Witness Name: Dr Robert J. Perry
Statement No.: WITN6920001
Exhibits: nil
Dated: 16th February 2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF DR ROBERT J. PERRY

I provide this statement in response to a request under Rule 9 of the Inquiry Rules 2006 dated 18 October 2021.

I, Dr Robert J. Perry, will say as follows: -

Section 1: Introduction

1. **Please set out your name, address, date of birth and professional qualifications.**

1. My name is Robert John Perry of GRO-C GRO-C and my date of birth is GRO-C 1950.

2. Qualifications:
   i. B.Sc (Hons) - Chemistry University of London (1971)
   ii. Ph.D Chemistry - University of Manchester Institute of
   iii. Science and Technology (1975)
   iv. Member of Royal Society of Chemistry M.R.S.C. C.Chem
   v. Registered/Accredited 'Qualified Person' (QP) for manufacture/release of pharmaceutical products as defined by EEC Directive 75/319/EEC. (no longer registered)

2. **Please set out your employment history with dates wherever possible, including the various roles and responsibilities that you have held throughout your career. In particular, please describe the roles, functions and responsibilities you had at PFC during your period as:**

   a. **Quality Control Inspector; and**

   b. **Director.**

   In your answer, please explain how your roles and responsibilities changed over time, and to whom you were accountable in discharging your role and responsibilities.

3. My employment history is as follows:

   i. Consultant - International Plasma Fractionation Association (2013 to Present)

   ii. Deputy Executive Director/Executive Director International Plasma Fractionation Association, Amsterdam (January 2007 - Present)

   iii. Self Employed (As above and other minor roles)

   iv. NHS Scotland/Scottish National Blood Transfusion Service Director— Better Blood Transfusion Programme (BBTP) (June 2005 - January 2007)

   v. Director of Pharmaceutical and Technical Projects National Services Scotland (May 2004 - May 2005)

   vi. Personnel Director SNBTS (Secondment) (August 2003 — 30 April 2004)

   vii. Director — Protein Fractionation Centre, Scottish National Blood Transfusion Service (1984-2003)

   viii. Quality Control Inspector — Protein Fractionation Centre (1981-1984)

   ix. Chief Analyst — Regional Sterile Supply Unit — West Midlands Regional Health Authority (1977-1981)

   x. Analytical Chemist — Severn Trent Water Authority (1975-1977)

   xi. University of Manchester Institute of Science and Technology Ph.D Student /Part Time Teaching (1972-1975)

   xii. Biochemist in Department of Chemical Pathology — Royal Postgraduate Medical School, Hammersmith, London (1971-1972)

4. In my role as Quality Control Inspector I was accountable to the PFC Director (Mr J G Watt) and following my appointment as Acting Director/Director I became accountable to the Committee of Management of the Common Services Agency (CSA), in common with other Regional Directors of SNBTS. This accountability was stated as being *"subject to the responsibilities of the National Medical Director (Dr J Cash)"* which in practice provided accountability for professional and medical issues.

5. In 1990 a SNBTS General Manager was appointed to whom I became accountable, again in practice, subject to the responsibilities of the National Medical and Scientific Director.

4. **Please set out your membership, past or present, of any committees, associations, parties, societies or groups relevant to the Inquiry's Terms of Reference, including the dates of your membership and the nature of your involvement.**

6. MEMBERSHIP OF KEY COMMITTEES ETC
    i. Member of SNBTS Management Board and Directors Committee Scottish National Blood Transfusion Service (1984-2004)
    ii. European Plasma Fractionation Association Member of General Assembly (1991-2005); Member of Executive Board/Treasurer (2001-2005)
    iii. Chairman - EPFA Standing Committee on Quality Assurance (1992-2005)
    iv. Member of UK Committee on Safety of Medicines (CSM) - Biological Sub-Committee (1986-1990)
    v. Member of B.P. Commission (Committee K, Blood Products) (Retired) (I do not hold a record of the dates of membership)
    vi. Member of UK Government Advisory Committees on Microbiological Safety of Blood and Tissues (ACVSB and MSBT) (1991 -2004)
    vii. Member of UK BTS/NIBSC Working Party on Blood and Blood Products

viii. Member of SNBTS Medical and Scientific Committee (1990-2004)

ix. Membership of various ad-hoc National and SNBTS Committees/Working Parties (1981-2007)

5. **Please explain how you kept abreast of medical and scientific developments and research in your field in the course of your career.**

KNOWLEDGE OF SCIENTIFIC AND MEDICAL DEVELOPMENTS AND RESEARCH

7. A broad range of mechanisms and fora existed to maintain awareness of scientific and medical developments concerning Plasma Derived Medicinal Products (PDMPs) and Transfusion Medicine in general. These included:-

- Regular and frequent exchanges of information and scientific publications between SNBTS medical and scientific staff and, in particular, regular surveillance of the relevant literature by Professor Cash, Dr Foster and others.
- PFC hosted a small library which identified and obtained key publications.
- Personal attendance at and/or presentations at national and international conferences and reports from colleagues (including those from SNBTS, BPL, Haemophilia doctors and others) highlighting key developments.
- Regular attendance at SNBTS and UK meetings including membership of the Biological sub-committee of the Committee on Safety of Medicines and ACVSB/MSBT.
- Regular updates on regulatory developments from EPFA/IPFA - of which SNBTS was a member.
- Informal networks of scientific and medical colleagues from European fractionators and the wider fractionation industry.
- Regular meetings with Scottish Haemophilia directors and periodic attendance at UK Haemophilia Centre Directors meetings.
- Membership of SNBTS Medical and Scientific Committee.

8. Gathering and evaluating information from the above was an important and regular feature of the work of all senior professionals within SNBTS.

Section 2: Previous statements and evidence

6. The Inquiry understands that you provided the following written statements and oral evidence to the Penrose Inquiry:

a. Statement to the Penrose Inquiry on Topic C1, dated 25 January 2011 (PRSE0001823)

b. Statement to the Penrose Inquiry on Topic B2, dated October 2011 (PRSE0003755)

c. Supplementary statement to the Penrose Inquiry on Topic B5, dated 14 June 2011 (PRSE0003769)

d. Statement to the Penrose Inquiry on Topic B3, dated 23 June 2011 (PRSE0002178)

e. Statement to the Penrose Inquiry on Topic C3, dated 2 September 2011 (PRSE0001258)

f. Statement to the Penrose Inquiry on Topic C4, undated and unsigned (PRSE0000145)

g. Statement to the Penrose Inquiry on Topic C3A, dated 12 September 2011 (PRSE0002320)

h. Statement to the Penrose Inquiry on Topic C3A, dated 28 September 2011 (PRSE0002938)

i. Transcript of oral evidence to the Penrose Inquiry on Topic C1, dated 24 March 2011 (PRSE0006011, pages 89-125)

j. Transcript of oral evidence to the Penrose Inquiry on Topic B2, dated 13 May 2011 (PRSE0006025, pages 1-71)

k. Transcript of oral evidence to the Penrose Inquiry on Topic B5, dated 24 June 2011 (PRSE0006038, pages 1-105)Transcript of oral evidence to the Penrose Inquiry on Topic B3, dated 13 September 2011 (PRSE0006045)

l. Transcript of oral evidence to the Penrose Inquiry on Topic C3, dated 28 October 2011 (PRSE0006058, pages 1-102)

m. **Transcript of oral evidence to the Penrose Inquiry on Topic C4, dated 23 November 2011 (PRSE0006068, pages 1-146)**
n. **Transcript of oral evidence to the Penrose Inquiry on Topic C3A, dated 7 December 2011 (PRSE0006074, pages 1-84)**

Please confirm whether these statements and the oral evidence are, to the best of your knowledge and belief, true and accurate. In particular, please confirm that your unsigned statement to the Penrose Inquiry regarding Topic C4 (PRSE0000145) is true and accurate. More generally, if there are any matters within your evidence to these previous inquiries that you do not consider to be true and accurate, please explain what they are and how the inaccuracy occurred. Please also identify any evidence you gave to the Penrose Inquiry which is not listed here.

9. I can confirm that to the best of my knowledge, belief and recollection my written statements and oral evidence provided to the Penrose Inquiry are true and accurate.

10. I do not know why my written statement regarding Topic C4 (PRSE0000145) is not signed, but in any event I can confirm that this is an accurate and true record.

7. What materials were made available to you when you gave evidence to the Penrose Inquiry?

11. All documentation identified and held by the SNBTS at the time of the Penrose Inquiry was available to me to assist in my evidence submissions.

8. Did anyone else assist you in preparing your evidence to the Penrose Inquiry? If so, who, and what assistance did they provide?

12. A number of SNBTS colleagues and ex colleagues were engaged in the identification and submission of historical records and documentation, which

provided assistance to me in identifying key documentation relevant to my evidence. I was the sole author of the evidence submitted.

9. **Please confirm whether you have provided evidence to, or have been involved in, any other inquiries, investigations, criminal or civil litigation in relation to human immunodeficiency virus ("HIV") and/or hepatitis B virus ("HBV") and/or hepatitis C virus ("HCV") infections and/or variant Creutzfeldt-Jakob disease ("vCJD") in blood and/or blood products. Please provide details of your involvement, and copies of your evidence if it is available to you.**

13. I have not been involved in any other Inquiries, litigation or investigations concerning HIV, Hepatitis or vCJD.

Section 3: Administration, organisation and governance at the PFC

10. **Please describe the administration and organisation of the PFC during the time you worked there and how this changed over time. In particular, please explain:**
    a. **the structure and staffing of the PFC, including the names, roles and responsibilities of key personnel;**
    b. **arrangements for funding the PFC, including, in broad terms, the level of funding, who was responsible for granting funding, and whether, in your view, the funding available to PFC was adequate;**
    c. **the PFC's remit, including the geographical area it covered, and the hospitals and haemophilia centres within its area.**

(a) PFC Structure and Staffing

14. The PFC operated with a departmental structure comprising the following departments:-

15. Manufacturing: Responsible for all aspects of product manufacture from bulk collection of plasma from Regional Transfusion Centres (RTCs) through to

return of manufactured plasma products to RTCs. Postholders: Mr W Grant, Mr M Crowston, Mr A Dickson, Dr R McIntosh.

16. Quality: Responsible for development and enforcement of Quality Systems, Quality Control laboratory testing of products and intermediates, approval of finished products for use and, latterly, regulatory compliance and product licencing following the removal of Crown Immunity status. Postholders: Dr R Perry (1981-84), Dr B Cuthbertson.

17. Research and Development: Responsible for product and process development and provision of troubleshooting and support to the Manufacturing Department. Also maintenance of the Centre's scientific database. Postholder: Dr P Foster

18. Engineering: Responsible for all aspects of building, plant and equipment maintenance. Postholders: Mr R Lines, Mr J Ducie.

19. Project Engineering: Responsible for specialist engineering support and in particular development and maintenance of IT systems throughout the centre – including manufacturing equipment and systems. Postholder: Mr E Walker.

20. Administration/Business Support Services: Responsible for PFC support services including Finance, Personnel Services, Transport etc. Latterly to include management of contracts with third party organisations. Postholders: Mrs J Campbell, Mr M Ivey, Dr K Reid

21. The heads of the above departments comprised the Local Management Team, reporting to the PFC Director.

22. There were some changes to this structure over time, including the subsuming of Engineering and Laboratory services into an enlarged Operations Department. I do not recall the dates of these changes.

(b) PFC Funding

23. The PFC, as an integral part of SNBTS, was funded through the Common Services Agency of the NHS in Scotland, which in turn received its funding for all its divisions from the then SHHD. My recollection is that the specific funding for SNBTS was ring fenced by SHHD and budgets for all SNBTS operational units were managed and monitored by the SNBTS Headquarters Finance Department.

24. PFC funding covered all operating and staff costs for the centre.

25. Requests for additional funding (both capital and revenue) were subject to internal overall SNBTS review prior to submission to CSA/SHHD for consideration and funding.

26. Although there may have been some disappointments and delays in response to funding requests, I do not recall funding being denied for key PFC developments and facility upgrading in response to statutory regulatory requirements.

27. Products were supplied to Health Boards in Scotland free of charge.

28. Funding for fractionation of plasma from Northern Ireland was included in the financial allocation to PFC from CSA/SHHD. I believe there was an interdepartmental transfer of funds between the Northern Ireland government department and SHHD, although I had no knowledge of the detail of this arrangement.

(c) PFC Remit

29. At the time of my appointment to SNBTS in 1981 the remit of PFC was to manufacture and supply a range of plasma derived products (Albumin, Coagulation Factor products and Immunoglobulin products as well as anticoagulant and infusion fluids) for the treatment of patients throughout Scotland. In the early to mid 1980's this remit was expanded to include bulk collection of plasma from Northern Ireland Blood Service and manufacture and

supply to Northern Ireland of plasma products from this plasma. This followed an agreement for this service between the Northern Ireland Health Department and SHHD.

30. It was considered (particularly by Professor Cash) an important principle that the distribution to Health Boards, hospitals and Haemophilia Centres of manufactured plasma products should only be via SNBTS (and Northern Ireland) Regional Transfusion Centres, which would be responsible for their onward distribution to Health Board hospitals and Haemophilia Centres. This arrangement was designed to reinforce the role of RTC medical staff for professional and operational liaison with prescribing doctors in Health Boards. This principle and practice was maintained throughout the period of plasma product supply from PFC.

11. Please describe the PFC's place within the SNBTS and the NHS more broadly, and how this changed over time. Please explain the arrangements in place, and the fora which existed, to facilitate collaboration and communication between organisations. Were such arrangements sufficient to ensure clear and effective communication and collaboration? In particular, please explain:

a. The PFC's relationship with the Scottish Regional Transfusion Centres ("RTCs").

b. The PFC's relationship with the Scottish Home and Health Department ("SHHD").

c. The PFC's relationship with the Department of Health and Social Security ("DHSS").

d. The PFC's relationship with any other bodies which controlled, supervised and/or advised the PFC

<u>PFC's Place within SNBTS and NHS</u>

31. PFC was the national manufacturing unit of the SNBTS. It operated within the managerial and professional structures of SNBTS, with a broadly comparable status in terms of size, influence and impact to that of its Regional Transfusion

Centres. Its existence and remit as a national unit created a natural focus for many of SNBTS's activities given the increasing importance and emphasis on plasma product self sufficiency and, in particular, the goal of meeting the needs of haemophilia patients in Scotland. The position and status of PFC within SNBTS remained largely unchanged throughout its existence.

32. A number of arrangements existed, both formal and informal, to provide effective communication and collaboration between all stakeholder organisations.

(a) Relationship with RTCs

33. At all levels of the organisation PFC had a close working relationship with RTCs, reflecting the interdependency between them and a strong shared sense of purpose. All SNBTS Directors (including PFC) met on a regular basis at Coordinating meetings chaired by Dr Cash, in his role as National Medical Director. The Director of the Northern Ireland Transfusion Service also attended these meetings following the implementation of the fractionation arrangement between Northern Ireland and Scotland, as well as periodic attendance by colleagues from England and Wales for topics of UK wide relevance. These meetings (held quarterly) were designed (as the name suggests) to coordinate the overall scientific, medical and operational activities of SNBTS centres, to ensure consistent policies and standards throughout the organisation and the wider UK Blood Services. These meetings were also the forum in which PFC activities would be discussed and considered – including plasma and product supply issues. There also existed less frequent, though regular, SNBTS Directors' meetings to which representatives from SHHD were invited and regularly attended. Agendas for the Directors meeting sometimes overlapped those from Coordinating Group meetings, but were primarily for the purpose of creating a fomal and routine structure for briefing SHHD on key developments and/or seeking their input into SNBTS decisions, when considered necessary.

34. Following the appointment of the SNBTS General Manager in 1990, the senior management of SNBTS comprised a SNBTS Board with a membership of RTC

Directors, PFC Director, National Science Laboratory (NSL) Director, Finance Director and Personnel Director, and a National Medical and Scientific Committee with a membership including RTC Directors, PFC Director and NSL Director. Other senior staff were periodically invited to attend for specific agenda items (eg from the Microbiological Reference Centre SNBTS Consultants, PFC Scientific staff.)

35. In addition to the above formal meetings, frequent meetings took place between SNBTS Directors and other staff on specific topics or as ad hoc working groups such as Quality Assurance (QA), Factor VIII, Plasma Quality etc.

36. Finally, there was regular and frequent written and telephone communication between staff at all levels in SNBTS and in particular between the National Medical Director (NMD), RTC and PFC Directors and RTC medical staff – the extent of this communication will be evident from the extensive SNBTS correspondence submitted to the Inquiry.

10 (b) PFC Relationship with SHHD

37. SHHD was an important point of contact for SNBTS. SHHD civil servants (in particular medical officers) were readily accessible to SNBTS. PFC interaction with SHHD was usually as part of an SNBTS team. A number of fora existed for direct and regular contact with SHHD.
    i. Attendance of senior Medical Officers from SHHD at SNBTS Director meetings
    ii. Deputy Chief Medical Officer (DCMO) and other senior officials' membership of CSA BTS Sub Committee, attended by all SNBTS Directors
    iii. Annual meeting of Scottish Haemophilia and Transfusion Directors convened by SHHD
    iv. Regular attendance of Medical Officers at Coagulation Factor Working Party meetings (reporting to Haemophilia and Transfusion Directors meeting above) chaired by Professor Ludlam.
    v. Regular 'update' meetings with SHHD officials and Medical Officers.

(c) PFC Relationship with DHSS

38. I do not recall there being a significant relationship with DHSS independent of SHHD. I personally attended meetings of ACVSB/MSBT chaired by the DCMO (England), but with SHHD officials also in attendance. Occasional meetings and discussions with DHSS will have taken place between myself and certainly Professor Cash and RTC Directors, but I cannot recall any details.

(d) PFC Relationship with other bodies.

39. PFC scientists worked with colleagues from the National Institute of Biological Standardisation and Control (NIBSC) on topics of mutual interest and were periodically co-opted on NIBSC working groups for e.g. development of National Guidelines for Blood Transfusion Services (the Red Book).

40. PFC was required to submit samples of finished products, intermediates and plasma pools for control testing and batch release to NIBSC as the national control laboratory.

12. More broadly, please describe the relationship between the SNBTS and the English NBTS. Please explain the arrangements in place, and the fora which existed, to facilitate collaboration and communication between the two blood services. Were such arrangements sufficient to ensure clear and effective communication and collaboration?

Relationship between SNBTS and English NBTS

41. The SNBTS and NBTS were administratively separate organisations with, respectively, ultimate accountability to the Secretary of State for Scotland and Minister of Health for E+W.

42. However they were both subject to the same professional guidelines and standards to which, to the best of my knowledge, they sought to harmonise their approach.

43. A range of fora and mechanisms existed to encourage and facilitate collaboration and communication including:-
    i. Attendance by SNBTS representative Director at NBTS Directors meetings and vice versa
    ii. Frequent communication between Professor Cash and Dr Gunson.
    iii. Creation of UK wide working groups such as SACTTI, with membership from all 4 services.
    iv. Joint approach to development of guidelines eventually resulting in the creation of JPAC
    v. UK Government and Health Departments' policies requiring uniform implementation of key developments particularly those concerning safety and quality.

44. My personal view is that these arrangements provided effective communication and collaboration, supported by a general collegiate attitude and common sense of purpose shared by transfusion professionals in the UK. However RTC Directors may have a more informed view since the PFC did not frequently or routinely interact with centres in England and Wales.

13. Please describe, during the time you worked there, the PFC's relationship with the Blood Products Laboratory ("BPL") and how that relationship changed over time. In particular, please describe:
    a. The official fora which existed to facilitate liaison between PFC and BPL.
    b. The relationships you maintained, in an individual capacity, with key personnel at BPL.
    c. Whether, in your view, the relationship between PFC and BPL was sufficient to ensure clear and effective communication and collaboration between the two laboratories. In your answer, please

provide examples of collaboration, or instances in which collaboration did not occur. Do you consider that there would have been merit in a joint UK approach to the development and production of blood products?

PFC Relationship with BPL

45. SNBTS and, in particular, PFC always considered its relationship with BPL to be very important, although as separate units under different UK jurisdictions there were few, if any, mechanisms or fora for regular formal liaison and collaboration. However there was a regular and productive scientific collaboration. I would refer you to the evidence submitted by Professor Marc Turner, which included information provided by Dr Foster (WITN3530007) . This statement provides further detail.

(a) Liaison between BPL and PFC

46. As mentioned above, I do not recall any formal liaison mechanisms between BPL and PFC, although Professor Cash was a consistent and strong advocate for closer and more formal cooperation between UK Blood Services concerning the development of safer NHS products. There was established a "Central Blood Laboratory Authority (CBLA)/CSA Liaison Committee" (which met annually) in the late 1980's, attended by the CSA General Manager, Professor Cash and myself and the CBLA CEO, Chairman and Medical Director. My recollection is that this was established to exchange information on the activities of SNBTS and CBLA and identify areas of potential collaboration. I cannot recall any specific actions which emerged from these meetings although the ongoing collaboration and communication between PFC and BPL scientists and operational managers continued, as outlined in the evidence of Professor Turner/Dr Foster mentioned above. I do not recall when these meetings were discontinued. I am not aware of or cannot recall any formal mechanisms being established by DHSS/SHHD or the Blood Services for formal cooperation concerning joint product development programmes.

(b) Relationships between myself and BPL Personnel

47. I personally established and maintained professional and personal working relationships with a range of senior BPL personnel involved in Manufacture, Quality Assurance, Marketing and Research and Development (at both BPL and PFL). These included Dr Lane (BPL Director), Dr T Snape (QA Manager), Dr J Smith and co-workers (R+D). These relationships were supported and maintained by periodic meetings, phone calls, correspondence and information sharing.

(c) Communication between BPL/PFL and PFC

48. Throughout my employment in SNBTS there was a close working relationship between PFC and BPL, whose origins predated my appointment to PFC. This was particularly evident in the field of research and product and process development, arising from the PFC head of R+D (Dr Foster) and PFL Director (Dr J K Smith) previously having worked together at PFC. Communication and collaboration was not underpinned by a formal mechanism, but I strongly encouraged information exchange, scientific collaboration and regular meetings between colleagues from both organisations. I believe these arrangements were effective and productive, although they fell short of a more formal arrangement advocated by Professor Cash. I do not recall there being any enthusiasm or action by SHHD or DHSS to strengthen or formalise these informal collaborative arrangements.

49. Examples of collaboration between PFC and BPL have been outlined in evidence submitted by Professor Marc Turner (WITN3530007 paras 202 – 212) and contributed to by Dr Foster. In addition to these examples there were regular visits between colleagues (including BPL/PFC Directors).

50. PFC/SNBTS had always been a strong advocate of using PFC capacity for the processing of both Scottish and a proportion of English plasma, but the option was rejected by DHSS (WITN 3530007 para 205).

51. Concerning product supply to the UK NHS, there were a number of occasions when BPL was able to supply products to SNBTS which it did not itself manufacture, or to provide a product for patients in Scotland pending the availability of a suitable product from PFC (eg High Purity FIX). Equally, PFC transferred product surplus to its needs (eg FVIII in the early 1980's) for use in England and also Immunoglobulin products (1990's), pending the availability of suitable products from BPL, and to support Hospitals in England where shortages existed at that time.

52. There may have been some merit in a joint approach for the development, production and supply of plasma products for the UK wide NHS (particularly for providing increased benefit of scale for PFC) but this did not apparently enjoy the support of DHSS or SHHD to the extent of serious consideration or study.

14. Please describe (i) the PFC's relationship, and (ii) more broadly, the SNBTS' relationship with the Northern Ireland Blood Transfusion Service, and how this changed over time. In particular, please explain:

a. What arrangements were in place, and what fora existed, in relation to the supply of blood products from the PFC to the NIBTS? Were such arrangements sufficient to ensure clear and effective communication and collaboration?

b. How did the supply of blood products to the NIBTS operate? Please describe all aspects of the supply chain, from the point of donation in Northern Ireland, to processing at the PFC, to the issue of blood products from the PFC for use in Northern Ireland.

<u>PFC/SNBTS Relationship with Northern Ireland Blood Transfusion Service (NIBTS)</u>

53. The relationship between PFC/SNBTS and the Northern Ireland Transfusion Service (NIBTS) was established in the early 1980's, following an agreement between the respective Health Departments of Northern Ireland and Scotland for the fractionation of plasma collected in Northern Ireland to be processed at PFC. PFC funding was increased to support this additional activity which, to the best of my recollection, increased the amount of plasma processed at PFC by

approximately 20%. Products supplied to NIBTS were coagulation factors (FVIII and FIX), Albumin and Immunoglobulin products.

(a) Communication and Collaboration with NIBTS

54. Reflecting this new relationship with PFC/SNBTS, the Director of NIBTS (Dr Morris McClelland) was invited to attend meetings of SNBTS Directors and he became a regular attendee, participating in discussions of both operational and professional issues. Similarly, the Director of the Northern Ireland Haemophilia Centre (Dr Elizabeth Mayne) was invited to join the regular meetings between SNBTS and Scottish Haemophilia Centre Directors (Coagulation Factor Working Party). Dr Mayne became a regular attendee of these meetings. The above arrangements created productive and effective mechanisms for communication and cooperation. Periodically, I would visit the NIBTS to update Dr McClelland and his staff on significant PFC developments and/or as an invited speaker at local (Belfast) meetings.

55. In addition, operational managers from both PFC and NIBTS communicated regularly concerning plasma collection and product supply arrangements. Also, colleagues from NIBTS were invited to and attended the annual SNBTS scientific meeting (ScotBlood). These arrangements remained largely unchanged for the duration of my SNBTS employment and my recollection is that all parties were content that they provided a useful and satisfactory forum for communication and cooperation.

56. Finally, prior to the initiation of the supply contract with NIBTS, PFC (myself and Dr Cuthbertson) conducted a quality audit in 1981 of the Northern Ireland Centre's arrangements for plasma collection, processing and in particular its diagnostic testing arrangements for markers of infectivity.

(b) The Operation of the NIBTS supply contract

57. To the best of my recollection the supply of plasma products to Northern Ireland operated as follows:-

i. Donor selection, blood collection, diagnostic testing and blood component preparation (including plasma for fractionation) and rapid freezing of plasma were undertaken by NIBTS under its supervision and subject to UK standards and guidelines.

ii. The above activities were subject to PFC quality audit and latterly (early 1990s) by Medicines Inspectors from the MCA.

iii. Frozen plasma was stored by NIBTS below -20 degrees C pending routine collection by PFC refrigerated vehicle and return to Edinburgh. The PFC vehicle also delivered plasma products to NIBTS in the same trip.

iv. PFC processed NIBTS plasma and after QA formal approval the finished products were returned to Belfast.

v. The quantity of product supplied to NIBTS was calculated on the basis of its pro-rata contribution to the overall plasma supply to PFC by both SNBTS and NIBTS.

vi. My recollection of the cycle time for these activities was between 3-6 months.

vii. Distribution of plasma products to hospitals and haemophilia centres in Northern Ireland was the sole responsibility of NIBTS.

15. Please describe, during the time you worked there, the PFC's relationships and your own individual relationships with pharmaceutical companies involved in (i) the collection, testing, manufacture or supply of blood and/or blood products, and/or (ii) the manufacture of diagnostic screening tests for viral infections

58. The PFC and particularly its scientific staff had a broad network of contacts with organisations involved in the manufacture and supply of plasma products. These were predominantly 'not for profit' organisations in Europe, US and Australia, with whom there was exchange of scientific information and other information concerning developments in the industry. However there was periodic contact with colleagues from the commercial sector of the fractionation industry, again primarily for the exchange of scientific information.

59. I am not aware of any significant contact between PFC staff and manufacturers of diagnostic screening tests. This is not surprising since PFC had no involvement in blood donation screening. However I am sure there would have been regular contact between diagnostic manufacturers and RTC colleagues who would have been important customers.

60. Please also see WITN3530007 paras 218 – 222 for further details.

16. Please describe the regulation to which the PFC was subject and how that regulation changed over time

61. Until 1991 the SNBTS/PFC operated under Crown Immunity. However throughout the period leading up to its removal in 1991, PFC, so far as was possible, sought to carry out its manufacturing activities in accordance with the procedures, guidelines and standards of the wider industry. This included successful Product Licence applications for coagulation factor and immunoglobulin products and periodic inspections and audit by the Medicines Control Agency (MCA). Following the removal of Crown Immunity in 1991 the PFC successfully transitioned to a fully licenced facility under the Medicines Act and related legislation and proceeded to obtain a portfolio of licences for its activities and products.

62. These included:-

i. Manufacturer's Licence
ii. Wholesale Dealer's Licence
iii. Manufacturer's Specials Licence
iv. Manufacturer/Importer's Authorisation for Investigational Medicinal Products [MIA (IMP)]
v. Product Licences/Marketing Authorisations for Coagulation Factor products, Immunoglobulin products and Albuminoid products.

63. The PFC continued to operate under MCA regulation until its closure.

17. To the best of your knowledge, please describe record-keeping

arrangements at the PFC during the course of your employment there, and how these arrangements changed over time. In particular, please explain:

a. **What records were kept by PFC regarding the research and development, manufacture, testing, quality control, and issue of blood PFC products?**
b. **What regulations and/or guidance, if any, governed record-keeping at the PFC? Pursuant to any such regulation and/or guidance, for how long were records kept by the PFC?**
c. **What records, if any, were kept by the PFC as regards the size of the donor pools used to manufacture batches of factor concentrates.**
d. **Who was responsible for record-keeping at PFC?**
e. **Do you personally hold any PFC records? If so, which records do you hold?**
f. **Where were PFC's records stored? To the best of your knowledge, have PFC's records been moved from their original storage facilities? If so, to what location have the records been moved?**
g. **To the best of your knowledge and belief, were any PFC records ever damaged or destroyed? If so, please explain how those records were damaged or destroyed and why.**

(a) Records - Research and development, manufacture, testing, quality control, and issue of blood PFC products.

64. To the best of my recollection all records of R+D activities, including experimental data, correspondence, notes and minutes of meetings, reports etc were held and maintained by the Head of Department. Records of product manufacture, QC testing authorisation for release and distribution and the inventory of Standard Operating Procedures for the entire Centre were held and maintained within the Quality Department. Records were stored in a number of ways, including hard copy, microfiche and latterly electronic storage. The documentation system was subject to regular review by MCA Medicines

Inspectors.

(b) Records - Regulation and Guidance on Record Storage

65. My recollection is that guidance on record storage for pharmaceutical manufacture, including duration of storage, was contained in the so called 'Orange Guide to Good Manufacturing Practice' and other guidelines for the industry. So far as I recall during my employment at PFC, manufacturing documentation/batch records of PFC products were kept securely without time limit.

(c) Records - Donor Pool Sizes

66. The volume and weight of plasma used for each manufacturing pool was recorded in the batch manufacturing record of each product batch. A knowledge of the mean plasma donation weight would permit a reasonably accurate estimate of the number of donors contributing to a particular product batch. The SNBTS had a system of full donation traceability and the precise number of donations in a plasma pool could be calculated, if necessary, using this system.

67. For example, RTCs sent plasma to PFC in bar coded boxes and maintained records of the donations contained in individual boxes. PFC recorded each box identification in the batch record. This system provided full traceability via PFC and RTC records of all donations entering a pool. . I can recall few, if any occasions when a precise calculation of the number of donations contained in a plasma pool was found to be necessary.

(d) Responsibility for Record Keeping

68. In addition to the responsibility and accountability of all staff for the accurate completion of pharmaceutical batch manufacturing documentation and all other activities with a potential impact on product quality, responsibility for maintaining centrally the Centre's system of pharmaceutical documentation, standard operating procedures and product batch records rested with the

Quality Department, Head of Department.

(e) Records held by myself

69. I do not now hold any PFC records. At the time of my employment, records of correspondence and documentation were held in a central (PFC) filing system, as well as in personal files held by PFC managers.

(f) Storage locations of PFC Records

70. Much of the documentation and records of PFC product manufacture were stored on the PFC site, although I believe there was also some external storage used. I cannot recall the details of this.

71. Inevitably, all PFC records were relocated following the demolition of PFC. There was an extensive cataloguing and retrieval of SNBTS records exercise carried out during the Penrose Inquiry, and current members of SNBTS will have knowledge of the current location of PFC records.

(g) Damage or Destruction of PFC Records

72. I do not recall any incidents which led to the damage or destruction of PFC records during my period of employment at PFC or their routine removal and/or intentional destruction.

18. Please describe, during the time you worked there, the facilities, staff and equipment used at the PFC to manufacture Factor VIII and IX concentrates. Please set out how these changed over time and your role, if any, in determining how the PFC's facilities should be redeveloped. You may wish to refer to PRSE0006025, pages 69-71.

73. A summary of Coagulation Factor products manufactured at PFC is contained in Table 10, p 44 of a report prepared by Dr Foster for the Penrose Inquiry (PRSE0001083). This report also summarises facility developments and

upgrades to PFC until its closure in 2008. Please see below.

It was expected that the intermediate-purity coagulation factor concentrates would be included in the range of products to be prepared at the new PFC facility being planned. However, the quantities to be manufactured were not known, as requirements for the treatment of haemophilia were uncertain (Scottish Home & Health Department, 1973[51]), especially in light of the dominant role being played by cryoprecipitate, which was prepared at Regional Transfusion Centres.

The development of freeze dried cryoprecipitate was explored at the Glasgow and West of Scotland Regional Transfusion Centre (Milligan, et al. 1981[52]) but was discontinued after Medicines Inspectors advised that the equipment and procedures did not reach the standard of Good Manufacturing Practice (GMP) expected in the UK.

Although the SNBTS continued to supply frozen cryoprecipitate on demand, its use in the treatment of severe haemophilia A was largely replaced by freeze dried Factor VIII concentrates, as this was the product of choice of haemophilia doctors and of patients and their representatives.

The different coagulation factor products supplied by the SNBTS for the treatment of people with haemophilia are listed in Table 10 below, with their date of introduction.

Table 10. SNBTS Coagulation Factor Products for the Treatment of Haemophilia

Date	Product	Purpose
1956[a]	Factor VIII concentrate (Cohn Fraction I), freeze dried.	Treatment of haemophilia A
1966[b]	Cryoprecipitate, frozen	Treatment of haemophilia A and other disorders of coagulation
1968[a,c]	Factor II,VII,IX&X concentrate (PPSB), freeze dried.	Treatment of haemophilia B and other disorders of coagulation
1971[a,c]	Factor II,IX&X concentrate (DEFIX) of intermediate-purity, freeze dried	Treatment of haemophilia B Treatment of haemophilia A with inhibitors to factor VIII
1974[a,c]	Factor VIII concentrate (NY) of intermediate-purity, freeze dried	Treatment of haemophilia A
Dec 1984[c]	Factor VIII concentrate (NY) of intermediate-purity, freeze dried, dry heat treated for 2 hours at 68°C	Treatment of haemophilia A

Date	Product	Purpose
Aug 1985[c]	Factor II,IX&X concentrate (modified DEFIX) of intermediate-purity, freeze dried, dry heat treated for 72 hours at 80°C	Treatment of haemophilia B
Sep 1985[c]	Factor VIII concentrate (modified NY) of intermediate-purity, freeze dried, dry heat treated for 24 hours at 68°C	Treatment of haemophilia A
April 1987[c]	Factor VIII concentrate (Z8) of intermediate-purity, freeze dried, dry heat treated for 72 hours at 75°C or 80°C	Treatment of haemophilia A
1991[d]	Factor VIII concentrate of high-purity, solvent/detergent treated	Treatment of haemophilia A
1992[a]	Factor VIII concentrate (Liberate) of high-purity, solvent/detergent treated	Treatment of haemophilia A
1993[a]	Factor IX concentrate (HIPFIX) of high-purity, solvent-detergent treated and dry heat treated for 72 hours at 80°C	Treatment of haemophilia B
1996[e]	Factor VIII concentrate (Liberate) of high-purity, solvent-detergent-treated and dry heat treated for 72 hours at 80°C	Treatment of haemophilia A

[a] prepared at the Blood Products Unit/ Protein Fractionation Centre at The Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh.

[b] prepared at Regional Transfusion Centres in Aberdeen, Dundee, Edinburgh, Glasgow and Inverness.

[c] prepared at the Protein Fractionation Centre, Ellen's Glen Road, Edinburgh

[d] prepared for SNBTS at the Centre Regionale Transfusion Sanguine, Lille, France from partially purified factor VIII solution prepared at PFC; the date of introduction is when the product was approved for clinical evaluation

[e] prepared at PFC; the date of introduction is when the product was approved for clinical evaluation.

6.3. Commercial Products

So great was the impact of treatment with coagulation factor concentrates that the demand exceeded the availability of products prepared by the NHS and created a market for imported concentrates produced by commercial manufacturers,

Health & Social Security, 1982[43]). The DHSS instead proposed that the fractionation of plasma for Northern Ireland be transferred from the BPL to the PFC. Consequently, the PFC began the fractionation of plasma from Northern Ireland in 1982.

The construction of the PFC was based on a building design which had been essentially completed in 1970. Government guidance on the construction of, and operation of facilities for, the manufacture of pharmaceuticals in the UK was first published in 1971 (DHSS, 1971[44]) and was substantially revised in 1977 (DHSS, 1977[45]).

A number of modifications were subsequently made to the PFC facility in order to comply with the most recent Medicines Control Agency (MCA) guidance and to increase the capability of the centre, including:

- internal modifications during the early 1980s to re-route process streams and to enhance the environment,
- construction of an extension, with specialist laboratories for microbiology, virology and a pilot-scale research laboratory, which was completed in 1982/83,
- construction of an extension in the early 1990s, with increased capacity for cold storage, aseptic dispensing, product inspection, labelling and packaging, product storage, engineering workshops, information technology and general warehousing.

Further equipment was installed to increase processing capacity, including:

- new equipment in 1981 for thawing plasma for the preparation of Factor VIII concentrate (Foster, et al. 1982[46]),
- new freeze driers in 1979 and in 1983 for the processing of coagulation factor concentrates,
- new equipment in the mid-1980s with increased capacity for the fractionation of plasma for the preparation of albumin and immunoglobulin (Foster, et al, 1986[47]),
- specialist ovens in mid-1985 for controlled, dry heat treatment of coagulation factor concentrates,
- automated equipment in 1987 for the formulation of albumin products,
- new equipment in the early 1990s for the preparation of high-purity Factor VIII concentrate, including equipment specially designed for virus inactivation by solvent/detergent treatment,
- new production equipment in 1998, to replace items potentially contaminated with the agent responsible for vCJD and which were not suitable for decontamination.

74. The manufacture of coagulation factor products utilised some equipment and facilities common to all products (eg Cohn Fractionation, Cold Storage, Sterile

dispensing, Freeze Drying, Inspection, Packaging and Warehousing) as well as dedicated process equipment specific to coagulation factor processing. Unlike much larger fractionation centres, PFC did not have specific facilities dedicated exclusively to individual products, but the use of common facilities and equipment for all products was segregated in time and by production scheduling.

75. I was closely involved as both Director and Quality Control Inspector in the identification of need for the development of PFC facilities and the preparation of cases for funding to CSA/SHHD. The importance and urgency of coagulation factor process developments as well as the need for expansion of the facilities to meet Medicines Inspectors requirements was recognised by SHHD and funding was made available in response to our requests.

76. All PFC staff were directly or indirectly involved in the manufacture, quality control, licencing, equipment maintenance, storage and distribution of all PFC products.

Section 4: Knowledge of risk of infections while at PFC

19. During your time at PFC, what was your knowledge and understanding of HTLV-III/HIV and AIDS and, in particular, of the risks of transmission from blood and blood products? How did your knowledge and understanding develop over time?

77. My personal knowledge of HTLVIII/HIV and AIDS was informed by published literature, news reports, contact and discussions with SNBTS medical and scientific colleagues, reports from UK and International meetings and conferences and haemophilia experts. My understanding of HTLVIII/HIV and AIDS and, in particular, it's relevance to blood and blood products, was further informed by opinion from UK and international experts in the field (including from SNBTS), Health department guidance, Haemophilia colleagues and others. As the pandemic developed over time (early 1980's) discussion of the

topic became a dominant and daily feature of the professional environment in which I worked. In common with many others working in the field of blood and blood products my understanding and interpretation of emerging information and data reflected the wider professional and expert interpretation of the causes, impact and epidemiology of this new disease.

20. How and when did you first become aware that there might be an association between HIV/AIDS and the use of blood and blood products? What steps did you take in light of that awareness?

78. I do not recall precisely when and in what circumstances I became aware of an association between HIV/AIDS and the use of blood and blood products. My earliest recollection is of informal conversations with the then PFC Director (Mr Watt), probably in late 1982 or 1983, and from early US reports of new and unexplained symptoms in some patients (eg in MMWR) circulated in SNBTS as part of the regular exchange of scientific information. I do not recall the PFC taking or being advised to take any specific actions other than the requirement to closely follow emerging UK and wider international reports. So far as PFC was concerned, the emerging reports concerning AIDS (particularly in the US) further reinforced the importance of eliminating any requirement for use of commercial coagulation factor products in Scotland (ie self sufficiency) and the increasing urgency for the development of heat treated products at PFC. These practical steps had already been established as high priorities for SNBTS/PFC throughout 1982 and 1983, although these were initially targeted towards NANBH.

21. What enquiries and/or investigations, if any, were carried out at PFC in respect of the risks of transmission of HIV/AIDS? What was your involvement? What information was obtained as a result?

79. I do not recall any specific practical actions being undertaken by PFC in response to early reports concerning AIDS other than paying close attention to emerging UK, International and regulatory (particularly FDA) opinion. Together with similar surveillance by Haemophilia Directors, RTC Directors and medical

staff and Professor Cash, the SNBTS had a fairly comprehensive overview of information available in the public domain. SNBTS and PFC staff regularly attended UK and International meetings and conferences in which AIDS increasingly featured in the scientific programmes and discussions. These activities provided up to date information and expert opinion concerning AIDS and also provided opportunity for detailed informal discussion with the wider international fractionation industry, blood services and clinicians. For example I attended the annual meeting of UK Haemophilia Centre Directors in October 1983 together with Dr Boulton and Dr Ludlam, at which a summary of the understanding of AIDS in both the US and UK was presented. My report from this meeting was referenced in the Penrose Final Report (PRSE0000040)

22. To the best of your knowledge, what was known by the Regional Health Authorities and/or the National Blood Transfusion Service ("NBTS") in the 1970s and 1980s about the risk of hepatitis - including Hepatitis B ("HBV") and Non-A, Non-B Hepatitis ("NANBH")/Hepatitis C ("HCV") - associated with blood and blood products? In particular:

a. How did knowledge of the risks of the transmission of hepatitis from blood and blood products develop over time?

b. What was the understanding of the relative risks of infection from (i) imported commercial factor concentrates, (ii) domestic factor concentrates, and (iii) domestic cryoprecipitate? How did this understanding change over time?

80. I have no knowledge of what was known by RHAs and NBTS about the risk of hepatitis in blood and blood products, although I would conjecture that such knowledge and understanding would have been comparable to that of SNBTS.

81. Whilst I cannot comment on the understanding of these risks specifically by NBTS and RHAs in the 1970s I believe the more widely held view of the risk of hepatitis transmission was that it was substantially greater from concentrates prepared from paid US donors, compared with those from domestic volunteer donors. This understanding arose from the known or estimated relative

prevalence of hepatitis in these populations. Cryoprecipitate was known to carry the lowest risk of transmission – at least by a single treatment event. By the early to mid 1980s it became known that NANBH was transmissible by most, if not all, domestically prepared concentrates but, it was thought, with a reduced initial severity of disease and longer incubation period.

23. From 1981, during your time at PFC, what was your own knowledge and understanding of hepatitis (including HBV and NANBH/Hepatitis C) and, in particular, of the risks of transmission from blood and blood products? How did your knowledge and understanding develop over time?

82. When I joined SNBTS in 1981 I had no appreciable knowledge of hepatitis, other than a superficial understanding of the condition (HBV) from my employment as a biochemist at the Royal Postgraduate Medical School in 1971/72.

83. In my role as Quality Control Inspector, my priority task was the development of centre wide pharmaceutical quality systems, standards, practices and documentation in response to Medicines Inspectors reports on PFC from 1979/80. This task also included providing support, education and assistance to SNBTS RTCs.

84. My knowledge and understanding of the topic and its relevance to the work of SNBTS/PFC developed rapidly following my appointment, primarily through the actions and mechanisms outlined in response to Question18 above and, in particular, through personal reading of the literature and participation in discussions with medical and scientific colleagues.

85. I also led the drafting and assembly of a formal product licence application to the MCA for the newly developed PFC Intravenous Immunoglobulin product, which required a general understanding of hepatitis (NANB, HBV) and its relevance to the safety of immunoglobulin products.

86. At no point from 1981 to date did I achieve an 'expert' scientific or medical understanding of hepatitis. I relied on obtaining expert knowledge from wider SNBTS staff. However I did develop a good working knowledge of the subject and its relevance to transfusion and plasma products.

24. How and when did you first become aware that there might be an association between hepatitis (including HBV and NANBH/HCV) and the use of blood and blood products?

87. I became aware of the association between hepatitis viruses and blood and blood products within weeks of joining SNBTS. This knowledge, though superficial initially, deepened with time through discussion with PFC colleagues (including Mr Watt) and wider SNBTS colleagues (including Professor Cash) and, in particular, following my appointment as Acting Director in 1984, when I was present at regular meetings of SNBTS Directors. I was aware that whilst albumin or immunoglobulin products generally did not transmit HBV or result in transaminitis (NANB) in recipients (although the reasons for Immunoglobulin products being free of this risk were not generally understood), I was aware that pooled coagulation factor products could result in transaminitis in haemophilia patients and some recipients of blood components.

88. Also, at this time, Professor Cash was increasingly expressing his view during informal discussions and conversations that manufacturers (including PFC) should begin to address the challenge of producing non-infective (with respect to hepatitis) products, and that a prevailing view amongst haemophilia care providers and the fractionation industry that risks of infectivity were greatly outweighed by the benefits of increased treatment would not be sustainable in the longer term.

25. What enquiries and/or investigations, if any, were carried out at PFC in respect of the risks of the transmission of hepatitis? What was your involvement? What information was obtained as a result?

89. The PFC/SNBTS carried out regular surveillance of the international scientific, patent and medical literature concerning the safety, quality and efficacy of plasma products. As a result of this, laboratory research on the pasteurisation of coagulation factor products began in Scotland in 1981. This was in response to the knowledge that a manufacturer (Behring) had demonstrated, at least in principle, that Factor VIII could be subjected to pasteurisation at 60° for 10hrs in the presence of stabilisers, albeit at a very low yield. Initially the work at PFC was focused on identifying stabilisers and conditions which might allow it to develop a pasteurisation process without breaching Behring's patented process.

90. In 1982 a SNBTS Factor VIII Study Group was established as an initiative by Professor Cash. The Factor VIII study group was an important development in SNBTS and was established to coordinate all available resources in SNBTS to meet its longstanding commitment to plasma product self-sufficiency and to establish this as a national priority. I attended this meeting together with Dr Foster and Mr Watt from PFC. At this time the PFC work on virus inactivation was only at a preliminary stage without any clear reportable outcomes. My recollection from the meeting is that safety issues were discussed in general, leading to agreement to establish a safety sub group.

91. The importance of product safety was certainly recognised in these discussions but so was the recognition that any method likely to improve safety would reduce product yield. Thus consideration of FVIII processing yield and FVIII content of plasma were considered essential prerequisites to progress on product safety, if the goal of self sufficiency was to be achieved and maintained.

26. What was your understanding of the nature and severity of the different forms of blood borne viral hepatitis and how did that understanding develop over time?

92. I have no formal training or education in medicine or clinical virology and my understanding of the nature and severity of viral hepatitis has always been informed by scientific and medical colleagues in SNBTS (particularly Professor

Cash in his role as NMD) and the wider UK, attendance at committees, meetings and conferences and from personal reading of reports and publications as the medical and scientific consensus developed over time.

93. My recollection is that whilst the clinical course and severity of disease in HBV infection was well understood in the early 1980's and before, the severity and longer term sequelae of NANB hepatitis were less clear. This picture developed rapidly through the early to mid 1980's when there emerged a clearer consensus on NANB hepatitis

94. In any event it became clear to me at an early stage in my employment in SNBTS that the transmission of NANB to eg haemophilia patients, was an unacceptable state of affairs – thus the decision to establish a SNBTS FVIII study group.

95. Notably, in the early 1980's research was conducted in SNBTS with the objective of identifying specific candidate markers and tests for NANB hepatitis.

27. On 23 September 1982, Dr J. Craske reported that seven of seven patients treated for the first time with NHS concentrates had developed NANBH (HCDO0000135_015, page 1). Prior to their publication, Dr Craske's findings were discussed at the UK Haemophilia Directors' ("UKHCDs") Annual Meeting held on 13-14 September 1982 (PRSE0000185, pages 3-4). In your written evidence to the Penrose Inquiry, you stated that you attended this meeting (PRSE0003755, page 2). What conclusions, if any, did you draw from these findings as to the risk of NANBH in NHS concentrates? If your conclusions differed as between Scottish (PFC) and English (BPL) concentrates, please say so. What action, if any, did you or others at the PFC take in response to the findings of this study? Please give reasons f or your answers.

96. The notes from the annual UK Haemophilia Directors meeting in September 1982 appear to have been written by myself. This was probably the first of such meetings of this group that I had attended since my appointment.

97. As recorded by Dr Foster in a report he prepared for the Penrose Inquiry (PRSE0001083 page 63), in the period 1977-1979 the incidence of clinically overt NANBH associated with the use of commercial concentrates was reported to previous and subsequent Haemophilia Directors meetings as being from 4 to 20 times greater than with NHS products (Craske J (1981). Haemophilia Centre Directors Hepatitis Working Party Report For Year 1980-81. Report to the 12th Meeting of UK Haemophilia Centre Directors held at the Royal Free Hospital London, 9th October 1981 [CBLA0001464]). For the period 1980-1982 SNBTS Factor VIII concentrate was associated with the lowest degree of overt transmission of NANBH in the UK (Craske J (1983). Haemophilia Centre Directors Hepatitis Working Party Report For Year 1982-83. Report to the 14th Meeting of the UK haemophilia Centre Directors held at the Oxford Regional health Authority, 171h October 1983.)

98. The study reported by Dr Craske in 1982 was followed up with a more detailed study of NANBH in previously untreated patients and published in August 1985 (Dr P Kernoff et al, British Journal of Haematology, 60 (3): 469-79).

99. I do not recall what specific conclusions I personally drew from Dr Craske's report in 1982, other than the reinforcement of my (and presumably others') understanding that at least immediate clinical outcomes were more favourable following treatment with NHS product vs US commercial materials and that minimising the need for use of imported US products remained a key objective for PFC/SNBTS. Also, and notwithstanding the suggestion from the above reports that the use of NHS products may have resulted in less severe infections, I took the view that the importance of SNBTS heat treatment development programmes remained undiminished.

100. Prior to this report (which I distributed to PFC/SNBTS colleagues) SNBTS had already established its FVIII Study Group and studies on heat treatment of FVIII were already underway in SNBTS with the first pilot batch of ZHT (pasteurised) being prepared in early 1983. Despite the latter report from Dr Craske in 1983, SNBTS did not take the view that there was likely to be a higher margin of safety of SNBTS products prepared from Scottish donors vs

BPL products from English and Welsh donors since there was little, if any, evidence of lower prevalence of NANBH in the Scottish population and there was close similarity of BPL and PFC products at that time.

28. You explained to the Penrose Inquiry that "*. ..as an operational manager in PFC, self-sufficiency was about maximising our output...every bottle of product that we could make from Scottish donors avoided the importation of a product from other sources, which we held and believed were less safe*" (PRSE0006025, page 58). Why did you believe that "*products from other sources*" were less safe than products made from Scottish donors? What evidence available to you at the time, if any, supported this belief? Please reconcile your answer with Dr Craske's findings, in 1982, that 9 of 9 first time recipients of concentrates contracted NANABH - irrespective whether the 9 concentrates were produced by the NHS or commercially (HCDO0000135_015).

101. My view and belief that blood donated and products prepared from voluntary unpaid donors in Scotland and the wider UK were likely to be safer than those from paid donors in the US commercial plasma industry were informed by (i) the near universal and widely published views of experienced UK and international professionals and experts (transfusion experts and prescribing doctors) (ii) the widely recognised WHO views and policies. (iii) Government health department policies on transfusion and (iv) historical studies by Professor Harvey Alter and others of US transfusion recipients from paid and voluntary unpaid donors following the US adoption and implementation of a voluntary unpaid blood donor system replacing the previous widespread use of paid donors. These views and beliefs did not extend to the supposition that unpaid donors would deliver a blood/plasma supply free of the risk of transmission of infectious diseases by transfusion, but that there would be a substantial reduction in the incidence of infectious donations, with a commensurate reduction of the viral bioburden in plasma pools. Recognition and acceptance of these benefits underpinned the policies of the UK Blood Services and the preferences of Haemophilia doctors.

102. It is important to note that the report by Dr Craske in 1982 of 9/9 previously untreated patients exhibiting evidence of NANBH was preceded by reports in 1981 and subsequently in 1983 and 1985 (Dr Kernoff et al) that the disease in recipients of NHS product was of longer incubation, less severe and shorter lived – these observations were consistent with the above views and data available at the time concerning the prevalence of NANBH in voluntary donor populations vs paid US donors.

103. Following the availability of diagnostic assays and quantification methods for HIV and HCV, there emerged further corroborative evidence of greatly reduced levels of virus disease markers in volunteer unpaid vs paid donations and plasma pools constructed from these donations. These are summarised in the report by Dr Foster prepared for the Penrose Inquiry (PRSE0001083 p 49).

28. Please provide details of any other information which informed your understanding of the severity and prevalence of NANBH/HCV in the UK donor population.

104. My recollection is that the development and implementation of diagnostic screening tests for HCV led to the rapid emergence of a detailed understanding of HCV prevalence in the UK donor and general populations and also in commercial paid donor populations. These studies were undertaken in the UK primarily by RTCs and public health colleagues, and the results will have been made available to me.

29. How did your understanding of the seriousness of HCV and HTLV-III/HIV impact the fractionation policies and practice in place at the PFC?

105. The increasing emergence of international evidence and expert opinion that NANBH should no longer be considered as a benign and self limiting disease led to a greatly increased emphasis by SNBTS (both RTCs and PFC)

on the goal of self sufficiency, increased plasma collection and its quality and research into options for the removal and/or inactivation of virus from PFC products.

106. The work of the FVIII study group established in 1982 was afforded a very high priority by SNBTS and particularly by Professor Cash. The PFC continued to research and progress methods for pateurisation (in solution) of FVIII as its preferred option. This included the development of in house methods for testing the efficacy of inactivation processes using "model" viruses. However there remained concern, including internationally, that the modification of FVIII manufacturing processes to include steps for virus inactivation could lead to the development of inhibitors in recipient patients, leading to potentially catastrophic consequences for the treatment of haemophilia.

107. As outlined in evidence presented to the Penrose Inquiry and in Chapter 23 of that Inquiry's Final Report, events in late 1984 led to an abrupt change in direction for the virus inactivation programme of work in SNBTS, and the rapid implementation (following consultation with Haemophilia Directors, SHHD, MCA and NIBSC) in December 1984 of FVIII heat treatment of freeze dried product at 68 degrees for 2 hours. Importantly, this included a comprehensive recall of all unheated material from the supply chain, including stocks held by haemophilia patients for home treatment.

108. These actions were taken in response to the devaststing news received in November 1984 that some haemophilia patients in the care of Dr Ludlam had tested positive for HTLV-III antibodies, and the disclosure at an international conference in Groningen, the Netherlands, that HTLV-III was vulnerable to heat inactivation at 68 degrees C in freeze dried preparations. Heat treatment of FVIII in the dried state subsequently became the preferred option for virus inactivation and HTLV-III inactivation became the dominant priority, recognising that such heating conditions might reduce NANBH infectivity but was unlikely to eliminate it. This culminated in further refinements of the PFC heat treatment process to permit heating of FVIII and FIX products at higher temperatures (80

degrees, 72hrs). Details of these subsequent developments and evidence are also described in the Final Report of the Penrose Inquiry (Chapter 24).

30. What advisory and decision-making structures were in place at PFC to consider and assess the risks of infection associated with the use of blood and/or blood products?

109. There were no medically qualified staff employed directly by PFC. The PFC Director was accountable to the Management Committee of the CSA, but subject to the responsibilities of the NMD, who was the de facto advisor to PFC on scientific and medical issues relating to patient treatment and safety. Directors and Medical staff from RTCs also contributed to such decision making and advisory processes. This was supplemented by regular consultation between SNBTS and SHHD medical officers, Scottish and Northern Ireland Haemophilia Directors (and other prescribing doctors), NIBSC and, notwithstanding the Crown Immunity status of PFC/SNBTS, informal contact and advice from the MCA.

31. What role, if any, did PFC have in advising those hospitals and haemophilia centres that it provided blood and blood products to, as to the risks associated with blood and blood products? Please give details of any steps taken in this regard.

110. The main advisory interface between PFC and users/prescribers of its products was via RTCs and their medical staff, in both Scotland and Northern Ireland. The importance of this principle was continuously reinforced by Professor Cash in his role as NMD. He believed that RTC medical staff should be the recognised experts for advice on the use of all products supplied by SNBTS. Adherence to this principle was also reflected in routine communications and meetings concerning PFC products and associated supply chain and product recall arrangements.

111. However these arrangements did not preclude direct contact between product users and PFC staff on specific topics, or their periodic attendance at

or presentations to groups of professional colleagues throughout Health Boards and hospitals.

112. PFC also provided product leaflets with each product dose, in line with the wider pharmaceutical industry and regulatory standards. These evolved over time but always included warnings of potential patient adverse reactions and risks associated with their use. Notification of adverse reactions were reported to PFC via RTCs.

32. When and in what circumstances did you first become aware of the risk of transmission of vCJD associated with the use of blood and blood products? How did your knowledge develop over time? What involvement, if any, did you have in responding to the risk of vCJD?

113. I do not recall when or in what circumstances I became aware of the potential vCJD risk from blood and blood products, but I am confident that it would have been around 1996, following the initial reports of a potentially new form of CJD in the UK population. As is well known, this was rapidly followed by concerns that the putative causative agent could be transmitted by blood, blood products and plasma products and some surgical procedures.

114. My knowledge (though not as an expert) developed in line with published scientific reports and through my network of contacts in the UK and internationally. I was further infomed at a UK policy level through my membership of MSBT at that time.

115. I participated in a consultative meeting convened by the MCA (prior to the UK announcement of a ban on the use of UK plasma) to discuss UK policy for the continued use (or otherwise) of UK plasma by BPL and PFC. This meeting led to a recommendation by the UK regulator to discontinue the use of UK plasma as a precautionary measure.

116. Dr Foster and I identified vCJD as an important topic for investigation and he initiated a range of studies designed to assess the likely removal of the

abnormal prion proteins (PrP^{Sc}) by PFC production processes. The results of these studies, which demostrated significant potential reduction of PrP^{Sc}, were presented to the MCA consultative meeting and also provided to the UK DoH as part of the contribution by SNBTS to UK vCJD risk assessments conducted by Det Norske Veritas.

117. Following the UK government decision to discontinue the use of UK plasma for plasma product manufacture, PFC was tasked to identify replacement sources of volunteer unpaid plasma and secure their supply. Recovered plasma was initially sourced from Germany (Bavarian Red Cross) and US not-for-profit Blood Centres. Plasma for Anti D Immunoglobulin manufacture could only be sourced from US paid donor sources.

33. More broadly, when and in what circumstances did the SNBTS become aware of any risks of transmission of vCJD associated with the use of blood and blood products? How did the SNBTS respond?

118. The wider SNBTS would have become aware (circa 1995/96) of the emergence of vCJD as a potential blood safety issue from its wide range of professional, scientific and Government contacts, and the wider UK Transfusion Services and advisory bodies. Prior to this, SNBTS staff will have been aware of the BSE epidemic and at least the theoretical possibility of the BSE infectious agent crossing species into humans – though this was initially considered to be an unlikely event.

119. The actions taken by SNBTS in response to this risk followed guidance issued by the UK Departments of Health and included:-

- Introduction of leucodepletion
- Importation of plasma for transfusion
- Revision of donor deferral criteria eg to exclude previously transfused donors

Section 5: Procurement of fresh frozen plasma ('FFP") by PFC and donor selection policies within SNBTS

34. Please explain the system by which the PFC procured FFP from RTCs during your employment there and how this system changed over time.

120. SNBTS RTCs were responsible for all aspects of donor selection and testing, blood donation, blood processing and plasma blast freezing, release for use and frozen plasma storage (<-20^{0}C) and retention of records to allow full traceability of plasma and blood components. FFP was stored at RTCs in boxes containing multiple plasma units and carrying unique identifiers.

121. PFC was responsible for bulk plasma collection from RTCs in Scotland and Northern Ireland using a refrigerated vehicle and entering it into bulk storage at PFC using the unique box identifiers. The PFC vehicle collected plasma from RTCs at regular intervals and also distributed finished products for clinical use.

122. PFC provided antibody quantification assay services to RTCs to assist in the identification of donors/donations suitable for hyperimmune immunoglobulin manufacture (eg Tetanus, HB, Zoster, Anti-D, CMV etc).

123. The above arrangements continued largely unchanged until the introduction of the UK ban on the use of plasma for fractionation from UK donors.

35. Please outline your knowledge of SNBTS donor selection policies during your employment at the PFC. In particular, please explain:

- **a. What steps were taken by the SNBTS to discourage donors at higher risk of transmitting infection, or to prevent them from donating?**
- **b. How did SNBTS policies regarding donor selection change following the emergence of (i) AIDS/HIV, (ii) NANBH/HCV, and (iii) HBV?**
- **c. Who was responsible for formulating donor selection policies? What role, if any, did the PFC play in formulating such policies?**

124. As outlined in question 34 above, responsibility for establishing, reviewing and implementing donor selection and deferral policies rested with RTCs, following guidelines and practices developed by the UK Transfusion Services. Although I was aware of such policies during my employment in SNBTS, the PFC did not play a significant role in their development or implementation. So far as I recall the policies for FFP did not differ from those established for blood and blood components, since they derived from the same donor source.

125. Accordingly I would defer to SNBTS RTC colleagues and ex colleagues concerning question 35 (a),(b) and (c).

36. Please refer to PRSE0001823. To the best of your knowledge:

a. To what extent did the PFC use FFP collected from prisons, borstals and similar institutions? Please identify and set out the number of institutions from which blood was collected and the frequency of sessions.

b. Why was it advantageous to collect blood from penal institutions? What

were the relative costs of doing so as compared to the cost of collecting blood at RTCs? Were prisoners in Scotland provided with any form of incentive to donate blood? If so, what incentives were provided?

c. What was your view of this practice?

d. You explained to the Penrose Inquiry that the collection of blood from penal institutions ceased in March 1984 (PRSE0001823, page 3). Who took this decision? Why was the decision taken at this particulate time?

126. Details of the collection of blood donations by SNBTS RTCs and the rationale for these activities has been examined by the Penrose Inquiry in Chapter 26 of the final report. I believe the evidence presented is accurate. More specifically, the SNBTS submitted detailed evidence to the Penrose

Inquiry concerning the collection of blood at penal institutions (PRSE0001307, PRSE0003909, PRSE0002164)

a. Information submitted to the Penrose Inquiry (PRSE0001307, PRSE0003909, PRSE0002164) indicates that approximately 1.1% (range of 0.1% - 2.38%) of blood donations collected in Scotland between 1974 and 1984 was from penal institutions. These data are summarised in Table 26.2 of the Penrose Report. This proportion would have been approximately the same for plasma (FFP) sent to PFC. I have no knowledge of the frequency of these sessions or their locations beyond that included for the West of Scotland RTC in the above reports
b. I have (and had) no knowledge of the rationale, advantages, relative costs or incentives offered (if any) to prisoners for this collection practice, beyond my general understanding that this practice was seen as making a contribution to the rehabilitation of offenders and perhaps provided some incentive to prison donors to participate in an activity outwith their normal daily routines.
c. I do not recall my view of recruitment of donors in penal institutions, or indeed whether I had a particular view. I do not recall being asked to express a view by Mr Watt or others on this topic.
d. The decision taken in March 1984 would have been taken by Dr Mitchel (Director, Glasgow and West of Scotland RTC). All other Scottish RTCs had ceased blood collection in penal institutions during or before1983. Also it had been noted by this time that RTCs in England and Wales had all but ceased this practice. These developments together with perhaps further persuasion by Professor Cash led to the decision being taken at this time.

37. To the best of your knowledge, what donor selection measures were taken, and when, to exclude donors at a high risk of HIV/HTLV-III from donating blood? What information was given to donors about the risk of HIV/HTLV-III?

In your view, were such measures adequate to protect recipients of PFC blood products from the risk of HIV/HTLV-III?

127. In the early 1980's there was a significant degree of professional autonomy amongst SNBTS RTCs, which were individually accountable for the safety of blood donations used for patient care, and the suitability of plasma supplied for fractionation at PFC. UK wide strategies for maximising transfusion safety were primarily reliant on the uniform and exclusive model for blood/plasma collection based on volunteer and unpaid donation, testing for hepatitis B (HbsAg) and adoption of WHO guidelines. These strategies were known to significantly reduce the incidence of transmission of hepatitis by transfusion and to reduce the level of hepatitis and other transmissable agents in plasma pools. It was equally recognised internationally that these measures alone would not and did not eliminate the risk of post transfusion hepatitis from blood and plasma products.

128. The development of measures to exclude donation by donors at high risk of AIDS/HTLVIII was begun in the SNBTS by Dr McClelland (SEBTS) in the Spring of 1983 and continued thereafter as described in evidence submitted by SNBTS to the Penrose Inquiry (PRSE0000954) and generally narrated in the report of the Penrose Inquiry (Chapter 28). The PFC (primarily its Director) would have been present at discussions between RTC Directors about such developments, but responsibility for communicating with donors and implementation of donor selection/exclusion policies rested with RTC Directors.

129. I do not recall any particular view I may have held of these developing strategies, or their adequacy in protecting recipients of PFC plasma products from the risk of HTLV-III other than the understanding that such measures together with the volunteer unpaid donor system would deliver a safer (though not free of risk) raw material for plasma product manufacture in the event that HTLVIII entered the UK blood supply. In the absence of a diagnostic test, donor selection was the only tool available at that time to exclude potentially infectious donations from entering the blood supply.

38. By mid-1983, Scottish RTCs had adopted a range of measures to exclude and/or inform donors at a risk of AIDS. These included: a leaflet

drafted by Edinburgh RTC which asked homosexual men and other groups not to donate blood (PRSE0000984); a leaflet distributed to donors at Glasgow RTC with a sticker asking them to consult doctors about AIDS (PRSE0004816 and PRSE0003620, page 5); and a decision by Aberdeen RTC to take no action to exclude or inform donors (PRSE0003620, page 5). In your view, were such measures effective in reducing the risk of HIV/HTLV-III in PFC blood products? Should further measures, or a more unified set of measures, have been adopted in Scotland at this stage?

130. The measures adopted in 1983 by SNBTS did not in fact prevent all HTLV-III infective donations entering the plasma pool, from which the batch of FVIII thought to have tragically infected patients in Edinburgh (Batch 3-009) was manufactured. Donations included in this FVIII batch were collected in late 1983. Despite efforts by SNBTS to identify the specific infective donation(s) in this plasma pool these were ultimately unsuccessful. It was also established from lookback procedures following the introduction of HIV testing that 6 infective donations (for HIV) were collected by SNBTS after 1983 and the associated plasma used in 6 batches of FVIII. Five of these batches were subjected to heat treatment and did not transmit HIV to recipients. Details are presented in a report submitted to the Penrose Inquiry (Actions Surrounding FVIII Batch 023110090, Dr B Cuthbertson, June 2010 (PRSE0002801)

131. It is evident therefore that the introduction of early donor exclusion measures did not entirely prevent the collection of infective donations, although it is likely that their introduction will have reduced the incidence of such donations.

132. I cannot judge the extent to which a more uniform application of such measures throughout SNBTS would have reduced blood donation by infected individuals, but clearly by today's regulatory standards it would be considered mandatory.

39. In September 1983, a UK-wide leaflet entitled "*AIDS and how it concerns*

***blood donors*" was distributed to RTCs (BPLL0007247, NHBT0020668, CBLA0001707). Were you or others at PFC involved in the production of this leaflet? If so, please explain the nature of your involvement. If not, please explain your view of this leaflet.**

133. I cannot recall having any personal involvement in the development and implementation of this leaflet and have no knowledge of Mr Watt's involvement, if any.

134. I do not recall having or expressing any particular view on this leaflet at the time or thereafter.

135. My limited understanding and knowledge of the genesis and content of this leaflet suggests to me that the aim of the leaflet was to inform donors and potential donors of the known facts concerning the emergence of a new disease (AIDS), to balance the only other source of public health information from media reports. It seemed also to be designed to address concerns and enquiries from the donor population concerning AIDS. Presumably this emphasis was considered to be proportionate to the perceived risk to transfusion in the UK at that time.

40. Please refer to SBTS0001837_001 a letter from Professor Cash dated 29 November 1984. Do you recall your response to the proposals that donors would be handed a leaflet at every session and leaflets will be sent to donors' homes who are not usually called to sessions? Did you agree with these proposals? To the best of your knowledge, how were these implemented in practice?

136. I was PFC Acting Director at the time of Professor Cash's letter to SNBTS Directors, and probably present at meetings where this was discussed. I have no recollection of whether I agreed or not with the proposals, but would probably have deferred to and supported the views of RTC Directors. I do not have knowledge of how the specific proposals were implemented, although I

believe there would have been a high degree of compliance with the request from Professor Cash.

41. On 27 November 1984, the Working Group on AIDS discussed a second AIDS leaflet (CBLA0011985, page 4). As to this:

a. It was stated that the 1985 leaflet would exclude all practising homosexuals from donating blood (CBLA0011985, page 4). Did you and/or others at PFC support this proposal? Please give reasons for your answer.

b. It was suggested that high-risk donors might be subject to "*intensive interviewing*" before donating blood (CBLA0011985, page 5). Did you and/or others at PFC support this proposal? Do you consider that donor interviews should have been introduced earlier? Please give reasons for your answer.

137. As mentioned previously, I was not closely involved in the development of donor selection/deferral policies and leaflets, although I would have been present at discussions of these topics by SNBTS Directors from 1984 onwards. In the absence of good evidence to the contrary, I would have supported the policies and practices agreed by them.

138. I do not believe I would have been called upon to express a formal view on this proposal. Dr McClelland represented SNBTS on this group, as an observer, together with Dr Bell from SHHD. The proposal was probably discussed by SNBTS Directors prior to the meeting and I would have lent my support to the views of more expert RTC colleagues.

139. In any event by late 1984 it had become increasingly apparent from emerging international data that practising homosexual men (now more accurately referred to as MSM) were a particularly high risk group for HIV/AIDS and it became widely accepted that they should be excluded from donation.

140. I do not believe I or others at PFC would have been called upon to express a formal view on this proposal. Moreover, I do not believe I had the

knowledge or competence then (or now) to judge whether these measures should have been introduced earlier, although I would suggest that the introduction of such measures would have required good epidemiological evidence to justify such targeting of particular groups.

42. To your knowledge, what additional information, if any, was given to SNBTS donors about the risk of them transmitting infection via their blood besides that contained in donor leaflets? When and how was such information provided?

141. I have no knowledge or recollection of additional information being provided to donors, either orally or as printed documents.

43. How effective, in your view, were leaflets and other communications at reducing the risk of donations from high-risk individuals?

142. I had no knowledge of the effectiveness of the evolving donor exclusion measures being developed at this time, although I recall being aware of anecdotal reports concerning donors who had self deferred at sessions or had been asked to do so by donor staff, but such reports fell far short of a quantitative or semi quantitative estimate of efficacy. I feel sure colleagues and ex colleagues from RTCs will be able to provide further detail.

143. The study of donor deferral policies and practices and their efficacy have continued to be subjects of detailed international studies up to the present time and, in particular, the measurement of donor compliance with exclusion and deferral policies.

44. On 19 August 1986, you attended a meeting of the SNBTS Co-Ordinating Group. Members discussed the reinstatement of HIV-positive donors whose antibody tests were initially positive but on repeated testing and confirmatory testing were negative over a period of several months. It was decided that the matter would be referred to EAGA for ruling

(PRSE0000883, page 3).

a. **What was your view on such donors being reinstated to the panel?**

b. **To the best of your knowledge, what was the outcome of the EAGA ruling? You may find MRCO0000003_113 of assistance in answering this question. How, if at all, was this decision communicated to you? Was this decision implemented so far as you are aware?**

144. My personal view on reinstatement of such donors would have reflected the expert medical view of RTC Director colleagues. If, indeed, it was their view that such donors should be reinstated I think I would have been supportive of such a position, since by that time and from the perspective of PFC we were increasingly confident of the efficacy of heat treatment processes for HIV inactivation.

145. I suspect, though I cannot be sure, that the SNBTS issue with 'transiently positive donors' was similar, though separate, from the issue considered by EAGA, in that the SNBTS cases concerned initial non repeatable screen positive, but negative on repeat and confirmatory testing, whereas those presented by Dr Gunson concerned repeatedly screen positive donations though negative by confirmatory tests. Also the SNBTS and EAGA meetings were separated in time by 15 months.

146. In any event, I have no recollection of the outcome of the EAGA ruling or whether it was communicated to me by Professor Cash. I have no knowledge of whether the decision was implemented by RTCs.

Section 6: Arrangements for allocating blood products within the SNBTS

General

45. **Please describe the arrangements in place within the SNBTS for the allocation of factor concentrates and/or other blood products produced at PFC to patients. In particular:**

a. **Please identify which haemophilia centres were supplied with products by the PFC and over what period of time.Please outline the respective responsibilities of the RTCs, the PFC, and the Haemophilia Centre Directors in allocating products to patients, and how these responsibilities changed over time.**
b. **Please explain which fora, if any, were established between the RTCs, the PFC and haemophilia centre directors to discuss and facilitate arrangements for the allocation of blood products to patients. Were meetings held regularly? Were they minuted? If so, by whom? What was discussed at these meetings?**
c. **Was the PFC in any way responsible for decisions about the choice of product used to treat patients in haemophilia centres and/or hospitals? If the PFC was not responsible for such decisions, did the PFC have any influence over the choice of product used to treat patients?**

147. As with all PFC products, coagulation factor products were supplied to RTCs in Scotland and Northern Ireland. RTCs maintained stocks of these products for distribution to Haemophilia Centres and also hospitals which used Factor IX (DEFIX) for reversal of anticoagulant therapy.

148. Until 1984 (and for the duration of the Northern Ireland contract) the quantities allocated and supplied to each RTC were determined by their proportionate contribution to the overall plasma supply to PFC (the Pro-Rata system). Thereafter the pro-rata system was abandoned in favour of a National approach to allocation based on regional need or, when demand exceeded supply, a population basis.

149. There were five Haemophilia Centres in Scotland and one in Northern Ireland. These were located in Edinburgh (RIE), Glasgow (GRI), Dundee (Ninewells), Aberdeen (ARI), Inverness (Raigmore) and Belfast (Belfast City Hospital). The centres in Glasgow, Edinburgh and Belfast were designated as Reference Centres. I believe there were designated and associated centres for

inpatient and outpatient treatment of paediatric patients in Glasgow (Yorkhill), Edinburgh (RHSC) and Belfast.

150. Each of these centres was supplied with coagulation factor products via their respective RTCs. There was no direct supply from PFC, except perhaps in exceptional circumstances.

151. PFC had no responsibility for allocation for supply of products to patients. Haemophilia Directors and their staff were solely responsible for prescribing and supply of products to individual patients in their care. Product stocks for this purpose were held in Haemophilia Centres and replenished as necessary from RTC stocks. Operational and professional liaison between Haemophilia Centres and RTCs was undertaken by RTC Directors or their nominated RTC Medical Consultant, who also liaised with PFC when required, including the reporting of adverse reactions and/or participation in product recalls.

152. A number of fora existed within the NHS in Scotland for liaison and communication between all those involved in plasma collection, product manufacture and supply and haemophilia patient care. These included:-

- The annual meeting of Haemophilia and SNBTS Directors convened by SHHD from the late 1970s onward. These were often chaired by senior medical officials from SHHD – including CMO/DCMO and minuted by SHHD officials, though I cannot be certain of this
- Regular (perhaps quarterly) meetings of a Coagulation Factor Working Party with membership from PFC, the wider SNBTS, Haemophilia Directors from Scotland and Northern Ireland and a SHHD medical representative. This working party was chaired by Professor Ludlam and minuted by a SNBTS attendee.
- Periodic ad hoc meetings between relevant parties to discuss specific topics or service developments – either minuted or outcomes recorded by correspondence

- Periodic and informal discussions between Haemophilia Directors and their staff and RTC Consultants, particularly concerning product availability and supply issues

153. The purpose of these meetings was to facilitate discussion, communication and agreed resulting actions between all stakeholders involved in haemophilia care, including:-

- SNBTS achievment and maintenance of product self sufficiency
- Developments in haemophilia treatment, particularly those with resource implications
- SNBTS coagulation factor product developments and requirements for clinical trials
- Consideration of SNBTS plasma and product supply and product stocks
- Identification of and agreement on strategies to minimise the risk to patients from viruses (existing and emerging) in donor populations
- Management of the transition from plasma derived products to recombinant alternatives

154. To the best of my knowledge and recollection, PFC had no involvement or influence whatsoever in the choice of product by prescribing doctors for the treatment of their patients. PFC had no medically qualified staff and any such involvement would have been considered highly inappropriate by myself, the wider SNBTS and haemophilia doctors. I can recall no instance when myself or other PFC colleagues were called upon to have any such involvement.

155. The PFC did not engage in any marketing or promotional activities for its products.

156. However, SNBTS strategies and policies for the development and supply of products for haemophilia treatment in Scotland and Northern Ireland were established and agreed in close collaboration with Haemophilia Directors, to ensure that Haemophilia Directors would consider PFC products suitable for

the treatment of their patients. This close collaboration did not preclude the freedom of Haemophilia Directors to source and purchase alternative products.

157. PFC products were at all times provided to the NHS in Scotland without charge to Health Boards.

158. I cannot comment on the extent of SNBTS medical staff involvement in the detailed care of patients, at the request of Haemophilia doctors, but my clear recollection is that the demarcation of responsibility between SNBTS (as a manufacturer) and prescribing doctors was carefully observed, not least by Professor Cash.

46. You explained to the Penrose Inquiry that, in early 1984, "*given the...really quite secure position in terms of product supplies, it seemed to me that we needed to review . ..the so-called pro rata system* " (PRSE0006025 , page 28). Please briefly describe the pro rata system which operated at this time. What was the rationale for the system? What were the advantages and disadvantages of the system, and why did you state that the pro rata system should be reviewed?

159. The SNBTS "pro rata" system for allocating PFC product supplies to RTCs was, I believe, established in the late 1970s, and subject to at least annual review by RTC Directors at a Co-ordinating Group meeting. The purpose of this system as I understood it was to provide an equitable system for PFC product distribution to RTCs, but also to incentivise RTCs to increase their plasma supply to PFC, through inter alia encouraging the clinical use of packed red cells instead of whole blood transfusion, so allowing plasma to be separated for fractionation by PFC. This was an important feature of the SNBTS strategy towards self sufficiency.

160. In practice the system appeared to deliver these outcomes. My understanding and recollection of the system was that quantities of product supplied to RTCs were calculated on the basis of the proportion of individual RTC contributions to the total plasma supply, after deductions (top slicing) of

circa 10% to support national stocks, R+D activities and projections of future product output from PFC.

161. RTCs with a greater proportionate contribution of plasma were rewarded with a greater supply of products (albumin, coagulation factors and Immunoglobulin products), thereby reducing the cost of commercial product purchase by Health Boards to meet shortfalls in supply vs clinical demand. This system was therefore based on RTC performance rather than national clinical need.

162. During 1983 I noted that increasingly large stocks of product were being held at PFC and RTCs which, on the calculated supply committments from the pro-rata system, were in danger of outdating. I recall informing Mr Watt of this situation, who in turn informed Professor Cash. I cannot recall the precise circumstances or reasons for this accumulation (though I believe it had much to do with the product yield improvements resulting from work by Dr Foster and his team), but with the knowledge of the supply shortages from BPL to England and Wales, I and others took the view that surplus product should or could be offered to the NHS in England. This, I recall, took place in 1984 with approximately 1-2 MIU PFC FVIII being supplied to BPL for distribution in England.. I believe also that Professor Cash wrote to Haemophilia Directors in Scotland exhorting them to consider the requirement for the continued use of commercial products when SNBTS products were readily available.

163. Soon after my appointment as PFC Acting Director in 1984, I further pursued this topic and advocated, in the light of the secure plasma and product supply situation and the knowledge that the use of whole blood for transfusions was increasingly infrequent, that the SNBTS should adopt a more national approach to the supply of PFC products, based on regional/population needs and eliminating the need for the pro rata system. This proposal was, I recall, agreed and welcomed by Directors as a more approriate National system for product supply, given the unequal and variable per capita distribution of haemophilia patients and their requirement for treatment (eg surgery) between Scottish regions. The annual "Pro rata meeting" was replaced with an annual

"Supply and Demand" meeting of Directors, to plan and establish future plasma and product supply projections and targets, which included estimates from Haemophilia Directors of their future needs for patients. The routine operation of the revised system of supply was based on RTCs establishing minimum stock levels for all products, based on their projected usage. PFC replenished these RTC stocks (when they fell below the agreed minimum level) from the national stocks held at PFC. The advantages of this revised supply system were (i) increased availability of products (ii) increased confidence in the security of supply (iii) supply based on clinical need (iv) simplified routine operation.

47. Were Scottish and/or Northern Irish patients treated with imported commercial factor concentrates during your tenure? In particular, please describe:

a. The extent to which patients were treated with imported commercial concentrates as opposed to those produced by the PFC.

b. Whether shortfalls in the availability of PFC products occurred. If so, what was the impact of these shortfalls on the type of products with which patients were treated?

c. What, in your view, were the key factors influencing the choice between PFC concentrates and imported commercial concentrates? Please explain the impact of clinical freedom on the relative use of PFC concentrates and imported commercial concentrates.

d. What influence, if any, did pharmaceutical companies have over decisions about the treatment of patients?

164. Commercial factor concentrates were used in Scotland and Northern Ireland, to varying degrees, throughout my employment in SNBTS. Details of the quantities of and rationale for the use of all products used for haemophilia patient treatment were submitted to the Penrose Inquiry (Self Sufficiency and the Supply of Blood Products in Scotland (PRSE0001083) and described in Chapter 21 of the Final Report. These details do not include products used in

Northern Ireland, for which no information was sought or presented. To the best of my knowledge there was no information held by SNBTS on the breakdown of product use in Northern Ireland, except for the understanding and knowledge from conversations with Dr Morris McClelland (Northern Ireland BTS) that supplies of PFC products were insufficient for all patient needs and accordingly were supplemented with commercial product purchase.

165. A detailed analysis of all products used for haemophilia treatment between 1970 and 1991 in Scotland (including comparison with the wider UK) was provided to the Penrose Inquiry by SNBTS and Haemophilia Directors (including from the UKHCDO). These are presented in the appendix to Chapter 21 (Tables 21.1 – 21.8) of the Penrose Inquiry Final Report.

166. My recollection is that there were periodic (though temporary) shortfalls in supply of FVIII products, or at least severe pressures on product stocks, primarily in the late 1980s through to the early 1990s. The reasons for these shortfalls were multifactorial, but included the progressive increase in demand, the requirement for the development, clinical trials and introduction of severely heated and High Purity FVIII products (Z8 heated to 80^0C/72hrs and Liberate) and periodic major building works which reduced PFC production capacity during these periods.

167. These were matters of concern to Haemophilia Directors, but occurred at a time when available commercial products were subjected to virus inactivation/removal processes. Clearly, increased quantities of commercial FVIII were used at these times (eg 1988/89) though I do not have details of how the use of these products may have impacted individual patient treatment.

168. It was not the role or responsibility of the SNBTS to exercise choice between its products and commercial alternatives. It was responsible for the development and manufacture of a range of products of a quality and safety (as judged by national and international standards) suitable for patients in Scotland, and latterly Northern Ireland, and in sufficient quantity to meet the clinical demand for such products. SNBTS received its funding from SHHD and

products were to be supplied free at the point of use and prepared from voluntary unpaid donations, in line with WHO guidance and government policy. The procurement of products not available from SNBTS or not considered suitable for patients was the responsibility of prescribing doctors and their respective Health Boards.

169. Therefore my views on the key factors are informed by the views expressed by Haemophilia Directors in the fora established in Scotland for formal cooperation between all stakeholders and periodic informal discussions. My understanding was that the key factors influencing the choice of Haemophilia Directors and indeed patients themselves included the following:-

- The widely accepted historical and contemporaneous evidence that volunteer unpaid donor sources of plasma provided a substantially safer source of plasma with respect to potential virus transmission, compared to that obtained from US paid donors, particularly in the absence of screening tests for HCV, HIV etc – though it was always recognised that this alone did not provide a guarantee of safety or freedom from risk. I believe this view was maintained until at least the early 1990s when coagulation factor products were subject to effective virus inactivation processes.
- Security and reliability of supply
- Product characteristics including product potency and efficacy, recovery and half life properties, vial content, dose size, ease of solubility and latterly product purity (ie content of other plasma proteins)
- Patient tolerance and freedom from adverse and allergic reactions
- Freedom from excessive risk of inhibitor formation.
- Cost of commercial products, since SNBTS products were supplied free at the point of use

170. I do not believe or recall that the last point above was a key consideration for Haemophilia Directors, although I would conjecture that Health Board managers may have required a justification for commercial product purchase.

171. Haemophilia Directors are better placed to answer this question. For my part I have no knowledge on the subject.

Batch dedication

172. By way of introduction and explanation, "batch dedication" as discussed below was a system for coagulation factor supply to patients, designed to minimise their donor exposure by reducing their use of multiple product batches within a specific time period (eg 3-6 months). The system implemented by SNBTS/Haemophilia Directors involved the assignment of individual patients by haemophilia centres to patient groups to which individual product batches were dedicated. Multiple product batches were held at RTCs with each batch dedicated for the exclusive use of individual patient groups.

173. The operation of this system required secure and large national product stocks, which were distributed regionally to support the batch dedication system envisaged. Its successful design and operation required close cooperation between PFC, RTCs and Haemophilia Centres. The primary role of PFC was to maintain supply of sufficient product batches to RTCs.

48. On 29 November 1983, Professor Cash proposed that the PFC consider batch issue to individual patients (PRSE0001537, page 2). What action, if any, did the PFC take in response to the proposal? What was your view of batch dedication systems at this time?

174. The letter referred to (PRSE 0001537) from Professor Cash was sent to all RTC Directors, as well as to the PFC Director indicating his understanding that any system of batch dedication designed to limit patient donor exposure required the close involvement of SNBTS RTCs and Haemophilia Centres for the effective routine operation of such a system. The role of PFC would be primarily to ensure the supply of sufficient product batches for the patient groups established. This letter would have been typical of the type of correspondence initiated by Professor Cash to seek the wider views of SNBTS Directors, on this occasion concerning the operational feasibility of such a

system throughout Scotland (ie "I would be most grateful for your thoughts on how this might be introduced in your region".)

175. I cannot recall what actions, if any, were taken by Mr Watt or those responsible for product distribution (ie RTCs) in response to the suggestion from Professor Cash. It is evident that both myself, Dr Foster and the PFC Production manager had sight of this letter. However, the priority concern of Professor Cash was clearly the risk of product outdating as a result of accumulating stocks of FVIII. At that time I shared this concern. My recollection is that RTC Directors acted on the request for information concerning product stocks which subsequently led to the supply of surplus FVIII to England and Wales and the introduction by myself in 1984 of a revised system for PFC product distribution to RTCs based on clinical need. (please refer to my answer to question 45).

176. Mr Watt left the employment of SNBTS shortly after this correspondence. Professor Cash reiterated his suggestion that efforts could be made to reduce patient exposure to multiple product batches at the annual SNBTS and Haemophilia Directors Meeting on 2nd February 1984 (evidence submitted to the Penrose Report (PRSE0001556) However to the best of my knowledge no further action was taken on this topic by Professor Cash, RTC Directors, Haemophilia Directors or myself until late 1984. In the intervening period PFC was focused on improved product supply arrangements and management of accumulating FVIII product stocks, development of heat treated coagulation factor products and its ongoing response to Medicines Inspectors' reports of PFC.

49. In mid-November 1984, a batch dedication system was proposed by D. B. L McClelland (PRSE0003308) and sent to you (PRSE0001095). As to this:

a. What discussions, if any, had taken place within the SNBTS regarding batch dedication prior to these proposals? What was the outcome of those discussions?

b. What was your view of batch dedication systems at this time?

177. I cannot recall any formal discussion on this topic within PFC or with RTC colleagues subsequent to the letter from Professor Cash (PRSE 0001537) and his suggestion to the annual meeting of Haemophilia and SNBTS Directors in February 1984 – although clearly the feasibility of such arrangements had been explored (at least informally) in January 1984 by Dr McClelland in his Centre (PRSE 0001095), although presumably with no specific outcomes or proposals at that time.

178. I cannot recall my view of the potential value and importance of batch dedication at this time (November 1984) and can only attempt to reconstruct what my view may have been.

179. Clearly SNBTS had just been made aware at this time (1st November 1984) of the strong probability that PFC FVIII had transmitted HTLV-III to a cohort of patients in Edinburgh, The identification by Drs Ludlam, McClelland and Boulton of the of the FVIII batch NY 3-009 as the product batch most likely to have transmitted infection to this cohort of patients also revealed that these patients had received product from other batches during the relevant period of their analysis. This information introduced a heightened sense of urgency within SNBTS for the implementation of actions to mitigate risks of further HTLV-III transmission to patients from SNBTS products including measures to reduce donor exposure. These measures would have included (probably in order of priority) the urgent implementation of heat treatment for coagulation factor products, its distribution to RTCs for onward supply to heamophilia centres and patients, further development of a more severely heated product (68^0C/24hrs), recall of unheated product stock from the entire supply chain and introduction of measures to minimise patient donor exposure (ie batch dedication).

180. These intiatives were uniquely available to SNBTS within the UK (and perhaps internationally) because of the close operational and working relationships between Haemophilia Directors, RTCs and PFC in Scotland/Northern Ireland and became the dominant focus of attention for PFC, and to an extent RTCs and haemophilia centres. SNBTS had recognised the

importance of minimising the donor exposure to patients and the essential contribution of PFC to support batch dedication systems with increased national and RTC product stocks, but also that the operational detail and implementation of such systems were primarily the role of RTCs, blood banks and Haemophilia centres, supported by a secure PFC supply of a sufficient number of product batches for subsequent allocation to patient groups.

50. On 21 November 1984, you wrote to C. A. Ludlam (PRSE0001796). To the best of your knowledge:

a. You previously met with Professor Ludlam on 14 November. What did you discuss? What was "*the situation*" which Professor Ludlam described?

b. What was the "*arrangement with Dr Boulton.*" How did this system differ from batch dedication to RTCs/individual patients? Please also refer to SBTS0000324_043.

c. You stated: "*There is of course no doubt that we can arrange for complete batches of approximately 1,000 vials to be sent to Edinburgh*

***...I would be happy to implement this immediately.*" How did this system differ, if at all, from batch dedication to RTCs? Given you were able to implement this system "*immediately,*" why did you not do so earlier?**

181. I do not recall what was discussed with Dr Ludlam on November 14th 1984. From the correspondence it would appear that discussion may have included Dr Ludlam expressing his wish to avoid receiving part batches of FVIII in his monthly allocation of product.

182. I do not recall the arrangements agreed with Dr Boulton, but from the correspondence cited it would appear to have concerned an agreement to supply to his Centre (SEBTS) product batches with a vial content close to 250iu/vial, to facilitate the guidance provided to haemophilia patients on home therapy. This was not designed or operated as a batch dedication system, but

rather a system which would simplify the training of patients to self infuse product in multiples of 250iu.

183. The supply of complete batches of products to RTCs did not necessarily constitute a system of batch dedication, which required the supply of multiple and complete batches to RTCs, with each batch being used for the treatment of designated patient groups. The letter from Dr Boulton (SBTS0000324_043) described the initial batch dedication system established in the Edinburgh Centre at the beginning of 1985, following the initial supplies of heat treated FVIII, and envisaged the subsequent establishment of six patient cohorts and the availability of reserve batches for each cohort.

184. The correspondence cited suggests that, notwithstanding Dr Ludlam's concerns expressed in November 1984, the majority of supplies to Edinburgh had in fact already comprised whole product batches prior to that date although clearly on some occasions part batches had been supplied by PFC. Subsequent to the above exchanges of correspondence, I am certain I would have provided clear instructions for whole batch issue to relevant operational managers in PFC, although I have no record of this. The policy of whole batch issue was superseded in early 1985 by the SNBTS system of batch dedication.

51. On 22 November 1984, you wrote to Professor Cash (PRSE0002485). You stated: "*...as an additional measure, to reduce patient exposure to ...HTLV III (and hepatitis) PFC will be implementing a policy of whole batch issue to RTCs ...This policy does not aspire to the ideal situation of batch dedication to individual patients but will provide some additional security. Thus, you should no longer receive issues made up from multiple batches*" (PRSE0002485, page 2). As to this:

- **a. Who took the decision to implement batch issue to RTCs rather than individual patients? What were the reasons for the decision?**
- **b. Why, in your view, was the "*ideal situation*" of batch dedication to individual patients preferable not adopted?**
- **c. Why, given the risk of hepatitis, had RTCs previously "*receive***

issues made up from multiple batches"?

185. I note that this letter (PRSE 0002485) was copied to the SHHD Senior Medical Officer and, judging by its content, will almost certainly have also been sent to RTCs to formally notify them of plans for introduction of heat treated product and requirements for action on their part. I cannot recall or reconstruct the specific details of discussions preceeding this letter but I am confident, given the importance of the topics covered, that they will have included prior discussions and agreement with Professor Cash, RTC Directors and most likely SHHD.

186. At the time of this correspondence the key priority and focus of SNBTS was to provide heat treated FVIII to haemophilia patients in Scotland (and Northern Ireland) at the earliest possible opportunity. This development required the heat treatment of existing product stocks, their quality control and release subject to satisfactory clinical evaluation. As the letter of 22nd November explains, only limited quantities of heat treated product were to be produced, sufficient for immediate supply to patients pending the outcome of a planned clinical evaluation. Thereafter, it was planned to subject all product stocks to heat treatment and arrange onward distribution to RTCs. The limited initial quantities of product available from this programme of work were insufficient for the simultaneous introduction of batch dedication for individual groups of patients, although such was envisaged following the availability of increased quantities of heated material subsequent to satisfactory clinical evaluation. Neither at this time nor subsequently was it envisaged or considered feasible to dedicate whole product batches to individual patients since this would have required upward of 200 product batches being available for issue at any time. This would be equivalent to approximately 40MIU FVIII (ie >4 times annual usage)

187. Although I have no detailed recollection of the detail of specific discussions, I believe am confident that the phased programme of work outlined in my letter would have followed discussion and agreement with Professor Cash, RTC Directors, Haemophilia Directors and SHHD.

188. The developments outlined above resulted, to the best of my knowledge, in Scotland becoming the first country in the world to make heat treated product available in sufficient quantity for all patients in December 1984. Also there were, to the best of my knowledge, no further patient seroconversions to HTLV-III in patients treated with SNBTS FVIII following these actions, despite the information gained subsequently of HTLV-III infective donations having entered PFC plasma pools.

189. As outlined above, insufficient stocks of heat treated product were available at the time of the transition to heat treated FVIII, although the implementation of a batch dedication system for groups of patients was established in early 1985 as increased stocks of heated material became available.

190. Prior to my appointment as acting Director in 1984, the "pro–rata" system for product distribution from PFC may have resulted in the distribution of part product batches to RTCs, particularly the smaller northern centres, although I have no recollection of the extent to which this may have occurred. In 1984 I instituted a revised national system of product distribution, as described previously, which resulted in increased levels of supply, so reducing the need for partial batch distribution.

191. My correspondence with Dr Ludlam (PRSE0001796) suggests that the supply of multiple batches (at least in 1984) was uncommon. In any event, the initial suggestion made by Professor Cash in 1983 to my predecessor (Mr Watt) and RTC Directors concerning aspirations to minimise donor exposure appears not to have been further pursued within SNBTS or amongst Haemophilia Directors. Partly, I would conjecture, as a result of more dominant concerns to develop virus inactivation processes within SNBTS and to maintain a secure overall supply of SNBTS product, which I believe remained the product of choice of both patients and their doctors.

192. Notwithstanding the above comments, I would with hindsight now consider the timing of introduction of batch dedication systems in early 1985 to

have been a lost or delayed opportunity, since product stocks in 1984 were at a level capable of supporting such a system. However, it was not evident (at least to me) which part of the overall arrangements for product supply to patients from PFC to RTCs, and finally to patients, was best placed to drive forward this initiative.

193. To the best of my recollection, I was not aware of other organisations in the UK or elsewhere implementing such systems at this time, or subsequently.

194. Also it would have been increasingly understood by the early 1980s that all FVIII products (from both paid donors and volunteer NHS donors) were capable of NANBH transmission, so emphasising the greater importance and urgency of the development of virus inactivation and removal strategies. It was also well known that commercial FVIII products were prepared from plasma pools containing 5-10 times more donations (and from higher risk paid donors) than those used by SNBTS, so reinforcing the dominant importance of "Self Sufficiency" in comparison with other possible initiatives.

52. On 27 December 1984, Professor Cash wrote to you with proposals for batch dedication. The proposals were "*quite simple*" and "*would permit a substantial reduction in batch exposure ...without disrupting ...supply*" (SBTS0000322_108). Given the simplicity of these proposals, why, in your view, did it take over a year for proposals to be put forward (PRSE0001537, page 2)?

195. The letter referred to in the above question is from myself to Professor Cash – not from Professor Cash to myself. The purpose of this letter was to brief Professor Cash on the possible arrangements for batch dedication which had been developed with RTC colleagues but also to seek his views on the proposal that the FVIII product to be prepared in early 1985 (ie NY 68^0/24hrs) should not be fed into the batch dedication system of supply until stocks of the 1st generation heat treated product (NY 68^0/2hrs) were exhausted.

196. Please see my response above to Question 51(c).

197. I do not know why this proposal was not progressed sooner within SNBTS and Haemophilia Centres. So far as PFC was concerned the topic was not raised with me as a priority for my attention following my appointment as acting PFC Director in January 1984 – its value and importance became clear to me with the news in October 1984 that HTLV-III had entered the Scottish donor population.

198. The benefits of reducing patients' exposure to donors was a significant factor in the preference for NHS products over commercial concentrates since PFC plasma pools were substantially smaller than those used by commercial manufacturers.

199. However it is possible to conjecture that had a system of batch dedication been in place during 1984 one of the patient cohorts established within the system would almost certainly have received repeated infusions of the FVIII batch (NY 3-009) which later in 1984 was found to have transmitted HTLVIII to the patients in Edinburgh. I cannot assess whether this outcome would have been better or worse (in terms of patient numbers) than that which occurred. This would have depended on the number of patients allocated to an infectious product batch and the impact of their repeated infusions from such a batch. However we can perhaps say with greater certainty that batch dedication at this time would not have reduced the incidence of NANBH to previously untreated patients.

53. In as much detail as you are able to, what meetings took place within the SNBTS, from November 1984 onwards, as regards batch dedication? Who attended these meetings? What was decided? You may wish to refer to PRSE0003102; SBTS0000382_129; SBTS0000322_108; PRSE0001427; SBTS0000242_044; SBTS0000383_046; and SBTS0000495_180, page 2

200. I have no detailed recollection of specific meetings, attendees or decisions taken concerning batch dedication beyond the cited information

available from SNBTS records from this period . However I can be certain that there were many formal and informal discussions over and above those cited. These will have taken place within PFC, with SNBTS Directors, Haemophilia Directors, SHHD and others. These will have been frequentduring the period of implementation (1st quarter 1985) but thereafter the system operated, to the best of my recollection, without major senior management intervention.

54. As regards SBTS0000242_044, do you hold a copy of the "*short paper*" you prepared for the Co-Ordinating Group? What did this paper say?

201. I do not have a copy or record of this paper and do not recall its content. I can conjecture that given the date of the request from Professor Cash's secretary and its purpose it would have contained an outline of the system developed following discussions with RTC Directors, the operational implications for PFC and RTCs and timings and actions necessary for implementation.

55. What issues affected the date on which the SNBTS was able to implement batch dedication, and the type of system adopted? What was your view of those issues? In particular:

- **a. Please refer to PRSE0003561, in which it is contemplated that the English NBTS might object if the SNBTS reserved products for its own patients. To your knowledge, did the SNBTS ever receive objections from the English NBTS? If so, who objected, when, and what was their objection?**
- **b. Please refer to PRSE0003102, in which Dr Cash raised the cost and operational implications of batch dedication, and the need to discuss with Directors (PRSE0003102).**
- **c. Please refer to PRSE0004110, in which you stated that "*there is an urgent need for commonality between regions or I suspect disaster may strike*" (PRSE0004110). Why did you consider there to be a need for "commonality"? What "disaster" were you concerned might strike?**
- **d. Please refer to PRSE0004616, in which D. B. L. McClelland states**

that batch dedication ought to allow the PFC time to develop heated products, and to SBTS0000324_073, page 2, in which you state you desire to "proceed cautiously" with batch dedication because of the transition to new product. Why were you suggesting this approach?

202. Following discussions in November 1984 and the resulting decisions to urgently roll out programmes for product heat treatment and batch dedication, the main issues affecting the timing and operational detail of their implementation will have been the anticipated progress in the manufacture of heated FVIII and its distribution to RTCs, anticipated annual product demand, projected short term and longer term stock levels and the collective agreement (or otherwise) to utilise all stocks of the first generation heated FVIII product (68^0C/2hrs) before commencing supply of its successor product (reformulated and heated to 68^0C/24hrs), later in 1985.

203. I do not recall the issue raised in the correspondence between Dr Hopkins and Dr Crawford (West of Scotland RTC) being further pursued or materially affecting SNBTS planning. I am not aware of any objections having been raised by the NBTS or others. Indeed the rapid introduction of FVIII heat treatment by SNBTS without the need to revert to commercial product supply during the transition was only possible because of the high and secure stocks available to support the concurrent programmes of heat treatment and batch dedication.

204. The correspondence cited between Professor Cash and myself concerning an idea outlined by Dr Crawford does not refer to the cost and operational implications of options already under consideration by SNBTS/Haemophilia Directors, but to a more complex system, presumably envisaged by Dr Crawford, and designed to reduce donor pool size and create designated plasma pools for each donor. In any event this suggestion was not pursued further.

205. My wish to see a common system adopted by all RTCs was driven by a desire to establish an operationally simple and robust system providing equitable benefit to all patients and Haemophilia Centres. In the absence of a convincing argument for bespoke systems for each region this seemed to me to be the most appropriate and efficient way forward. My reference to a possible "disaster" is probably an exaggeration!. My concern related to the potential problems which would arise if individual RTCs chose to operate different product supply and allocation systems with their respective haemophilia centres.

206. The Letter to Dr Boulton (SBTS0000324_073) expressed my wish to proceed "a little more cautiously" because at that time (i) detailed arrangements for introduction of batch dedication were not as advanced in other RTCs as those being developed in Edinburgh and had yet to be collectively discussed and agreed by SNBTS Directors (ii) agreement had not been reached concerning arrangements for the transition from the NY 68^0C/ 2hr product to its successor (NY 68^0C/24hr) (iii) the manufacture of NY 68^0C/24hr had only just commenced.

56. You explained to the Penrose Inquiry that batch dedication was introduced within the SNBTS during 1985 (PRSE0006025, page 26) To the best of your knowledge, on what date was batch dedication introduced? If the date differed across regions, please say so.

207. Batch dedication systems were implemented in SNBTS progressively during the first quarter of 1985, as stocks of heat treated FVIII became available from PFC. Initially the number of patients allocated to individual product batches by RTC/Haemophilia Centres would have been relatively large although the number of groups would have been increased fairly quickly by RTC/Haemophilia Centres as product was heat treated and released by PFC. For example the correspondence from Dr Davidson (Consultant Haemaologist, Glasgow Royal Infirmary) (PRSE 0003810) indicates that the initial system in the West of Scotland RTC and Glasgow Royal Infirmary comprised three

patient groups. Similar progress had been made in the Edinburgh RTC in mid January with the creation of initially 3 patient groups.

208. Clearly the implementation was not simultaneous across all regions because of the need for coordination between RTCs, Blood Banks and Haemophilia Centres. Details of the numbers in each patient group (agreed between individual RTCs and their respective Haemophilia Directors) and the operational arrangements established would have been different in each region, but broadly similar in principle.

57. Please describe the batch dedication system(s) which were ultimately adopted within the SNBTS. Were different systems used for different regions or patients? If so, why? In your view, could and/or should a system of batch dedication have been introduced earlier? Please refer to PRSE0002485; , PRSE0002675 page 2; PRSE0001427; SBTS0000322_108; PRSE0004616; PRSE0003810; SBTS0000395_019; PRSE0002080; and WITN0252018.

209. The batch dedication system ultimately established by SNBTS and Haemophilia Directors is outlined in the references cited and in particular SBTS0000322_108 and PRSE0001427.

210. In essence each RTC and their associated Haemophilia Centres allocated all patients treated with SNBTS products into individual Batch Dedication Groups, which were supplied and replenished from PFC stocks and reserve batches held at RTCs. I do not recall how many patients each group would typically comprise, but my recollection is that they were calculated to ensure that individual patients would be exposed to only one product batch in a 3-6 month period.

211. This system was predicated on the availability of large national product stocks and the agreement that all stocks of the initial heat treated FVIII product (68^0C/2hrs) would be used prior to the introduction of its successor product

(68^{0}C/24hrs) manufactured in 1985. The PFC involvement in the system extended only to maintaining stocks of product at RTCs for each patient group.

212. I believe the system described could have been implemented in 1984 using unheated product stocks being routinely issued at that time.

213. At the annual meeting of Haemophilia and SNBTS Directors held on 2nd February 1984 Professor Cash had raised in his annual report the desirability of action/cooperation between SNBTS and clinical colleagues to reduce patient exposure to multiple batches of coagulation factors (see PRSE0004741 from the Penrose Report). The minutes from this meeting (PRSE0001556) record Professor Cash's suggestion, but do not record any specific follow up action and appear not to have afforded the topic a high priority. In any event, the topic was not further pursued until events concerning transmission by SNBTS FVIII of HTLV-III to patients in Edinburgh injected a greater degree of urgency and priority to the topic.

214. As stated previously, I believe this was a lost opportunity although I cannot comment with any authority on whether the introduction of batch dedication following this meeting would have reduced the number of patients infected with HTLV-III from SNBTS FVIII.

58. What issues arose after a system of batch dedication was established? Was batch dedication ultimately discontinued? If so, when did this occur and why? Please refer to SBTS0000325_018; PRSE0001927 page 1; and SBTS0000495_180, page 2.

215. Following its introduction in early 1985 I do not recall any specific or significant issues associated with the batch dedication system. However as mentioned previously, the security and reliablity of this supply system was dependent on large national product stocks. These were maintained (albeit at a diminishing level), but were progressively reduced as a result of product yield penalties from product heat treatment and, in particular, the introduction of the severely heated product Z8 (80^{0}C/72hrs) in 1987 and increasing product

demand. I cannot recall the details, but I believe the reducing national stock levels may have required a revision or temporary suspension of the batch dedication system by RTCs and Haemophilia Centres (particularly as a result of the issues raised by Professor Cash in his letter to Dr Ludlam, PRSE0001927) to create fewer patient groups. However, by mid 1987 and with the introduction of Z8 there was increasing confidence in the virus safety of SNBTS FVIII for both HIV and hepatitis C, thereby reducing (though not eliminating), the perceived importance of batch dedication as a tool to reduce donor exposure.

216. Batch dedication was eventually discontinued as a result of the above. However I cannot recall when this occurred, but was probably in 1988 or 1989.

59. On 11 November 1991, you wrote to Professor Cash regarding batch dedication. You stated: "*the scientific value of these measures cannot and will not be proved*" (LOTH0000045_002). Why did you hold this view? What effect, if any, did batch dedication have in reducing the risk of infection from PFC blood products?

217. I do not recall the context of this correspondence or the reasoning for the statements made.

218. However, in 1991 we knew that our initial heat treatment conditions (68^0C/2hrs, applied to all SNBTS/Haemophilia Centre stocks of FVIII) resulted in no further transmissions of HTLV-III to recipients of SNBTS FVIII products. We also knew that previously untreated and minimally treated patients were susceptible to NANBH transmission by both 68^0C/2hr and 68^0C/24hr heated products. Thus the beneficial impact of batch dedication alone with respect to HIV transmission was unmeasurable (but probably close to zero) as a result of the simultaneous introduction of heat treatment. The beneficial effect on NANBH transmission was also probably unmeasurable or at best marginal due to the prevalence of NANBH in the donor population and its likely presence in every product batch. Finally, the small number of previously untreated and minimally treated haemophilia A patients exposed to SNBTS products between

1985 and the introduction of Z8 (80^0C/72hrs) in 1987 precluded the possibility of any meaningful calculation of the frequency of NANBH transmission in different patient batch dedication groups.

219. I am aware of at least one infrequently treated patient being infected with NANBH from a heat treated PFC product (NY 68^0C/24hr) subsequent to emergency treatment in 1986.

220. Thus the benefits of batch dedication could be not be scientifically quantified or proven – although I remain of the view that at the time batch dedication was an important management option at a time when the risk of pathogen transmission to patients could not be quantified with any certainty.

221. In conclusion I believe the system of batch dedication developed and implemented by SNBTS/Haemophilia Directors was probably uniquely available in Scotland as a result of (i) its achievement of self-sufficiency and availability of large and secure national product stocks and (ii) the close working relationships which existed between SNBTS (PFC and RTCs) and Haemophilia Directors. I know of no other arrangement in the UK, the EU or elsewhere where batch dedication was practised.

Section 7: Development and production of freeze-dried cryoprecipitate

Introductory Comments

222. Consideration and discussion of this topic largely predated my employment in SNBTS. My principal role following my appointment was to lead the development of quality management systems, documentation systems and identification of actions necessary to bring the PFC into pharmaceutical "GMP compliance" following the report of the UK Medicines Inspectors (Messrs Flint and Purves) in 1980. This role also included advising SNBTS RTCs on actions necessary concerning their collection and supply of plasma to PFC. In 1983 I also led the assembly of a comprehensive product licence application for a

newly developed Intravenous Immunoglobulin product and its submission to the UK Medicines Control Agency. I initially had no knowledge of clinical issues affecting product selection for patient care, although my knowledge and understanding of this important context developed over time through exposure to discussions within SNBTS and elsewhere.

60. **In January 1980, Dr G. S. Gabra reported the development of a lyophilised cryoprecipitate ("freeze-dried cryoprecipitate"/"FDC") which offered many of the advantages of NHS concentrate but with a '*reduced hepatitis risk*' (PRSE0001701, pages 2-3). Dr Gabra and others further described freeze-dried cryoprecipitate in a letter to the British Medical Journal published on 11 October 1980 (BPLL0002088). To the best of your knowledge:**
    a. **When did Dr Gabra begin to develop this product? You may wish to refer to PRSE0001701, page 3.**
    b. **In May 1979, Dr Gabra presented the findings of a clinical trial to the West of Scotland blood club (PRSE0001701, page 5). Were you ever aware of the results of this trial? If so, what did the results show?**
    c. **What was your view of the freeze-dried cryoprecipitate developed by Dr G. S. Gabra? Please explain: (i) whether, in your view, freeze-dried cryoprecipitate was an appropriate treatment for patients and, if so, which patients; and (ii) whether, in your view, freeze-dried cryoprecipitate was suitable for production at RTCs and/or the PFC. If not, why not?**
    d. **In reaching your view, what weight, if any, did you give to the following:**
        i. **FDC was produced from small pools of five cryoprecipitates and carried a reduced hepatitis risk (PRSE0001701, pages 2-3).**
        ii. **FDC was produced using a simple method which could be adopted at minimum expense at RTCs (PRSE0001701, page 2).**
        iii. **FDC had a yield of around 50% of fresh donor plasma**

(PRSE0001701, page 2), and an average Factor VIII content of 542 iu per bottle (PRSE0001701, page 7).

e. FDC was suitable for home therapy: it was easily stored, carried a predetermined dosage, and could be rapidly reconstituted in distilled water (PRSE0001701, page 2). Has your view of freeze-dried cryoprecipitate changed over time? If so, how?

223. I have no knowledge or recollection of when this development commenced.

224. I have no knowledge or recollection of this trial or its results.

225. I do not recall having, or being called upon to express an informed view of this development. If my view had been requested it is most likely that it would have been informed by the views of Mr Watt, Dr Foster and Professor Cash, and guided primarily by considerations of pharmaceutical quality assurance and GMP compliance rather that strategic issues of product selection or supply.

226. I had neither the knowledge nor professional competence to judge the suitability or otherwise of this product for patient treatment.

227. My current view concerning the suitability of FDC for production by RTCs is that it would have been possible, subject to significant investment in facilities (eg clean rooms) and equipment (eg freeze driers), to meet the quality standards required for routine production in a GMP compliant environment. It was not a suitable process for incorporation into the pharmaceutical manufacturing facilities and quality assurance systems at PFC, which had been designed and developed for relatively large scale batch processing. Moreover, such a product could not be standardised and was unlikely to have been suitable for virus elimination/inactivation processes.

228. If I had held a view at the time I believe it would not have been dissimilar to the above.

229. As stated above I do not recall developing a view on this subject although the view of my predecessor (Mr Watt) and Professor Cash are evident from their correspondence cited above. My comments below reflect knowledge and experience gained during my SNBTS employment rather than an informed view at the time in question.

230. This is clearly the case for a single product infusion but for the routine treatment of a severe haemophilia patient this benefit diminishes significantly with time. In a paper submitted by SNBTS to the Penrose Inquiry (PRSE0003480, pages 35/36) it was estimated that the probability of infection with NANBH/HCV rises to approximately 85% for a severe haemophilia patient treated with cryoprecipitate over a period of 24 months. This point was made by Mr Watt in his correspondence with Professor Cash, although he did not provide calculations in support of his view.

231. I do not recall any cost estimates being submitted or examined for FDC at RTCs, but I do not believe these would have been "at minimum expense" given the requirement for facility and equipment development.

232. I believe this would have been a reasonable estimate of product yield, although in the early 1980's there was a significant increase in PFC FVIII product yields.

233. I am not sure these claims of FDC being suitable for home therapy would necessarily have been shared by all (or a majority) of haemophilia treaters at that time. My understanding was that such products contained variable FVIII activity, had large infusion volumes and were prone to adverse and allergic reactions in recipients. Whilst such products could be and were used in haemophilia care elsewhere, Coagulation Factor Concentrates, I believe, were increasingly the product of choice and benchmark for the treatment of severe haemophilia in adults from the early 1980s onward although cryoprecipitate continued to be used for the treatment of mild disease and in children.

234. My view of freeze dried cryoprecipitate has not changed over time.

61. On 15 September 1980, Professor C. A. Ludlam wrote to Dr C. R. Rizza, stating that the "*Protein Fractionation Centre in Edinburgh ...are considering the possibility of preparing Freeze Dried thaw-siphon cryoprecipitate for home therapy.*" (LOTH0000012_131). To the best of your knowledge, what was the outcome of these proposals? Was FDC still under consideration by the PFC at the start of your employment there? If so, what was your view of these proposals? Did the PFC ever produce FDC for home therapy? If not, why not? Please provide as much detail as you are able to. You may wish to refer to: SBTS0000223_063, page 5 and PRSE0000840.

235. This predated my employment at PFC. I presume that this topic was still being discussed and considered in SNBTS in 1980, leading to Dr Ludlam seeking the views of his UK colleagues. I am not aware of any documents amounting to a 'proposal' or programme of work on this topic at PFC or in the wider SNBTS. The views of the PFC Director at that time were however clear and that PFC should continue to focus its efforts on the continued development of FVIII concentrates. I cannot recall any serious consideration of the topic within PFC. To the best of my knowledge PFC did not at any time prepare FDC for home therapy or any other use.

62. On 4 March 1981, the Haemophilia and Blood Transfusion Working Group, including representatives from the PFC and the SHHD, discussed the production of freeze-dried cryoprecipitate (PRSE0000181, page 2). As to this:

a. Were you aware of this discussion? If so, what was your view?

b. A multicentre trial of FDC was proposed. Was this trial ever conducted? If so, what were the findings? If not, why not? Please give as much detail as you are able to.

c. Dr G. A. McDonald "*suggested that FDC could be a research and development project at PFC but Dr Foster said that PFC did not have resources for this at present*" (PRSE0000181, page 2). Were you made aware of this proposal? If so, what was your view of it?

Did you agree that PFC lacked resources to embark on this project?

d. **The Working Group agreed to discuss results of the West of Scotland pilot evaluation at the next meeting. To the best of your knowledge, did this discussion take place? If so, what was the outcome?**

236. I was certainly not aware of this discussion at the time since I had only been in post for a matter of days at this time. I did perhaps subsequently become aware of this topic but primarily from a historical perspective only. Accordingly I am unable to provide any useful, competent or relevant information on questions (a),(b),(c) or (d).

237. I do not recall the proposed trial of FDC being conducted. It may have been, but without any involvement of PFC. But I suspect not.

238. I was not made aware of this proposal at the time although subsequently I would, I believe, have shared Dr Foster's view.

239. I have no recollection of whether the results of a pilot evaluation were ever discussed.

63. Please refer to SBTS0000269_004, a letter from Professor Cash to J. G. Watt dated 25 October 1982. To the best of your knowledge, please explain:

a. **The relationship between freeze-dried cryoprecipitate and the Medicine's Inspectorate Reports (SBTS0000269_004).**

b. **Professor Cash contemplated that FDC might be produced at the PFC (SBTS0000269_004). At this time, had you become aware of this possibility? If so, how and when did you become aware of it? What was your view as to the feasibility of producing FDC at PFC? How, if at all, had your view changed since the matter was first proposed in March 1981 (PRSE0000181)?**

240. I believe, though cannot be sure, that this letter would have been sent to RTC Directors in addition to Mr Watt. I believe Professor Cash's reference to a future SNBTS response to Medicines Inspectors' reports may have concerned the need to consider the remedial actions and investment required to respond to criticisms from the Inspectors following a series of visits to SNBTS RTCs at the beginning of 1982, which may have included criticism of the freeze drying facilities, equipment in the West of Scotland RTC and its suitability for the preparation of therapeutic products. In his letter Professor Cash was signalling his apparent lack of enthusiasm for any further development of FDC by SNBTS and the need to bring discussion of FDC to a conclusion. However he also acknowledges that such a product development may be considered by Haemophilia Directors to be appropriate and necessary. If such a view emerged from further discussion, Professor Cash wished to establish whether the necessary equipment and facility investment required by SNBTS should be in the West of Scotland RTC or PFC.

241. In any event, discontinuation of the FDC project was announced at the annual meeting of SNBTS and Haemophilia Directors in January 1983.

242. I cannot recall if or when I became aware of FDC production at PFC as a serious possibility or probability. However, had I been called upon to express a view by either Mr Watt or Professor Cash, I would have considered such a development to be incompatible with the functioning of PFC as a GMP Manufacturing facility without significant investment in plant, facilities and equipment to establish a suitable facility on the PFC site. Also, at this time PFC had secured funding for critical developments in facilities and equipment necessary to respond to Medicines Inspectors' criticisms and this work was planned or already underway. I was directly involved in these developments and at no time can I recall being asked to factor into planning the possibility of FDC manufacture at PFC.

64. Please refer to SBTS0000269_003, Mr Watt's reply to Professor Cash, dated 25 October 1982. To the best of your knowledge, please

explain:

a. **Mr Watt stated that Scottish demand for Factor VIII could be met from PFC concentrate and "*the argument that we need freeze-dried cryo because of higher yield is no longer relevant*" (SBTS0000269_003, page 1). Did you agree with this assessment? Please give reasons for your answer. What other factors, if any, informed the decision whether to produce FDC at the PFC? Was Scottish demand for Factor VIII, in fact, met by PFC concentrate alone in the period following this letter? If not, please state how demand was met.**

b. **Mr Watt alluded to "*the type of more purified product, suitably pasteurised, toward which we are moving*". To what was this a reference? (SBTS0000269_003, page 1). At the time of this letter, what plans, if any, did the PFC have to produce pasteurised products. Please provide as much detail as you are able to.**

c. **Mr Watt stated that "*the hypothesis that single donor products reduce the risk of infection'* had never been examined statistically and that doubted whether this was a '*significant factor in the lifetime of a patient.*" (SBTS0000269_003, page 1). Did you agree with this assessment? Please give reasons for your answer.**

243. I believe this assessment was broadly correct, although I cannot recall if I had sight of this letter at the time. Progressive increases in plasma supply, together with significant product yield improvements were resulting in increased output of PFC FVIII, leading to substantial increases in product stock. In the period 1981-1984 the consumption of PFC FVIII in Scotland rose from 3.48 to 6.89 MIU, the use of cryoprecipitate fell from 0.9 to 0.3MIU and the use of commercial FVIII used fell from 1.24 to 0.05 MIU. Throughout this period SNBTS annual production of FVIII concentrate exceeded the overall clinical use of all FVIII products in Scotland. However, increasingly small amounts of commercial FVIII continued to be used until 1985. In addition, SNBTS product stocks rose to approximately 12 months supply in 1984, which permitted the

rapid implementation of heat treatment for FVIII and its supply to all patients in Scotland in late 1984.

244. Details of SNBTS FVIII product supply and clinical use in Scotland between 1979 and 1985 are presented in evidence submitted to the Penrose Inquiry (Self-Sufficiency and the Supply of Blood Products in Scotland (With Particular Reference to the Treatment of Haemophilia A), Dr P Foster, January 2011, p 58) and are provided below for ease of reference.

Table 16. Production of Factor VIII Concentrate by SNBTS and Clinical Use of Factor VIII Concentrate in Scotland, 1979 to 1985

Year	Amount of FVIII Produced by the SNBTS[a] (m iu)	Amount of SNBTS FVIII used Clinically[b] (m iu)	Amount of commercial FVIII used[b] (m iu)	Total Amount of FVIII used Clinically[b] (m iu)
1979	2.74	1.76[c]	0.72[c]	2.48
1980	3.73	3.87	0.96[d]	4.83
1981	5.58	3.48	1.22	4.70
1982	6.68[a]	4.75	0.52	5.27
1983	9.81[a,e]	5.73	0.39	6.12
1984	8.18[a,f]	6.89	0.05	6.94
1985	6.73[a]	5.67	nil	5.67

245. Other factors influencing the decision concerning FDC at PFC included knowledge that factor concentrates were becoming the treatment of choice by both patients and haemophilia treaters, a realistic prospect at that time of a pasteurised product becoming available, lower incidence of adverse reactions and freedom from the need to use commercial product. Also PFC had embarked on a programme of work to address Medicines Inspectors' criticisms and this did not include the ability to prepare FDC.

246. SNBTS submitted to the Penrose Inquiry a detailed account of its development programmes concerning coagulation factor products (SNBTS Briefing Paper on the Development of Heat Treatment of Coagulation Factors, November 2010, Dr P R Foster), (PRSE0002291).

247. The key events in the development of a PFC pasteurised product were:-

- First experiment on FVIII pasteurisation using carbohydrate and amino acid stabilisers – September 1981
- First pilot batch of pasteurised FVIII (ZHT) – February 1983
- Initial clinical trial of FVIII ZHT which resulted in adverse reaction in one of three patients - January 1984
- Preparation of fifth pilot batch of ZHT – March 1984
- Preparation of final pilot batch of ZHT – September 1984.

248. The development of this product did not proceed further and PFC refocused its efforts on heating of freeze dried products in response to the knowledge gained for the first time in late 1984 that HTLV-III could be susceptible to inactivation by heat treatment at 68^0C for 1-2 hrs and that the existing PFC FVIII product could withstand such treatment.

249. As above I cannot recall if I had sight of this letter at the time. Had I done so I would have understood the rationale for his view, but probably would have had insufficient knowledge or experience to judge its accuracy. Also the views expressed by Mr Watt only concerned the risk of hepatitis transmission (NANBH and HB) as this correspondence predated the understanding of risk of AIDS from coagulation factor products.

250. Please also see my response to question 60 (d) (i) above.

65. On 11 January 1983, Dr Boulton wrote to Professor Cash, stating that "*with the onset of a properly pasteurised product, some of the cases for small pool or single donor material, such as cryoprecipitate, will be less strong*" (SBTS0000269_002, page 1). As to this:

a. Did you agree with this assessment? Please give reasons for your answer.

b. What plans, if any, did the PFC have to produce pasteurised blood products at this time? If the PFC had no such plans, please explain, in your view, why Dr Boutlon envisaged the "*onset of a properly pasteurised product*" at this time?

251. I do not believe I had sight of this letter at that time – the annotation suggests it was copied to Dr Foster only.

252. In any event had I seen the letter I would have supported Dr Boulton's assessment.

253. Dr Boulton would have been aware of these plans and involved in the clinical trial of the pasteurised product ZHT.

254. Please see my response to question 64 (b) above.

Section 8: Production of blood products at the PFC

66. Please describe, during the period you worked there, the range of blood products manufactured by the PFC and how those products were used by patients, including how this changed over time.

255. The following plasma derived medicinal products (PDMPs) were manufactured at PFC:-

- Albumin products (Resuscitation, burns, shock, renal disease and other applications)
    - Stable Plasma Protein solution (4.5%) – replaced latterly with 5% Human Albumin
    - Human Albumin (20%)
- Factor VIII (Treatment of Haemophilia A)
    - Intermediate purity NY (unheated, 1974-1984)
    - ZHT Pilot batches for clinical evaluation. (Pasteurised 60^0C/10hrs, 1983) Development discontinued September 1984
    - Intermediate Purity NY (Heat Treated 68^0C/2hrs, December 1984 – 1985)
    - Intermediate purity NY (Heat Treated 68^0C/24hrs, 1985 -1987)
    - Z8 (Heat Treated 80^0C/72hrs, April 1987 – 1991)

- High Purity FVIII (Liberate, treated with solvent/detergent (SD) for virus inactivation, introduced in 1991)
- High Purity FVIII Liberate HT, (SD + 80^0C Heat treatment) approved for clinical trial 1996

- Factor IX (Treatment of Haemophilia B, Reversal of anticoagulant therapy)
  - DEFIX (Prothrombin Concentrate containing factors II, IX and X, Late 1960s to 1985)
  - DEFIX (Heat treated at 80^0C/72hrs, 1985 onward)
  - High Purity FIX for haemophilia B (SD + Heat treatment at 80^0C/72hrs, approved for clinical trial 1993 but superseded by recombinant products)
- Intramuscular Immunoglobulin Products (Prophylaxis and/or treatment of infectious diease and antenatal prophylaxis for pregnant Rh negative mothers). These products were prepared to specifications defined by the British Pharmacopoeia (BP)
  - Human Normal Immunoglobulin
  - Anti –Tetanus IgG
  - Anti - Hepatitis B IgG (HB)
  - Anti -Zoster IgG
  - Anti- Rabies IgG
  - Anti- RhD IgG (prophylaxis of Rhesus disease of newborn babies)
- Intravenous Immunoglobulin (IVIgG) (Developed in early 1980s and granted product licence mid 1980s. Developed and used for treatment of Primary Immunodeficiency initially, but subsequently clinical uses expanded rapidly to include Acquired/Secondary immunodeficiency and a wide range of neurological and other conditions. By the early 1990s IVIgG was the "driving product" for PFC and the wider international fractionation industry and remains so
  - Intravenous Immunoglobulin (normal)
  - Hyperimmune IVIgG – anti Hepatitis B
  - Hyperimmune IVIgG – Anti-Tetanus
  - Hyperimmune IVIgG – Anti-D
  - Hyperimmune IVIgG – CMV

- Other products under development for clinical trial but which did not become part of PFC licenced product range
    - Fibrinogen concentrate
    - Fibrin Sealant

67. Please explain, during the time you worked there, the process by which the PFC manufactured Factor VIII concentrate, and how this changed over time. Please explain, as far as you are able to:

a. How the process employed at PFC differed from (i) that used at BPL, and (ii) that used by commercial manufacturers.

b. Any problems which resulted from the manufacturing process at PFC and how these were overcome.

256. I do not have in my possession and cannot recall all details of the manufacturing processes and process modifications developed and implemented by PFC during the course of my employment in SNBTS. However, some of the important detail and its chronology, and in particular that which relates to the implementation of virus inactivation processes adopted, is contained in documents submitted to the Penrose Inquiry (1. Events concerning the safety of blood and blood products with special reference to the treatment of haemophilia, October 2009 and 2. SNBTS briefing paper on the development of heat treatment of coagulation factors, Dr P Foster, November 2010). (PRSE0003480 and PRSE0002797).

257. To the best of my recollection and knowledge all FVIII manufacturing processes at PFC commenced with the preparation of bulk cryoprecipitate from frozen plasma pools. This initial step was (and remains) common to most, if not all, fractionators. Notably however, this initial process step at PFC utilised a continuous thawing process rather than the conventional bulk tank method widely used by the industry and was found to substantially increase FVIII recovery in this step.

258. The resultant bulk cryoprecipitate was subsequently subjected to an extraction procedure to further purify the FVIII fraction, aluminium hydroxide adsorption to remove unwanted coagulation factors, formulation to stabilise the

FVIII activity, sterilisation by filtration, dispensing and freeze drying, heat treatment (latterly), visual inspection of individual vials, quality control analysis and labelling and packaging.

259. My understanding is that the above steps were broadly comparable to processes employed in the industry generally for the preparation of "intermediate purity" FVIII products in the 1970s and early 1980s. Subsequent developments at PFC in the mid 1980s and early 1990s (for Z8, Liberate and Liberate HT) included additional purification steps such as Zinc precipitation and ultrafiltration, modified freeze drying conditions and severe heat treatment (Z8) and ion exchange chromatography, solvent detergent virus inactivation and severe heat treatment (Liberate and Liberate HT).

260. A more detailed description of the processes for the manufacture of FVIII at PFC between 1980 and 1991 was provided to the Penrose Inquiry and included in its final report (Chapter 20 Figures 20.1 and 20.2). These are reproduced below for ease of reference.

261. Figure 20.1 from Penrose Report (Fractionation scheme)

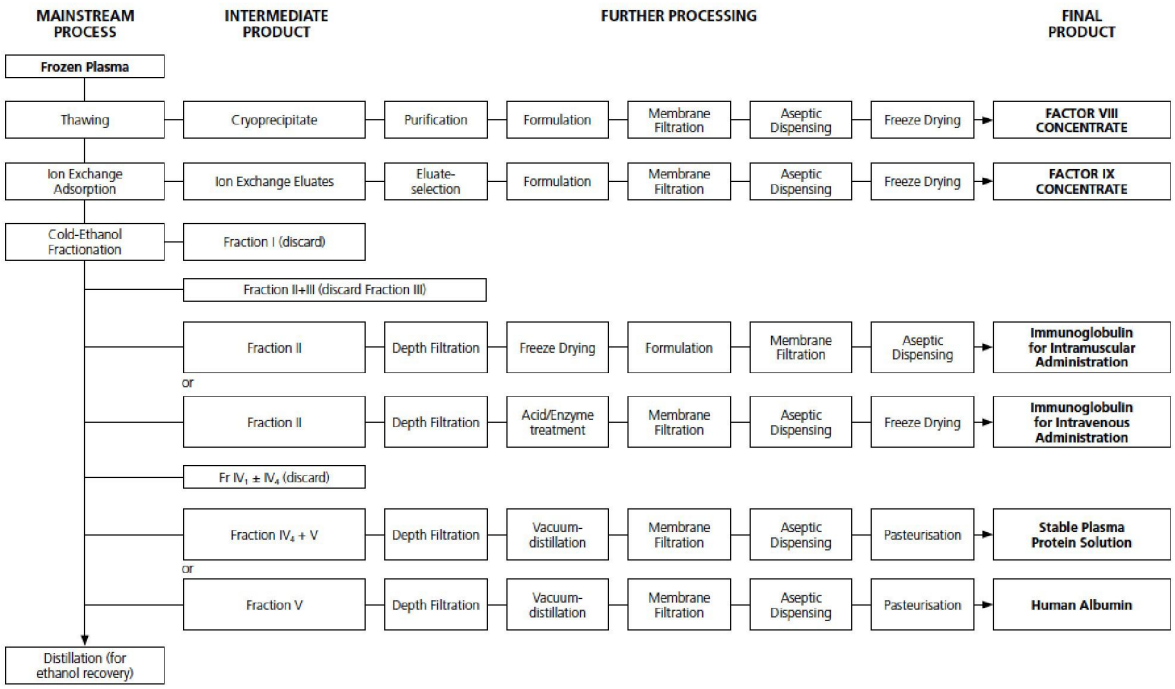
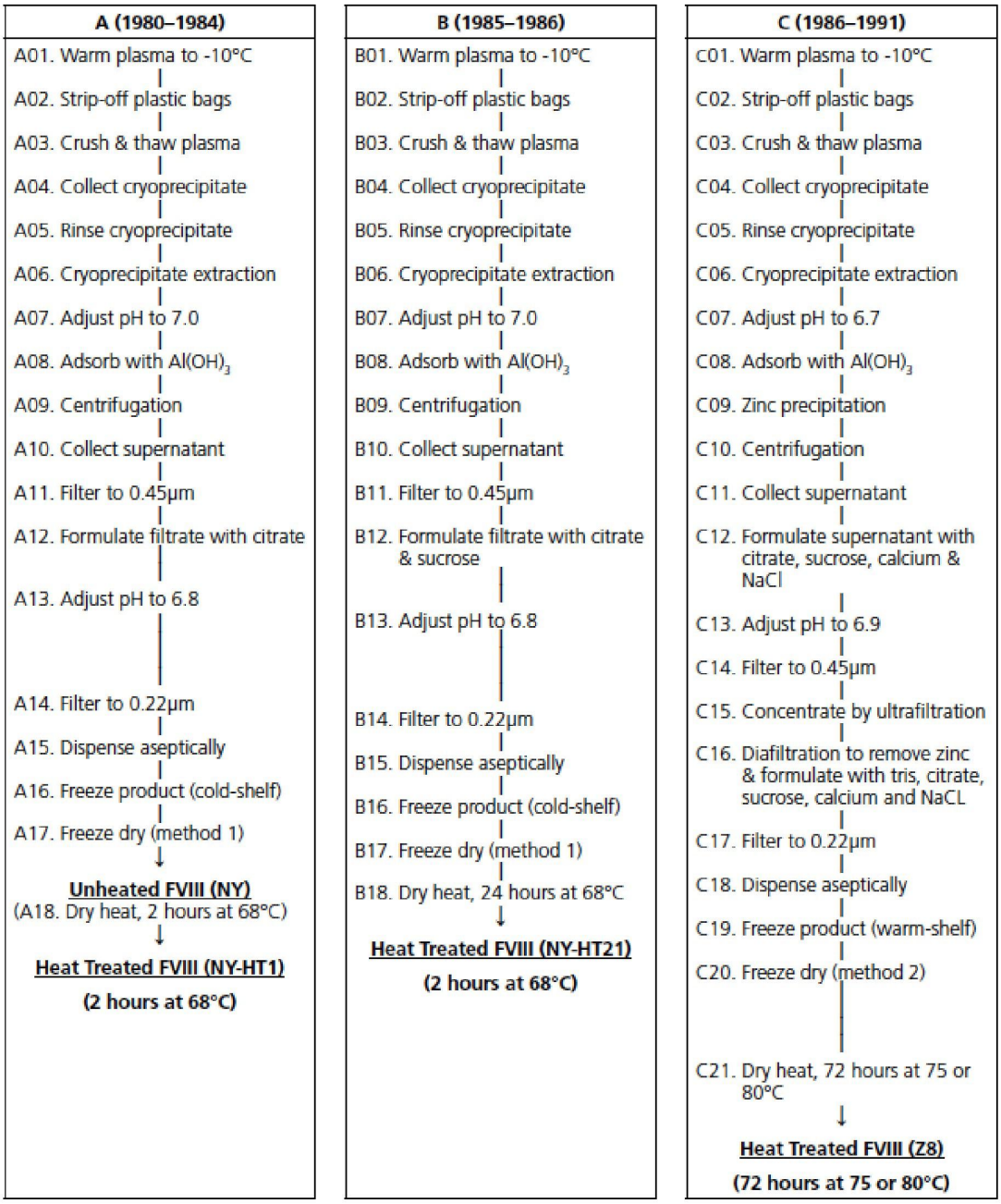


Figure 20.2 from Penrose Report (FVIII Manufacturing Processes 1980-91)



262. I do not recall the detailed difference between PFC FVIII manufacturing processes and those employed by BPL. I do not personally possess details of the BPL processes, although these would have been known to PFC R+D staff, with the exception at the time of its High purity FVIII product (Replenate), which was manufactured under a confidential licence agreement between BPL and a commercial fractionator (Baxter).

263. I am aware that the processes employed at PFC for the production of its NY products in the l970s and early 1980s were broadly similar and equivalent to those of the BPL product 8A, manufactured and supplied during the same period.

264. Concerning differences between the BPL 8Y and PFC Z8 products, my recollection is that Z8 was essentially a simplified version of 8Y, and both products were, in part, the result of collaboration between the two centres and in particular Dr J Smith (PFL) and Dr P Foster (PFC) and their respective co-workers.. The key differences between 8Y and Z8 were described in evidence submitted to the Penrose Inquiry (Ref. Events concerning the safety of blood and blood products with special reference to the treatment of haemophilia A, SNBTS October 2009), within an appendix submitted with this document (Appendix A, The Development of Hepatitis-Safe FVIII Concentrate By the Scottish National Blood Transfusion Service Dr P Foster, Dr R McIntosh, 1999, p10). This appendix concerned concerning evidence provided to the Scottish Executive Investigation of HCV transmission to patients in the 1980s. (PRSE0003480).

265. For ease of reference the relevant sections of this evidence to the Scottish Executive Investigation are reproduced below (PRSE0000131).

8. DIFFERENCES BETWEEN SNBTS (Z8) AND BPL (8Y) PROCESSES

8.1 The Z8 process developed by SNBTS[54] was essentially a simplified version of the 8Y process developed at PFL Oxford[56], which had itself been derived from the earlier ZHT (para 5.4) pasteurisation process being developed by SNBTS [37-39].

8.2 In both the 8Y and Z8 processes Factor VIII was prepared from cryoprecipitate, followed by a precipitation step to remove contaminating proteins. This step was followed by the concentration and formulation of Factor VIII prior to freeze drying and heat

treatment.

8.3 In the 8Y process the first precipitation step used a relatively high concentration of heparin as precipitant[56] whereas in the Z8 process we used zinc combined with a low concentration of heparin57. There were two main reasons for this:
Firstly heparin, at high concentrations, interferes with the Factor VIII assay method used by PFC at that time and additional development of assays would have caused a significant delay.
Secondly, and most importantly, we had discovered that the degree of purification obtained by the 8Y process was not necessary for 80°C 'dry' heat treatment to be achieved. Therefore, by using the zinc/heparin precipitation procedure, with which we already familiar, we were able to avoid a major area of additional work that would have been needed to implement 80°C heat treatment at PFC.

8.4 In the 8Y process, Factor VIII was concentrated by precipitation/centrifugation and the recovered precipitate resuspended then formulated using gel filtration. We had studied the same precipitation procedure during our work on pasteurisation but had found ultrafiltration to be a superior technology for this purpose, both in performance and ease of operation.
We had no experience of gel filtration of Factor VIII but, as formulation could also be achieved using ultrafiltration, our preference for ultrafiltration at the concentration step obviated the need for the extra stage in the process using unfamiliar gel filtration technology.

8.5 We judged, therefore, that rather than begin work on a new product with new process steps, we could introduce an 80°C heat treated product more rapidly by adapting existing SNBTS developments for this purpose.

8.6 In early 1985, there was no readily available equipment that could be purchased immediately for the heat treatment stage. At PFC, equipment which we had designed for the pasteurisation of Albumin at

60°C was able to operate at up to 70°C and this was utilised to enable the heat treatment of Factor VIII at 68°C to be introduced promptly.

8.7 During this period, PFL Oxford developed a specialised heat treatment oven for heating dried products, in conjunction with a manufacture experienced in this technology. PFC collaborated in this development and purchased equivalent ovens from the same manufacturer as soon as they became available.

266. In common with most or all commercial pharmaceutical companies, details of manufacturing processes utilised by commercial fractionators were not available in the public domain and generally were considered commercial proprietary information, with confidentiality being closely guarded. Some superficial information was available in the public domain through marketing literature (eg purity, specific activity, virus removal/inactivation strategy, etc) but contemporaneous details of their manufacturing methods would not have been available. Their methods would have used cryoprecipitation as the initial process step and clearly downstream processing, formulation and finishing steps would have been broadly in the same sequence as those of PFC.

267. However, I am unable to provide an informed comparison with their detailed and proprietary processes.

268. FVIII is widely recognized as a large and highly unstable molecule, susceptible to spontaneous degradation, activation, deactivation and instability. It is particularly vulnerable in vitro to often small changes in its chemical and physical environment, including phase changes (eg frozen to liquid and vica versa) and, in common with many proteins, to physical shear forces. These properties were not well understood at the time, particularly in the 1970s and 1980s. It was for some time considered inconceivable that a protein molecule with these characteristics could be subjected to physical processes or chemical treatments capable of removing or inactivating endogenous viruses, whilst preserving its biological activity. This view changed in 1981 following the announcement from Behrigwerke of its FVIII pasteurisation method.

269. As potential solutions to these challenges began to emerge in the early 1980s, the dominant priority for PFC, the wider SNBTS and the international fractionation community became the need to develop product development strategies demonstrably capable of reducing the risk of virus transmission whilst maintaining and increasing product supply levels to avoid (for Scotland at least) the need to import products from paid US donors. It was the scale of this challenge which led Professor Cash to create the SNBTS FVIII Study Group in 1982.

270. The coagulation factor product development strategies (ie heat treatment of freeze dried product) developed and adopted by SNBTS were robust, reliable and effective, although not without the requirement for periodic intervention, troubleshooting or action to maintain FVIII self sufficiency for all patients in Scotland. Specific problems encountered included:-

i. Lower than expected product yields on scale up of new processes
ii. Periodic problems of extended product solubility times
iii. Progressive increase in demand for FVIII
iv. Maintaining plasma quality in terms of its FVIII content
v. Production capacity, particularly the design of manufacturing processes being constrained by the requirement to operate the Centre within a normal working day. This constraint was the result of employment terms and conditions imposed by the UK NHS Whitley Councils, which proscribed the operation of and payment for multiple shift operation. This was resolved eventually in the early 1990s with the implementation of a staff pay and grading structure specifically for PFC following the granting of a variation order from SHHD. An overlapping shift system was subsequently implemented to increase PFC production capacity
vi. The simultaneous requirement for a major building programme in the early 1990s to address Medicines Inspectors' criticisms concerning storage and necessary upgrading to production areas
vii. Delays in conducting clinical assessment of PFC Factor VIII products and in particular the initial assessment of Z8 arising from Haemophilia

Director concerns over indemnification of patients participating in such trials

68. With reference to any documents which you hold and to the best of your knowledge, please describe the size of the plasma pools used to manufacture Factor VIII at the PFC for the years 1981-1994 inclusive. For each year, please state:

a. The number of donations in the average-sized plasma pool.

b. The range of pool sizes used, expressed in terms of the number of contributing donations.

c. The number of batches of Factor VIII concentrate produced.

You may wish to refer to: PRSE0000912, pages 57-58; SBTS0000238_009, pages 8-9; and SBTS0000041_126, page 1. If you are able to provide figures for the period prior to 1981, please do so - you may wish to refer to: PRSE0003960, page 2, Table 1.

271. I hold no documents or records to inform my answer to the questions posed in this question, other than information contained in the Penrose Inquiry reports and papers submitted to it in evidence. My responses are therefore derived from memory, assumptions and calculations inferred from these sources.

272. PFC did not hold records of the number of donations in individual plasma pools. The unit of measurement used for the manufacturing processes at PFC was total plasma weight/volume entering process and the numbers and unique bar code identification of boxes of plasma from which individual donations could be identified from RTC records, if necessary.

273. Approximate numbers of donations could be calculated from knowledge of the average weight of individual recovered plasma donations (approximately 200-250g). The size of plasma pools was determined by the capacity of the freeze driers used for FVIII manufacture and the amount of plasma supplied to PFC.

274. Between the late 1970s and early 1980s plasma pool sizes varied between 300-550 kg equating to approximately 1200 donations and 2200 donations respectively.

275. During the latter part of the 1980s, production batch sizes progressively increased to accomodate increasing plasma supply to PFC (details in the table below from the information submitted to the Penrose Inquiry - PRSE0001083, p35 - including Northern Ireland) and the consequential requirement to increase production capacity through increased batch size and installation of larger freeze driers and other processing equipment. To the best of my recollection, batch sizes increased to approximately 1000kg, equivalent to approximately 4000 individual donations.

276. Following the introduction of the high purity FVIII concentrate in the early 1990s (known to be free of risk of virus transmission), it became possible to store and combine intermediate FVIII fractions (processed cryoprecipitate), resulting in plasma equivalent batch sizes of circa 1500kg (equivalent to approximately 6000 individual donations).

277. Throughout these periods PFC product batch sizes were determined by the routine supply of plasma and were therefore significantly smaller than those from other fractionators (eg BPL) and substantially smaller than typical batch sizes of commercial fractionators using paid donor plasma.

278. Annual Supply of Plasma to PFC 1975-98:

Year[a]	Amount of Fresh Frozen Plasma (Kg)[b]			Total FFP
	To Cryoprecipitate[c]	To Concentrate[d]	Total	Kg per 10^6 pop.
1975/76	8,497	5,514	14,011	2,677
1976/77	5,471	10,176	15,647	2,990
1977/78	6,216	12,563	18,779	3,588
1978/79	6,752	12,973	19,725	3,780
1979/80	6,477	17,416	23,893	4,593
1980/81	5,498	21,597	27,095	5,213
1981/82	3,341	30,463	33,804	6,522
1982/83	2,963	35,509	38,472	7,446
1983/84	2,520	42,423	44,943	8,717
1984/85	2,767	41,434	44,201	8,593
1985/86	3,633	40,740	44,373	8,653
1986/87	2,677	44,105	46,782	9,142
1987/88	2,915	42,597	45,512	8,913
1988/89	2,341	49,011	51,352	10,099
1989/90	2,480	59,995	62,475	12,286
1990/91	1,720[e]	70,953	72,673	14,292
1991/92	2,110[e]	73,585[f]	75,695	14,886
1992/93	2,030[e]	67,321[f]	69,351	13,443
1993/94	2,290[e]	71,208[f]	73,498	14,454
1994/95	2,390[e]	73,273[f]	75,663	14,850
1995/96	2,390[e]	72,495[f]	74,885	14,666
1996/97	2,320[e]	67,283[f]	69,603	13,632
1997/98[g]	2,560[e]	63,771[f]	66,331	13,019

[a] financial year from 1st April to 31st March

[b] from statistics tabled at meetings of SNBTS Directors; excludes clinical FFP.

[c] assumes one unit of cryoprecipitate is obtained from 0.2 Kg plasma; cryoprecipitate was used to treat haemophilia A and other disorders of haemostasis

[d] after deduction of the weight of plastic, which accounted for 6% of the weight.

[e] mainly for treatment of coagulation disorders other than haemophilia.

[f] inclusive of plasma collected by plasmapheresis.

[g] preparation of fractionated plasma products from UK-plasma was banned in 1998.

These data demonstrate both the magnitude of the year-on-year increase in the quantity of plasma obtained and the increasing emphasis on the preparation of Factor VIII concentrate at the SNBTS Protein Fractionation Centre (PFC) instead of cryoprecipitate at Regional Transfusion Centres. This is illustrated in Table 7 below.

279. See response to question 68 above.

280. I do not hold and cannot recollect any information or data regarding such details. However in the reference cited (SBTS0000238_009, p7), Dr Foster reported that between 74-83 batches of FVIII were produced in the years 1980-84. To the best of my recollection this pattern of production was relatively unchanged, with increased output being achieved through increased batch size rather than increased frequency of processing.

281. Also, and importantly, FVIII batch size was in part determined by the logistics and capacity for downstream processing of the other plasma fractions (albumin, immunoglobulin) derived from the supernatant of the initial FVIII cryoprecipitation step.

69. With reference to your answer to Q.68, please describe the circumstances and decisions which led the PFC to increase the size of the pools used to manufacture Factor VIII concentrate. Please explain, with regard to each occasion when the pool sizes were increased:

a. Who made the decision to increase the size of the pools?

b. What were the circumstances and the rationale for those decisions?

c. What consideration, if any, was given to the likelihood that increasing the size of the pools would increase the risk of infection?

d. In your view, were decisions to increase the size of the pools justified? Please give reasons for your answer.

282. These were primarily the result of operational proposals and considerations and were taken by myself following consultation with senior PFC operational managers (eg Dr Foster, Dr Cuthbertson, Production Managers).. SNBTS Directors and Professor Cash would have been broadly aware of such developments through regular meetings and briefings and also at regular meetings of the FVIII Study Group established in 1982.

283. The circumstances and rationale for these decisions and developments was the progressively increasing demand for coagulation factor products and other products prepared by PFC (albumin and particularly Immunoglobulins), and increased plasma supply to PFC. These developments led to increasing pressure on the manufacturing capacity of PFC and particularly its overall freeze drying capacity. Increasing plasma pool size and, as a result, the associated product batch size increased both the efficiency of the centre and

its capacity. Also, small batch size resulted in a proportionately higher rate of finished product loss from fixed QC sampling regimes. Thus the primary and dominant rationale was to increase and sustain a secure supply of all PFC products for patients in Scotland and minimize or eliminate the need to import commercial products prepared from paid US donors. As a relatively small fractionator, PFC pool sizes were significantly less than those of BPL and other larger European not-for-profit fractionators/blood services and substantially less than those of commercial fractionators. Modest increases in plasma pool size at PFC were implemented in the knowledge that they remained much lower than those used by commercial fractionators,whose products would have required to be imported and used if PFC/SNBTS had not kept pace with clinical demand.

284. It may have been evident that increased pool size increased donor exposure, but the increased risk to patients from use of imported products would have been much greater if PFC had not increased production output through its increases in batch size.

285. Also, the increased batch size of FVIII facilitated the implementation of the SNBTS batch dedication system and prolonged the period in which individual groups of patients were exposed to a single product batch.

286. In simple terms, not to have increased pool size and production capacity would have exposed patients to greater risks.

287. In my view, and taking account of wider national and international context and timescales in which these decisions were necessary, the decisions were wholly essential and justified. See my responses to 69 (a), (b) and (c) above.

70. Please explain, during the time you worked there, the process by which the PFC manufactured Factor IX concentrate, and how this changed over time. Please explain, as far as you are able to:

a. How the process employed at PFC differed from (i) that used at

BPL, and (ii) that used by commercial manufacturers.

b. Any problems which resulted from the manufacturing process at PFC and how these were overcome.

288. Throughout the 1970s, 1980s and early 1990s, the PFC (and its predecessor Blood Products Unit at Edinburgh Royal Infirmary) manufactured a Factor IX complex (Prothrombin Complex Concentrate, DEFIX) containing coagulation factors II, IX and X and used primarily for the treatment of haemophilia B, reversal of anticoagulant therapy and on occasion treatment of haemophilia A patients with inhibitors for whom it was found to have some efficacy.

289. I do not hold and cannot recollect all details of the manufacturing process but I recall the process included the following key steps.

i. Adsorption of factors II, IX and X using DEAE cellulose from the supernatant of the initial cryoprecipitation step
ii. Elution of the FIX complex and freezing pending further processing (referred to as DE Eluates)
iii. Pooling of DE Eluates and formulation
iv. Sterilisation by filtration
v. Dispensing into final containers
vi. Freeze Drying
vii. Inspection, Labeling and Packaging
viii. QC analysis and batch release

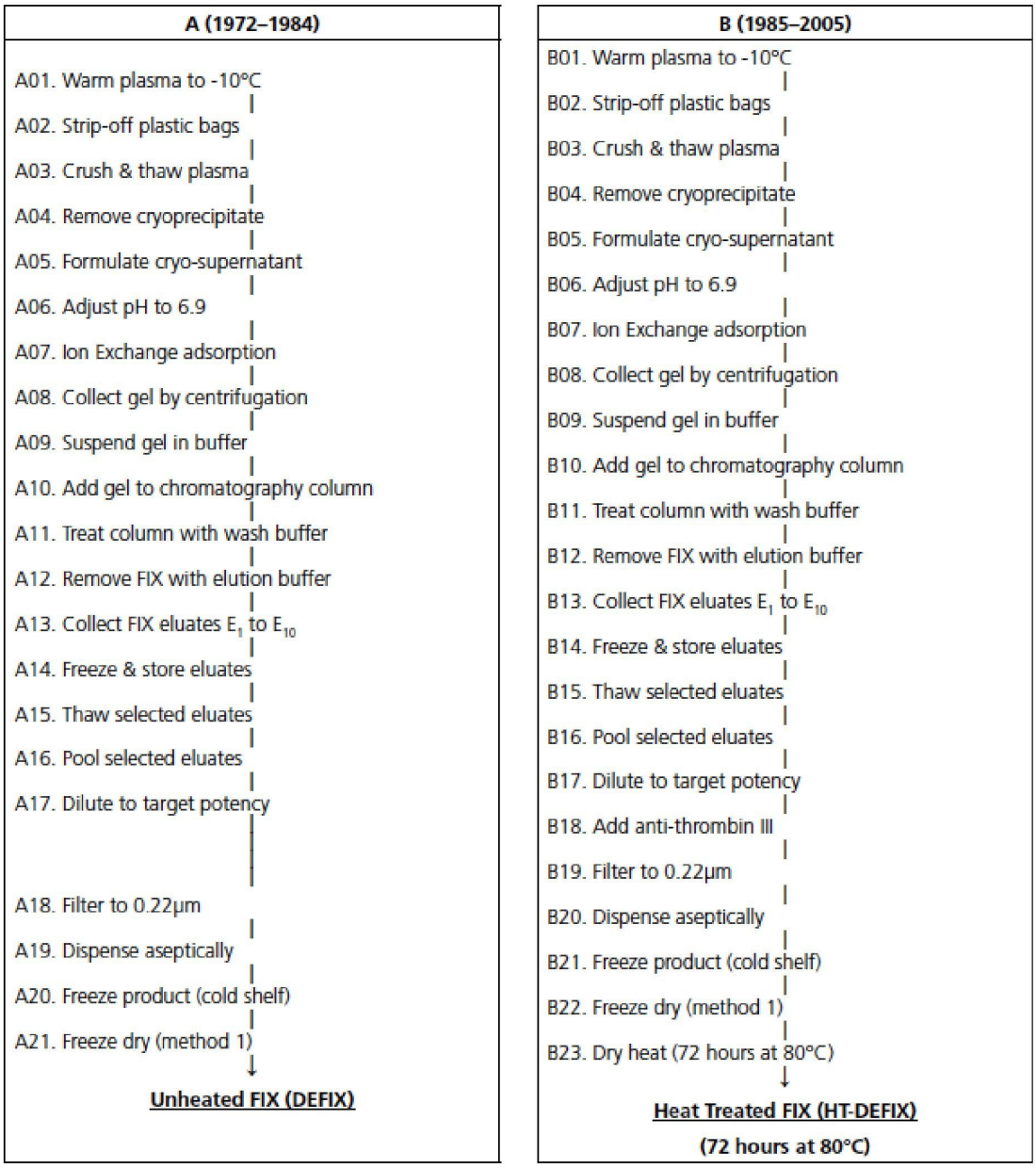
290. In 1985 the product formulation was adjusted to permit heat treatment of the product at 80^0C/72hrs. These were minor modifications and required little redesign of the manufacturing process. These developments were completed in early 1985. However, Professor Cash expressed concern that the product might be more thrombogenic following severe heat treatment, and accordingly the product was subjected to studies in animal models to demonstrate freedom from this effect. The product (HT DEFIX) was released for routine clinical use in October 1985 following its earlier (July 1985) clinical evaluation in patients. In the intervening period, haemophilia directors purchased commercial heat

treated FIX for patient treatment. HT DEFIX continued to be used throughout the 1980s and early 1990s for treatment of Haemophilia B and for the reversal of anticoagulant therapy, until 2005.

291. PFC developed a high purity FIX product in the early 1990s which became available for clinical evaluation in 1993. I cannot recall details of this process but it was based on the method published by colleagues in Lille CRTS, France (Dr T Burnouf).

292. A more detailed description of the processes for the manufacture of DEFIX and HTDEFIX at PFC between 1972 and 2005 was provided to the Penrose Inquiry and included in its final report (Chapter 20 Figure 20.3). It is reproduced below for ease of reference.

293. PFC Factor IX Manufacturing Processes 1972-2005:



294. The DEFIX and HT DEFIX products and processes were virtually identical to those used at BPL for their 9A product. The thrombogenicity studies described above and considered by Professor Cash as a pre-requisite to the clinical use of HT DEFIX were carried out in collaboration with BPL, with comparable and satisfactory outcomes for both HT DEFIX and Heated 9A.

295. I cannot recall details of commercial products available at the time, but my recollection is that few (if any) of the contemporaneous commercial PCC

products were subjected to the severe heat treatment applied by PFC and BPL in 1985.

296. Details of manufacturing processes of commercial fractionators were (and still are) carefully protected by confidentiality, patent or both.

297. I cannot recall any examples of specific problems arising from the PFC FIX manufacturing process, at least none which inhibited product supply or safety.

71. With reference to any documents which you hold and to the best of your knowledge, please describe the size of the plasma pools used to manufacture Factor IX at the PFC for the years 1981-1994 inclusive. For each year, please state:

a. The number of donations in the average-sized plasma pool.

b. The range of pool sizes used, expressed in terms of the number of contributing donations.

c. The number of batches of Factor VIII concentrate produced.

You may wish to refer to: PRSE0000912, pages 57-58; SBTS0000238_009, pages 8-9; and SBTS0000041_126, page 1. If you are able to provide figures for the period prior to 1981, please do so - you may wish to refer to: PRSE0003960, page 2, Table 1.

298. I hold no records and can find no information from previous submissions to the Penrose Inquiry to inform my responses on this topic.

299. To the best of my recollection, the manufacturing logistics of FIX manufacture at PFC differed from FVIII manufacture. Only a proportion of individual plasma pools assembled for FVIII manufacture were subjected to ion exchange (DEAE Cellulose) adsorption following the initial cryoprecipitation step and, because of the lower clinical demand for FIX, not all plasma pools/or the supernatant from cryoprecipitation were subjected to this process step. The intermediate fractions obtained from this step (DEAE Eluates) were stored

frozen for subsequent selection (based on a range of analytical parameters), pooling (one or more eluates) and final processing to DEFIX or HT DEFIX (1985 onward). Since FIX was manufactured from the same plasma pools used for FVIII manufacture the number of donations contributing to FIX batches would be the same as for the associated batch of FVIII.

300. The detailed information requested may be available from detailed analysis of product batch records and internal reports which may still be held by SNBTS, but meantime I am unable to provide, with any confidence, reliable responses to questions 71(a),71(b) and 71(c) in terms of figures requested.

72. With reference to your answer to Q.71 above, please describe the circumstances and decisions which led the PFC to increase the size of the pools used to manufacture Factor IX concentrate. Please explain, with regard to each occasion when the pool sizes were increased:

a. Who made the decision to increase the size of the pools?

b. What were the circumstances and the rationale for those decisions?

c. What consideration, if any, was given to the likelihood that increasing the size of the pools would increase the risk of infection?

d. In your view, were decisions to increase the size of the pools justified? Please give reasons for your answer.

301. The circumstances and decisions leading to increased pool sizes for FIX were a natural consequence of decisions to increase pool sizes for FVII since both products were derived from the same starting plasma pool.

302. See response to 69 (a) - (d) above.

303. With the benefit of current knowledge, it is possible to conclude that product batch size and donor exposure were not significant factors in patient safety following the introduction of severe heat treatment of FIX in 1985, since it is now known through routine patient testing and surveillance undertaken by

Haemophilia Directors that no Haemophilia B patients seroconverted to HIV or displayed evidence of NANBH following the introduction of HT DEFIX in October 1985. Therefore it can be concluded that this process was effective in inactivating both HIV and hepatitis viruses. However, whilst there was some justified optimism concerning the efficacy of 80^0C treatment, there was insufficient evidence at the time to conclude with certainty that this was the case.

73. Please refer to PRSE0000912, a report by Dr G. S. Gabra dated 1983. Pages 57-58 list the sizes of 9 plasma pools produced at the PFC in 1982. As to this:

a. Are these pool sizes an accurate representation of those used at the PFC in 1982? If not, in what way are the pool sizes inaccurate?

b. How many contributing donations were contained in the pools of (i) 320kg, and (ii) 550kg?

Why did the pool sizes vary between 320kg and 550kg? You may wish to refer to your answer to Q.71 and/or Q.72

304. Dr Gabra would have obtained these data from PFC colleagues for inclusion in his report.

305. I have no reason to believe these data are inaccurate and, to the best of my knowledge, were typical of the batch size at the times quoted.

306. As described previously, PFC batch size was expressed and recorded in kg/litres as these were the parameters used for manufacture. Pool size expressed in donations can be estimated by applying a conversion factor of 4-5 donations per kg:-

- 320kg equates to between approximately 1280 and 1600 donations.
- 550kg equates to between approximately 2200 and 2750 donations.

307. Pool sizes were 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.

74. Please refer to SBTS0000238_009, a report produced by the PFC during your employment there. The tables on pages 8-9 list, *inter alia*, the sizes of some plasma pools at the PFC from 1980-1984.

e. As regards Table 3 (SBTS0000238_009, page 8):

i. What is meant by "*Batches In-Process*"?

ii. Please confirm that the column marked "*Plasma (L)*" lists the pool size of each respective batch in litres. If this is not the case, please explain what this column refers to.

iii. Are these pool sizes an accurate representation of the size of the pools generally used at the PFC from 1980-1984? If not, in what way are the pool sizes an inaccurate representation?

iv. How many contributing donations were contained in the pools of

(i) 114 litres, and (ii) 540 litres?

v. Alternately, insofar as the table may refer to the number of vials per batch, how many contributing donations were contained in a batch which produced 255 vials?

vi. Why, in 1982-1983, did the pool sizes used at the PFC vary in size between 283 litres and 540 litres?

vii. Why, during the period 1978-1983 - in which the risk of NANBH was increasingly recognised and the risk of HIV emerged - were pool sizes at the PFC increased from as low as 114 litres to up to 540 litres? Who took decisions to increase the pool sizes at the PFC and why did they do so? Did you agree with these decisions? Please give reasons for your answers.

viii. Why, given that the risk of infection per batch can only be properly ascertained by reference to the number of contributing donations, did the PFC use kilograms, litres and/or vials as a metric of pool size? Were the number of

contributing donations recorded elsewhere. If not, why not?

f. As regards Table 4 (SBTS0000238_009, page 9):

i. Please confirm that the column marked "*Plasma (L)*" lists the pool size of each respective batch in litres. If this is not the case, please explain what this column refers to.

ii. Are these pool sizes an accurate representation of the size of the pools generally used at the PFC from 1980-1984? If not, in what way are these pool sizes an inaccurate representation?

You may wish to refer to your answers to Q.69-73.

308. In response to the above:

i. "Batches in Process" typically referred to production batches which either had not completed QC testing and/or inspection and Quality Assurance (QA) release for use or which had not met one or more QA release parameters and were held for further investigation and/or rework to meet QA release control parameters.

ii. To the best of my knowledge "Plasma L" refers to the plasma pool size used for manufacture of the individual batches listed.

iii. The pool sizes listed were typical of those used in the period 1980-84.

iv. Contributing donations to pools of 114 litres and 540 litres were approximately 450 and 2100 donations respectively.

v. Please also see my response to 73 (b) above.

vi. The stated batch size for NY669 (255 vials) would have equated to a plasma pool size of approximately 255 litres, assuming a process yield of 250IU/litre and a vial content of 250IU. This was typical of the smaller pool size used at the time. Alternatively, the figure of 255 vials may represent a proportion of a larger product batch which did not meet visual inspection criteria.

vii. The pool sizes in 1982/83 varied between 283 and 540 litres, for the reasons described in 73 (c) above.

viii. The period 1978-1983 largely predated my employment at PFC, which began in 1981. Prior to that date the amount of plasma supplied to PFC had begun to accelerate rapidly as a result of the efforts of RTCs to increase plasma collection to meet the aspiration towards self-sufficiency. From 1978, plasma supply had risen from approximately 12,000kg to 42,000kg per annum (excluding plasma supplied by Northern Ireland for processing). Plasma pool sizes were initially very small in comparison with other fractionators, probably reflecting the low volumes of plasma supplied at that time, but these increased progressively to increase PFC production capacity for coagulation factor products as plasma supply increased. It will have been evident to my predecessor (Mr Watt) prior to my arrival that meeting increasing production targets for FVIII supply using batch sizes as low as 114 litres was operationally and economically unsustainable within a facility designed and configured for larger batch sizes and the use of shared processing facilities (eg Sterile dispensing, freeze drying) for its wider product range. It certainly became evident to me in 1981, early in my SNBTS career, that meeting product supply targets required a step change in plasma pool size, although it was equally evident that the pool sizes ultimately envisaged and adopted remained substantially lower than most fractionators – particularly those in the commercial paid donor sector whose batch sizes were upwards of 5,000 litres, and from paid donors. It was the requirement to avoid the need to import products from such sources that drove the PFC development and manufacturing strategies.

309. Decisions concerning product pool sizes will have been taken by the PFC Director and operational managers, with the knowledge of the National Medical Director who would have been aware of the implications concerning donor exposure, but also the imperative to increase PFC manufacturing output.

310. Put simply, had PFC not increased its batch size in the early 1980s, output of FVIII would, at least in the short and medium term, failed to meet increasing product demand for Scottish patients, resulting in the need for

importation of commercial products. This would not have been a good or desirable outcome from the perspective of HTLV-III or NANBH transmission.

311. The parameters used to control PFC manufacturing processes were, inter alia, plasma weight and volume entering the initial process. These parameters were used to monitor eg process performance and yield, and were readily convertible into estimates of donation numbers if required, and accurately to specific donations through the PFC batch manufacturing record and records held by RTCs. I cannot be certain, but I believe latterly plasma consignments included individual donation identifiers, but these were only used for the purpose of retrieving individual donations subject to recall.

312. As regards Table 4 (SBTS0000238_009, page 9):

i. I confirm that, to the best of my knowledge, the column marked "Plasma (L)" lists the pool size of each respective batch in litres.
ii. To the best of my knowledge and recollection the pool sizes quoted in this document are typical of those in use between 1980 and 1984.

Section 9: Introduction of virally inactivated blood products

75. What role, if any, did the PFC have in promoting the development of viral inactivation for factor concentrates (i) from the late 1970s to 1983 and (ii) from 1983 onwards? In particular:

a. Was the need for virally inactivated products raised by you or anyone else at the PFC during these periods? If so, please give details. If not, why not?

b. What collaboration and information-sharing, if any, took place between the PFC and (i) BPL, and (ii) commercial manufacturers?

313. During the 1970s PFC was engaged in research concerning the development of a purified FIX product using Polyethylene Glycol precipitation, which it was believed had the capability of reducing (though not eliminating) hepatitis virus levels in FIX. This product was known as Supernine. I cannot

recall whether this development product was subject to clinical evaluation. However at the time of my joining SNBTS/PFC (1981) my recollection is that this development had been largely discontinued.

314. In May 1981 Dr Foster (PFC) obtained a German publication from Behrigwerke concerning a method for pasteurisation of FVIII. Whilst this process delivered a very low product yield (~8%) this publication demonstrated for the first time, in principle at least, that it was possible to stabilise FVIII to heat treatment. This led to the first experiments at PFC on pasteurisation of FVIII and marked the beginning of the PFC virus inactivation programme for FVIII and the high priority afforded to this topic. Professor Cash would have been made aware of this development and also the observation and inference that the commercial fractionation industry was beginning to apply their substantial resources to this topic and that SNBTS must do likewise, if it was to continue to be the supplier of choice for coagulation factor products in Scotland. It was for this and other reasons that Professor Cash established the SNBTS FVIII Study Group in 1982, drawing upon the PFC R+D resources and wider scientific and medical staff in SNBTS and elsewhere.

315. In 1983 the development of virus inactivation methods for coagulation factor products dominated PFC's and the wider SNBTS research and development programmes, although not to the exclusion of other important developments such as the development and licensing of its Intravenous Immunoglobulin product. By this time these developments required little, if any, promotion since their importance had become self evident to SNBTS, Haemophilia Directors and to SHHD.

316. The senior BPL/PFL scientist leading their development of coagulation factor products was Dr J K Smith. Prior to his appointment at BPL/PFL he was Deputy Director at PFC, where he established a close working relationship with Dr Foster and others. This relationship was maintained throughout his employment atBPL/PFL, and particularly during the critical periods during the 1980s. There was as a result extensive information-sharing and collaboration concerning the development programmes of both organisations, including

regular meetings, conversations and exchanges of experimental data between scientific and other senior staff. These interactions were supported and encouraged by senior SNBTS managers, including myself, my predecessor (Mr Watt) and to the best of my knowledge and recollection, the BPL Director. Details of these were summarised and provided to the Penrose Inquiry (PRSE0002797, pages 29-31), including the formal collaborations concerning joint virus inactivation and thrombogenicity studies. I believe these relationships were instrumental in the successful development of UK coagulation factor products free from the risk of virus transmission.

317. Concerning interaction and collaboration with the international commercial industry, I can recall little if any scientific collaboration or information sharing, since the details of their evolving processes were held in strict commercial confidence. PFC and BPL staff may have been aware in general terms of inactivation strategies being pursued, but technical or scientific details were not publicly accessible.

76. Please describe, in as much detail as you are able to, the research and development of virally inactivated blood products which occurred at the PFC from the late 1970s to 1988. Please refer to PRSE0001885. To the best of your knowledge, please explain:

a. Dr Cash has stated that the PFC pursued viral inactivation "*since before 1982*" (PRSE0001885, page 4) What efforts to inactivate factor concentrates took place at the PFC prior to 1982? Was funding and support was made available to pursue this research?

b. What action did the PFC take when they became aware, in 1981, that

Behringwerke were developing the viral inactivation of factor concentrates (PRSE0001885, page 5)?

c. Throughout 1982-83, the PFC made efforts to pasteurise factor concentrates in solution. Please describe these efforts, how these efforts were funded, and any problems which arose. Please describe the results of (i) the preliminary clinical evaluation and

(ii) the pilot-scale study of scale up (PRSE0001885, page 6).

d. **During 1982-83, the SNBTS were aware of the dry heat method but doubted whether it could be applied to PFC products whilst maintaining yield (PRSE0001885 page 6). Did concerns as to yield preclude the PFC from researching dry heat treatment during this time? What other factors, if any, precluded research into this area? Did the PFC consider changing manufacturing methods in order to pursue the dry heat method? If not, why not?**

e. **You explained to the Penrose Inquiry that "*at least 60 percent of my***

***interest was in making sure that the process [delivered] a product yield that would continue to allow us to supply products in Scotland*" (PRSE0006058, page 29-30). What did you mean by this? Did you consider self sufficiency a higher priority than heat treatment?**

f. **Why was a heat treated Factor IX concentrate not made available at**

the same time as heated Factor VIII? You may wish to refer to PRSE0001885, page 7.

g. **What other problems arose in the development of virally inactivated blood products? How were these problems overcome?**

h. **In your view, could and/or should the PFC have achieved viral inactivation of (i) Factor VIII concentrate and (ii) Factor IX concentrate more quickly than it did? Please give reasons for your answer.**

318. A fairly detailed and comprehensive account of the development of virus inactivated coagulation factor products at PFC/SNBTS was submitted to the Penrose Inquiry (PRSE0002797). I believe this is a true and accurate record and I can add no further detail to this account.

319. Document PRSE0001885 referred to in the question is in fact a report from myself to Dr Cash.

320. As described previously and in the paper (PRSE0002797) submitted to the Penrose Inquiry, PFC research into virus inactivation through heat treatment began in September 1981, immediately following knowledge of the research being carried out by Behringwerke.

321. This initial research was carried out by existing PFC scientists and, to the best of my knowledge, additional funding was neither required nor sought by the then PFC Director, Mr Watt.

322. As stated above, this was the event which triggered the PFC virus inactivation (heat treatment) development programme. First experiments were carried out in September 1981 by Dr A Macleod (Senior Scientist in PFC R+D Department).

323. I can add no further clarity or detail on these developments in addition to that included in the narrative of the Penrose Inquiry Final Report (Chapter 23 paras 39-142) or the information submitted to this Inquiry (PRSE0002797 seee pages 55-57).

324. I was aware of and participated in discussion of the programme of work being led by Dr Foster and his co-workers on this topic, but I was not closely involved in the detailed experimental work being undertaken. My recollection is that the work, which was initially targeted at NANBH, presented significant scientific and technical challenges, not least the requirement to establish a product formulation and stabilisers which were capable of delivering a viable product yield and absence of damage to the FVIII molecule, whilst also delivering 'adequate' levels of virus inactivation – and using a strategy which circumvented the patented method described by Behringwerke.

325. In particular, I recall being concerned (from a QA perspective) that the process envisaged would require a significant redesign and configuration of

PFC manufacturing facilities for removal of high concentrations of carbohydrate stabilisers following the pasteurisation process and product reformulation in a secure processing environment, to eliminate the possibility of post pastuerisation virus contamination of the final product. During the development it had become evident (from virus inactivation studies at PFC using model viruses) that pasteurisation in solution offered higher levels of virus inactivation than heat treatment of freeze dried product. This observation reinforced the SNBTS decision to prioritise pasteurisation as its preferred strategy.

326. This preference was supported by Haemophilia Directors, although they had expressed concerns over neo-antigen formation (ie heat induced damage to the FVIII molecule) leading to generation of antibodies in patients – a complication considered at the time to be potentially more serious clinically than NANBH.

327. The research undertaken led to the successful pilot scale manufacture of a pasteurised FVIII product considered suitable for clinical evaluation in mid 1983.

328. To the best of my knowledge the above activities were carried out within existing PFC/SNBTS resources and did not require, or were not constrained by funding – at least none that I was made aware of by Mr Watt.

329. A clinical evaluation of the above pilot scale batch was undertaken by Dr Ludlam in the Edinburgh Haemophilia Centre in late 1983. My recollection is that whilst clinical parameters, such as half life and recovery, were satisfactory in all three patients, one patient suffered an adverse effect which was considered by Dr Ludlam to be a significant cause for concern. Professor Cash agreed with this assessment.

330. This outcome signalled the need for further development of the process, including a requirement for increased product purification and the exploration of the use of alternative stabilisers and product formulation.

331. Please also see my response at 76 (c) above.

332. I can find no reference or inference in PRSE0001885 to suggest that product yield from dry heat treatment was a key factor in determining the PFC preferred strategy at this time. On the contrary, our concern was the poor yield reported by Behrigwerke from their preliminary work on pateurisation. The PFC preferred strategy was based on a belief at the time that pasteurisation was likely to be a better candidate treatment for NANBH inactivation, notwithstanding the technical and scientific challenges it presented. Also, during the course of the early 1980s, PFC/SNBTS was in regular contact with BPL/PFL and became aware of their work on dry heat treatment. I recall that this led to PFC/SNBTS maintaining its focus on pasteurisation whilst keeping in close contact with BPL/PFL on their study of dry heat treatment (and vica-versa). This arrangement allowed and supported a UK NHS wide approach to the challenge of producing virus inactivated coagulation factor products within the NHS.

333. The dual goals of producing safe coagulation factor products and "self sufficiency" were not considered (at least by myself and others in SNBTS) to be mutually exclusive. Rather they were part of the same strategic goal for SNBTS. As I explained to the Penrose Inquiry, the successful development of a safe but low yielding product available to only a fraction of patients was not a desirable or viable option, since imported product made from US paid donors would be required to supplement PFC supply. Equally, the development of a high yielding product available to all patients, but with a residual risk of disease transmission, was an equally undesirable outcome. Thus the goals of "self sufficiency" and "virus safe" products were an indivisible single objective.

334. FIX is a much smaller molecule than FVIII, and less vulnerable to damage and/or inactivation by heat. Initial studies in 1984/85 revealed that PFC FIX product (DEFIX) could be subjected to severe heat treatment at 80^0C for 72hrs with little requirement for process modification. However heated FIX product prepared for clinical evaluation resulted in elevated QC release parameters, designed to control the known risk of thrombogenicity in patients.

Further studies on product formulation and in particular the addition of small amounts of Anti -Thrombin III available from BPL, resulted in a satisfactory results in QC tests for thrombogenicity. However, Professor Cash advised that the heat treated product should be subjected to additional studies using in-vivo trials in animal models previously developed by SNBTS, prior to clinical evaluation in patients and routine issue. These studies were initiated in early 1985 in collaboration with BPL and, pending their successful completion, SNBTS discontinued its supply of unheated FIX and commercial heated concentrates were purchased as an interim arrangement. SNBTS introduced its heated FIX product (HT DEFIX) in September/October 1985. These actions were supported by Haemophilia Directors and to the best of my recollection, SHHD.

335. Problems encountered by PFC/SNBTS in its development of its "virus safe" product portfolio were, I believe, similar to those of the wider industry, and particularly those of the Not-for-Profit sector. In addition to the scientific and technical challenges described elsewhere, operational problems included:-

- Yield penalties from heat treatment
- Occasional problems of extended solubility time of heat treated products
- Production capacity and plasma supply to meet escalating demand for coagulation factor products and other key products, such as Intravenous Immunoglobulin
- Availability within PFC of pilot scale GMP manufacturing facilities for preparation of material suitable for clinical trial

336. Other problems included:-

- Access to patients from a small population for clinical evaluation of new and modified products - this progressively led to a requirement to conduct clinical trials outwith the UK, particularly as patients in Scotland were treated with recombinant products in line with international developments
- Indemnity for patients recruited by Haemophilia Directors for clinical trials of SNBTS products
- Regulatory developments which progressively increased the number of patients required for product evaluation and licensure

337. Prior to the end of 1984 it was not known that:-

- HTLV-III had already entered the UK/Scottish donor population
- HTLV-III was relatively heat labile and susceptible to inactivation by dry heat treatment.
- Heat treatment would not cause neo-antigen formation in heat treated PFC products.
- Dry heat treatment of PFC FVIII at 68^0C/2hrs was possible without major loss of FVIII activity.

338. It was however known that NANBH virus(es) were unlikely to be inactivated by dry heat treatment and in particular dry heat treatment regimes being trialed by commercial companies eg Hyland whose dry heat treated product continued to transmit NANBH in late 1983 and 1984. As a result PFC continued to progress its preferred strategy of pasteurisation until late October 1984 when HTLV-III infections in recipients of PFC FVIII were reported and critically, the first reports of HTLV-III inactivation by dry heat treatment emerged from US laboratory studies.

339. These events, together with knowledge from PFC studies that its existing FVIII product would tolerate heating at 68^0C for short time periods resulted in a review of its strategy and the decision to immediately adopt dry heat treatment as an interim measure to mitigate any further risk of HTLV-III transmission. I do not believe these actions would have been justified earlier in 1984 and may not have received the support of Haemophilia Directors without more extensive clinical evaluation.

340. Scotland became the first country in the world to make a heat treated FVIII product available for all of its patients in December 1984, approximately two months after receiving the news from Dr Ludlam of patient seroconversions to HTLV-III. It is highly unlikely that these actions could have been taken more quickly or at an earlier date.t

341. My recollection is that pasteurisation of both FVIII and FIX were studied at PFC in parallel with pasteurisation processes to be used for both products. However, it was decided at an early stage in the development of a pasteurised FIX product that such a product should be subjected to in-vivo studies of its thrombogenicity in a suitable animal model prior to clinical evaluation or routine clinical use. These studies were designed, collaborations established and the methods validated during 1984.

342. When PFC learned in late 1984 that HTLV-III could be inactivated by dry heat treatment and that its FIX product (DEFIX) could withstand severe dry heat treatment, the PFC/SNBTS (with the prospect, though not certainty, that such treatment might also reduce NANBH infectivity) decided to focus its efforts and resources on the preparation of a FIX product heated to 80^0C/72hrs in the dried state, with a view to conducting the above thrombogenicity studies in early 1985. Further reformulation of the product was required prior to the start of these studies in March 1985, and its subsequent release for clinical evaluation in July 1985 and issue for routine use in August. Between April and October 1985, Haemophilia Directors purchased supplies of heat treated FIX products from commercial sources pending completion of the SNBTS safety studies.

343. Thus the primary reason for the later supply of HT DEFIX (~9 months later than FVIII) was the need to conduct the above safety studies. The decision to temporarily discontinue the initial strategy of pasteurisation in favour of dry heat treatment strategy for FIX followed the same rationale as for FVIIIFor these reasons together with the requirement for additional thrombogenicity safety studies I do not believe this product could have been introduced at an earlier date.

77. On 21 November 1985, you attended the meeting of the SNBTS Factor VIII Study Group (PRSE0003428). Please explain the nature and extent of your role in the testing of heat-treated Factor IX amongst liver patients. What were the results of these studies?

344. I cannot recall any personal involvement in a study of the use of HT DEFIX in liver patients or indeed whether this study was established. Such a study may have taken place with the involvement of SNBTS medical staff, but I have no knowledge or recollection of this.

78. On 13 May 1985, the PFC received a memorandum from Dr P. L. Yap regarding a study on anti-HTLV-III immunoglobulin (SBTS0000038_095). To the best of your knowledge, please explain:

a. What was the purpose of the study?

b. What was your role and/or the role of the PFC in the study?

c. What were the results?

d. What was the significance of the heat treatment and beta-propiolactone treatment used in the study with regard to the viral inactivation of blood products more generally?

345. I recall only some very informal discussions with SNBTS colleagues and others concerning the possible therapeutic value of a hyperimmune immunoglobulin product prepared from donors who had been infected with HTLV-III. The concept or idea of "passive immunisation" was similar to that recently pursued by blood services concerning the use of convalescent plasma from donors who had recovered from Covid-19 infection as a possible therapeutic option for treatment of Covid-19 patients.

346. I do not recall any serious or formal discussion of this proposed study within SNBTS.

347. My understanding is that the study sought to evaluate the prophylactic value of a hyperimmune immunoglobulin product (anti-HTLV-III antibodies) in preventing the acquisition of HTLV-III in a male gay population known to be at high risk for infection with HTLV-III.To the best of my knowledge and recollection neither I nor PFC had any involvement in this study. I believe my view at the time (and certainly now) would have been that the practical, health and safety and containment issues associated with the large scale preparation of an immunoglobulin product from a plasma pool assembled from HTLV-III

viraemic and infectious donations would have been formidable. In the absence of any evidence that such an approach had some clinical efficacy, my view would have been that such an undertaking was well beyond the resources and facilities at PFC.

348. I do not recall if the study proceeded in any way, but I suspect not.

349. I have no knowledge of the progression or outcome of this or other similar studies elsewhere.

350. My understanding is that the heat treatment and beta-propiolactone treatment of the source plasma to be used for manufacture was designed to inactivate HTLV-III in the plasma pool prior to its conventional fractionation into an immunoglobulin product. As well as heat treatment, beta-propiolactone was also known to be effective for the inactivation of viruses, although in doing so it did cause a degree of modification to some plasma proteins potentially affecting their efficacy (eg Immunoglobulins). This treatment was not suitable for application to coagulation factor products.

79. Please refer to CBLA0002217, a letter from you to Dr Lane dated 15 July 1985. You stated that it was unlikely that heat treated Factor VIII products would "*achieve freedom from NANB*." Please explain why you held this view. More generally, what impact, if any, did scepticism as to the prospects of inactivating NANBH have on the development of heat treated products? In your answer, please discuss (i) the period from the mid 1970s to early 1980s, prior to the onset of HIV/AIDS, and (ii) the period from 1983/94 onwards, following the onset of HIV/AIDS.

351. The inference in this question of "scepticism" on my part (or the wider SNBTS) is not correct. The correct interpretation is that the view expressed in my letter specifically refers to the PFC heat treated FVIII product (NY 68^0C/24hrs) manufactured by PFC at that time and that it was unlikely to be free of the risk of NANBH transmission. It was not an expression of scepticism in more general terms. This view expressed to Dr Lane was informed by

international reports of FVIII products heat treated using similar conditions continuing to transmit NANBH together with results of SNBTS validation studies using model viruses.

352. As described previously in this statement, the SNBTS research and development programme of virus inactivation was initiated in 1981, with the clear objective of eliminating the risk of hepatitis transmission by its coagulation factor products. Events and information received in late 1984 resulted in an urgent refocusing of its efforts from hepatitis to HTLV-III/HIV, in the belief that the latter represented a greater and more serious immediate threat to patients. In late 1985 following the introduction of HIV donation testing and routine issue of its NY 68^0C/24hr product, PFC/SNBTS focused its efforts on elimination of NANBH, but also on the desirability of increasing the margin of product safety with respect to HTLV-III/HIV. This led to the development and introduction of Z8 (80^0C/72hr).

353. Whilst there was no scepticism evident during this period there was a cautious attitude towards over optimistic claims within the industry of product safety, especially with respect to NANBH transmission.

80. In as much detail as you are able to, please explain the PFC's efforts to achieve viral inactivation effective against NANBH as well as HTLV-III/HIV. Please refer to PRSE0004139 and PRSE0006058, pages 39-41. As to these:

a. Dr Cash's notes for a Directors meeting held in March 1986 stated that "*some heat treatment regimes are not effective with regards to non-A, non-B hepatitis*" (PRSE0004139, page 6). When did the PFC first become aware of this? What action, if any, did the PFC take as a result?

b. You explained to the Penrose Inquiry that, in early 1986, the SNBTS believed that "*if you achieve ...non-infectivity for non-A non-B hepatitis, you are almost certainly going to achieve non-infectivity with respect to HIV. So non-A non-B hepatitis was still the gold standard at the time*" (PRSE0006058, page 41). What did

you mean by the "*gold standard*"?

c. **Dr Cash's notes state that the SNBTS had plans to "*validate our heat treatment process with respect to HTLV-III*" (PRSE0004139, page 6, paragraph 2(iii)). Please describe the validation which took place. Why, when NANBH was the "*gold-standard*", did the SNBTS not validate the blood products with respect to NANBH as well as HTLV-III/HIV?**

d. **In your view, could and/or should the PFC have achieved viral inactivation against NANBH sooner than it did? Please give reasons for your answer.**

354. Details of the PFC/SNBTS development programme for virus inactivation of coagulation factor products are described in the paper prepared for and submitted to the Penrose Inquiry (PRSE0002291). I believe this is an accurate and comprehensive account of the key developments and their rationale between 1981 and 2006.

355. Scotland was the first country in the world to make available a Factor VIII product free of the risk of NANBH for all its patients.

356. PFC/SNBTS became aware of these observations during 1985, primarily from literature, conference reports and international colleagues. I cannot recall any precise dates. The reports concerned reported transmissions of NANBH to susceptible patients treated with commercial dry heat treated products with comparable temperature and time profiles to those used by PFC at that time.

357. Although PFC/SNBTS may have hoped that these heat treatment conditions might, at least, reduce product infectivity, these emerging data were not unexpected and PFC had, in any event, continued its research into

methods for more severe heat treatment of its NY product. This work was not successful and in late 1985 PFC proposed a strategy for the development of a higher purity product (Z8) capable of heat treatment at 80^0C/72hrs.

358. This strategy was presented to the annual meeting of SHHD/Haemophilia Directors/Transfusion Directors by Professor Cash in March 1986 (PRSE0004139). Work on this strategy had begun prior to this meeting.

359. I used this expression in my oral evidence to the Penrose Inquiry to simply emphasise that, notwithstanding the introduction of dry heat treatment regimes in the mid 1980s, to address the risk from HTLV-III/HIV, the original objective of the industry to eliminate the risk of NANBH transmission had yet to be realised – at least by dry heat treatment. It was understood at this time that NANBH was more resistant than HTLV-III to dry heat treatment and if one could eliminate transmission of NANBH using this technology it was highly likely, if not certain, that elimination of HTLV-III risk would also be achieved. Perhaps "ultimate objective" is a better expression.

360. I believe the validation study described by Professor Cash was a laboratory "spiking study" in which known quantities of HTLV-III were added to product prior to freeze drying and heat treatment and the residual virus levels quantified after treatment. By 1985/86, HTLV-III could be cultured *in vitro* and quantified. The study envisaged was the result of an offer of collaboration by Professor Robin Weiss, London (UK retrovirus expert) and would have been carried out in a containment facility and involved the addition of HTLV-III to a solution of FVIII, followed by freeze drying and heat treatment. Residual live virus would be quantified after each process step. The results were typically expressed as $\log^{10}$ inactivation. (eg 3 log inactivation = 1000 fold reduction). PFC had been conducting such laboratory studies since 1982 using a range of model viruses (though not direct measurement of HTLV-III) and had undertaken studies on behalf of BPL/PFL.

361. I cannot recall if these studies proceeded in the timescales forecast by Professor Cash, or indeed if the collaboration came to fruition. My recollection (which may be incorrect) is that these studies were ultimately performed in collaboration with the University of Edinburgh and carried out in their containment facilities. I have no record or detailed recollection of the results of the study.

362. Clearly such direct measurement of HTLV-III inactivation only became possible following its discovery, isolation and *in vitro* culture.

363. In contrast, the virus(es) thought to be associated with NANBH had not been identified and isolated in the mid 1980s and would not be so until 1989. Thus any measurement of process efficacy with respect to NANBH could only be estimated indirectly from studies using model viruses (eg Vaccinia, Polio, Herpes). Such studies were already being conducted at PFC. They did not provide direct evidence of process efficacy but rather served as a tool for comparing the relative efficacy of different heat treatment conditions.

364. Direct measurement/validation with respect to NANBH/HCV would not be possible until circa 1990 and until then the only direct validation available for NANBH was clinical trials in susceptible patients using serial measurements of ALT as a surrogate for NANBH infection. These trials were initiated by SNBTS and Haemophilia Directors under the supervision of Dr Ludlam following the introduction of the PFC severely heat treated FVIII product (Z8) in 1987 and successfully demonstrated freedom of NANBH transmission by this product.

365. My personal view is not and cannot be objective. However, I believe

the decisions taken and strategies adopted at the time were reasonable and evidence based. They were progressed within the resources available and with a sense of urgency and purpose. With the benefit of hindsight it may be possible to identify points during the development period where some timescales could have been shortened (eg delays in provision of patient indemnification by SHHD). Time saved in this and perhaps other ways may have provided earlier access to the Z8 product (75-80^{0}C/72hrs) for clinical evaluation and routine use but would probably only have amounted to a few months.

366. However, importantly, the system of batch dedication agreed with Haemophilia Directors had been implemented since 1985 and this included agreement that the introduction of successive new FVIII products into the supply system should only take place when stocks of the previous product were exhausted. Therefore the date of access to the Z8 product was determined by residual stocks of its predecessor product (NY 68^{0}C/24hr), rather than the timing of clinical trials. These stocks were calculated to last until ~April 1987, effectively and prospectively establishing this as the date for the routine supply of Z8. FVIII (Z8) was subsequently shown to be free of the risk of NANBH transmission following the results of the study described above (80 c) in previously untreated and minimally treated patients conducted by Scottish Haemophilia Directors.

81. Please refer to PRSE0002057, pages 26-27. The document describes a meeting between Dr Foster, Dr Cuthbertson, Dr McIntosh and yourself held on 23 December 1985. The meeting recommended the development of an 80°C FVIII in response to concerns that heating at 68°C (the Z8 Programme) was inadequate to inactivate HIV. To the best of your knowledge, please describe the circumstances and purposes of this meeting. What topics were discussed and what conclusions were reached? How quickly did the PFC switch to higher heating conditions

following the realisation that 68 degrees may have been insufficient to kill HIV and NANBH? If you hold a record of this meeting, please say so.

367. My recollection is that there was no formal record prepared of this internal PFC meeting.

368. I do not recall who identified the need for this meeting. It could have been myself or, more likely, Dr Foster, who provided a document for discussion entitled "FVIII Progress and Options". A meeting such as this would not have been unusual at PFC given the importance and priority of the FVIII development programme and, although there is a suggestion that it was convened in response to possible concerns over the efficacy of 68^0C/24hr heat treatment with respect to HIV inactivation, I believe its broader purpose was to review overall progress of the FVIII development programme and consider future options in the light of (i) Obstacles encountered in the development of the NYU high purity FVIII product (ii) Discoveries and observations made by Dr McIntosh offering an alternative and simpler route to a severely heat treated product – albeit of lower purity.

369. The prevailing view from this meeting was that virus safety and product yield were more important than product purity per se, and it was agreed to recommend to Professor Cash and subsequently Haemophilia Directors that resources should be focused on modifications to the existing FVIII product and its heat treatment to 80^0C/72hrs. This became known as the Z8 programme. When this objective had been achieved a return to the high purity NYU process development was envisaged.

370. The Z8 product became available for clinical trial in late 1986 and introduced into routine use via the batch dedication arrangement in April 1987.

82. Please refer to PRSE0003814, a letter from you to Dr Boulton dated 7 July 986. As to this:

a. You stated that the Phase IV (high purity) product was "*more than equivalent to 8Y, it's much better!*" Please explain in what way

the Phase IV product was superior to 8Y. What data did you hold, if any, which supported this proposition?

b. You stated that you intended to supply Phase III product to "*virgins*" in order to demonstrate a product of virucidal equivalence and remove the need to go South. Please explain what you meant by removing "*the need to go South.*" You may wish to refer to PRSE0006074, pages 22-25.

371. I believe this claim of "superiority" referred to the anticipated purity of the Phase IV product (NYU high purity), which was intended to be substantially greater than 8Y. At the time of writing this letter it remained our intention to develop this product as a successor to Z8. In the event, this product was not progressed further to clinical trial or routine use in light of increasing confidence in the safety of severely heat treated FVIII products (8Y and Z8) with respect to NANBH and HIV.

372. At the time of writing this letter it was our intention to have Z8 available for issue in September 1986 and, in particular, for the treatment of previously untreated and minimally treated patients. This product was considered to be equivalent to 8Y in terms of virus safety, thereby removing the requirement for supplies of 8Y for such patients, if so requested by haemophilia directors.

83. Please refer to PRSE0000968, a memo from you to Dr Foster and Dr Cutherbertson dated 22 December 1986. You discuss a modification to the Z8 freeze drying cycle and expressed your unease at the fact the modification could have been introduced many months previously. To the best of your knowledge, please explain why the modification was not introduced earlier? What impact, if any, did the delay in introducing this modification have on the risk of infection to which recipients of Z8 were exposed?

373. I cannot recall the details of this event in 1988 but my concerns are evident from my comments.

374. At the time of this incident PFC had been under considerable supply pressures for FVIII and also reports of extended solubility times of Z8 in routine use. I would surmise that my comments arose from my judgement that these problems may have been mitigated by an earlier and timeous implementation of a relatively minor process modification concerning details of the FVIII freeze drying cycle and proposed by the PFC R+D department. My memo sought to initiate a review of management processes and actions to improve future and detailed technical surveillance of PFC manufacturing processes.

375. I had no concerns at the time or subsequently that the delayed introduction of the modification to the freeze drying cycle would have an impact on product safety, including the risk of infection to patients. All product issued prior to the introduction of the modification fully met the QA/QC release criteria.

Section 10: Development and implementation of screening tests and testing at the PFC

376. SNBTS donor recruitment, selection, deferral policies and donation testing waswere undertaken exclusively by Regional Transfusion Centres (RTCs) under the direction and responsibility of RTC Directors and medical staff and coordinated by the SNBTS National Medical Director. Policy decisions concerning implementation of screening tests for 'new' pathogens such as HIV and HCV were taken by UK Departments of Health, including the designation of a uniform start date throughout the UK and the identification of suitable confirmatory assays. Clearly the UK Blood Services contributed to evaluations of candidate test systems to establish their performance in an operational environment and also played a central role in the development of "testing algorithms" to provide uniform guidance on actions to be taken on screening test results and the development of guidance for management/counselling of donors found to be test positive.

377. The PFC and its staff were not directly involved in or responsible for any of the above activities although I would have been aware of developments through my presence and participation in SNBTS Directors meetings.

378. I was a member of the ACVSB during the period of evaluation and implementation of HCV test systems.

84. Please briefly explain the decisions and actions taken by the SNBTS in relation to the testing of blood donations during the 1970s, 1980s and early 1990s. Please describe what methods of testing were used and when in relation to (i) HBV; (ii) NANBH/HCV; and (iii) HIV. Please describe the efficacy of these methods and any problems which arose.

(i) HBV

379. My understanding is that screening for HBV (HbsAg) began in Scotland in the early 1970s using counter immune electropheresis (CIEP). This was followed by the use of the more sensitive and specific reverse passive haemaglutination (RPHA) method in the mid 1970s and finally the use of radioimmune assay (RIA). I do not know if these screening systems were used uniformly or at the same time throughout Scotland, but my recollection is that on my arrival in SNBTS in 1981 the RIA method was being used in all regions.

(ii) NANBH/HCV

380. HCV antibody testing was introduced in September 1991 in line with instructions received from the UK DOH/SHHD. Prior to that date I was aware that implementation of testing had started in the West of Scotland RTC as part of UK pilot studies and also that all RTCs in Scotland commenced testing before that date to ensure that all blood components supplied on and after the agreed UK wide implementation had been tested. My recollection is that initial implementation was carried out using the so called 2nd generation test system which had much higher sensitivity and specificity than its predecessor. This was later followed by the adoption of 3rd generation test systems and other developments and improvements made by diagnostic companies. SNBTS, I believe, developed its own HCV confirmatory assay using the highly sensitive and specific PCR technology.

381. HCV antibody testing was highly effective in identifying infective donations but was unable to detect donors in the early phase of infection prior to onset of the antibody response (the so called "window phase")

(iii) HIV

382. HIV antibody testing was introduced in October 1985 and found to be effective in identifying infectious donations. However, and like HCV, the test was unable to detect "window phase" donations.

85. In your view, what other measures, if any, could and/or should have been taken by the SNBTS in relation to the testing of blood donors in order to further reduce the risk of infection from blood and blood products? Please give reasons for your answer.

383. I cannot identify any measures or approaches that could have been taken or explored in relation to donor testing beyond those taken – perhaps with the exception of the ever present option of surrogate testing. I am sure the Inquiry will wish to examine this topic in some detail, as did Lord Penrose. My own view of this topic, from the perspective of a fractionator working with large plasma pools, is that whilst surrogate tests may have had some value in removing a proportion of potentially infective individual donations from the blood supply, there would remain a greater proportion undetected which would continue to be present in most, if not all plasma pools.

86. In 1993, you were a member of Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation ("MSBT") when it decided not to recommend routine anti-HBc screening (MHRA0020214). This issue was further discussed by various committees throughout the 1990s and 2000s. Please refer to NHBT0017532 and NHBT0001954_001. To the best of your recollection:

a. What arguments were made for and against the introduction of anti-HBc testing during this time?

b. What was your own view of routine anti-HBc screening? How did

you view change over time, if at all?

c. **In your view, why was this discussed periodically by various committees without a final decision? In your view, was continued reassessment appropriate?**

384. I have no recollection of involvement in consideration of this topic within SNBTS or more widely. I therefore have no useful insight into the topic beyond the issues outlined in the cited papers. Clearly I was present at meetings where the topic was discussed (MSBT, SACTTI) but I would not have been called upon to provide an authoritative (or any) view as a fractionator. My observation today is that this particular issue was perhaps typical of small microbiological risks of transfusion being identified and in which the cost/benefit of practical intervention becomes an important consideration.

385. I think the arguments for and against this intervention are well summarised in the minutes of the MSBT meeting (MHRA0020214).

386. I do not believe I held a particular view at the time or, if I did, I cannot recollect what it might have been. I would have been aware of the topic and certainly held the view that it was of little relevance to plasma product manufacture, since by this time (1993) there was increasing confidence in the efficacy of virus inactivation processes in dealing with any residual risks from potentially imperfect screening assays.

387. I am unable to answer this question. However I can offer the observation that blood service organisations generally had become more acutely aware (especially in light of the tragic events in the 1980s) of residual microbiological risks which had not been resolved. This would naturally lead to periods of prolonged surveillance and interest in residual risk issues – however small.

87. In early 1985, you co-signed an article sent to The Lancet regarding false positive HTLV-III/HIV test results (PRSE0002407). To the best of your recollection:

a. **Why was this article not published?**

b. How long of a delay did you believe would have been caused if HTLV-III/HIV screening were delayed until a test with greater specificity became available?

c. What considerations went into deciding on an acceptable level of false positive test results? Who made these recommendations? Did you agree with these recommendations?

d. What impact, if any, did the issue of false positive test results have on the implementation of HTLV-III/HIV screening at PFC?

e. Has your view of false positives changed since the time of this letter? If so, how has your view changed?

388. My understanding is that the letter was in fact published on 2nd March 1985 (See Penrose final report paras 30.42 – 30.44 and PRSE0004824).

389. At the time the above letter was drafted the development of test kits and their evaluation was at a relatively early stage, but with some rather alarming early estimates of false positivity. My understanding of the purpose of the letter was to highlight some important broad conditions for the implementation of donor screening. As well as false positivity rates the letter highlighted the wider public health imperative for public access to screening to avoid or minimise the possibilityrisk of at risk/concerned members of the public attending donor sessions primarily to obtain their HIV status. In any event, these concerns were acted on throughout 1985, leading to the availability of test kits for evaluation and routine use in October 1985

390. I am unable to judge whether a requirement for improved test specificity was the rate limiting factor in the development and supply of HIV test kits.

391. I was not involved in the development, evaluation or routine use of large scale test systems. However, I was aware of the critical importance of test specificity and sensitivity for donors and patients respectively. From the early (and alarming) data emerging from initial studies, which led to the Lancet letter, it was self evident that such levels of false positivity could have a major impact on individual donors, collective donor confidence in the transfusion service itself

and create a very substantial donor counselling burden for medical staff. Evaluation of the HIV test kits becoming available was undertaken by the Public Health Laboratory Service (PHLS), on behalf of UK Health Departments, with input from Transfusion and Virology experts.

392. Also, the UK Expert Advisory Group on AIDS (EAGA) had been established early in 1985, and I believe that group would have exercised oversight/supervision of on-going evaluations – including establishing test kit performance criteria.

393. Diagnostic test kits used in the US were subject to approval by the US FDA prior to their routine use.

394. PFC did not undertake routine screening of individual donations for HTLV-III/HIV or any other microbiological marker of infectivity. This was undertaken by RTCs prior to plasma release for shipment to PFC. However, my recollection is that PFC subjected product batches and their associated plasma pools to HTLV-III/HIV testing using the test kits approved for use by the DOH. PFC would have had equal concerns to those of RTCs regardingconcerning test specificity, since false positive results obtained for plasma products would have been problematic for product release.

395. Also, PFC implemented heat treatment of FVIII in December 1984 and subsequent routine patient surveillance revealed no further transmissions of HTLV-III from PFC products used after this date. Therefore, the date of implementation of HTLV-III screening (including any delay attributable to the issue of false positive test results) had no material or measurable impact on the virus safety of PFC products supplied during 1985 and beyond. However, it is acknowledged that this outcome could not have been predicted with certainty during 1985. Confidence in that outcome grew following the introduction of HTLV-III testing and retrospective identification (from look back studies) of infective (or potentially infective) donations having entered plasma pools used for the manufacture of heat treated products, which did not subsequently transmit infections to recipient patients. My recollection is that there was a high

degree of confidence in the HIV safety of PFC coagulation factor products by early 1986 when all patients had been transferred to the NY 68^0C.24hr product manufactured from HTLV-III/HIV tested plasma.

396. My view of the consensus opinions expressed in the letter have not changed with time, except to observe that the subsequent development of test technologies with much improved sensitivity and specificity progressively diminished (though not eliminated) issues associated with false positive test results.

88. Please explain when the PFC began to test blood products for HTLV-III/HIV? How was the date for implementation of HTLV-III/HIV testing decided?

397. HTLV-III/HIV testing of PFC plasma products was introduced prospectively for all new product batches following the availability of the approved test kits in 1985. This test was also used retrospectively in the testing of previous batches of products, and in particular those known (from look back) to have contained HTLV-III positive donations in the plasma pools used for their manufacture. The test systems used were those developed for single donation screening and it was anticipated that plasma pooling and purification methods would inevitably lead to antibody dilution and therefore greatly reduced sensitivity of these tests when applied to plasma products and particularly coagulation factor products which contained very low levels generally of immunoglobulin (antibodies).

398. I cannot recall the precise date on which this testing was implemented. However to the best of my recollection no batches of FVIII were found to contain HTLV-III/HIV antibodies using these tests either before or subsequent to the introduction of donation screening, perhaps as a result of the limitations described above.

399. More sensitive methods suitable for the detection of HIV in coagulation factor products (ie PCR) were not developed until 1991

400. In 2008 a vial of FVIII NY 3-009 (the product batch implicated in the transmission of HIV to Edinburgh patients in 1984) was discovered and submitted to NIBSC for testing of markers (antibodies and viral RNA) of HIV infection using their highly sensitive Nucleic Acid Amplification Test methods (NAT). The report from NIBSC indicated detection in this sample of very low levels of HIV markers in some test systems but that the results should be treated with caution.

89. Please describe the implementation of HTLV-III/HIV testing at the PFC. In particular:

a. **What was the process for screening blood products? Was testing conducted on individual donations or pooled samples? What confirmatory testing procedure was used, if any?**
b. **What action was taken, if any, with regard to blood products manufactured prior to the introduction of HTLV-III/HIV testing? Were untested products recalled, quarantined or issued with additional warnings? If so, please give details. If not, why not?**
c. **What action was taken when donations, pools, or blood products produced at the PFC were found to be infected with HTLV-III/HIV? Please set out the steps that were taken, with respect to (i) the recall, quarantine or issue of the infected batch, (ii) passing information to third parties, and (iii) identifying recipients of previous donations from that donor.**
d. **What impact, if any, did the introduction of HTLV-III/HIV testing have on the risk of infection from blood products produced at the PFC?**

401. As described previously, microbiological screening of plasma supplied to PFC was carried out on each individual donation by RTCs prior to dispatch to PFC.

402. Samples from plasma pools (or more precisely pools of cryosupernatant) were subsequently taken by PFC for testing.

403. Vials/bottles from batches of finished product were taken for microbiological testing.

404. I cannot recall whether the testing in (ii) and (iii) above was carried out at PFC or on behalf of PFC by an RTC microbiological testing laboratory.

405. I cannot recall what confirmatory testing procedure was used for plasma pool or finished product samples.

406. In any event I cannot recall any instances of HIV positive pools or product batches which may have required confirmation testing.

407. Products prepared from plasma collected before the introduction of HIV testing remained in the supply chain and, with the exception of small quantities of NY FVIII heated at 68^0C/2hrs being recalled and withdrawn from use in November 1985 as a safety precaution, were neither recalled, quarantined or issued with additional warnings beyond those already included on the product packaging and product information leaflets.

408. At the time of introduction HTLV-III/HIV testing of individual blood/plasma donations, PFC coagulation factor products were subjected to heat treatment at 68^0C/24hrs and distributed via the SNBTS batch dedication system. The batch dedication system required relatively high overall stocks of product for successful operation, which would have been substantially depleted if non-HTLV-III tested plasma and product batches prepared from such plasma had been recalled/destroyed. Indeed, such action would have led to an immediate and medium term supply failure of PFC products, pending the rebuilding of product and plasma stocks from tested plasma. This would have required commercial product purchase, if available, and of products prepared from US paid donor plasma, which similarly had not been tested for HTLV-III/HIV. Accordingly SNBTS and Haemophilia Directors and SHHD took the view that continuity of SNBTS product supply was in the best interests patients.

It was further recognised that during a period of continuous and incremental product improvement by PFC and other manufacturers a policy of withdrawal and/or recall of products prepared prior to the latest improvement was neither in the best interests of patients or sustainable. Such a policy at an international/global level would have led to a collapse of global supply.

409. For these reasons UK regulatory authorities and Health Departments did not advocate or require such action.

410. To the best of my recollection, additional warnings or information was not provided with PFC products or required by regulatory authorities following the use of HTLV-III tested plasma. Haemophilia directors were fully briefed on and supported the above approach to product supply and, I believe, shared the increased confidence in the efficacy of PFC's heat treatment processes with respect to HIV. In particular, they were aware of the continued supply of heat-treated products from non-HTLV-III tested plasma within the batch dedication system after October 1985 which continued, I would estimate, until mid 1986.

411. Following the introduction of HIV antibody testing in October 1985 and its application to testing of PFC products, I cannot recall any instance evidence of HIV antibody being found in PFC products, either before or after its introduction. However, PFC did receive reports arising from SNBTS HIV look-back procedures of HIV antibody positive (and potentially positive) donations supplied to PFC. Six batches of PFC products were identified which were derived from confirmed HIV antibody positive donations, although no such donations were retrospectively identified as having contributed to FVIII Batch 023110090 (NY 3-009), which was originally implicated in the HIV transmission to Edinburgh patients. The actions taken in connection with this batch are contained in a report submitted to the Penrose Inquiry (Actions Surrounding FVIII Batch 023110090 (NY 3-009), 09/06/2010, Dr B Cuthbertson). I believe this report provides an accurate report of the actions taken by PFC/SNBTS in response to this HTLV-III transmission event. The summary conclusions of the report were that:-

- The infectivity of the batch was deduced from epidemiological data available in 1984. It seems likely that this assumption was correct, but it has never been proven.
- The actions taken at the time were well documented and most of the documentation is still available and described in this paper.
- None of the donors whose plasma was used to make batch NY 3-009 was ever identified as being HIV positive
- When the possible infectivity of batch NY 3-009 was discovered, a decision was taken to quarantine any further plasma donations from the same donors, pending investigation. This investigation did not identify an infective donor and the quarantine was ended when heat treatment at 68°C for 24 hours was ready to be introduced, i.e. all of the quarantined units of plasma were used to make product heated at 68°C for 24 hours, a process with published evidence of efficacy in inactivating HIV.

412. In respect of:-

(i) the recall, quarantine and issue of infected (and potentially infected) batches, to the best of my knowledge and recollection all such products will have been recalled following their identification, although many will have already been used by the time of introduction of routine HIV testing. However there was no general recall of product manufactured from non HIV tested plasma.this time.

(ii) passing information to third parties, details of product batches suspected or known to contain antibody positive donations will have been notified to RTCs and/or Haemophilia Centres for follow up actions including, I believe, patient surveillance.

(iii) identifying recipients of previous donations from that donor, the initial identification of individual antibody positive donations and previous donations (look-back) were undertaken by RTCs and reported to PFC.

413. Finally and importantly, PFC/SNBTS has found no evidence of HIV transmission to Haemophilia or other patients treated with PFC plasma products following the introduction of FVIII heat treatment in December 1984,

including from those product batches which were found from look-back studies to have contained HIV antibody positive donations.

414. I am not aware of any reports of HIV transmission attributable to PFC products subsequent to the introduction by PFC of heat treatment in December 1984. Virus inactivation processes applied to plasma products made the most significant contribution to the safety of pooled plasma products and this remains the case to the present day.

415. At the time of introduction of HIV antibody testing of individual donations in October 1985, all PFC plasma products were already subjected to heat treatment processes validated for their ability to inactivate viruses and therefore its introduction had no measurable impact on the incidence of HIV virus transmission by PFC plasma products. However, donation testing was recognised internationally by the fractionation industry and regulatory authorities as an important contributor to product safety – alongside donor recruitment, selection and deferral and pharmaceutical virus removal/inactivation processes. In this respect, donation testing for HIV contributed significantly to achieving progressive increases in the "margin of safety" of plasma products by minimising the virus bioburden in plasma pools. The smaller the concentration of virus in plasma pools, the greater is the assurance of their removal or inactivation during plasma processing.

90. What funding and operational support was the PFC provided with to facilitate the implementation of HTLV-III/HIV testing? What effect, if any, did the level of funding and support have on the date when the PFC was able to commence testing?

416. I do not recall any issues of funding or operational support affecting the date of implementation of HIV testing within PFC/SNBTS. The implementation date for individual donation testing was determined by UK Departments of Health and with a clear instruction that this date would apply to all UK Blood Services. The requirement for testing of pooled plasma products would have been determined by the Medicines Control Agency (MCA). I cannot recall when

this was mandated or the date PFC commenced routine testing of its products on a voluntary basis. The vast bulk of HIV testing (including donor counselling) was undertaken by RTCs, to whom funding was allocated by SHHD via the CSA. I cannot recall if there were any significant costs associated with the testing of PFC products but I believe they would have been included in the overall cost estimates for SNBTS as a whole.

91. The Inquiry understands that after the PFC had completed virus marker testing for HTLV-III/HIV on pooled blood products, samples were sent from each batch to the National Institute for Biological Standards and control ("NIBSC") to complete further testing (PRSE0002556, page 21, section 9.5). As to this, please explain:

a. How the testing procedure differed between PFC and the NIBSC? What tests were used by each organisation?

b. Whether the PFC informed the NIBSC of the results of their own testing prior to them undertaking their own testing.

c. What steps were taken when a sample was found positive by the NIBSC?

d. Whether the test results obtained by the NIBSC ever differed from those found by the PFC? If this occurred, please describe the circumstances and the action taken following the discovery of the discrepant results in as much detail as you are able to.

e. How quickly were the test results from the NIBSC returned? What steps, if any, were taken to either quarantine or supply the products pending the NIBSC test results?

417. I cannot recall details of the assay methods used by PFC and NIBSC or any significant differences in sensitivity or specificity.

418. The testing of PFC product samples was a voluntary arrangement between NIBSC and PFC and included assays for FVIII potency and other parameters as well as for markers of virus contamination.

419. These arrangements were discontinued in 1985 at the request of NIBSC but were re-established in January 1987 for all PFC products.

420. I cannot be sure of the specific date but my recollection is that in the late 1980s routine testing for anti-HIV and HBsAg in plasma pool samples was undertaken by both PFC and NIBSC. This was extended to include anti-HCV testing in the early 1990s.

421. At this time the testing of plasma pools and products by NIBSC became mandatory.

422. I believe PFC was required to submit details of its test methods to NIBSC together with the results of its own testing (ie positive or negative). To the best of my knowledge NIBSC would not test samples unless already found to be negative by the manufacturer.

423. I cannot recall any instances of discrepant results between PFC and NIBSC (ie PFC negative and NIBSC positive). They may have occurred but would have been was a rare occurrence. Such a discrepancy would have been followed by further laboratory investigation. The product batch would not have been authorised for use until both NIBSC and PFC results were negative.

424. I cannot recall such details with any certainty but they will be available from individual batch records held by SNBTS. My guess is that the turnaround time was 2-4 weeks. Product would not have been authorised for issue by PFC until these results were available.

92. On 18 July 1986, you attended a meeting of the AIDS Scientific and Technical Working Group at which an evaluation on several ELISA kits conducted by Dr Garrett was discussed (CBLA0002313, page 3). The Inquiry understands that a Government-led evaluation of HTLV-III/HIV test kits took place from May-October 1985 (LCAN0000001_002, page 53). To the best of your recollection, please explain how often evaluations of HIV/HTLV-III test kits took place outside of the

Government-led evaluation. Were new generation kits automatically evaluated before their implementation? What impact, if any, did these evaluations have on the tests used by the PFC?

425. The evaluations led by Dr Garrett described in CBLA0002313 concern the development of assay systems and standards suitable for testing of plasma products. Typically these required adaptation and modification of test systems originally designed and validated for individual blood donation testing and involved collaboration between NIBSC and plasma product manufacturers active in the UK market. The "AIDS Scientific and Technical Working Group" was established by NIBSC to promote collaboration on the development, evaluation and validation of test methods for use in the blood transfusion services and UK plasma fractionation centres.

426. Concerning the evaluation of HIV test kits for routine donation screening, this process was led by the PHLS on behalf of UK Departments of Health. Despite this insistence on a central Government–led evaluation, my recollection is that the UK Blood Services contributed to this process with operational field trials of candidate test kits in a routine high throughput environment. In particular I recall that in Scotland the West of Scotland RTC developed expertise in this area and contributed significantly in 1985 to the initial introduction of donor HIV screening.

427. The continued development and implementation of new generation test kits was, as far as I recall, always preceded by multicentre evaluation and field trials prior to their approval for use. However the evolution of suitable systems for plasma product testing led by NIBSC proceeded relatively independently from those developed for large scale donor screening.

93. Did the PFC outsource any confirmatory testing for pooled blood products other than to the NIBSC? If yes, please please state the organisation, the testing procedure used and the steps were taken when a sample was found positive.

428. NIBSC was the UK official national reference and control laboratory for biological pharmaceuticals. It was the authoritative reference centre for PFC's quality control test procedures.

429. I cannot recall whether PFC had any other formal relationship with external organisations for confirmatory testing or other purpose. SNBTS maintained a formal relationship with eg the Scottish Centre for Infection and Environmental Health (SCIEH) and Edinburgh University for the purpose of acting as microbiological reference centres for confirmatory testing of screen positive/indeterminate individual donations but not, I believe, for plasma products.

94. Please describe the implementation of anti-HCV testing at the PFC. In particular:

a. What was the process for screening blood products? Was testing conducted on individual donations or pooled samples? What confirmatory testing procedure was used, if any?

b. What action was taken, if any, with regard to blood products manufactured prior to the introduction of anti-HCV testing? Were untested products recalled, quarantined or issued with additional warnings? If so, please give details. If not, why not?

c. What action was taken when donations, pools, or blood products produced at the PFC were found to be infected with anti-HCV? Please set out the steps that were taken, with respect to (i) the recall, quarantine or issue of the infected batch, (ii) passing information to third parties, and (iii) identifying recipients of previous donations from that donor.

d. What impact, if any, did the introduction of anti-HCV testing have on the risk of infection from blood products produced at the PFC?

430. As described previously (eg question 87), microbiological screening of plasma supplied to PFC was carried out on each individual donation by RTCs prior to dispatch to PFC.

431. Samples from plasma pools (or more precisely pools of cryosupernatant) were subsequently taken by PFC for testing.

432. Vials/bottles from batches of finished product were taken for microbiological testing.

433. I cannot recall whether the testing in (para 430) and (para 431) above was carried out at PFC or on behalf of PFC by an RTC microbiological testing laboratory.

434. I cannot recall what confirmatory testing procedure was used for plasma pool or finished product samples.

435. In any event I cannot recall any instances of HCV positive pools or product batches which may have required confirmation testing - but they may have occurred rarely.

436. Products made from untested plasma were not recalled, quarantined or issued with additional warnings.

437. Following the introduction of anti-HCV testing in 1991, UK and EU regulations permitted the continued use and supply of plasma products prepared from non-HCV tested plasma until 1995. Small quantities of specialist products (eg hyperimmune IgG products) may have been recalled after this date.

438. At the time of introduction of anti-HCV testing most, if not all plasma products used in the UK were considered to be safe with respect to virus transmission as a result of universal adoption of effective virus inactivation processes, including severe heat treatment used in the UK by BPL and PFC. This had been demonstrated in clinical trials of NHS FVIII and FIX products.

439. I am aware of no evidence of virus transmission (HB,HCV,HIV) by its coagulation factor products following the introduction of severely heat treated FVIII and FIX in 1987 and 1985 respectively.

440. Individual donations found to be HCV antibody positive during RTC screening were not sent to PFC for processing.

441. I cannot recall when the routine testing of plasma pools for HCV antibody was introduced by the MCA/NIBSC as a mandatory requirement, but I believe it was approximately 1993/94, when most manufacturers' plasma pools will have contained only HCV tested donations. Similarly, I cannot recall when the routine testing of finished products for anti-HCV became mandatory, but I believe it would have been coincident with plasma pool testing.

442. Plasma pools or finished product found to be reactive for HCV antibodies would have been rejected and not entered into further manufacture or the product supply chain. Detailed standard operating procedures existed to guide the actions necessary in such circumstances, but I cannot recall their detailed content. In any event I cannot recall specific instances of such events although they may have occurred – though rarely.

443. The identification of recipients of previous donations from donors found to be HCV positive was undertaken by RTCs as part of the SNBTS look-back study. The PFC had little or no involvement in this important study.

444. The PFC complied with all the requirements prescribed by UK Departments of Health, UK and EU Regulatory Agencies and NIBSC following the introduction of HCV testing.

445. The introduction of HCV antibody testing for individual blood donations had a profound and positive effect on the safety of the blood supply in all countries.

446. However by the time of introduction of HCV testing by SNBTS, PFC products were already considered to be free of the risk of HCV transmission, following the introduction of severe heat treatment between 1985 and 1987, including products manufactured from non-HCV tested plasma pools.

447. Therefore, the measurable impact of HCV testing on the risk of infection from blood products produced at the PFC was minimal. However, its introduction served to increase their "margin of safety" with respect to HCV transmission.

95. What funding and operational support was the PFC provided with to facilitate the implementation of anti-HCV testing? What effect, if any, did the level of funding and support have on the date when the PFC was able to commence testing? You may wish to refer to PRSE0006068, page 134-135.

448. I do not recall funding or support for HCV testing carried out by SNBTS/PFC being a rate determining factor for its routine introduction. My personal views offered to the Penrose Inquiry concerning perceived delays to the UK wide implementation (PRSE0006068, page 134-135) remain unchanged.

449. In brief summary, I held a view in mid 1990 that (1) there was now available a test system capable of preventing approximately 60% of cases of post transfusion NANBH, (2) that FDA licensure of the test was imminent, (3) that confirmatory testing systems were at an advanced stage of development and (4) other countries had already introduced testing and were apparently managing the outstanding issues with the test.

450. My feeling was that there was by mid 1990 at least, a sound basis to recommend in principle that HCV testing should be introduced in the UK and that further delays in making this recommendation (for what seemed to me to be an increasingly inevitable outcome) could in the future be seen as excessively cautious.

451. There were further subsequent delays to UK wide implementation of testing as a result of the late abandonment of the 1st generation test, in favour of its successor 2nd generation test, and the insistence by the Departments of Health that testing should commence on a single date. This resulted in successive delays to implementation, from the originally proposed date of April 1991 to July and finally September which, it was felt, was determined by the readiness (financial, administrative and operational) of all UK Blood Services.

452. In any event, and from a PFC perspective, these delays did not to the best of my knowledge have a detrimental effect on the safety of PFC products. I am aware of no evidence of HCV transmission by PFC or BPL products following the introduction of severe heat treatment of coagulation factor products (Z8 and 8Y) between 1985-87.

96. During your time at the PFC, what differences, if any, did you perceive between the approach of the English Blood Transfusion Service and the SNBTS to the introduction of anti-HCV screening within the RTCs? You may wish to refer to PRSE0000145.

453. As mentioned previously I was not closely involved in scientific, technical or policy decisions concerning the introduction of HCV testing by SNBTS RTCs, or did I consider myselfconsidered to have any particular expertise or expert knowledge in this area. My personal involvement was primarily through my membership of ACVSB and presence at SNBTS senior management meetings, and occasionally UK meetings where the topic was discussed. I therefore had a good working knowledge of the policy and scientific issues associated with the introduction of HCV testing, but my personal views would not have significantly influenced the decisions and considerations of those leading its UK introduction.

454. I am not sure I understand what is meant by "...the *approach* of the English Blood Transfusion Service and the SNBTS to the introduction..." but my recollection of impressions I gained at the time was that the UK Blood

Services welcomed the prospect of a test capable of reducing or eliminating the risk of HCV transmission by transfusion, and that their views concerning the issues to be addressed prior to routine implementation were well aligned. These included test sensitivity and specificity, essential requirement for robust confirmatory assay, Transfusion Service led field trials of candidate tests, donor counselling implications, testing algorithms etc. Also, initially at least, there was a clear and shared understanding of the benefits of a UK wide start date.

455. Approaches to these issues were discussed and actions coordinated between the UK services at the recently formed Advisory Committee on Transfusion Transmitted Diseases (ACTTD). This meeting was chaired by Dr Gunson and membership included senior managers from SNBTS (Professor Cash and Dr Mitchell).

456. There were concerns expressed within SNBTS (particularly during 1991) regarding on-going postponement of the UK start date, when SNBTS itself was funded and operationally ready to proceed. SNBTS considered the option of seeking authority from SHHD to proceed ahead of the agreed UK start date, but was rejected.

457. My views presented both in writing and orally to the Penrose Inquiry concerning the introduction of HCV testing in Scotland remain unchanged.

458. In brief summary I believe there were a number of shortcomings in the overall UK management process ultimately leading to a relatively late implementation of HCV testing in Scotland and throughout the UK. These included:

i. Unnecessary secrecy and confidentiality associated with the considerations of ACVSB and other 'behind the scenes' discussions.

ii. Absent or confused processes for communication of ACVSB decisions to operational managers.

iii. A late recommendation in principle (in my view) by ACVSB and DOH for the introduction of HCV testing. This appeared to be driven primarily by scientific rigour rather than urgent public health considerations.

iv. The apparent absence of a clear plan, timescale, strategy or policy guidance (from either DOH or SHHD) for the introduction of testing, following the decision in principle by ACVSB in July 1990 to introduce testing.

v. The progressive (and largely unexplained) deferral of the UK start date from April to July to September 1991, believed to have been caused at least in part by administrative and funding issues between the English services and DOH, rather than operational readiness.

vi. With hindsight, and given its readiness (both operational and financial) to introduce testing in early 1991, the failure of SNBTS to robustly argue a case for earlier introduction of testing in Scotland with SHHD/Scottish Ministers including the public health consequences of delays. Equally an SHHD apparent reluctance to consider such an option preferring instead to be guided exclusively by timescales determined by DOH.

97. You explained to the Penrose Inquiry that, in 1989, the ACVSB were cautious about introducing anti-HCV screening at RTCs in the absence of a confirmatory test. You noted that Dr Gunson was enthusiastic, while colleagues such as Dr Tedder and Dr Zuckerman took a more cautious approach (PRSE0006068, page 52, and NHBT0000043_039). In your view, should anti-HCV screening have been introduced earlier or was it justified to wait until a confirmatory test became available? Please give reasons for your answer.

459. I should emphasise that in making the observations below they are made from the perspective of a well informed SNBTS manager, but with no authoritative expertise, operational experience or detailed scientific/medical understanding of the issues associated with large scale microbiological screening of blood donations and associated duties of care to donors.

460. In 1989 it was not known if the emerging candidate test systems were or would become suitable for routine donor screening. Although on-going studies internationally were providing useful and encouraging data, they also highlighted potential problems of specificity and sensitivity in large scale trials,

which would require robust confirmatory test systems prior to implementation. However the availability of a confirmatory assay was not the only criteria or condition set by the DOH for this new development. The DOH (and ACVSB) had already agreed that prior to routine introduction in the UK, a suitable test system must include satisfactory sensitivity and specificity characteristics, a confirmatory assay, licensure by the US FDA, acceptable performance in UK field trials in RTCs and a cost/benefit analysis – although my recollection is that cost/benefit analysis diminished in importance in future considerations.

461. These pre-conditions of test implementation had been met by mid 1990 or the prospect of them being met was imminent. However, there remained significant concerns by some experts concerning the suitability and efficacy of available confirmatory tests. Also there was emerging data concerning the efficacy of the tests in detecting infectious donations. This was reported as being approximately 60%. It was further known and reported around this time that Blood Services in a number of countries had (or were about to) already implemented HCV testing – including Japan, Australia, France, Finland, the US, Austria, Netherlands (Amsterdam), Canada, Germany and Belgium.

462. It was reasonable to assume that these countries had taken these decisions notwithstanding the shortcomings of the available tests.

463. The above observations led me to develop the personal view that it would have been appropriate to at least provide a clear recommendation to ministers of the need for similar and urgent actions by the UK Blood Services. Both Dr Gunson and I expressed this view to the ACVSB in April 1990. This view was not recorded in the minute of this meeting.

464. On 21 January 1991, Ministers approved the UK-wide introduction of HCV testing on a single date to be agreed by the UK blood services. This date was subsequently agreed as July 1st 1991. The intervening period was considered necessary to resolve the remaining issues concerning confirmatory testing and to agree a UK-wide policy for counselling of donors. I believe this implementation was achievable had it not been decided to conduct further

extensive evaluation of the second generation tests which were becoming available in early 1991. This led to further delays to the commencement of testing and a new target date of September 1st 1991, using second generation tests.

465. In conclusion, the extended timescale for UK wide introduction of HCV testing was not determined solely by the issue of confirmatory testing, but also by the need for donor counselling policies and procedures, extended test kit evaluations and the late abandonment of the first generation tests in favour of the successor second generation tests. The SNBTS commenced HCV testing of all donations in its largest centre in May 1991 as part of an extended UK evaluation, but my understanding is that all other centres were also funded and ready to test on or before this date.

466. Finally, and as previously stated, I believe any delays or perceived delays in the introduction of HCV testing had little, if any, impact on the safety of plasma products prepared in the UK. Indeed, prior to February 1991 there was on-going consideration (eg by NIBSC) of the potential implications of anti-HCV testing on the safety of plasma products derived exclusively from anti-HCV negative donations, particularly in light of the views of some experts who had suggested that the presence of HCV antibody donations in plasma pools might actually contribute to plasma product safety through its neutralising effect on any HCV present. This effect was considered important in the case for anti-HBs in plasma pools. The US had, at that time concluded that anti-HCV positive plasma donations should continue to be included in plasma pools for fractionation.

467. My understanding now is that there is an acknowledgement within the UK blood services that the introduction of HCV testing could and should have been undertaken sooner. I cannot judge when this might have been possible. My views on this subject which were provided to the Penrose Inquiry remain unchanged.

98. During the time you worked at the PFC, what was your view of surrogate testing as a potential method of donor screening to reduce the risk of (i) HTLV-III/HIV, and (ii) NANBH/HCV. How has your opinion changed over time? Please answer with reference to specific surrogate test methods.

468. Regarding (i) HTLV-III/HIV, I cannot recall any consideration within SNBTS, or more widely, of possible candidate surrogate tests for this virus, either in the context of blood components or pooled plasma products My recollection is that immediately following the international consensus that the causative agent of AIDS was most likely to be a virus, successful efforts to identify the virus and subsequently develop tests suitable for diagnosis and blood donor screening followed rapidly, leading to the development of specific and sensitive tests in 1985. This relatively short period (~2-3 years) would not have provided sufficient time for the identification of candidate surrogate tests, their evaluation and validation, and establishing policies for donor care and counselling for those found positive. In any event, I am not aware of any candidate surrogate tests which were considered potentially useful.

469. Regarding (ii) NANBH/HCV, I can recall much discussion of ALT and anti HBc testing within SNBTS, UK wide and internationally throughout the 1980s. These discussions focused primarily on the efficacy of surrogate tests to reduce post transfusion hepatitis from blood components, rather than the safety of pooled plasma products. My view at the time and subsequently was that ALT and or anti-HBc testing were unlikely to have a significant impact on plasma product safety, given their low anticipated detection rate (the majority of NANBH infectious donations would not be excluded) and the prevalence of NANBH in the general and donor population. A small number of countries introduced surrogate testing for NANBH including Germany, Italy, the US, Luxembourg, France, Switzerland and Malta. I am not aware of any evidence that plasma products made from ALT/anti-HBc tested donations in these countries were safer with respect to NANBH than those from untested donations.

470. Thus, whilst the topic of surrogate testing received much attention and consideration by colleagues in RTCs both in the UK and Internationally, the focus of PFC (and most other fractionators) remained on the development of pharmaceutical virus inactivation procedures.

99. On 3 March 1987, you attended a meeting of SNBTS Directors at which it was agreed: "to recommend to the SHHD that surrogate testing for NANB should be implemented with effect from 1 April 1988 as a national development requiring strictly new funding. Each Director should let Dr Cash know what funds would be required in his/her region, assuming that both core testing and ALT would be undertaken in the Transfusion Centres" (PRSE0004163, page 6). Did you agree with this recommendation? What response did this recommendation receive from SHHD? Please provide as much detail as you are able to.

471. I do not recollect the details of this meeting or the discussions which led to the recommendation to SHHD, although clearly I was present at the meeting and did not raise any objections to the proposal. PFC was not closely involved in the detailed consideration of this topic, which was primarily driven by RTC interest in the continued NANBH transmission by blood component transfusions. By this time (March 1987) the PFC supply of severe heat treated FVIII was imminent, with the prospect of eliminating NANBH transmission by coagulation factor products – with or without surrogate testing of individual donations. I believe my view at that time would have been that the introduction of surrogate testing would have few, if any, operational implications for PFC and I would have been content to support the expert views of RTC colleagues.

472. I cannot recall being involved in the follow up to this recommendation, although it is evident from subsequent events that SHHD did not endorse or support the SNBTS proposals. Details of subsequent discussions between SNBTS and SHHD concerning this and associated events have been narrated in the Penrose Inquiry Final Report, Chapter 27.

100. On 15 June 1987, you co-signed a letter to The Lancet, entitled "Testing blood donors for Non-A, Non-B Hepatitis: Irrational, perhaps, but inescapable" (SBTS0000177_106). One argument for surrogate testing was to reduce the level of infectivity in products produced from pooled plasma fractions (SBTS0000177_106, page 2). Given the size of the pools used to manufacture blood products, as well as the imprecise nature of ALT and anti-HBc testing, to what extent would such a surrogate testing programme have reduced infectivity?

473. This letter to the Lancet was written in an attempt to provoke action within the UK and gain support for the introduction of surrogate testing based on wider arguments than those concerning clinical risks of NANBH transmission by blood components, which had already been (unsuccessfully) deployed. It was acknowledged in the letter that surrogate testing was a controversial subject both in the UK and internationally and that there was no clear scientific basis for its introduction. Deployment of the specific argument that surrogate testing might increase, albeit marginally, the safety of pooled plasma products was not based on a scientific consensus that this was the case, but rather on concerns that the introduction of surrogate testing in eg US, France and Germany could lead to perceptions amongst consumers that plasma products prepared from ALT/anti-HBC tested plasma donations (particularly those from US commercial companies) and marketed as such, may result in the preferred use of these products over NHS products. This and the other considerations cited in the letter were the reason the letter was entitled "Irrational, perhaps, but inescapable".

474. As correctly inferred in the above question, there was no scientific evidence to support a view that surrogate testing would reduce the infectivity of plasma products, given the poor specificity and sensitivity of such tests, plasma pool size and the estimated prevalence of NANBH in the general and donor population. To the best of my knowledge such benefits had not been or were not subsequently demonstrated.

475. The PFC view at the time of publication of the letter was that the introduction of surrogate testing would add little benefit to the safety of coagulation factor products, which were now being subjected to effective virus inactivation processes. However, I did share the concerns over product liability issues and the potential impact of marketing strategies by US commercial fractionators. On this basis I was content to support the views expressed in the letter and to be a co-signator.

101. A report prepared by Dr H. H. Gunson in August 1987 set out the conclusions of a Council of Europe Working Group established to consider the introduction of routine surrogate testing for NANBH (NHBT0008816_002). The Working Group concluded it could not make a recommendation as to the introduction of surrogate testing in light of the following:

a. The use of surrogate tests as a public health measure to reduce the incidence of NANBH remained controversial
b. There was no guarantee that there would be a significant reduction of NANBH
c. The introduction of surrogate testing could lead to a severe depletion of blood donors which could compromise the blood supply in some countries.
d. If surrogate testing was introduced, provision would have to be made for interviewing, counselling, medical examination and treatment of anti-HBc positive donors and donors with raised ALT.

Were you aware of the Working Group's report? If so, did you agree with the conclusions reached by the Working Group? If not, why not?

476. I cannot recall if I was aware of this report by Dr Gunson, but I may have seen it and/or been present at discussions concerning its content. In any event, I believe I would not have been surprised at its content, which broadly reflected

the lack of international consensus on the topic and the concerns consistently stated by UK and EU Blood Services.

102. The aforementioned report stated: "if a stance is taken that blood should have maximum safety then the tests would be introduced" (NHBT0008816_002, page 6, paragraph 8). In your view, did the decision not to introduce routine surrogate testing amount to a decision not to provide "maximum safety"?

477. I am unable to offer a useful interpretation of this statement in the report. I am not aware of the status of this report, which appears only to summarise the views of members of the Council of Europe Working Group. It was unable to make any recommendations and suggested that actions must be considered by individual countries, based on their local assessments.

103. In October 1989, Dr Gunson, the Chairman of the Advisory Committee on Transfusion Transmitted Diseases ("ACTTD"), recommended: "The routine introduction of non-specific tests should be deferred, unless this is necessary for the acquisition of product licences in the UK for fractionated plasma products" (NHBT0000188_072, paragraph 7.5). In November 1989, the Advisory Committee on the Virological Safety of Blood ("ACVSB") concluded that there was no case for surrogate testing for NANBH (NHBT0005043, page 5). Were you aware of these decisions made by ACTTD and ACVSB? If so, did you agree with these decisions? If not, please explain why you disagreed with the recommendations.

478. I believe I would have been aware of the recommendation of ACTTD and the subsequent endorsement of this recommendation by the ACVSB in November 1989.

479. I do not recall the details these particular events, but I am confident that I would have supported these decisions and would not have been surprised at

them, since there was by this time a very realistic prospect of a specific and sensitive test for HCV.

104. Please explain whether surrogate testing for ALT or anti-HBc was ever adopted by the PFC during the time you worked there. If surrogate testing was adopted by the PFC, please explain:

a. What surrogate testing procedure was adopted? Was testing conducted on individual donations or pooled samples? What confirmatory testing procedure was used, if any?

b. What action was taken, if any, with regard to blood products manufactured prior to the adoption of surrogate testing? Were untested products recalled, quarantined or issued with additional warnings? If so, please give details. If not, why not?

c. What action was taken when donations, pools and/or blood products were found to be infectious? Please set out the steps that were taken, with respect to (i) the recall, quarantine or issue of infected batches, (ii) passing information to third parties, and (iii) identifying recipients of previous donations from that donor.

d. What impact, if any, did the adoption of surrogate testing have on the risk of infection from blood products produced at the PFC?

e. What funding and operational support was the PFC provided with to facilitate the implementation of surrogate testing? What effect, if any, did the level of funding and support have on the date when the PFC was able to commence surrogate testing?

f. What were the circumstances in which the PFC stopped surrogate testing? Please provide as much detail as you are able to.

480. To the best of my knowledge and recollection there was never any consideration of implementing ALT or anti-HBc at PFC on individual donations supplied by RTCs or plasma pools prepared at PFC. This would not have been operationally feasible and/or would not have provided any meaningful results. ALT testing is not designed for testing of plasma pools and anti-HBc assays were insufficiently sensitive for pooled samples.

481. I am also not aware of any other fractionator employing these tests in this way.

Section 11. Product recall

105. From 26 October to 3 November 1984, Drs McClelland, Ludlam, Cash and Boulton initiated the recall of Factor VIII batch 023110090 (NY3-009) after recipients tested positive for HTLV-III/HIV (PRSE0000828). As to this:

- **a. In your view, should batch 023110090 have been recalled earlier? Should the recall have been initiated on 29-30 October, when the seroconversions were first linked to the product (PRSE0000828, paragraph 3)? Please give reasons for your answer.**
- **b. When did you and/or the PFC first become aware of the situation which led to the recall of batch 023110090? Were you/PFC aware of the situation at any point prior to Dr McClelland's phone call on 3 November (PRSE0000828, paragraph 5)?**
- **c. Please refer to PRSE0002869, page 2, paragraphs 6-7 and handwritten comments, which states: *Further investigation by PFC ...investigation of FVIII + donors associated DEFIX Batch (DE831) also recalled ...product recalled quarantined pending investigation"*. To the best of your knowledge, what actions did the PFC take in response to this incident? In particular:**
  - **i. When was the decision taken to recall Defix batch DE831? Who made this decision and why? What was the association between Dfefix batch DE831 and Factor VIII batch 023110090?**
  - **ii. As to the investigations referred to above, when did these take place? Who was involved? What was the nature and extent of those investigations? What were the findings, if any?**
  - **iii. When were the recalls of Factor VIII batch 023110090 and Defix batch DE831 completed? Did any delays,**

communication issues arise, or any other problems occur? If so, please provide details.

iv. **Did any patients receive treatment with Factor VIII batch 023110090 or Defix batch DE831 after recall was initiated on 3 November 1984? If so, why did this occur? Please provide as much detail as you are able to.**

v. **What other actions, if any, did the PFC take in response to this incident? Did the PFC take any steps to recall any other blood products as a result of the incident?**

483. My understanding from the records available concerning these events, the detailed report submitted to the Penrose Inquiry (Actions Surrounding FVIII Batch 023110090 (NY 3-009)), and the memorandum from Dr McClelland (PRSE0000828), is that the initial actions by PFC to remove this batch (which was supplied only to Edinburgh and Aberdeen RTCs) from use were taken on 1st November 1984, by telephone to Aberdeen BTS. Drs Ludlam and McClelland would have been aware that no stock remained at SEBTS and the Edinburgh Haemophilia Centre.

484. The timing of this recall was based on the judgements and assessments by Drs McClelland, Ludlam and Boulton and Professor Cash, that batch 023110090 (NY 3-009) was the most likely candidate batch to have transmitted HTLV-III. This analysis would have taken some time to complete subsequent to the initial reports received by Dr Ludlam on 26th October 1984.

485. I do recollect being absent from the Centre (at the Groningen Conference) when this information was communicated to PFC (to Dr Cuthbertson in my absence) on 1st November 1984. I believe I was made aware of the information and the actions taken immediately on my return to the Centre on 5th November 1984.

486. DEFIX, Batch number DE831, was formally recalled on 7 November 1984. DEFIX DE831 had been issued to Glasgow, Edinburgh and Dundee, and had all been used apart from 1 vial returned from Glasgow. No HIV infections

were reported in any recipient. It is possible and probably likely that this recall was initiated by telephone prior to this date. This product batch was identified for recall as a precautionary measure because it had been prepared from the same plasma pool used for the preparation of NY 023110090. This decision would have been taken by myself and Dr Cuthbertson, probably following consultation with Professor Cash.

487. Details of investigations regarding this incident and the associated timelines were submitted to the Penrose Inquiry in a report dated June 2010 (Actions Surrounding FVIII Batch 023110090 (NY 3-009)) and cover the period from 1983 to 2009. The practical implementation of the recalls and detailed follow up actions were carried out by Dr Cuthbertson (QA Manager at PFC).

488. The batch of FIX associated with this incident did not transmit HIV to patients.

489. The removal of these product batches from the supply chain (ie 41 unused vials from Aberdeen) would have been completed immediately following the initial recall notifications of 1st November (FVIII 3-009) and on or before 7th November (DEFIX 831). The information contained in PRSE0002869 indicates that the recall documentation from Aberdeen was completed on 9th November and on 20th November by the Edinburgh Centre. I have no detailed records or reports in my possession concerning details of actions taken in respect of the FIX recall (DEFIX 831). I am not aware of any delays, communication issues or other problems concerning these recalls, which were carried out in accordance with documented procedures and Standard Operating Procedures.

490. At the time of the recall all product supplied from FVIII Batch 023110090 to the Edinburgh RTC and Haemophilia Centre had been used for patient treatment. The remaining product (41 vials) in the Aberdeen Centres were immediately removed from the supply chain. Therefore, to the best of my knowledge, FVIII Batch 023110090 was not used for patient treatment beyond the date of the recall. Haemophilia Directors in post at the time may be able to confirm this. I have no documentation or reports in my possession concerning

the recall of DE 831, but I have no reason to believe its use would have continued following the product recall since the sole remaining vial of this product was recovered from Glasgow..

491. Details of all investigations regarding this incident and the associated timelines were submitted to the Penrose Inquiry in a report dated June 2010 (Actions Surrounding FVIII Batch 023110090 (NY 3-009)) and cover the period from 1983 to 2009. These included extensive actions to attempt to identify infectious donation(s) which may have contributed to the plasma pool used for the preparation of this FVIII batch. However these were unsuccessful and no infectious donations were identified.

492. I cannot remember any other PFC product recalls, either directly or indirectly associated with this incident.

106. On 6 December 1984, you initiated the recall of unheated PFC Factor VIII concentrate. Please refer to PRSE0002675 and PRSE0001885. As to these:

a. Please describe, in as much detail as you are able to, the circumstances in which the decision was taken to recall unheated factor VIII concentrate.

b. Did you at any point prior to 6 December contemplate the recall of unheated factor VIII concentrate? If so, why did you not initiate the recall earlier? Did you at any point prior to 6 December contemplate recalling unheated factor VIII concentrate and concomitantly replacing those stocks with (i) a commercial alternative, whether heated or unheated, (ii) cryoprecipitate, or (iii) not replacing stocks for an interim period?

c. Why were unheated factor IX concentrates not recalled at this time?

d. In as much detail as you are able to, please set out the response of the Regional Transfusion Directors ("RTDs") to the recall. Were you satisfied by their response? If not, why not? Did any delays or communication issues arise, or any other problems occur? If so,

please provide details.

e. **Did any patients receive treatment with unheated PFC factor VIII concentrate after 6 December? If so, why did this occur?**
f. **Please confirm that unheated factor VIII was also recalled from Northern Ireland. Did any particular issues arise with respect to Northern Ireland?**

493. The question as posed is not quite accurate since the formal recall of all stocks of unheated product was not anticipated to commence until the beginning of January 1985. On 6th December 1984 I wrote to RTC Directors outlining the arrangements for the supply of heat treated FVIII to begin on 10th December 1984 and subsequent withdrawal of unheated product to begin in January 1985. This programme of product "exchange" was designed to provide patients with as early as possible access to heat treated product, with the intention that most patients would be able to be treated with heat treated product during and after the week beginning 10th December, but with the overall goal that all patients could be treated in this way from 1st January 1985. In this respect, the programme was not a product recall, which is a term usually applied when products are removed from the market because of known or suspected defects or quality and safety concerns. It is therefore better described as a product exchange which was initiated on 10th December 1984.

494. The decision that PFC/SNBTS could and should supply a heat treated FVIII product as soon as possible was based on (i) information received in November 1984 that a batch of PFC FVIII was associated with the transmission of HTLV-III (ii) new information received that HTLV-III could be inactivated in coagulation factors by heat treatment. (iii) pre-existing knowledge that current PFC coagulation factor products could withstand heat treatment with acceptable recovery of FVIII activity (iv) PFC/SNBTS havinghaving established very secure product and plasma stocks which were considered an essential prerequisite to the product exchange programme envisaged for December 1984.

495. The withdrawal from the supply chain of unheated FVIII was a natural

follow-up action, with the intention of ensuring that this product was not inadvertently supplied to patients in 1985 and beyond. It was further envisaged that unheated product returned to PFC could be heat treated and reissued.

496. As described in my answer above, the recovery of unheated product stocks from the supply chain was the final part of the PFC/SNBTS product exchange programme developed during November 1984. To the best of my knowledge there was never any consideration of a formal recall of PFC unheated FVIII prior to the estimated earliest date on which PFC was able to supply its replacement heated product. Notwithstanding the discovery in November 1984 of HTLV-III transmission by PFC FVIII, it remained the view of Haemophilia Directors, SNBTS Directors and SHHD that the continued supply of PFC FVIII was preferable to its replacement, even temporarily, with commercial concentrates known by this time to carry a very significant risk of HTLV-III.

497. During the period of 5-6 weeks between the notification of HTLV-III to SNBTS and the supply of a heat treated product on December 10th most (though probably not all) patients would have continued their treatment without additional batch exposure.

498. To the best of my knowledge the use of cryoprecipitate was not considered as an interim treatment regime for all patients in the period between the initial notification to SNBTS of HTLV-III transmission by a batch of PFC FVIII (NY 3-009) in late October 1984 and the distribution by PFC of heat-treated FVIII (NY 68^{0}C/2hr) on the 10th December 1984. Such a significant change in treatment regimes for haemophilia patients throughout Scotland and Northern Ireland (ie treatment with cryoprecipitate) would only have been considered by SNBTS if such action had been proposed and requested by Haemophilia Directors. I cannot recall SNBTS receiving such a request, although there may have been dicussions concerning this between Professor Cash and Dr Ludlam. Also, in my view it would not have been considered possible to create this capability in RTCs at such short notice (or at all) and for such a short interim period of 5-6 weeks. To the best of my knowledge the capacity in RTCs for the

large scale preparation of cryoprecipitate did not exist without major investment in and procurement of additional equipment, storage facilities, distribution arrangements and quality systems. In my view such developments would have required careful planning, implementation and validation over a period of many months.

499. Similarly, the PFC was not designed and equipped for, or experienced in the preparation of single donor cryoprecipitate as an immediate and short term interim measure. Such action would have required extensive modifications to its manufacturing facilities and quality and documentation systems. These constraints would have been understood and recognised by RTC Directors (and also Haemophilia Directors) as being a non-viable option.

500. Finally, not replacing stocks for an interim period would have resulted in the immediate need for the purchase of commercial alternative product – which I believe would have been considered at the time to be the worst of all options.

501. My recollection is that unheated DEFIX remained at issue until a safe and secure supply of commercial FIX had been identified to cover the period during 1985, when the PFC HTDEFIX was subjected to safety studies.

502. There was at this time no evidence of HTLV-III transmission by unheated DEFIX, including the product batch associated with NY 3-009.

503. So far as I can recall, RTDs were involved in and supportive of the decisions taken between November 1984 and early 1985 concerning the supply of coagulation factor products, including the details of the product exchange programme briefed to them on December 6th 1984.

504. RTDs and their staff were supportive, cooperative and helpful throughout this period. Both I and the wider PFC staff were satisfied with the response of RTDs and their staff during the recall and product exchange process. I do not recall any delays, communication or other issues affecting the speed, effectiveness or security of this process.

505. As explained above in the introduction to my answers to question 106, heated FVIII was not supplied to RTCs until 10th December 1984 at the earliest, and initially in relatively small quantities. The exchange programme envisaged the use of heated FVIII commencing on or soon after this date, with 100% of patients being transferred to this product by 1st January 1985.

506. Decisions concerning the operational arrangements, the timing for transfer of individual patients onto heat treated product was the responsibility of Haemophilia Directors.

507. Unheated FVIII was recovered from Northern Ireland (Belfast) at the beginning of January 1985 in the same way as for Scottish Centres. I do not recall there being any particular problems or issues associated with these actions.

107. **You explained to the Penrose Inquiry that the PFC "*ceased to supply unheated Factor IX, I think it was May 1985 but we didn't formally recall it, we quarantined it because we weren't confident that commercial supplies were necessarily reliable or that they may result in unpredictable clinical reactions***
***...Between May and October 1985, my understanding is that all patients in Scotland would have been treated with commercial product. Or certainly that's the system that we set up"* (PRSE0006045, page 98-99; please also refer to PRSE0002938). As to these:**

a. **Why did the PFC initially decide to quarantine unheated Factor IX rather than recall it? In your view, was the quarantine effective in reducing the risk of infection for patients? Please give reasons for your answer.**
b. **To the best of your knowledge, did any patients receive treatment with**

unheated PFC Factor IX between May - October 1985? If so, why did this occur? Please provide as much detail as you are able to.

c. Please describe the recall of remaining stocks of unheated Factor IX which took place in October 1985 (PRSE0002938). Were stocks recalled from (i) RTCs, (ii) haemophilia centres, (iii) hospitals and/or (iv) patients? What happened to the recalled stock?

508. I believe this decision was taken on the advice of clinical colleagues who had concerns over the security of supply of heat treated commercial FIX at that time (May 1985). Also, these products had not been subjected to the animal studies being applied to the PFC HTDEFIX. Unexpected adverse events from the use of these replacement products may may have led to the need for urgent supplies of unheated DEFIX which was known to be clinically well tolerated. Thus it was decided to maintain stocks of unheated DEFIX in strict quarantine at RTCs and for emergency use only. To the best of my knowledge, the quarantined product was not used on any occasion for this purpose.

509. I presume the quarantine process and interim use of commercial heat treated FIX products was effective in reducing the risk of infection because it was never found to be necessary to use the unheated/quarantined DEFIX pending the introduction of HTDEFIX in October 1985.

510. To the best of my knowledge, the quarantined product was not used on any occasion for patient treatment between May and October 1985.

511. HT DEFIX was supplied to RTCs in Scotland and Northern Ireland on the 1st October 1985. Once satisfactory stocks had been established and the product confirmed to be satisfactory in clinical use, the unheated DEFIX product was withdrawn from the supply chain. By this time quarantined stock would only have been held at RTCs.

512. To the best of my knowledge the recovered stock was destroyed and/or used for research purposes at PFC.

108. Please describe, during the time you worked at the PFC, your own and the PFC's involvement in any other recalls of blood products from

patients, hospitals, haemophilia centres or RTCs in Scotland and Northern Ireland.

513. In common with all pharmaceutical manufacturers, the PFC had documented procedures (Standard Operating Procedures) for guiding the management response and necessary actions following reports of PFC product defects, adverse events, RTC reports of post transfusion virus transmission or suspected virus transmission by blood components or other information potentially impacting on the safety or quality of PFC products. I was involved in the development of these procedures and their review in my role as QC Inspector and Director.

514. From time to time PFC received such reports which were recorded as "incident reports" by the QA Department and subjected to investigation,appropriate action and follow up, including discussion with senior SNBTS medical staff. I cannot recall examples of reports which led to a formal product recall as a precautionary measure but I believe they occurred, albeit rarely.

515. To the best of my knowledge, records of such incident reports and actions taken will have been retained by SNBTS.

109. Do you consider that, at any other time, blood products could and/or should have been recalled from within the UK? If so, which products and/or batches should have been recalled and when? If not, why not?

516. I have no knowledge of any examples of failures to implement product recall where this could or should have occurred. This is particularly the case for events in England and Wales, where there was no SNBTS/PFC involvement in, or knowledge of, the details of plasma product supply from BPL or other suppliers.

110. What formal policies and procedures were in place as regards the recall of PFC products? How did these change over time? In your view, were such policies and procedures adequate? From your experience, did clinicians generally comply with recall requests? If not, why did they not?

517. PFC policies and procedures concerning all aspects of product manufacture and supply (including product and plasma recall) were determined by a comprehensive documentation system of "standard operating procedures". This system, typical of the pharmaceutical industry, and regularly examined by Medicines Inspectors, was progressively developed, refined and subjected to regular review. I recall the development and implementation of detailed policies and procedures to guide actions and decisions concerning the potential need for product recall, but I cannot recall their detailed content or their evolution over time. However I was concerned that clear prospective policies and guidance existed to manage reports of eg potential plasma infectivity and the criteria to be used to guide decisions on release or recall of product batches made from such donations. The draft SOP cited below, at Question 111, (NHBT0008069) is an example of the type of documentation developed for the management of recalls.

518. My recollection is that the operational policies developed provided a good framework for decision making, but were not able to cover every eventuality or reports received.

519. I cannot recall any circumstances or incidents in which clinicians or others did not comply with PFC recall requests.

111. In 1991, you corresponded with Professor R. S. Tedder regarding plasma notifications and product recall. Please refer to NHBT0000042_108; NHBT0008068; NHBT0008069; PRSE0002280; and DHSC0003532_062. As to these:

a. On 22 March 1991, you wrote to Dr Tedder (NHBT0008068) enclosing a PFC SOP (NHBT0008069). The SOP stated that recall of plasma should be initiated wherever "*blood components are*

***implicated in the transmission of any viral infection ....no matter how many other units are implicated.*" What was the rationale for this policy? Professor Tedder and others expressed concerns that PFC plasma notification requirements placed an undue burden on RTCs where a large number of donations were implicated. What was your view of such concerns?**

b. **Plasma notifications were tabled for discussion at the ACVSB on 25 February but deferred until the next meeting (PRSE0002280, page 10). In a letter to you on 7 March 1991, Professor Tedder stated that the matter remained "*unanswered*" (NHBT0000042_108). Plasma notifications were finally addressed by the ACVSB on 21 June 1991 (DHSC0003532_062, page 10-11). Why did this delay occur?**

c. **At the ACVSB on 21 June, Dr Lane stated: the "*commercial view was that if a test were performed on the donation at the time of donation and properly validated, then the commercial manufacturer was prepared to abide by it since viral inactivation procedure was good enough*" (DHSC0003532_062, page 10-11). As to this:**

d. **Dr Lane appears to imply that reports of post-transfusion hepatitis played no role in commercial plasma notification. To the best of your knowledge, was Dr Lane correct? What role, if any, did you consider that reports of post-transfusion hepatitis should play in NBTS plasma notification policy?**

e. **In your view, did heat treatment render systems of plasma notification ineffectual?**

f. **Was this matter taken further following the ACVSB on 21 June? If so, please give details.**

520. I think my rationale for this requirement was simply that early notification to the fractionator of all donations which were transfused to a recipient who subsequently developed an infection, provided the opportunity for the fractionator to remove these from stock before they were pooled. There was no requirement placed on the RTC to prove the infective status of individual units,

but only to identify units under investigation. I did not believe this placed an undue burden or pressure on RTCs to identify the infected donation from all those potentially implicated.

521. Plasma notifications were addressed at the ACVSB meeting of 21 May 1991 not 21 June 1991.

522. I do not remember the reason for the delay of further consideration for this topic, although it may have been a shortage of time at the meeting, a lack of priority, urgency or importance of what may have been regarded by the committee as an operational topic, a preference that discussion included a contribution from Dr Lane (BPL) or a combination of these.

523. Dr Lane was correct, since the commercial plasma industry only collected plasma for fractionation by plasmapheresis and there was no collection by them of blood components for direct transfusion to patients. Thus there could be no reports of post transfusion hepatitis or any other infectious disease.

524. My view at that time was that because UK and EU blood services collected mainly "recovered" plasma (ie plasma separated from whole blood donations) the surveillance of hepatitis and/or other infectious diseases in recipients of blood components associated with plasma units created the opportunity to remove at least some infective or potentially infective donations from plasma pools if notified to the fractionator timeously. The importance or value of this diminished with increasing confidence in plasma product safety as a result of heat treatment and other virus inactivation processes.

525. In my view not entirely. I believed (and still do) that removal of plasma donations which may be infectious from a plasma pool should have been undertaken whenever possible. Retrospective notifications of post transfusion infection is not possible for commercial plasma collection systems, but can be of value in the collection of recovered plasma. Also, the importance of excluding infectious and potentially infectious donations from a plasma pool has

continued to the present day – as evidenced by the introduction of additional NAT testing of plasma/blood donations in the 1990s, ongoing attention to appropriate donor selection and deferral criteria and the enforcement of these measures by current regulations for blood and plasma products.

526. Plasma product safety is dependent on the cumulative benefits of (i) Donor selection (ii) Minimising virus levels in plasma pools (iii) Application of virus inactivation technologies.

527. The ACVSB meeting referred to was on 21 May 1991. I believe this matter was not considered further on a UK wide basis – at least by ACVSB.

Section 12: Your relationships with commercial companies

112. Have you at any point:

a. **Provided advice or consultancy services to any pharmaceutical company involved in the manufacture and/or importation and/or sale of blood products?**
b. **Received any pecuniary gain in return for performing an advisory/consultancy role for a pharmaceutical company involved in the manufacture, sale and/or importation of blood products?**
c. **Sat on any advisory panel, board, committee or similar body, of any pharmaceutical company involved in the manufacture, importation or sale of blood products?**
d. **Received any financial incentives from pharmaceutical companies to use certain blood products?**
e. **Received any non-financial incentives from pharmaceutical companies to use certain blood products?**
f. **Received any funding to prescribe, supply, administer, recommend, buy or sell any blood product from a pharmaceutical company?**

If so, please provide details.

528. I have provided briefing 2008 to the National Bioproducts Institute, South Africa (NBI) – a not-for-profit organisation based in Durban, South Africa and a member of IPFA. I was paid a fee for my work on behalf of NBI.

113. What regulations or requirements or guidelines were in place (at any time relevant to your answers above) concerning declaratory procedures for involvement with a pharmaceutical company? If you were so involved, did you follow these regulations, requirements and guidelines and what steps did you take?

529. I had no knowledge of such requirements, regulations or guidelines preceding or during my consultancy work for NBI.

114. Have you ever undertaken medical research for or on behalf of a pharmaceutical company involved in the manufacture, importation or sale of blood products? If so, please provide details.

530. I have not undertaken such work.

115. Have you ever provided a pharmaceutical company with results from research studies that you have undertaken? If so, please provide details.

531. No

116. If you did receive funding from pharmaceutical companies for research, did you declare the fact that you were receiving funding and the source of the funding to your employing organisation?

532. I did not undertake such work.

Section 3: Other Issues

117. Please explain, in as much detail as you are able to, any other issues that you believe may be of relevance to the Infected Blood Inquiry. To assist, we have provided a list of issues (attached).

533. I have not identified any further issues

Statement of Truth

I believe that the facts stated in this witness statement are true.

GRO-C: Dr Robert J Perry

Signed _____

16th February 2022

Dated _____