr Smith, **WITN3433001**, para 56; *'Heat-treated NHS factor VIII concentrate in the United Kingdom – a preliminary study'*, Clin.Lab.Haemat,1986, 8, 85-92 **PRSE0000608**.
[40] **CBLA0000016_034**, para 63.
[41] Written statement of Dr Smith, **WITN3433001**, para 56.
[42] Memo from Dr Smith to Dr Lane and others dated 3 January 1984 **CBLA0001786**.
[43] Memo from Dr Smith to Drs Lane and Snape dated 16 January 1984 **CBLA0002487**.

"this special product" to allow treatment of two infant patients of Dr Aronstam, who was asked to establish the supply through Dr Smith.[44]

31. Between September and November 1984, according to Dr Smith's statement to the Inquiry, there was a commitment to 8Y (higher purity, dry heated 80°C/72h) manufacture at BPL. As a stop-gap measure against AIDS, all suitable batches of IP Factor VIII in quarantine stock and in the pipeline would be heated at 70°C/24h.[45]

32. In 1984, Dr Smith continued as a point of contact to promote collaboration between BPL/PFL and PFC. On 26 September 1984, Dr Perry (SNBTS) wrote to Dr Lane and outlined the aim to increase processing capacity of Factor IX; technical problems had been encountered and Dr Perry anticipated that BPL/PFL might have either overcome such problems or would be able to offer some assistance. Dr Smith and Dr Snape were named as the most appropriate point of contact for the arrangement of visits to BPL and PFC for the acceleration of progress.[46] Further correspondence between Dr Lane and Dr Perry on 1 October 1984 indicated that Dr Lane considered joint discussions to be of value and that Dr Smith and Dr Snape should be contacted.[47]

33. On 12 October 1984, a memorandum from Dr Snape was sent to Mr Wesley, (in charge of fractionation at BPL) and Dr Smith concerning dry heated concentrates, asking for urgent consideration of the possibility of introducing a routine dry-heating step in the finishing of Factor VIII and IX concentrates.[48] In his draft proof of evidence for the HIV Litigation, Dr Smith explained that in the autumn of 1984 he, Dr Lane and Mrs Winkleman had made the decision to focus all efforts on developing dry-heated products rather than using wet heating. He stated:

> *"My recollection is that Dr. Lane, Mrs. Winkleman and I decided in September 1984 that we would go all out for a dry-heated product. Although wet heating was still an option we did not see how it would be applicable in the conditions which existed in the old manufacturing plant; heating in*

[44] Letter from Dr Lane to Dr Aronstam, **CBLA0001817.**
[45] Written statement of Dr Smith, **WITN3433001**, para 56.
[46] Letter from Dr Perry to Dr Lane, **CBLA0001897**.
[47] Letter from Dr Lane to Dr Perry, **CBLA0001901**.
[48] Memo from Dr Snape to Dr Smith and Mr Wesley, **CBLA0001908**.

solution requires a great deal of later processing and much of the manufacture in the old plant was "open" processing which would have led to a risk of re-contamination with infective plasma solutions after heating ... It is clear that we definitely decided to go ahead with a dry-heated product before we heard the proof that HIV was heat-labile and by 12th October we were moving very quickly towards developing dry-heated product."[49]

34. On 12 November 1984 Dr Smith and others produced a memo setting out the options for treatment of coagulation factor concentrates; the identified options for Factor VIII concentrates were: the restricted pool intermediate concentrate 8CRV; dry-heated 8CRV or HL; a new concentrate of higher specific activity, 8Y, which had been *"under intensive development only since July"*; or Factor VIII heated in protective solution. The memo recorded that PFL's programme *"gives 8Y the highest priority"* and that the present intention was *"to confirm the stability of 8Y to dry heat and possibly exploit it routinely"*. Options for Factor IX were dry-heated 9D and 9D heated in protected solutions.[50]

35. On 13 November 1984 a meeting was held, attended by (amongst others) Dr Smith, Dr Lane, Dr Snape and Mr Pettet, to consider options for heat treatment of Factor VIII; a note of the meeting produced on 19 November by Mr Wesley recorded that it was recognised that *"every effort must be made to start heat treatment as soon as possible"*; *"a very provisional date of 1.4.85 was set"* as the target date for implementation of heat treatment.[51]

36. On 20 November 1984, a memorandum was sent from Dr Smith to Drs Lane, Harvey and Snape concerning the distribution and allocation of dry-heated '8CRV' to particular categories of patients.[52] In his draft proof of evidence in the HIV Litigation Dr Smith said:

"This memorandum was prepared prior to the Haemophilia Centre Directors meeting on 10th December and sets out our position on the availability of

[49] Draft proof of evidence in the HIV Litigation, **CBLA0000016_034**, para 132.
[50] Memo from Dr Smith and others dated 12 November 1984, **CBLA0001920**.
[51] Memo from Mr Wesley dated 19 November 1984, **CBLA0001923**.
[52] Memo from Dr Smith to Drs Lane, Harvey and Snape, **CBLA0001926.**

heat-treated concentrates. The purpose of the memorandum was to provide Dr Lane with ammunition for telling the Haemophilia Centre Directors that we could provide the most vulnerable patients with heated concentrate immediately if the clinicians were prepared to put forward the names of those they considered to be special cases. We estimated that in order to meet this demand we would need a 1,000 vials per month of heated concentrate were needed and believed we could probably meet this requirement. I believe Dr Lane put this offer forward at the meeting on 10th December although it was not taken up. As it happened heated HL from BPL was not issued until January 1985 [Is this date correct?] [sic] because of a quality control problem, even though we had stocks of heated 8CRV available. One of the reasons we were selective in the use of dry heated 8CRV is that we wanted to test the effect of heating on transmission of NANBH in susceptible patients and I make this point clear in the memorandum."[53]

37. Dr Smith attended the meeting of Haemophilia Reference Centre Directors and others on 10 December 1984 at BPL.[54] A memo from Dr Smith to Drs Lane, Snape and Harvey on 12 December 1984 set out steps to be taken in light of the decisions at the meeting on 10 December, noting that *"days are precious if BPL/PFL are to be seen to be doing our utmost to help the HCDs"*.[55]

38. In the meantime Dr Smith had been part of a visit to the PFC on 29-30 November 1984 to discuss SNBTS policy on Factor VIII. Dr Smith's memo recording his conclusions from the visit referred to the seroconversions in patients receiving only Scottish concentrate and reported that *"Under clinical pressure to "supply something or they will buy US heated concentrate", they are recalling large batches and subjecting these and their current stock (approximately one year) to dry heat. Their concentrate will not stand 24 hours at 70° and the exposure is much briefer, shorter than they or I could be happy about"*.[56] Dr Smith observed in his draft proof of evidence for the HIV litigation that *"the Scots however were in a slightly different*

[53] Draft proof of evidence of Dr Smith in the HIV Litigation, **CBLA0000016_034**, para 133.
[54] Notes of meeting, **CBLA0001948**.
[55] Memo dated 12 December 1984, **CBLA0001952**.
[56] Memo dated 3 December 1984, **CBLA0001942**.

position from us, in that they had a number of patients seroconverting to HIV from product produced at PFC. We never had that intense pressure in England".[57]

39. On 6 February 1985, Dr Smith was present for most of the meeting with the Haemophilia Directors' Hepatitis Working Party, at which he and Dr Snape were invited to comment on BPL's proposals for supply of heat-treated Factor VIII concentrates.[58] There was a discussion of the clinical trials for 8Y.[59] Dr Smith wrote to Dr Rizza and other participating centre directors on 12 February 1985 setting out proposed arrangements for the use of 8Y in named patients as part of a trial.[60]

40. After successful phase 1 tests, 8Y was available in April 1985 on clinical trial for those with no prior exposure to concentrates, or minimal exposure to cryoprecipitate.[61]

41. In early July 1985 Dr Smith wrote to Dr Hill (Birmingham Children's Hospital) regarding the clinical trial of 9A concentrate, explaining that *"I do not need viral data at this stage and we put no restriction on your choice of patient, but we expect you to treat a few severe haemophilia B patients in otherwise robust health."* The letter set out the observations and information with which Dr Smith expected to be provided about the use of concentrate and response of patients, adding that BPL/PFL would *"do everything possible to ensure that patients helping with this stage of the trial will continue to be supplied with heated NHS concentrate, if that is what you wish, and with the same batches until they are exhausted".*[62]

42. On 31 July 1985, Dr Brian Colvin wrote to Dr Lane regarding children with Haemophilia B who had had concentrates, requesting the provision of heated concentrates for such children, following a suggestion from Dr Smith.[63] On 6 August

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[57] Draft proof of evidence of Dr Smith in the HIV Litigation, **CBLA0000016_034**, para 137.
[58] Minutes of meeting of Hepatitis Working Party on 6 February 1985, **HCDO0000562**. Dr Smith had also attended the previous meeting of the Hepatitis Working Party on 15 September 1984, **HCDO0000561**, at which he reviewed the progress of studies of small pool Factor VIII at Oxford.
[59] Memorandum from Dr Snape to Dr Lane, **CBLA0002031**.
[60] Letter dated 12 February 1985, **CBLA0002035**.
[61] Written statement of Dr Smith, **WITN3433001**, para 56.
[62] Letter from Dr Smith to Dr Hill dated 8 July 1985, **BWCT0000152**.
[63] Letter from Dr Colvin to Dr Lane, **BART0000536_004**.

1985 Dr Smith informed Dr Colvin of an arrangement that had been approved for the supply of 8Y for children with haemophilia A.[64]

43. In August-September 1985, 8Y was, according to Dr Smith's statement, available to all patients whose Haemophilia Centre Directors preferred it. A protocol for the follow up study of patients receiving 8Y required clinicians to report to Dr Snape or Dr Smith their interpretation of investigations of signs of hepatitis (clinical or laboratory) in such patients.[65] After September, there were no further issues of IP Factor VIII heated under milder conditions.[66] Then, in October 1985, severely heated Factor IX (9A) was available to all HCDs.[67]

44. A Regional Transfusion Directors meeting at BPL on 8 October 1985 reported Dr Smith's review of the virus inactivation programme: *"so far 8Y is a super product in terms of its ability not to transmit hepatitis"*.[68]

45. In an article in a 1986 Haemophilia Society Bulletin Dr Smith claimed that BPL had *"leap-frogged the competition with two entirely new heat-treated concentrates of Factor VIII and Factor IX, developed from the lab bench to national products in under a year"*. The article reported that *"All the laboratory and clinical reports suggest that we have many thousand-fold 'overkill' of the AIDS virus and none of the susceptible first-treatment haemophiliacs in the trial have shown any signs of hepatitis so far"*.[69]

46. In a paper written for a May 1986 Symposium on Standardisation in Blood Fractionation, Dr Smith reported the '*Interim results of surveillance for NANBH in patients receiving heated concentrates produced in England'*, concluding that *"... this collection of data of variable quality does not carry the full authority of a formal prospective clinical trial. However, when all reservations have been made about*

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[64] Letter from Dr Smith to Dr Colvin **BART00000536_001.**
[65] **CBLA0002035.**
[66] Written statement of Dr Smith, **WITN3433001**, para 56.
[67] Written statement of Dr Smith, **WITN3433001**, para 56.
[68] Notes of the Regional Transfusion Directors meeting, BPL, 8 October 1985, **CBLA0002263.**
[69] The Haemophilia Society Bulletin (1986) Vol. 34 No. 3, **PRSE0003186** p.6. The precise date of publication is unclear, but the formal request for the article was made by letter dated 12 February 1986 to Dr Smith from Mr Watters: **BPLL0007328.**

imperfect follow-up data, the weight of this varied evidence justifies our asking clinicians to put many more previously untreated patients into a more formal trial, using even more batches of product. Although these are only interim results on a limited number of batches, we think we are justified in thinking that the severe heating has been more effective in preventing transmission of NANBH than the milder heating accorded to the Hyland and Armour products in studies published last year. It is too early to know whether NANBH transmission has been eliminated by severe dry heating, or whether we may see transmission by only a few batches, as has occurred with Alpha's factor VIII concentrate heated in heptane".[70] The interim results were also shared by Dr Smith at a meeting of HCDs in October 1986.[71] A letter from Dr Smith to Dr Kernoff dated 19 August 1986 revealed that much of the data had already been presented to most HCDs at the Blood Club in March 1986.[72] A meeting had also taken place between BPL and SNBTS at PFC on 17 March 1986, at which Dr Smith *"outlined clinical trial results of the 8Y F VIII product so far. While results cannot be considered conclusive at this stage, he indicated that no cases of virus infection have occurred (attributable to 8Y material) after 12 months experience of 8Y in virgin haemophiliacs".*[73]

47. A subsequent report entitled *Effect of dry-heating of coagulation factor concentrates at 80°C for 72 hours on transmission of Non A Non B Hepatitis*, by the Study Group of the UK Haemophilia Centre Directors on Surveillance of Virus Transmission in Concentrates, of which Dr Smith was a member, was published in the Lancet in October 1988.[74]

48. On 31 August 1987, Dr Perry wrote a memo to Dr Foster regarding Factor VIII Development Strategy and Timetable, suggesting there was a need to:

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[70] Develop.biol.Standard, Vol 67, pp323-325 **PRSE0004378.**

[71] Memo from Dr Smith to Dr Lane and Dr Snape dated 28 August 1986, attaching draft of proposed contribution to HCDs' meeting on 15 September, **CBLA0002332_001.** The paper by Dr Smith was shared, by Dr Rizza, with Reference Centre Directors at their meeting on 22 September 1986, **PRSE0001101**; and presented to Haemophilia Centre Directors at their meeting on 9 October 1986, **PRSE0004317**.

[72] Letter from Dr Smith to Dr Kernoff dated 19 August 1986, **OXUH0003754_047**. A memo dated 10 March 1986 from Dr Smith to Drs Lane, Snape and Harvey and all participants in the 8Y study also set out an interim report on the surveillance for NANBH: **BPLL0006186_002**.

[73] Note of a meeting held at PFC on 17 March 1986, **PRSE0003764.**

[74] Lancet, October 8 1988, **PRSE0000044.** The first draft of the report was produced by Dr Smith in March 1988: see **CBLA0002405**; the results were discussed at a meeting held at NIBSC on 30 March 1988: see **CBLA0002406.**

"Consider whether there is any merit in joining forces with Jim Smith to broaden our perspective on FVIII developments. This idea may be somewhat bizarre but nevertheless worth considering given the resources at his disposal."[75]

[75] Memo from Dr Perry to Dr Foster, **SBTS0000282_157**.

Self-sufficiency

49. In his statements, Dr Smith set out his opinion as to the principal reasons why the UK did not become self-sufficient in blood products. In particular, he made a distinction between England and Scotland's approach. He said:

> *"The concept of "UK" self-sufficiency is an empty one. Although national self-sufficiency in blood products was strongly endorsed by WHO [PRSE0003476], no-one could claim that the principle, and its consequent responsibilities, were embraced as energetically in England as in Scotland. I believe that, at some decision-making levels, "illegal governmental assistance", and "restraint of trade" were adduced as serious impediments, despite the EU's adoption [PRSE0002575] of the WHO position. At the clinical level, where the other important decisions were made, an influential group of HCDs saw it as limiting the clinician's choice of the best product available for his patient; Scottish clinicians, no less fervent for their patients' welfare, seemed to cope with that challenge."*[76]

50. Following his move from Edinburgh to Oxford in 1975, Dr Smith expressed surprise at the lack of a national approach in England to self-sufficiency. He said:

> *"I was shocked by this lack of appetite for self-sufficiency at a national level. The situation I found in Oxford already provided a worked example of commitment and co-ordination which might have been adopted, with local adjustment, in any of the English Regions. The Oxford HC in Churchill Hospital treated many more patients than average, partly because families with haemophilia migrated to the Centre which, under Dr McFarlane and Dr Biggs, had always offered more generous treatment from the beginning... About 50m from the HC, and working under the most trying conditions, Dr Grant and later Dr Gunson at Oxford RTC made heroic efforts to provide the fresh plasma for PFL's production of F.VIII, all of which went next door to the*

[76] Written statement of Dr Smith, **WITN3433001**, para 164. It should be noted that Dr Smith was a member of the working party on self-sufficiency in blood products set up by Dr Gunson: **CBLA0000016_034**, para 110; and see the preliminary report of the working party at **CBLA0001377.**

HC. I was never given a convincing technical reason why, with BPL playing the role of PFL in the Virtuous Triangle, the same could not have been done in every Region, long before the surge in about 1982."[77]

51. Dr Smith contrasted the position in Scotland and England:

> *"PFC was virtually always able to meet the core Scottish demand for their FVIII and FIX [PRSE0001083]. England could make the heavily-nuanced claim in 1985 only because so many clinicians were choosing to buy imported products. The BPL claim ... became progressively more realistic after 1987 due to a better balance between the RTCs' and BPL's efforts, and BPL's development of more "attractive" FVIII products – only to see them pre-empted by the UKHCDs' recommendation in 1997 that the UK HCs should only use recombinant coagulation factors, in which BPL had not invested. The vCJD disaster of the late 1990s dealt the killing blow to the regrettably brief co-operation between the RTCs and BPL..."*[78]

52. Dr Smith was asked in his Inquiry statement to consider the role of the supply of plasma; the manufacturing capacity of BPL/PFL and PFC; the estimated and actual demand of the use of blood products; financial and other resources; and management and decision-making structures. He said in response that from 1982, RTCs did all that was asked of them and were not the limiting factor in the production of Factor VIII in England and Wales.[79] He added:

> *"Given a suspended death sentence in 1979, BPL had to push the capacity of the old Coagulation Factor plant to its creaky limits until 1987, then began to catch up with demand fairly quickly in the new B.27. Although calculations of demand had varied rather widely, the design capacity of the new Coagulation Factor plant was adequate, and even accommodated several challenging changes of product and processes until BPL ceased to be a national asset. Throughout the 1970s, the HCDs, often with Dr Biggs or Dr Rizza of Oxford*

[77] Written statement of Dr Smith, **WITN3433001**, para 166.
[78] Written statement of Dr Smith, **WITN3433001**, para 166.
[79] Written statement of Dr Smith, **WITN3433001**, para 167.

OHC as their spokesperson, faithfully kept their projections of demand up to date and ever more emphatic. The upward trajectory of demand, accelerated at times by new concepts such as prophylaxis and home therapy, could at any time have been extrapolated to the likely date of commissioning a new building, and therefore a decision-making process. We were constantly being reminded that it was not DH practice to spend large sums on "speculations". The design of the new BPL Coagulation Factor plant had to take appropriate cognisance of this."[80]

53. Dr Smith suggested that the political climate at the turn of the 1980s was not naturally favourable to expenditure in the public service. In his opinion, it was once convinced that a modern fractionation service could be a sound investment, given the high cost of commercial product, that the government then accepted the need for spending on the redevelopment of BPL.[81]

54. Dr Smith considered that a 5-year programme of re-building BPL would have had to have started in about 1978, not in 1982 as actually happened, in order to have had impact. He said,

"I contend elsewhere that, to prevent infections with HIV and at least staunch the surge of new HCV infections in the next generation, we would have to have had safe products before 1983. Even if heating had been more than a gleam in the eye in 1982, a 5-year programme of re-building BPL would have to have started in about 1978, not in 1982 as actually happened. The projections of UK need, made about 1975-78 on the basis of Scottish demand, notably by Dr Cash, were not taken seriously in England, except perhaps by some HCDs. The one-off bounty in 1975 by the then Minister of Health [PRSE0004264] was spread far too thinly. Very little reached BPL and it did not stimulate even ground studies for a building commensurate with the task."[82]

[80] Written statement of Dr Smith, **WITN3433001**, para 168.
[81] Written statement of Dr Smith, **WITN3433001**, para 169.
[82] Written statement of Dr Smith, **WITN3433001**, para 170.

55. Dr Smith asserted that substitution of UK products for imported ones would have made little or no difference to NANBH transmission to severely-affected patients, and even to infrequent users unless a small-pool strategy had been adopted for them. He asserted that it transpired only slowly that 8Y did not transmit NANBH and that it would have protected infrequent users from April 1985.[83]

56. In relation to HIV, Dr Smith stated that BPL could claim that 8CRV/HL concentrate subjected to 60°C or 70°C heating was available from August 1983 and, judged in retrospect, its use then would have forestalled HIV transmission by imported concentrates until the latter began to be dry-heated. By January 1985, when BPL's heated IP product was unequivocally "available", all imported concentrates still on the market were, he said, probably as safe from HIV as BPL's: *"As far as HIV was concerned, 8Y simply guaranteed overkill."*[84]

Knowledge of risks of hepatitis and AIDS

57. Dr Smith described his knowledge (and his perception of the knowledge of others) regarding the risks of hepatitis as follows:

    57.1. In his statement to the Inquiry, he stated that, in relation to NANBH, *"the risks of treatment were considered worth taking, in both blood transfusion practice and the treatment of haemophilia"* and that NANBH was *"universally considered to be an acute infection, producing only relatively mild symptoms, or none at all"*, with few reports of serious chronic disease associated with NANBH until the 1980s.[85]

[83] Written statement of Dr Smith, **WITN3433001**, para 172.
[84] Written statement of Dr Smith, **WITN3433001**, para 173.
[85] Written statement of Dr Smith, **WITN3433001**, para 32.

57.2. Asked about the respective positions of fractionators and clinicians, Dr Smith observed that *"They were receiving the same, sometimes conflicting messages, e.g., about long-term liver damage associated with chronic NANBH infection, at the same time, but the impact was different. Fractionators were saying "we know that it keeps getting harder to justify using large-pool coagulation products and we are working to make your decisions easier, but there are gaps in our basic knowledge which make it difficult to get a toe-hold on testing and inactivation of NANBH". Meanwhile, clinicians had to make hard daily choices based on their own interpretation of the danger, and make risk-benefit assessments on individual patients. Most would continue to recommend or use concentrates, aware of the risks. Fractionators have no place in telling clinicians how to make these choices."*[86]

57.3. He recalled lively debates in conferences and medical journals about the justification of liver biopsy in haemophiliacs and pathologists' differing interpretations of what samples were claimed to show. *"Most clinicians treating haemophilia were not seeing unusual incidences of late, symptomatic liver disease, perhaps because they had not been alerted to looking for it systematically. The ultimate consensus was that the majority of those infected with NANBH developed chronic hepatitis, and about 15-20% of those went on to have cirrhosis and other serious liver disease, usually after a delay of many years."*[87] It should be noted that Dr Smith was present at the 1980 symposium in Glasgow which explored "Unresolved Problems in Haemophilia" and explored in particular issues relating to hepatitis risks.[88]

57.4. In his draft proof of evidence in the HIV litigation, Dr Smith explained that it was in 1982 that thoughts were moving towards heat inactivation, but that the work was being undertaken against the background of HBV *"ceasing to be of much practical concern, and hepatitis Non-A Non-B, not yet being recognised for the serious condition it later emerged to be"*.[89]

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[86] Written statement of Dr Smith, **WITN3433001**, para 37.
[87] Written statement of Dr Smith, **WITN3433001**, para 39.
[88] **CBLA00000016_034**, para. 98 and **CBLA0001150**.
[89] **CBLA00000016_034**, para. 38.

57.5. A similar point emerged in Dr Smith's first Penrose statement, where he emphasised *"how little pressure there was from the haemophilia treaters and patients to take NANBH seriously in this period before 1983"*.[90]

57.6. One of the notes attached to Dr Smith's first Penrose statement repeated that NANBH *"was widely perceived as a mild, transient illness with only very rare serious sequelae"*.[91] Dr Smith recalled Dr Preston as being a notable exception.[92]

58. Insofar as AIDS/HIV was concerned:

58.1. Dr Smith's first Penrose statement suggested that *"There was some resistance among haemophilia clinicians to the idea that AIDS was caused by a blood-borne virus"*[93].

58.2. He imagined that by 1983 most blood transfusion professionals had concluded that the patterns of AIDS transmission strongly suggested involvement of a blood-borne virus.[94]

58.3. In common with blood transfusion colleagues, fractionators were *"more pressingly concerned with blood-transmissible pathogens than were haemophilia clinicians, and would have concluded that AIDS was caused by a blood-borne virus, at least as the initial event"*.[95]

58.4. In his oral evidence to the Penrose Inquiry, Dr Smith recalled first hearing about AIDS from an American colleague who brought back a cutting from the

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[90] **PRSE0004045**, para. 6. It is not clear what the factual basis might be for Dr Smith's reference to patients (as opposed to clinicians) not applying pressure to take NANBH seriously. It might be said that patients would need to have been informed of the risk by their clinicians in order to be in any position to do so.
[91] **PRSE0004045**, JKS Note 1.
[92] **CBLA00000016_034**, para. 35. See also the reference to Drs Preston and Mannucci being "Cassandras": **PRSE0004045** p. 28.
[93] **PRSE0004045**, para. 16; see also **WITN3433001**, paras 42-3 and para. 105 (referring to *"those clinicians whose long resistance to the viral hypothesis was well established"*).
[94] Written statement of Dr Smith, **WITN3433001**, para 44.
[95] Written statement of Dr Smith, **WITN3433001**, para 45.

Boston Globe – perhaps in 1982 – and that *"very shortly"* it was apparent that *"it was being transmitted pretty obviously through blood-borne routes"*.[96]

[96] **PRSE0006059** pp.70-71.

The relationship between PFL/BPL and PFC

59. In his written statement to the Inquiry, Dr Smith described informal lines of communication between PFL/BPL and PFC. He also listed what he described as *"some of the most important and tangible debts we owed to PFC"*:[97]

- *"Sharing the results of unsuccessful approaches by the SNBTS virus study group to virus inactivation, e.g., gamma-irradiation, so that we did not have to spend fruitless effort on them."*
- *"Providing details of a zinc/heparin method to separate FVIII from much of the unwanted fibrinogen at an intermediate stage. After a serendipitous discovery at PFL, this evolved into a processing step essential in what became 8Y."*
- *"Providing details, as PFC work developed, of promising pasteurisation processes for FVIII and FIX."*
- *"Sharing early Reports from some conferences which we could not attend, most significantly concerning Behringwerke's progress on pasteurising FVIII, and Rubinstein's on dry-heating."*
- *"Sharing access to the dog DIC trials which confirmed that 9A was not thrombogenic."*
- *"Sharing the results of PFC's attempts to explain the resistance of 8Y and other formulations to high temperatures."*
- *"Carrying out exacting virus spiking experiments on dry-heated FVIII and FIX, before BPL had acquired its own virus lab."*

60. Comparing the facilities in Scotland with those in England, Dr Smith noted that PFC's premises had been developed more recently when compared to BPL/PFL and that space had been allowed for R&D and pilot operations. PFC employed more scientists than PFL but they were not all simultaneously working on coagulation factors. PFC had an emphasis on chemical engineering which was absent from PFL and BPL. PFC also benefitted from the SNBTS R&D Lab, also in Edinburgh, although those

[97] Written statement of Dr Smith, **WITN3433001**, para 91.

resources were not all devoted to coagulation factors. However, Dr Smith emphasised that he did not take as close an interest in PFC's facilities as in its ideas and capacities and their willingness to share them with PFL.[98]

61. With regards to the relationship between PFC and PFL/BPL during the development of heat-treated concentrates, Dr Smith said:

> *"From Responses to Q.28a and 28b and others in passing, it should be clear that this relationship was extremely rewarding, at first in PFL's favour, and perhaps more equally when NANBH was eclipsed by AIDS and we both had to accelerate exploitation of our dry-heating experiences."*[99]

An example of the discussions between PFC and PFL/BPL appears in Dr Smith's note of a visit to PFC and to SNBTS headquarters in February 1983.[100]

62. When asked whether PFC had unused capacity to fractionate additional large quantities of plasma and thereby produce, store and supply additional blood products, Dr Smith said:

> *"I would guess that, in 1975, PFC's original 1973 plant could have handled an extra 200 L of plasma per week, perhaps with some expansion of staff (already a contentious issue) and finishing capacity. However, BPL was already receiving less FFP than it was ready to process, an imbalance which continued until 1982. Between 1982 and 1987, BPL was stockpiling FFP, and that is the time when any surplus capacity at PFC would have been most valuable. I have no information on whether PFC would have been able to help at that time, or whether SNBTS was ever asked."*[101]

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[98] Written statement of Dr Smith, **WITN3433001**, para 93.
[99] Written statement of Dr Smith, **WITN3433001**, para 98.
[100] Memo dated 15 February 1983 from Dr Smith, **CBLA0002481**; see also **CBLA00000016_034**, para. 122 and **PRSE0004045** p6 (referring to *"a correspondence between scientists with a clear sense of their responsibilities. We were both well aware of a degree of tension between the upper layers of our respective organisations but agreed (without as I recall having to discuss the question) that this must not be an obstacle to pooling what information we could each gather"*).
[101] Written statement of Dr Smith, **WITN3433001**, para 162.

63. Dr Smith added that there was no way that all of PFL's assets could have been shoe-horned into PFC, in the mid-1980s or earlier, and somehow continued to work in parallel, and commented that it turned out to be fortunate that PFC and PFL were pursuing different paths to global heat-inactivation, while still able to help each other's efforts.[102]

64. In one of Dr Smith's written statements to the Penrose Inquiry he responded to the question of whether difficulties at a senior level inhibited in any way the exchange of information between BPL and PFC in respect of the development of 8Y. He said:

> *"As early as 1980, and with a persistence much to his credit, Dr Cash had been trying to persuade BPL to have formal meetings at which SNBTS and BPL scientists would discuss the status of their current projects, and perhaps evolve common criteria and policies. (During much of this period there was no central NBTS in E&W to be represented at the table, only individual RTCs). The Inquiry does not document the belated fruition of his pressure - a series of formal encounters, chaired alternately by Dr Cash and Dr Harvey (BPL's R&D Director). I had thought the first of these happened in 1985, when we reached a consensus on thrombogenicity studies and the run-up to synchronised issue of dry-heated FIX in the autumn, but that is not documented and my recollection must give way to recorded facts. More importantly, there were several exchange visits between PFL and PFC scientists from 1983 to 1985. These were prompted by pressing scientific interests, quite technical, informal and very practically focused. I can only imagine that they had at least tacit blessing from senior levels. For reasons offered in JKS Note 6[103], we did not quiz each other about national policies or intentions. The later, formal meetings were rather guarded, valuable in providing supporting evidence on product quality, but lacking any revelations which accelerated a hepatitis-safe Factor VIII in Scotland. This is not to say that anything was actually withheld by either side. (One of the unfortunate features of such formal, en bloc meetings is that they produce two "sides".*

[102] Written statement of Dr Smith, **WITN3433001**, para 163.
[103] This is an addendum to Dr Smith's statement to the Penrose Inquiry in relation to Topic C3, at **PRSE0004368**, pp.7-11.

This is less likely in one-to-one encounters between individual scientists with urgent matters to discuss).”[104]

65. Also as part of his statement to the Penrose Inquiry, Dr Smith was asked about the lack of PFC representation on the CBLA Central Committee on Research and Development in Blood Transfusion that first met on 21 June 1983. He was also asked whether the committee was truly a UK committee or limited to England and Wales. Dr Smith answered as follows:

> *“I do not recall knowing the membership of the Committee; its precise remit; whether it had any new money to disburse; or its clout to make policy. With the PEN 016 series I am reading its minutes for the first time. Nothing leads me to question the rationale laid out by Mr Smart at the first meeting [PEN 016 1156]: CBLA had asked for a non-executive committee of experts who could advise them about forward developments in transfusion, and confirm that BPL and BGRL were pursuing sound policies in relation to their allies and co-dependents. Later, Dr Gunson implies that the CCRD was suggested by DHSS, but any Southern chicanery seems to be negated by equal representation of MRC, DHSS and SHHD, plainly as courtesy "observers" rather than active participants. Dr McClelland was invited as having broad-ranging expertise in transfusion matters, and doubtless also for his quiet but authoritative demeanour. It is stated categorically at the first meeting that the CCRD had no new money to allocate and was purely advisory. In the way of committees, it may in time have acquired a new slant - the new chairman, Dr Gunson apparently seeing it as a useful force in promoting UK convergence on transfusion policies [PEN 016 1158]. Dr Bell bridled at this, and it might have been better if the committee had at this point considered carefully whether a new remit and membership were required, to avoid confusion and suspicion. It may be noted that from the beginning Dr Bell had been sceptical about the relevance of the CCRD to SHS' needs, given that it had no cash or muscle [SGH 007 0761], This seems to me to be nearer the mark than Dr*

[104] Written statement of Dr Smith in relation to Topic C3 in the Penrose Inquiry, **PRSE0004368**, p5, para 5(a).

Cash's continuing fears that the CCRD was an English plot to exclude Scotland from transfusion policy decisions and UK grants.

These tempests need not detain the Inquiry too long. In practice, the minutes do not reflect much active interplay or debate between Scottish and English ideas. BPL's current progress was reported to the CCRD regularly - there is literary evidence that I supplied notes to Dr Lane from time to time but there appears to have been no active discussion of that progress, or even any discreet touch on the tiller. The CCRD received the reports rather passively, which may indicate that they did not feel qualified to comment, or were satisfied that we were not missing some obvious line of enquiry. There is no record of the CCRD being invited to advise on comparable reports from PFC. This is exactly as one would expect from its original remit to advise CBLA - not CSA, which showed no sign of wanting to join in, presumably happy with the expertise within its own jurisdiction.

The Committee did not weigh heavily on my shoulders, but that may be thanks to Dr Lane's practice of protecting his staff from unrewarding distractions, even if it meant taking some extra weight himself. The work of my colleagues was not affected by nervous micro-management from above."[105]

66. Dr Smith was further asked, if there had been a representative of PFC present, would an earlier or fuller exchange of information between BPL/PFL and PFC in respect of the development and clinical use of 8Y, including severe heating, have occurred. He said:

"The short answer is: No. Had there been more active, fractionation-oriented participation of SNBTS in the CBLA's Committee (I mean no disrespect to Dr McLelland whom I know to be very well-informed), it would not have advanced PFC's virus-safe concentrates by a day. PFC scientists had reliable access to anything we knew (where it was not tied up with third parties - none of which proved to be important), and evaluated it against their own strong

[105] Written statement of Dr Smith in relation to Topic C3 in the Penrose Inquiry, **PRSE0004368**, p6.

policies, at least as rationally and rigorously as I would have in their position. JKS Note 6 further explains my view that Scotland's progress was not practically impeded by a lack of shared information, or absence from any committee."[106]

[106] Written statement of Dr Smith in relation to Topic C3 in the Penrose Inquiry, **PRSE0004368**, p6.

Resources at PFL/BPL

67. Dr Smith noted in his statement to the Inquiry that if the new BPL had been built by 1980, *"people like me would have had a more orderly life and might have been able to create more options for virus reduction. As it was, we spent a lot of time working around builders renovating the old premises and in introducing training in modern pharmaceutical practices in preparation for the new BPL."* He would have wanted the kind of physical facilities in England necessary to exploit pasteurisation, something explored at the PFC, and observed that it was *"conceivable that had PFL been able to combine efforts with PFC we might both have arrived at a common goal sooner"*, although he added that *"even in retrospect that seems unlikely"*.[107]

68. According to Dr Smith, a number of resources would have been beneficial, and might have made Dr Smith's team more confident of success, but would not have accelerated the programme in relation to heat treatment significantly. More coagulation assays might have allowed optimisation of the process more thoroughly. But the 8Y path to successful pasteurisation was, according to Dr Smith, *"remarkably smooth"*. Hitches during scale-up were few and relatively easily solved. Having facilities at BPL for virus spiking might have allowed the covering of more variables and to measure the additional inactivation at higher temperatures, however, it would not have led to earlier availability of 8Y and 9A products.[108]

69. Dr Smith suggested that the volume of dry-heated products might have increased faster in a larger new facility but said that the most vulnerable patients did not require large amounts of product; that 8Y was already available to this group by April 1985; and that even the less severely heated product had been available on a named patient request since 1983 and would in retrospect have been safe from AIDS.[109]

[107] Written statement of Dr Smith, **WITN3433001**, para 95.
[108] Written statement of Dr Smith, **WITN3433001**, para 101.
[109] Written statement of Dr Smith, **WITN3433001**, para 103.

70. Dr Smith's statement also recorded that there were never any facilities or staff for virus work at PFL, and none at BPL capable of handling highly pathogenic viruses until completion of the new R&D Department in the late 1980s.[110]

[110] Written statement of Dr Smith, **WITN3433001**, para 88.

Pool Sizes and PFL/BPL

71. Dr Smith's statement to the Inquiry outlined the kinds of starting pool being used or proposed, before the advent of 8Y: normal pools, small pools, and limited-donor pools. These were described as follows.

72. Normal pools: The default at PFL was about 200L (800 single donations), and up to 1500L (6000 donations) at BPL.[111] The standard product made from these pools was a 250 IU vial of IP concentrate (8CVR at PFL, HL at BPL).

73. Although PFL pools were smaller than those at BPL they were never less than 300 donations and at no time fitted within the small-pool definition.[112]

74. Small Pools: Smaller pools were, in the early days of FVIII, estimated between 30-40 donations. Dr Smith observed that the upper limit of what might be called a small pool in 1980 should be defined by considering the incidence of an infection in the donor population and the annual consumption of the product by the patients treated with the product. In the early 1980s, Dr Smith may have assumed an incidence of NANBH in blood donors of 1:1000; using that incidence, a 100 L pool would have a 0.5 chance of producing an infective batch. Small pools thus offered little protection to the adult with severe haemophilia, according to Dr Smith's thinking. Pools smaller than 100 L would improve the odds somewhat but 100 L was at PFL the smallest pool that was possible without changing the technology in important ways and taking heavy losses.[113]

75. If the intention was to protect the most vulnerable, it was *"just about possible to include some small-pool compromise as a planned part of a new comprehensive fractionation facility"*. Thus, a pool of 20 donations (5 L) might produce 5 vials of 250 IU to treat one of the *"vulnerable"* group of patients in one year. The risk of infection would be 0.02 per year which was *"realistically the best offer available*

[111] Written statement of Dr Smith, **WITN3433001**, para 114; see also paras 121 and 124.
[112] Written statement of Dr Smith, **WITN3433001**, para 136.
[113] Written statement of Dr Smith, **WITN3433001**, paras 115-116; see also paras 122 and 127.

once a clinical decision is taken to treat the patient at all". Dr Smith described this as *"one aspect"* of his *"contingency thinking"* in the early 1980s, *"unable to see on the horizon a quick solution through validated screening of donations or some as yet-unspecified means of inactivating NANBH, which at that time posed the most immediate threat"*.[114] However, the 10-20 donation small pools proposed in 1981 as a contingency measure were never developed.

76. Limited-donor pools: This concept, according to Dr Smith's statement, derived from the arrangement instituted by Dr Angela Robinson, whereby 0.5 L of plasma would be collected every month from experienced blood donors whose last four blood donations had elicited no case of symptomatic hepatitis in their recipients. These were dubbed "Green 4 donors" and the donations were to be quarantined for 6 months in case a late infection intruded. Successive collections of plasma from these donors might be stored and combined to provide "limited-donor" pools within PFL's minimum capacity of 100 L. [115] PFL produced a small number of 100 L batches of 8CVR from Green 4 plasma in about 1982-3.

77. Only Leeds RTC was involved in collecting the Green 4 plasmapheresis donations. Dr Smith believed that originally the Green 4 products, unheated, were intended to be used by Dr Rizza in Oxford HC, mainly to give an insight into whether the laborious method of accrediting donors might make a difference to NANBH infection rates for at least the most susceptible patients. Dr Rizza appeared to have reported verbally to Dr Smith some apparent transmissions from this unheated product, which would be consistent with one or two of even these highly-selected donors being infective. The project then became caught up in the demand for heated products.[116]

78. According to Dr Smith, both small pools and limited-donor pools were last resort possibilities for protecting vulnerable patients, at least for a year or two. They were not projects subjected to detailed examinations of feasibility.[117]

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[114] Written statement of Dr Smith, **WITN3433001**, paras 118-119.
[115] Written statement of Dr Smith, **WITN3433001**, para 120; see also 123 and 128.
[116] Written statement of Dr Smith, **WITN3433001**, para 129; see also draft proof of evidence in the HIV litigation, **CBLA0000016_034**, paras 91-95.
[117] Written statement of Dr Smith, **WITN3433001**, para 137.

79. In terms of the practicalities of limited-donor pools, Dr Smith considered that they were not a practical possibility on a larger scale in the period 1982-1985. It would have taken almost as much equipment and trained staff to process each of the ten 100 L pools as to process a single 1000 L pool. The quality control burden would also rise in proportion to the number of pools processed. BPL could not have accommodated the additional staff and equipment to run multiple 100 L pools of accredited plasma. Recruitment and training would have been another issue. Location of the site near Borehamwood always made recruitment and retention of staff difficult.[118]

80. Ultimately, Dr Smith's statement explained, the proposal for small pool or donor-limited pools was overtaken by the success of broad-spectrum virus inactivation from 1985 onwards.[119]

[118] Written statement of Dr Smith, **WITN3433001**, paras 154-155.
[119] Written statement of Dr Smith, **WITN3433001**, para 156.

Reversion to cryoprecipitate

81. Dr Smith set out his views about reversion to cryoprecipitate in his Inquiry witness statement. He asserted that a return to cryoprecipitate was not a practical possibility in the period of 1982 to 1985, adding that the provision of cryoprecipitate was always considered the responsibility of RTCs at the request of the haemophilia clinicians (the Inquiry has, of course, heard evidence from RTDs that a reversion to cryoprecipitate would have been a practical possibility).[120] Dr Smith was asked whether a return to cryoprecipitate was considered in the UK and answered as follows:

> *"Considered by whom? Not by fractionators, for the reasons already stated. Not by RTCs, who did not relish the scale of expansion predicated. Not the staff of HCs, for whom the dissolution and pooling of frozen gobbets of cryo was a fiddly job requiring air-filtration facilities and training in aseptic technique. Only a new "factory" ... probably producing freeze-dried cryo, would have had the capacity to replace all large-pool concentrates."*[121]

82. Dr Smith also thought of cryoprecipitate as a pharmaceutically-inferior medication which should be replaced as soon as possible. Quality control of cryoprecipitate was based on a few random samples from hundreds of discrete batches. There were variations in the Factor VIII content of individual bags which were inevitable. The process of reconstituting and pooling bags of cryoprecipitate, especially in a home environment, was bacteriologically unsafe. Dr Smith believed that it was quite common for patients to become intolerant of cryoprecipitate, exhibiting distressing allergic reactions. For those severely affected by haemophilia, he asserted that freeze-dried cryoprecipitate would have been an unrecognisable regression and that the additional virus protection would be illusory in any case.[122]

[120] Written statement of Dr Smith, **WITN3433001**, para 146.
[121] Written statement of Dr Smith, **WITN3433001**, para 148.
[122] Written statement of Dr Smith, **WITN3433001**, para 149.

83. Dr Smith conceded, however, that by 1983 to 1984 a patient in the mildly-affected group might justifiably have insisted on cryoprecipitate rather than a concentrate.[123]

84. Dr Smith emphasised that it was the business of the clinician, not the fractionator, to assess the risks and benefits for different patients and categories of patients; he also suggested that there was no widespread demand for centrally-produced cryoprecipitate, even at the height of the HIV risk before donor screening in 1985, on the grounds of existing capacity, lead-times for construction, pharmaceutical quality, and tolerance issues.[124]

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[123] Written statement of Dr Smith, **WITN3433001**, para 150.
[124] Written statement of Dr Smith, **WITN3433001**, para 151.