Witness Name: Dr Peter Foster
Statement No.: WITN6914001
Exhibits: WITN6914002 – WITN6914070
Dated: 7th March 2022

INFECTED BLOOD INQUIRY

WRITTEN STATEMENT OF PETER R FOSTER

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

I, Dr Peter R Foster, will say as follows:

CONTENTS

Section 1: Introduction

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

1.1 Name, Address, Date of Birth.

(i) Peter Reynolds Foster.

(ii) GRO-C

(iii) GRO-C 1945.

1.2 Professional Qualifications:

BSc. MSc. PhD. CS. CSci. CEng. FIChemE.

1.3 Degrees

(i) BSc (1st Class Hons, Chemical Engineering), Heriot Watt University, 1968.

(ii) MSc (Biochemical Engineering), University College London, 1969.

(iii) PhD (Biochemical Engineering, thesis entitled '*A study of protein solubility for the design of a fractionation stage in a continuous enzyme isolation process),* University College London, 1972.

1.4 Membership of Professional Bodies

(i) Graduate Member, The Institution of Chemical Engineers, 1968.

(ii) Corporate Member, The Institution of Chemical Engineers,1976.

(iii) Chartered Engineer, The Engineering Council, 1976.

(iv) Fellow, The Institution of Chemical Engineers, 1983.

(v) Clinical Scientist, The Health & Care Professions Council, 2000.

(vi) Chartered Scientist, Science Council, 2004.

Please set out your employment history, including the various roles and responsibilities that you have held throughout your career, as well as dates.

2.1 Appointments

(i) Senior Biochemist, The Scottish National Blood Transfusion Association Protein Fractionation Centre (PFC), January 1973 to March 1974.

(ii) Head of the R&D Department, The Scottish National Blood Transfusion Service Protein Fractionation Centre (PFC), April 1974 to February 2009.

2.2 NHS Grade

(i) Senior Biochemist, January 1973.

(ii) Principal Biochemist, April 1976.

(iii) Top Grade Biochemist, October 1983.

(iv) Clinical Scientist, Grade C, July 1990.

(v) PFC Department Manager, Grade 8, June 1991.

(vi) Biomedical Scientist, Head of Service, December 2007.

2.3 Roles and Responsibilities

(i) The planning, managing, undertaking and reviewing of PFC process and product developments and contract R&D activities.

(ii) The line management and financial management of the PFC R&D Department.

(iii) The planning and direction of the PFC Library and scientific information services.

(iv) Maintaining an awareness of relevant scientific and medical literature.

(v) Contributing to the overall management of PFC, including its out-of-hours, on-call service.

(vi) Contributing to the preparation of PFC's regulatory submissions.

(vii) The protection of PFC's intellectual property.

(viii) Assisting SNBTS with requests under the Freedom of Information Act.

Further information is available in my CV [WITN6914002]

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 members and the nature of your involvement.

3.1 International

(i) The European Plasma Fractionation Association (EPFA).

- Representing EPFA at meetings of the European Medicines Evaluation Agency concerning prions and blood products, 1999-2003.

- Chair of EPFA expert group on Transmissible Spongiform Encephalopathy, 2003- 2004.

3.2 National Committees

(i) Attendee at annual planning meetings of SNBTS Directors, Scottish Haemophilia Directors and the Scottish Health Service, 1981-2008.

(ii) Attendee at meetings of the CJD Incidents Panel expert group on plasma fractionation, 2003-2004.

(iii) Attendee at a meeting of the SaBTO expert group on prions, 2009.

3.3 SNBTS Committees

(i) Member, SNBTS Coagulation Factor Study Group, 1982-1989.

(ii) Member, SNBTS Product Development Group, 1990-2006.

(iii) Member, SNBTS Steering Group on CJD, 1998-2006.

(iv) Member, SNBTS Research Advisory Group, 1999-2006.

3.4 PFC Committees

(i) Member, PFC Heads of Dept/Management Team, 1974-2008.

(ii) Chair, PFC Development Management Team,1986-2006.

(iii) Chair, PFC Steering Group on CJD, 1996-1997.

3.5 Membership of Learned Societies

(i) The British Blood Transfusion Society, Founder Member, 1983.

(ii) The British Science Association.

(iii) The British Society for Haemostasis and Thrombosis (former member).

(iv) The Society of Chemical Industry (former member).

(v) The New York Academy of Sciences (former member).

Section 2: Previous statements and evidence

Evidence to the Penrose Inquiry

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

4.1 I had access to all of the documents that I had obtained and retained over my career, including my appointments diaries. I also had full access to documents held in SNBTS/PFC files as well as in the SNBTS/PFC library.

See also my responses 6.2 and 6.3 below.

Did anyone else assist you in preparing your evidence? If so, who, and what assistance did they provide?

5.1 I was given advice on terminology by my solicitor to try to ensure that scientific and technical matters were expressed in a way that a lay reader would understand.

See also my responses 6.2 and 6.3 below.

Please explain the background behind your authorship of the two SNBTS submissions to the Penrose Inquiry listed as documents 1 and 2. In particular, who proposed and organised the papers for submission, who assisted in their preparation, and by whom, if anyone, were the final versions approved.

6.1 Background

(i) That a Scottish Public Inquiry would be held was announced in April 2008. Lady Cosgrove was appointed to chair the Inquiry, but she resigned from the post in the Autumn of 2008.

(ii) As PFC was in the process of being closed, I was assigned by SNBTS to work on preparations for the Public Inquiry. Dr Brian McClelland, former Director of the Edinburgh Regional Blood Transfusion Centre, was also assigned by SNBTS to work on preparations for the Public Inquiry. We shared an office for this purpose.

(iii) In January 2009, Dr McClelland and myself were discussing what SNBTS could do to prepare for the Inquiry, given that:
- a new chair of the Inquiry had still to be selected.
- no terms of reference had been published
- no specific procedures for the Inquiry had been published.

(iv) Given the complexity of the subjects, and the period of time covered, we thought that it could be helpful to the Inquiry if SNBTS could begin to gather factual information that might

be relevant.

(v) Dr McClelland and I drew up a list of topics we thought that the Inquiry might examine and I selected the names of potential authors from current or recently retired SNBTS experts.

(vi) I assigned myself to write papers on self-sufficiency and virus inactivation.

(vii) Draft versions were circulated to Professor Cash and other senior staff to check for errors and omissions, with the final version being approved by the author.

(viii) The first request for a witness statement that I received from the Penrose Inquiry included the topic of self-sufficiency. In my response (PEN.015.0101) [PRSE0000545] I decided to append the paper that I had prepared on this topic (PEN.013.1125) [PRSE0001083].

(ix) In responding to the request from the Penrose Inquiry for a witness statement on the development of heat treatment (PEN.012.1438) [PRSE0003349], I decided to append the paper that I had prepared on this topic (PEN.013.1309) [PRSE0002291].

(x) When the Penrose Inquiry learned of the general existence of these papers, they instructed SNBTS to provide all of them to the Public Inquiry.

(xi) I was also the main author of a SNBTS background paper entitled *"Events concerning the safety of blood and blood products with special reference to the treatment of haemophilia"* (PEN.013.0220) [PRSE0003480].

6.2 Document 1 (The Development of Heat Treatment, PEN.013.1309) [PRSE0002291].

(i) I was assisted in the preparation of this document by Dr Ronald V McIntosh and by Dr Bruce Cuthbertson, both of whom had been involved in the work described.

(ii) I was greatly assisted in the preparation of this document by having given evidence to previous investigations/inquiries and by having recently written a comprehensive account of infections associated with plasma products, including the development of virus inactivation technologies, for a chapter in the textbook Transfusion Microbiology, published in 2008 by Cambridge University Press [WITN6914003]. I had also co-authored similar chapters in three earlier textbooks (see my response 80.3 for details).

(iii) On reviewing my paper (PEN.013.1309) [PRSE0002291], it contains two errors:

- on page 44, bottom line, the figure of 10ml should be 15ml.
- on page 62, at 8-13 June 1968, the Congress referred to was that of the World Federation of Hemophilia (WFH) in Milan, not the Congress of the International Society of Thrombosis & Haemostasis (ICTH) in San Diego.
- I accept full responsibility for both these errors.

6.3 Document 2 (Self-Sufficiency, PEN.013.11125)

(i) I was assisted in the preparation of this document by Dr Anne G Welch who obtained data for me from PFC/SNBTS files on the supply of plasma and the production of Factor VIII concentrate and cryoprecipitate by SNBTS. Dr Welch had worked in my department at PFC since 1977 and, following her retirement, had been re-appointed by SNBTS to support work on the Public Inquiry. Although she had never worked on coagulation factors, she knew where to find relevant records, having done this for anti-D immunoglobulin throughout her career.

(ii) I was assisted by Professor Ian M Franklin who gave me a copy of a report concerning the use of Factor VIII concentrate by the West Midlands Regional Health Authority (see page 68, table 23).

(iii) I was assisted by Mr Neil Billing, SNBTS project manager for the Penrose Inquiry, who obtained information on the licensing of commercial Factor VIII concentrates in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) – see pages 46-47, table 11.

(iv) On review, my paper PEN.013.1125 [PRSE0001083] contains three errors:
- on page 50, in the heading for table 13, the year 1981/82 should be 1983/84.
- on page 51 in the first line after table 13, the year 1981/82 should be 1983/84.
- on page 57, in footnote c to Table 15, Table 13 should be Table 14.
- I accept full responsibility for these errors.

Please confirm whether the contents of:

a) your statements to the Penrose Inquiry recorded at documents 3 – 7 above;
b) the transcripts of your oral evidence to the Penrose Inquiry, recorded at documents 8 – 12 above; and
c) The Heat Treatment Briefing Paper recorded at document 1 above

(your "*Evidence to the Penrose Inquiry*") are true and accurate. If there are any matters contained within your Evidence to the Penrose Inquiry that you do not consider to be true and accurate, please explain what they are and how the inaccuracy occurred.

7.1 To the best of my knowledge my evidence to the Penrose Inquiry is true and accurate, except for the errors noted at 6.2 (iii) and 6.3 (iv) above.

For clarification, the Heat Treatment Briefing Paper cited as document 1 is PEN.0131309 [PRSE0002291] and cited document 4 the "Second Penrose Statement" should be PEN.012.1797 [PRSE0001478].
The document given as document 4 (PEN.012.1852) [PRSE0000814] provides technical details of the manufacturing processes used at PFC.

My evidence to the Penrose Inquiry included documents that have not been cited:
- A revised response to questions on topic B3 (PEN.0121.797) [PRSE0001478].

• Additional information concerning self-sufficiency (PEN.018.0571) [PRSE0003147].
• See also my comments on page 163, at section 81.2.4 concerning additional evidence.

What materials were made available to you when you gave evidence to the Archer Inquiry?

8.1 Background
(i) When the Independent Inquiry under Lord Archer was announced both Professor Ian Franklin, SNBTS National Medical Director, and I believed that people with knowledge of the subject should offer to give evidence.

(ii) Professor Franklin requested permission from the Scottish Health Department for both of us to give evidence to the Archer Inquiry. This request was granted and he informed the Archer Inquiry of our offer to give evidence.

(iii) This offer was accepted by the Archer Inquiry, with Professor Franklin being scheduled to give evidence before me, as I had holiday arrangements planned.

(iv) As I had received no guidance from the Inquiry, I had intended to make an oral presentation and then to answer questions. However, when I returned from holiday, I discovered that Professor Franklin had provided the Inquiry with a written statement.

(v) I decided that I too should provide a written statement. Although I had full access to PFC files, I prepared this from memory due to time constraints. This written statement was the basis of my evidence to the Archer Inquiry.

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

9.1 I had no assistance in preparing my evidence to the Archer Inquiry, except for a submission that I prepared jointly with Professor Franklin, see para 10.2 (iii).

Please confirm whether the Archer Statement and the Archer Transcript (your "*Evidence to the Archer Inquiry*") are true and accurate. If there are any matters contained within your Evidence to the Archer Inquiry that you do not consider to be true and accurate, please explain what they are and how the inaccuracy occurred.

10.1 My Evidence to the Archer Inquiry
I confirm that my evidence to the Archer Inquiry was true and accurate, to the best of my knowledge, at the time that it was given.

10.2 Additional Information Submitted to the Archer Inquiry
(i) Warnings.

- When I gave evidence to the Archer Inquiry I was asked by Lord Archer if I could provide the Inquiry with examples of warnings that had been issued with coagulation factor concentrates.

- I sent the Archer Inquiry examples of warnings that had been issued with PFC products and

with some commercial products [PRSE0002726].

- I had obtained the examples of warnings concerning PFC products from PFC product batch files and from PFC Product Licence Applications.

- I had obtained the examples of warnings issued with commercial products from product leaflets that I had collected over the years from company sales booths at commercial exhibitions that were held at conferences and symposia.

(ii) Evidence from the Haemophilia Society.

- I submitted a paper to the Archer Inquiry concerning the testing of coagulation factor concentrates for HIV in order to clarify points made by the Haemophilia Society that I believed were incorrect [WITN6914004].

- I submitted a paper to the Archer Inquiry concerning information on the development of heat treatment of Factor VIII concentrates in order to clarify points made by the Haemophilia Society that I believed were incorrect [PRSE0001214].

(iii) Non-A, Non-B Hepatitis from Cryoprecipitate.

- Following his evidence to the Archer Inquiry, Professor Franklin was requested by the Inquiry to provide an assessment of the risk of non-A, non-B hepatitis infection via treatment with cryoprecipitate.

- Professor Franklin invited me to assist him with this assessment.

- Professor Franklin identified a number of treatment scenarios involving cryoprecipitate and I calculated the probability of NANBH infection for each of these scenarios, assuming a prevalence of non-A, non-B hepatitis infection in blood donors of 0.3%, which was the figure that had been given to the Archer Inquiry by Professor Howard Thomas [WITN6914005].

10.3 Additional Information Not Submitted to the Archer Inquiry.

(i) Whilst attending the Archer Inquiry I was asked why English plasma had not been processed at PFC. My response was that I did not know why.

(ii) Following my evidence to the Archer Inquiry, minutes of relevant DHSS meetings from 1977, and other relevant papers, were included amongst documents released by the Department of Health.

(iii) I therefore prepared a note for the Archer Inquiry to update my answer to the question that had been put to me, as I now had information that had not been available to me previously [WITN6914006].

(iv) By the time I had completed this update to my evidence, it had been announced that a Public Inquiry would be held in Scotland.

(v) SNBTS decided that precedence should be given to the Scottish Public Inquiry because, unlike the Archer Inquiry, it was to be held on a statutory basis under the Inquiries Act.

(vi) Consequently, my updated evidence was not submitted to the Archer Inquiry.

(vii) The Archer Inquiry also decided that the Scottish Public Inquiry should be given precedence and excluded Scotland from its findings.

(viii) Although I was questioned by Lord Penrose on the reasons why English plasma had not been sent to Scotland, my explanation (Penrose Inquiry transcript 10th May 2011, pages 82-83 [RLIT0001068]) was not included in the Final Report of the Penrose Inquiry.

Please provide a copy of your report and any other evidence submitted to the Lindsay Tribunal. What were the circumstances in which you came to give evidence to the Lindsay Tribunal? Please confirm whether this evidence is true and accurate. If there are any matters contained within your Evidence to the Lindsay Tribunal that you do not consider to be true and accurate, please explain what they are and how the inaccuracy occurred.

11.1 Background

(i) I was requested to attend a meeting at SNBTS HQ with a solicitor for the Lindsay Tribunal, which I believe had been arranged by the National Director of SNBTS, Mr Angus McMillan-Douglas.

(ii) From memory, I believe that I was asked to describe the development of Factor VIII concentrates at PFC.

(iii) Before attending the meeting I had examined the file of correspondence between PFC and the Irish Blood Transfusion Service Board and had discovered correspondence from 1975 in which the PFC director Mr Watt had offered to process plasma from the Republic of Ireland at PFC. (see 11.2 (ii)).

(iv) This correspondence was of particular interest to the solicitor for The Lindsay Tribunal and I was subsequently invited to give evidence to the Tribunal.

(v) This request from The Lindsay Tribunal was made in 2000 whilst the Scottish Executive was undertaking an investigation into a claim that PFC had "*delayed the introduction of heat treatment*".

(vi) Because the Investigation by the Scottish Executive had not been completed, a request by SNBTS to the Scottish Executive Health Department for me to give evidence to the Lindsay Inquiry in person was not authorised.

(vii) I believe that this position changed following representations to the Scottish Government from the Minister of Health for the Republic of Ireland and I was allowed to give evidence in person.

11.2 Evidence to the Lindsay Tribunal

(i) I have no memory of writing a report specifically for the Lindsay Tribunal.

(ii) The transcript of my oral evidence [LIND0000320] indicates that I provided the Tribunal with the correspondence noted in 11.1(iii) above [WITN6914007] and my report concerning the development of Factor VIII concentrate at PFC that had been submitted to the Investigation being undertaken by the Scottish Executive, see para 14.4.3(i).

What materials were made available to you when you gave evidence to the Lindsay Tribunal?

12.1 I had full access to all of the files at PFC.

Did anyone else assist you in preparing your evidence to the Lindsay Tribunal? If so, who, and what assistance did they provide?

13.1 The report which described the development of Factor VIII concentrates at PFC was authored by myself and Dr Ronald V McIntosh of PFC.I drafted the report, which was then reviewed for accuracy by Dr McIntosh who had been involved with much of the work described, see para 14.4.3(i).

Please confirm whether you have provided evidence or have been involved in any other inquiries, investigations, criminal or civil litigation on matters relevant to the Inquiry. Please provide details of your involvement.

14.1 USA Multi-District Litigation, MDL-986

(i) I was requested by the National Director of SNBTS, Mr David McIntosh, to attend a meeting at SNBTS HQ with lawyers from the United States and was instructed to give my full co-operation, as it was the practice of SNBTS to do its best to assist with any inquiries. I believe that this was in late-1994.

(ii) I attended with the PFC Director Dr Robert Perry. We were questioned on the development of Factor VIII concentrates at PFC, particularly our work on heat treatment. I understood that the lawyers (Mr Barr and Mr Hammes) were representing US commercial manufacturers of coagulation factor concentrates. They explained that the companies were facing legal action on the grounds that heat treatment should have been developed much earlier. They were therefore meeting scientists who had been involved in developing heat treatment to learn how they had achieved this and if it could have been done sooner.

(iii) I subsequently attended two further meetings to be questioned on evidence being presented by the Plaintiffs. I was particularly asked to give my opinion on evidence from Dr Frank Putnam, the main expert for the Plaintiffs, in which Dr Putnam described why he believed that pasteurisation of FVIII could have been achieved much earlier than it had been. I did not agree with Dr Putnam (see my response to question 33).

(iv) I subsequently took part in three deposition hearings (two in Edinburgh and one in London) at which I was questioned and cross-examined by US lawyers for the Plaintiffs.

(v) Following the deposition hearings, I was invited by the Defendants to give evidence as an expert witness.

(vi) I declined to travel to the USA to give evidence in person and instead agreed to give video testimony in Edinburgh.

(vii) As the Defendants wanted their expert witnesses to all give their trial testimony in person, I was reclassified as a fact witness rather than an expert witness.

(viii) My trial testimony was filmed in Edinburgh on 8th December 1997. I believe that this was shown at a number of court hearings, all of which found in favour of the Defendants. The transcript of my trial testimony is attached [WITN6914008]. I can provide a copy of the video (in DVD format) if requested.

(ix) I was later asked by Mr Barr to comment on an expert report from Dr Nicholas P Jewell concerning HIV infections in the UK, which was largely based on data that had been published by Cheinsong- Popov et al. (Br Med J 1986, 293, 168-9) [BAYP0000008_303]. I have not retained the expert report by Dr Jewell, but my comments on it are attached [WITN6914009].

(x) I was also asked by Mr Barr to describe impediments to the development of solvent-detergent treatment of coagulation factor concentrates. My response is attached [WITN6914010]. See also my response at 33.3.

(xi) I was provided with a considerable amount of documentation by Mr Barr. I have retained three of these documents for personal scientific interest (see question 80):

- The transcript of a deposition taken from Dr Horst Schwinn, the biochemist who discovered the method of pasteurising Factor VIII concentrate that was developed during the 1970's by the German company Berhringwerke.

- An expert report from Carol K Kasper MD.

- A Canadian legal judgement, which included information on the transmission of HIV to patients in the UK by heat treated Factor VIII concentrate from Armour Pharmaceuticals.

14.2 The Finlay Tribunal of Inquiry (Ireland)

(i) In February 1996, I was contacted by a solicitor representing the Blood Transfusion Service Board (BTSB) of Ireland who wanted my advice concerning plasma fractionation.

(ii) I was given permission to meet with him by Dr Robert J Perry, PFC Director.

(iii) When we met, he asked me if the process used by BTSB to prepare anti-D immunoglobulin could be assumed to be as safe from hepatitis C transmission as anti-D

immunoglobulin prepared by the traditional method of cold-ethanol (Cohn) fractionation.

(iv) My opinion was that such an assumption would be incorrect. I was not called to give evidence to the Finlay Tribunal of Inquiry by BTSB, presumably because my opinion would not have been in accordance with the position of BTSB.

(v) The Finlay Tribunal of Inquiry did not consider the method of preparation of anti-D by BTSB to have been responsible for hepatitis C infection in recipients of anti-D, despite the same, non-standard, method of anti-D preparation having been implicated in the hepatitis C infection of over 2500 women in East Germany (Meisel H, et al. Lancet 1995,345, 1209-1211 [DHSC0002549_067]; Foster PR, et al Lancet 1995, 346, 372 [HSOC0010138_003])

(vi) My opinion that the method of preparation of anti-D at BTSB was responsible for the hepatitis C infections in recipients of anti-D, is included in the chapter on plasma products that I co-authored in the 2008 textbook Transfusion Microbiology (WITN6914003, page 266).

14.3 Deas Mallen Souter

(i) In the late 1990s I was contacted by Mr Anthony Deas of the solicitors Deas Mallen Souter, who was seeking information concerning virus inactivation.

(ii) I sought permission from the SNBTS National Director Mr Angus-McMillan Douglas who said that I should meet with Mr Deas and co-operate fully.

(iii) I met Mr Deas and Mr Mallen at PFC where I answered all of their questions concerning methods of virus inactivation.

(iv) They then asked me if I could tell them the date at which testing of blood donors for hepatitis C had been introduced in the UK.

(v) I did not know the answer, but I obtained the date from Dr Bruce Cuthbertson, Head of the PFC Quality Department, who was working nearby, and gave it to Mr Deas.

(vi) I subsequently received a written account of the meeting from Mr Deas which he asked me to check for errors and to sign.

(vii) His note of our meeting contained so many errors that I decided to write my own account, which I signed and sent to him.

(viii) I do not have a copy of this correspondence and have not been able to obtain it from SNBTS, but it may be available from Deas Mallen.

(ix) Deas Mallen solicitors went on to co-ordinate the Plaintiffs in the High Court action against the National Blood Authority that was heard by Mr Justice Burton.

14.4 Investigation by the Scottish Executive (2000)

14.4.1 Background

(i) In May 1999, I was told by the SNBTS National Medical Director Professor Ian Franklin that he had met Mr Philip Dolan, Chair of Scottish Haemophilia Forum, who was seeking information on the different factor VIII concentrates that had been produced at PFC and their dates of introduction.

(ii) Professor Franklin had told Mr Dolan that he could obtain this information from me following a presentation that I was due to give at a symposium on vCJD in Edinburgh on 21st May 1999.

(iii) Mr Dolan approached me following my presentation and I gave him the information that he had requested. I told him that we would be pleased to provide him with any further information or clarification.

(iv) I did not hear from Mr Dolan and was therefore surprised to find a report on the BBC television news in August 1999 that PFC had "*delayed the introduction of heat treatment*".

(v) This report was repeated by numerous media outlets, with PFC being accused of "*blunders*" and "*errors*" and of infecting 4000 patients throughout the UK with hepatitis C.

(vi) I then saw Mr Dolan interviewed on ITV news where he stated that all commercial companies had introduced 80ºC heat treatment before PFC. This was not correct. No commercial company had developed 80ºC heat treatment before PFC and commercial companies had been some 5 years later than PFC in supplying FVIII to the UK that was safe with respect to hepatitis C (see cited document 1, PEN.013.1309, page 22) [PRSE0002291].

(vii) SNBTS did not correct these media reports, preferring instead to await an Investigation by the Scottish Executive.

(viii) Following this adverse media coverage, I began to draft an account of the development of Factor VIII concentrates at PFC, with emphasis on the development of heat treatment.

(ix) Before I had completed this, I was informed that it had been arranged that SNBTS would make a presentation to the Haemophilia Society.

(x) I was pleased to learn of this, as it was consistent with my earlier offer to Mr Dolan to provide him with further information or clarification.

(xi) This event took place in Edinburgh on 25th November 1999, where I made the presentation on behalf of SNBTS [WITN6914011].

14.4.2 Evidence to the Investigation by the Scottish Executive in 2000

(i) My account of the development of Factor VIII concentrates at PFC, with Dr R V McIntosh as a co-author, was submitted by me to the SNBTS National Director Mr McMillan-Douglas in early December 1999 [PRSE0000131].

(ii) Additional questions from the Scottish Executive were received by SNBTS in February 2000. The response from SNBTS was largely written by me [PRSE0001249].

(iii) I had no communication with the officials from the Scottish Executive who conducted the Investigation.

(iv) The Scottish Executive published its findings in October 2000 [GGCL0000010], concluding:
"*The facts strongly suggest that SNBTS made very reasonable progress in developing products with reduced viral risk, relative to activity elsewhere. We accept that they were not the first. Scientific knowledge and technical expertise in this area were developing rapidly during the period in question, spurred on by the drive to eliminate HIV. It is worth remembering that commercial products available during the time in question were not proven to be HCV-safe (and many were subsequently withdrawn). We accept SNBTS's assertion that they were able to provide sufficient hepatitis C inactivated Factor VIII to cover the needs of all haemophilia patients in Scotland by 1988 – we know of no other country which could make the same claim".*

14.5 Investigation by the Health & Community Care Committee of the Scottish Parliament (2001)

(i) Following publication of the findings of the Scottish Executive, the Health & Community Care Committee (HCCC) of the Scottish Parliament conducted its own investigation.

(ii) I was instructed by the SNBTS National Director, Mr Angus McMillan- Douglas, to attend a hearing of the HCCC on 14th March 2001.

(iii) I was not informed of the purpose of the hearing, nor was I given any questions in advance. I was therefore unable to provide a written statement or prepare any answers.

(iv) I attended the hearing with Mr Angus McMillan-Douglas, Professor Ian Franklin and Dr Brian McClelland. A transcript of the proceeding is published on the website of the Scottish Parliament [WITN6914012].

(v) The HCCC subsequently sent SNBTS some additional questions. I contributed to the SNBTS response, which is published on the website of the Scottish Parliament [WITN6914013].

(vi) The final report of the investigation by the HCCC agreed with the findings of the Investigation by the Scottish Executive in respect of SNBTS and is available on the

website of the Scottish Parliament [WITN6914014].

Have you ever felt that any undue pressure was placed on you whilst providing your evidence relating to the matters of relevance to this Inquiry? If so, from what source?

No

Section 3: Your Role and the SNBTS Protein Fractionation Centre

Please outline the roles, functions and responsibilities you had at the SNBTS Protein Fractionation Centre ("PFC") during your employment there from Senior Research Scientist in 1973 through to your period as Development Manager from 1991 until February 2009.

16.1 Roles and Responsibilities

(i) Senior Biochemist engaged in research & development, 1973-1974,see 16.2(i).

(ii) Head of R&D involving:

- Planning, managing, undertaking and reviewing of PFC process and product developments and contract R&D activities, 1974-2008.
- Line management and financial management of the PFC R&D Department,1974-2008.
- Planning and direction of the PFC Library and scientific information services, 1974-2008.
- Maintaining a continual awareness of scientific and medical literature, 1973- 2009.
- Contributing to the preparation of PFC's regulatory submissions.
- Protection of the intellectual property of PFC/CSA by the publication or patenting of relevant findings.
- Assisting SNBTS in responding to requests under the Freedom of Information Act (Scotland), 2004-2008.

16.2 Principal Scientific & Technical Contributions

(i) 1973-1975: Evaluating and re-designing equipment for the cold-ethanol (Cohn) fractionation of human plasma using computer controlled, continuous-flow (continuous small volume mixing, CSVM) technology. This project included the development by Westphalia Ltd of a new centrifuge for the recovery of protein precipitates that provided both an increased capacity and increased refrigeration compared with traditional centrifuges. This new multi-chamber centrifuge was subsequently used at PFC for the recovery of cryoprecipitate and, I believe, is now used world-wide for this purpose. I was also responsible for the commissioning of the CSVM process at the new PFC centre in Liberton.

(ii) 1974-1977: Leading an SNBTS team to increase the factor VIII activity of plasma collected by SNBTS, which resulted in the factor VIII activity of plasma to PFC being increased significantly.

(iii) 1976-1981: Contributing to studies aimed at removing hepatitis viruses from Factor IX concentrates by precipitation (in collaboration with Dr Alan J Johnson, New York University Medical Center).

(iv) 1976-1981: Leading studies to identify the causes of loss of factor VIII during the manufacture of Factor VIII concentrate. Implementing procedures to increase the yield of factor VIII, including the design of equipment for thawing plasma continuously which increased the yield of factor VIII at PFC by about 50% by 1981.

(v) 1980-1986: Discovering that the addition of the anticoagulant sodium citrate was a main cause of instability of factor VIII during the manufacture of Factor VIII concentrate and developing the addition of calcium to prevent progressive loss of factor VIII activity during processing. This discovery assisted in the introduction of virus inactivation technologies and the further purification of factor VIII without an unacceptable yield reduction.

(vi) 1982: Discovery of a new method for reducing the fibrinogen content of Factor VIII concentrate without loss of factor VIII, by precipitation of fibrinogen with zinc (in collaboration with Dr Milan Bier, University of Arizona).

(vii) 1981-1986: Undertaking research and development of methods of heat treatment of Factor VIII and Factor IX concentrates.

(viii) 1984-1990: Undertaking research and development of the chromatographic purification and formulation of factor VIII solutions. This work included the identification (in collaboration with Dr A J Johnson, New York University Medical Center) of a new ion exchange matrix (Q-Sepharose, Pharmacia Ltd) for the purification of factor VIII, which I believe is now in widespread use for the manufacture of Factor VIII concentrates, and the discovery of a means of formulating high purity factor VIII without having to add albumin as a stabiliser, as the addition of albumin not only reduced the product purity but also exposed recipients to many more donations.

(vix)1985-1992: The development of a simplified method of cold-ethanol fractionation for the preparation of Human Albumin, including the identification of new precipitation conditions and the development of automated diafiltration (in conjunction with Amicon Ltd) for the removal of residual ethanol.

(x) 1990-1994: Project Manager for the development of the SNBTS high-purity Factor VIII concentrate, Liberate®, based on a method of manufacture developed by Dr T Burnouf at the regional fractionation centre in Lille, France.

(xi) 1995-1996: Author of Pharmaceutical Expert Reports for the Product Licence applications for SNBTS high-purity Factor VIII concentrate (Liberate®) and Human Albumin (Alba®).

(xii) 1997-2006: Estimating and measuring the extent to which the agent responsible for vCJD might be removed by processes used at PFC for the manufacture of Plasma Derived Medicinal Products.

(xiii) My publications and PFC patent applications are listed in my CV [WITN6914002].

Please outline the organisation of PFC during your time there, including:

a. its structure, staffing and hierarchy;

Response to Question 17a.

17.a (1) Blood Products Unit/PFC, Edinburgh Royal Infirmary, 1950-1974

(i) The Blood Products Unit (BPU) was established in 1950 within the new Edinburgh Regional Transfusion Centre for the purpose of developing fractionated plasma products. Dr Drummond Ellis was appointed to head the unit, reporting to the Regional Transfusion Director, Dr Robert A Cumming.

(ii) Dr Ellis left the BPU in 1967 to join BPL and was replaced by Mr John G Watt who was originally given the title "Superintendent", later changed to 'Scientific Director'.

(iii) Mr Watt appointed chemist Dr James K Smith in 1968, with Dr Smith being assigned the role of Deputy Scientific Director.

(iv) To avoid confusion with Blood Products Laboratory (BPL), the BPU was renamed the Scottish Protein Fractionation Centre (PFC) in April 1970. Mr Watt was given the designation 'Scientific Director' and managed PFC independently from the Regional Transfusion Director, Dr Robert A Cumming.

(v) I joined the PFC in January 1973 as a senior biochemist and was assigned to work on troubleshooting the new continuous flow process for ethanol fractionation that Mr Watt had designed for the central fractionation process at the new PFC facility under construction at Liberton, in the south of Edinburgh.

(vi) At that time there were about 25 staff working in a number of different sections; the senior staff being Mr Watt, Dr Smith and Mr Grant (Production Manager).

(vii) Mr Barry White, a chemical engineer, was appointed in January 1973 to establish an engineering department. He became heavily involved with the construction of the new PFC facility, representing Mr Watt at site meetings.

(viii) In early 1974, a meeting of senior staff was convened by Mr Watt to consider a new organisational structure for the centre. The following departments were agreed and a person was assigned by Mr Watt to head each department. These were:

- Production; Department Head, Mr William (Bill) Grant.
- Quality; Department Head, Dr James K Smith.
- Engineering; Department Head, Mr Barry J White.
- R&D; Department Head, Dr Peter R Foster
- Administration; Department Head; Mrs Janette Campbell (appointed 1975)

17.a (2) PFC (Liberton) 1974-2008.

(i) PFC staff were given access to the Administration block of the new centre from April 1974. This included facilities for the Quality Department, the R&D department and Administration, including a Library.

(ii) Facilities for Production and Engineering became available at the end of 1974.

(iii). Up to this point, Production had continued at the Royal Infirmary site. It was only from January 1975 that commissioning of the new centre by PFC staff could begin.

(iv) Mr Watt had estimated that a total of about 120 staff would be required for the new centre and a process of recruitment began.

(v) The departmental structure remained as in 17.a(1)(ix) except that in 1979 the Engineering Department was divided into Project Engineering and Engineering & Building Maintenance.

(vi) To the best of my knowledge, the PFC Directors and Department Heads were:

- Director: Mr John G Watt (1967-1983), Dr Robert J Perry (1984-2004), Dr Katherine G Reid (acting, 2004-2006), Mr Richard Blythe (interim, 2006-2007), Dr Ronald V McIntosh (2007-2008).
- Production Head: Mr William Grant (1955-1990), Mr Martin Crowston (1990-1993),
- Mr Alan J Dickson (1993-2002), Dr Ronald V McIntosh (2002-2007), Mr Derek Radin (2007-2008).
- Quality Head: Dr James K Smith (1974-1975), Ms Moira Patterson (1975-1980),
- Dr Robert J Perry (1980-1983), Dr Bruce Cuthbertson (1984-2004), Mr Fraser Leslie (2004-2006), Mr Derek Edwards (206-2007), Ms Susan Goldwyre (2007-2008).
- Engineering Head: Mr Barry J White (1973-1979).
- Engineering & Building Maintenance Head: Mr Rowland Lines (1979-2005), Mr Steven Gilligan (2005-2007), Dr John Rudge (2007-2008).
- Project Engineering Head: Mr Ewan Walker (1979-2006), Dr John Rudge (2006- 2007).
- Research & Development Head: Dr Peter R Foster (1974-2008).
- Administration/Business Services Head: Mrs Janette Campbell (1975-1983), Mr Michael Ivey (1984-1995), Ms Isobel Ferguson 1995-1997), Dr Katherine G Reid (1997-2004), Ms Gwynneth Clay (2005-2007), Mrs Denise Wilson (2007-2008).

(vii) Virology Section

A PFC virology section was established in January 1974, with the appointment of Dr Bruce Cuthbertson. As PFC did not possess the facilities necessary for work with viruses, Dr Cuthbertson and technical support staff were seconded to work at Ruchill Hospital under Dr Robert (Bobby) Sommerville, Scotland's then leading clinical virologist. The main purpose of

this work was to establish analytical methods to screen donors for specific antibodies. Dr Sommerville was formally appointed as a consultant to PFC by Mr Watt.

The virology section transferred to PFC (Liberton) when a containment level 3 facility for handling dangerous pathogens was constructed within a Microbiology Extension to PFC that was built in the early 1980s, where it was managed within the Quality Department.

Following Dr Cuthbertson's appointment as Head of the Quality Department in 1984, Dr Katherine G Reid was appointed to head the Virology Section to be replaced by Dr Helena Hart in 1989 and Dr Carol Bienek in 1998.

Management of the Virology section was transferred from the Quality Department to the R&D Department in 1995.

(viii) Further information on the history of PFC is available in a paper written by me that was published in 2016 [WITN3530032].

b. how the PFC was funded;

Response to Question 17b

17.b PFC Funding

(i) PFC was funded by the Scottish Home and Health Department/Scottish Health Department, via the Common Services Agency (CSA) and SNBTS. To the best of my knowledge there were three exceptions:

- Finance to purchase an item of equipment for R&D was provided by Celltech Ltd. in 1990 as their contribution to a joint project on freeze drying/dry heat treatment.

- Studies on the removal of infectivity related to vCJD were financed from a European research fund, via a consortium that had been established for this purpose, circa 2000.

- The development and production of a Botulinum Toxin Immunoglobulin was funded by The Ministry of Defence, Defence Science &Technology Laboratory from about 2000 to 2008.

(ii) Products manufactured at PFC were supplied free of charge to the NHS in Scotland.

(iii) From about the late 1990's PFC was required to generate commercial income for NHS (Scotland), in addition to meeting Scotland's needs for plasma products. This was done by:

- Selling surplus plasma products (eg. Albumin to India, Intravenous Immunoglobulin to Regional Health Authorities in England).

- Undertaking contract part-production for biotech companies (eg. dispensing and freeze drying of a product for Pharmaceutical Proteins Ltd).

(iv) In the period 2000-2005, PFC generated £16.6m from commercial activities. See the response to a question in the Scottish Parliament concerning the funding of SNBTS [WITN6914015].

c. the decision-making process within PFC, and in particular how decisions were taken on which projects should be pursued.

Response to Question 17c

17.c Decision Making within PFC

(i) Decision making within PFC was generally taken by the Director in consultation with Department Heads.

(ii) When I was assigned to the role of Head of R&D, Dr Smith gave me a list of all current R&D projects, together with a brief status report for each project. From 1974 to 1982, decisions on which projects to be pursued and their relative priority, were taken by the PFC Scientific Director, Mr Watt, following verbal consultation with myself.

(iii) From January 1982, decisions on which projects to pursue at PFC in respect of coagulation factor concentrates were either confirmed or taken by the National Medical Director of SNBTS, Dr John D Cash, who established a committee for this purpose, named the Coagulation Factor Study Group, which he chaired, see para 3.3(i). Decisions are recorded in the minutes of the meetings.

(iv) In 1986, I established a PFC committee to progress development projects known as 'The PFC Development Management Team'. This was chaired by me and included amongst its members the PFC Director, the Head of Quality and senior scientific staff from R&D. Subsequently the Head of Production was included, see para 3.4(ii). Decisions are recorded in the minutes of the meetings.

(v) In 1990, Professor Cash extended the remit of the SNBTS Coagulation Factor Study Group to encompass all PFC's product developments. The name of the committee was changed to the Product Development Group. Following the retirement of Professor Cash in 1996, the committee was chaired by Professor Franklin who replaced Professor Cash as SNBTS National Medical and Scientific Director and continued to operate until 2006, see para 3.3 (ii). Decisions are recorded in the minutes of the meetings.

(vi) Between scheduled meetings, proposed changes to R&D strategy or priorities would be agreed verbally by PFC staff with the PFC Director who would then agree them verbally with the SNBTS National Medical Director.

(vii) Proposals concerning the development of products for the treatment of people with haemophilia were put to Haemophilia Directors by Professor Cash for their agreement, see para 3.2(i). These proposals and the subsequent decisions are recorded in the minutes of the meetings.

The Penrose Final Report described the administrative arrangements concerning the external management of the PFC in the 1970s and 1980s at Chapter 17 of the Penrose Final Report. Its conclusion, as summarised at 17.93, was that *"Both before and after 1974 the Regional, and latterly the national Medical and PFC Scientific Directors of the Service had largely autonomous control of their respective organisations, exercised independently of the [Common Services Agency]."* Please state whether you agree with this conclusion, and explain any disagreement. Please provide any further detail that you consider to be relevant to the Inquiry.

I had no direct involvement with Common Services Agency (CSA). However, to the best of my knowledge I believe that the conclusion at 17.93 is correct, but would note that:

- The CSA was legally responsible for the SNBTS, including the PFC.
- SNBTS finances were managed by the CSA, including all financial transactions, including those of PFC.
- SNBTS staffing matters were handled via the CSA.

- A CSA Blood Transfusion sub-committee met regularly to take decisions on matters of SNBTS administration, including the authorisation of overseas travel and attendance at courses and conferences.

- I believe that a proposal from Mr Watt in 1975, concerning staffing arrangements for PFC, which included a proposal for shift-working, was not taken forward by the CSA Blood Transfusion sub-committee as the members did not think it would be accepted by Trades Unions.

- SNBTS Directors were not members of the CSA Blood Transfusion sub- committee, but they were allowed to attend as observers.

Further information may be obtainable from Dr Brian McClelland, who was directly involved with the CSA for much of the period in question.

In October 1981, the PFC was the subject of a number of criticisms following a Medicines Inspectorate Report. Please comment on whether, in your view, those criticisms were justified and, if they were, why the failings identified had arisen. Please explain what role you took in rectifying the issues identified, and – insofar as it is within your knowledge - the steps taken by the wider PFC management. Please explain what effect these remedial actions had on the development of blood products at PFC, and in particular what effect (if any) they had on work on viral inactivation of blood products (and the speed at which viral inactivation was achieved).

19.1 Background to the October 1981 Inspection of PFC

(i) Pharmaceutical manufacturing facilities in the UK are required to comply with guidance issued by the Department of Health/DHSS.

(ii) This guidance was first issued by DHSS in 1971 and was entitled 'Guide to Good Pharmaceutical Manufacturing Practice' and published by HMSO.

(iii) A second edition of the Guide was issued in 1977 [PRSE0002339], in which "*the whole text was revised, some entirely new sections added*" (see introduction to the third edition 1983, page 3 [SBTS0000423_004]).

(iv) To the best of my knowledge the design of PFC had been completed before any guidance had been issued by DHSS and was therefore based on then current international standards, such as the USA Code of Federal Regulations 21, part 221, as well as lessons learned from the established plasma fractionation facilities that Mr Watt had visited.

(v) When the new PFC building had been completed, Mr Watt requested that it be inspected by The Medicines Inspectorate to determine if it met the DHSS guidance that had been issued in 1971.

(vi) His request for an immediate inspection was declined. He was advised instead to apply for a Manufacturer's Licence by providing complete details of PFC's manufacturing facility and its operation. This application was submitted in 1976 and a Manufacturer's Licence for PFC was granted in 1976 for a period of five years, which was the standard practice of the Medicines Division of the Department of Health.

(vii) Mr Watt was then advised to submit applications for Product Licences, beginning with coagulation factor concentrates.

(viii) An application for a Product Licence for PFC's Factor VIII concentrate was submitted and approved in 1978 and an application for a Product Licence for PFC's Factor IX concentrate was submitted and approved in 1979.

(ix) I believe that Mr Watt appreciated that PFC did not fully meet the 1977 GMP Guidelines, but he did not attempt any remedial action until an inspection could be carried out because he wanted to agree any actions with the inspectorate and to have their report to provide independent justification for any finance required.

(x) The first inspection of the PFC facility by the Medicines Inspectorate took place over a two-week period in December 1979/January 1980 and was undertaken against the DHSS guidance that had been published in 1977.

19.2 The First Inspection of PFC, 1979/80

(i) To assist their inspection, the inspectors (Mr John Flint and Dr John Purves) requested that a member of PFC staff be assigned to accompany them to take notes on their behalf. I was assigned to that role.

(ii) It was clear from the outset that their primary concern was the risk of bacterial contamination. It was explained to me that this concern was due to the '*Devonport Incident*', in which a number of deaths had occurred in a hospital in Devonport in 1972 from treatment with infusion solutions that had not been sterilised correctly.

(iii) The main concern that they identified at PFC in this regard was the use of a screw cap bottle (that had been designed and approved by the Medical Research Council) that was used for Albumin solutions, as they believed that bacterial growth might take place within the glass grooves of the screw section. They were also concerned at the absence of facilities for bacteriological testing at PFC, which was being done for PFC at an external laboratory.

(iv) Another major concern of the Inspectors was that finished products were being stored off-site, which they viewed as insecure. This was due to the area that was originally provided for this purpose having been converted for the preparation of coagulation factor concentrates, to accommodate a demand for these products that had not been anticipated when PFC was designed.

(v)The Inspectors also explained to me that the main cause of errors in the manufacture of pharmaceutical products was mix-ups due to the crossing of production lines. In contrast to conventional pharmaceuticals, plasma fractionation involved the manufacture of multiple products from a common feedstock, making the segregation of product lines more challenging.

(vi) Plans to address all of the issues raised at the inspection were drawn up by Mr Watt in conjunction with the Heads of Production (Mr Grant), Quality (Dr Perry) and Engineering & Building Maintenance (Mr Lines).

(vii) I was not involved in this exercise, but I was generally aware of the plans and that they were agreed with the Inspectorate and with the SHHD.

19.3 The Inspection of October 1981 (BNOR0000572)

(i) I was not involved with this inspection, but I believe it was carried out to follow up progress with the plans to modify PFC that had resulted from the first inspection.

(ii) As these plans involved significant building modifications, I believe that many of the points raised at the first inspection had still to be resolved and that in this respect the report of the inspectors was correct.

(iii) Paragraph 4.4 of the report concerns upgrading the operation used for removing frozen plasma from its plastic pack and preparing it for processing to obtain a "*clearer starting material*", meaning a reduction in bacterial content. The level of bacteria in this area had increased due to an action taken by the inspectors during 1981. Previously, individual donations of plasma were pooled at Regional Transfusion Centres into 2 litre or 5 litre plastic packs, prior to being frozen, then sent to PFC for frozen storage. Although this pooling procedure was done using sterile connectors, the inspectors were concerned that bacterial contamination might still be possible, and the practice was banned. This resulted in plasma then being sent to PFC (and BPL) as individual donations in plastic bags, each holding about 250 ml.

These individual donation bags had been exposed to the general environment of blood donor sessions, which ranged from village halls to regional transfusion donor centres. Not only was a much greater quantity of plastic being received and handled at PFC, but the surface of the plastic was more heavily contaminated with bacteria than the 2 litre and 5 litre packs used previously. This resulted in a higher level of bacterial contamination in this process area at PFC. To resolve this problem PFC staff quickly developed a suitable method of cleaning the plasma packs after they were removed from frozen storage but before they were opened.

19.4 Impact on Virus Inactivation

(i) I believe that the impact of the remedial actions agreed with the Medicines Inspectorate on the timescale for achieving virus inactivation were positive in two respects.

(ii) The first of these is that permission was granted for the construction of a Microbiology Extension to PFC, for which plans had been drawn up in the mid-1970s, but which had not previously been authorised by the SHHD.

(iii) The main reason for approval being given for this extension was the provision of bacteriology laboratories, which had been included in its design, which the Medicines Inspectorate had requested to enable PFC to be able to carry out its own bacteriological testing on-site.

(iv) Also included in the design of the Microbiology Extension were a category 3 containment facility for work with dangerous pathogens (i.e. viruses) and an R&D pilot plant.

(v) The R&D pilot plant enabled large volume studies to be undertaken on pasteurisation of factor VIII, which led to the development of both 8Y (at BPL) and to Z8 at PFC, both of which were free from transmission of hepatitis C.

(vi) The PFC Virology Laboratory enabled virus inactivation studies to be undertaken with live viruses at PFC, including studies with HIV on behalf of BPL as well as for PFC.

(vii) A scheduled 3-month closure of plasma processing at PFC, to carry out planned remedial actions, coincided with evidence that HIV could be inactivated by dry heat treatment and a decision being taken by SNBTS to apply this technology to PFC's existing product. To achieve this, batches of FVIII concentrate had to be returned from storage, labels had to be removed from each vial by manual scrapping, followed by heat treatment, inspection, quality control, labelling, re- packaging and distribution.

(viii)The 3-month closure of plasma processing meant that additional PFC staff were available to assist with these tasks, enabling PFC to be able to distribute supplies of heat treated Factor VIII for Scotland and Northern Ireland on 10th December 1984.

(ix) The remedial building works were completed as planned, with the processing of plasma being re-started on 20th January 1985.

(x) Further information on the regulation and inspection of PFC, including the topic of Crown Immunity, is available in an SNBTS paper on Regulation that was provided to the Penrose Inquiry (PEN.017.2723) [PRSE0002556].

Please explain what knowledge (i) you, and (ii) PFC management in general had of the donor selection policies and practices of SNBTS in respect of the plasma that was provided to PFC for fractionation. In particular, what knowledge was there that plasma donated by prisoners was used in the early 1980s? What, if any, concerns did you have about this practice and what, if anything, did you do to raise them?

(i) To the best of my knowledge, SNBTS Regional Transfusion Directors were responsible for donor selection.

(ii) I had no knowledge of donor selection policies and practices, other than guidance in a pamphlet that was published by DHSS in 1979, a copy of which was available in the PFC library [PRSE0003128]. I am not aware of any further guidance on donor selection by

DHSS/SHHD. Guidance on donor selection was published in 1983 by the Council of Europe (see section 63.1(viii)), but I was not aware of this at the time.

(iii) This matter was the responsibility of Regional Transfusion Directors and, although I cannot speak for others, I do not believe that PFC management in general was aware of SNBTS policies and practices in this respect. However, the PFC Director was a member of the SNBTS Directors Committee and would have been aware of any discussions on this topic from their attendance at these meetings. SNBTS Directors meetings were confidential. The minutes and associated papers were held in confidence and were not available either to myself or to PFC management in general.

Please explain what knowledge (i) you, and (ii) PFC management in general had of the donor selection policies and practices used in Northern Ireland in respect of the plasma that was provided to PFC for fractionation in the early 1980s. Did those policies and practices result in plasma from Northern Ireland being treated any differently to plasma from Scotland?

See my answer to question 20.
I was not involved in the selection and scheduling of plasma for processing, but I believe that plasma from Northern Ireland was processed together with plasma from Scotland, once standard validation studies had been completed.

Section 4: The relationship between PFC and the Bio Products Laboratory ("BPL")

Please explain, in general terms, the nature of the relationship between PFC and BPL, including the level and regularity of your interaction with BPL management and scientists during your employment with PFC (nb. please construe references to BPL to also include the associated Plasma Fractionation Laboratory ("PFL") in Oxford).

Please identify or refer to relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

22.1 Personal Communications Between Staff of PFC and BPL/PFL
(i) Shortly after I joined PFC, I was assigned the task of leading a delegation of PFC staff to BPL. This group was made up of all of PFC's scientific and technical professional staff at that

time; excluding the Director (Mr Watt), his deputy (Dr Smith) and the Production Manager (Mr Grant).

(ii) The purpose of the exercise was to enable middle-ranking PFC staff to meet their counterparts at BPL to encourage dialogue between them.

(iii) A similar delegation from BPL visited PFC when the new facility opened in 1975.

(iv) Dr Smith left PFC in mid-1975 to join PFL/BPL and we maintained an on-going dialogue, which involved correspondence, exchange of reports and face-to-face meetings (usually held at PFC). For examples, see PEN0131309, pages 56-65.

(v) I also knew Dr Peter Feldman well. He led the development of Factor IX concentrates at PFL/BPL. Before he joined PFL, his PhD had been sponsored by PFC and I had been his industrial supervisor. During his PhD he had spent a period working at PFC.

(vi) I was familiar with Dr Mike Harvey who was head of R&D at BPL during the 1980s. Dr Harvey's scientific interest concerned the application of affinity chromatography to the preparation of Albumin, whereas my priorities at this time concerned coagulation factor concentrates, for which Dr Smith was responsible at BPL/PFL.

(vii) I always encouraged my staff to dialogue with their counterparts at BPL/PFL. I am aware that this was usually done by telephone and may not have been recorded.

(viii) Examples include Dr Ronald McIntosh (PFC R&D) communicating regularly with Mrs Lowell Winkelman and Mr David Evans at PFL on coagulation factor developments and Dr Anne Welch (PFC R&D) communicating regularly with Dr Mike Kavanagh, Mr John More and Mr Dave Wesley at BPL on matters concerning immunoglobulins and albumin.

(ix) I believe that PFC Head of Quality, later Director of PFC, Dr Robert Perry, had a close working relationship with the Head of Quality at BPL/PFL Dr Terry Snape.

(x) Other PFC departments acted in a similar manner to R&D in having regular dialogue with their BPL counterparts, examples included:

- Head of Quality, Dr Cuthbertson with his BPL counterpart Dr Snape.

- PFC Quality Control staff communicating directly with Mr Geoff Sims who headed the coagulation QC lab at BPL.

- The PFC Section Head responsible for freeze drying (Mr John Sinclair) communicating directly with his counterpart at BPL Mr Kevin Kinnarney.

(xi) PFC staff would meet their BPL/PFL counterparts at scientific conferences and symposia, including meetings at the National Institute for Biological Standards & Control (NIBSC) where Dr Trevor Barrowcliffe was the acknowledged world authority on the assay and standardisation of Factor VIII concentrates.

22.2 Formal Collaborations (that I can recall from memory)

(i) Following the Medicines Inspection of BPL in 1979, it was apparent that a new facility was required. A project group was formed, under the chairmanship of Dr Peter Dunnill of University College London, to undertake a technology review. A number of PFC staff, myself included, were invited to participate in meetings held at BPL.

(ii) When research began at PFC on the pasteurisation of coagulation factors, the possibility that heat treated Factor IX might be thrombogenic (ie. cause thrombosis)
was a major concern to Dr Cash. He believed that a suitable animal model should be established to determine safety in this respect. PFL was invited to collaborate in the study, with Dr Smith agreeing to do so. As the PFL Factor IX concentrate was manufactured using the same method of preparation as PFC, identical findings were obtained by both groups. Ultimately both PFC and PFL Factor IX concentrates had to be reformulated to bring a laboratory test for thrombogenicity within limits after heat treatment. This required the addition of the protein Anti-thrombin III. This protein was prepared routinely at PFL, but not at PFC. Therefore, PFL supplied PFC with Anti-thrombin III for this purpose and continued to do so throughout the life of PFC's heat treated Factor IX concentrate in question.

(iii) The PFC Microbiology Extension that was constructed in the early 1980s included a category 3 containment facility suitable for undertaking studies with live pathogenic viruses. A steam sterilisable pilot-scale freeze drier was also available. As BPL did not possess these facilities, PFC agreed to undertake virus inactivation validation studies on behalf of BPL, that were needed to obtain Product Licences for their heat treated coagulation factor concentrates. This work was undertaken by the PFC virology section head Dr Katherine Reid, under the direction of Dr Bruce Cuthbertson, Head of Quality at PFC.

22.3 Other Collaborations/Assistance (that I can recall from memory)

(i) In the late-1970's, the yield of PFC factor VIII increased to a point where freeze drying capacity was about to limit output. The purchase and installation of additional freeze drying capacity typically took about 18 months. One way of continuing to increase output before a new freeze drier could be installed was to add an extra shelf to the existing freeze drier. This could be done only by reducing the height of the FVIII vial. BPL used a shorter vial than PFC, but this was made specifically for them and was not available generally. The PFC Production Manager, Mr Bill Grant, arranged for a supply of these shorter vials from BPL, who continued to supply them to PFC until the early 1990s, when a high-purity FVIII was developed for which a standard small vial could be purchased.

(ii) In 1982, a problem developed with an assay that was essential for the quality control of immunoglobulins. Dr Ronald McIntosh (PFC R&D) was assigned to work on this problem. He immediately contacted BPL for advice, only to discover that they had the same problem. Dr McIntosh went on to solve the problem and shared his findings with BPL.

(iii) Information on PFC's R&D concerning pasteurisation of factor VIII was shared with Dr Smith of PFL during 1983/84. It was in applying the information from PFC in May 1984, that PFL discovered a way of further purifying factor VIII that led eventually to the development of its new Factor VIII concentrate 8Y, which was ultimately found to be free from transmission of non-A, non-B hepatitis.

(iv) In January 1985, I was given the specification of an oven for dry heat treatment that had been designed by BPL in conjunction with Pickstone Ltd., a company that specialised in the manufacture of precision ovens. PFC ordered an equivalent oven from Pickstone in January 1985, which was delivered in July 1985.

(v) In 1990, a standard depth filter that was essential for the preparation of immunoglobulin and albumin products was withdrawn from use. An alternative had to be identified and validated. Staff at PFC (Dr Anne Welch and Mr Christie Turnbull) and BPL (Mr John More) worked closely together to resolve this issue as quickly as possible.

See also my third written statement to the Penrose Inquiry, cited document no. 5 (PEN.012.1438) pages 21-24 [PRSE0003349].

Please explain the extent to which relations between PFC and BPL assisted or impeded from time to time the achievement of common goals, for example, viral deactivation and self-sufficiency.

I believe that the very close working relationships between staff of PFC and BPL/PFL assisted the achievement of many common goals, including virus inactivation. See also my response to question 22.

In particular, please address the following points:

a. **the frequency and nature of communications between PFC and BPL including meetings, correspondence and telephone conversations (whether formal or informal);**
b. **the subject matter of those communications;**
c. **the personnel involved, in particular the heads of R&D at the respective bodies during your tenure of that position at PFC;**
d. **collaboration on any R&D projects;**
e. **the general "tone" of the relationship between SNBTS/PFC and BPL and the extent to which that might have changed over time and according to the personalities involved and their seniority;**
f. **the extent to which any preference for less formal routes of information exchange assisted collaboration and reciprocity in achieving common aims.**

In this respect, you may be assisted by reference to the First Penrose Statement (§ 4.2), the First Penrose Supplementary Statement (§ A.2 et seq), the Third Penrose Statement (§10 and 12, in particular), the Fourth Penrose Statement (§ 1, 7 and 9), the Heat Treatment Briefing Paper (§ 4.2) and The Archer Statement (p15).

(i) See my response to question 22.

(ii) This informal information exchange was mostly undertaken as required and, to the best of my knowledge, was always carried out in a friendly and helpful manner.

(iii) I believe that more formal arrangements could have resulted in important information being delayed, filtered, diluted and possibly mis-represented inadvertently by more senior managers, who themselves may not have had direct knowledge or experience of the scientific and technical matters involved.

(iv) In my opinion the less formal routes of information exchange, in which staff of PFC

and BPL/PFL were engaged, were generally much more productive than formal arrangements would have been.

In Dr Cash's Second Penrose Statement, he states (§10.2): "*On appointment as NMD in 1979 I discovered that the relationship between Mr. Watt (Director of PFC) and his counterpart at BPL (Dr. Lane) was greatly strained. Before and after Mr. Watt left the SNBTS (December 1983) I made considerable efforts to repair the professional interface between SNBTS and BPL.*"

Is Dr Cash's characterisation of the relationship between Mr Watt and Dr Lane one that you recognise? How did the relationship between Mr Watt and Dr Lane affect the overall relationship between the two organisations?

(i) I rarely met with Dr Lane and had no knowledge of any difficulty between him and Mr Watt.

(ii) Mr Watt did not usually discuss any external problems with staff of PFC, as he always took great care to avoid anything that might distract PFC staff from their duties within PFC.

(iii). If there was any difficulty between Mr Watt and Dr Lane, I do not believe that this was known by the staff of their respective organisations, nor do I believe that it affected the overall relationships between the staff of both organisations.

In Dr Cash's Second Penrose Statement (§12.11) he describes attempting to bring together the management teams of PFC and BPL in December 1980 to explore a joint UK approach to the manufacture and research of Factor VIII concentrates for the whole of the UK, but that this was rejected by BPL management with support from the DHSS and the knowledge of the SHHD. Dr Cash further recalls that he "*took the view that as at December 1982, the efforts at bridge building had, before and after 1979, all come from the SNBTS and had been comprehensively rejected by BPL and DHSS.*"

At §12.2 Dr Cash refers to his suspecting that you were aware that in 1980 he had sought to persuade Dr Lane of BPL that "*we really ought to be making collaboration between BPL and PFC open, intensive and a high priority, and that this proposal had been rejected.*"

The PFC was also not represented on the CBLA Central Committee on Research and Development in Blood Transfusion, which first met on 21 June 1983. In the Fourth Penrose Statement (§ 8(i)) you state that you were unaware of the CBLA Committee.

In your view:

a. **Do you agree with this characterisation of BPL, the DHSS, and the SHHD being apparently "uninterested" in such a joint UK approach between PFC and BPL?**
b. **If so, why, in your opinion, did this lack of interest occur?**
c. **Would there have been merit in such an approach?**
d. **What, from your perspective, would have been the advantages and disadvantages of such an approach?**
e. **Would such an approach have been likely to have resulted in the earlier introduction of factor concentrates that inactivated (i) HIV, and (ii) HCV?**
f. **How, if at all, did the exclusion of the PFC from the CBLA Committee affect the work of the PFC, in particular in respect of providing virally inactivated factor concentrates?**

(i) I have no knowledge of the views of DHSS or SHHD other than as given in my response to question 22, in which an agreement that plasma from England be processed at PFC was not implemented by DHSS/SHHD.

(ii) Dr Cash was not directly involved with day-to-day work within PFC. Therefore, I am sure that he did not appreciate the extent to which the staff of PFC and BPL/PFL were already co-operating informally and how productive this was, making more formal co-operation unnecessary.

(iii) I am sure that "*the exclusion of PFC from the CBLA Committee*" (paragraph 26f of the question) had no effect in providing virus inactivated factor concentrates, as direct informal communications were already taking place between the scientists involved. See also my answer 24 (iv).

In your First Penrose Statement (§5.3) you list a number of other plasma fractionation organisations and related bodies with whom the PFC communicated. Please explain the nature of that communication in relation to each of those institutions.

a. **Please state what, if any, policies, protocols or practices governed PFC's communications with private pharmaceutical companies.**

b. **Please comment on the extent to which, if at all, concerns about patents inhibited or limited co-operation with BPL or other laboratories, companies or organisations.**

c. **Please identify, and explain, any areas in which you feel PFC did not have access to information or co-operation that it may reasonably have expected to obtain (for example, because a particular organisation was not open to such co-operation). Comment on what, if any, effect this had on PFC's production of blood products and its work on viral inactivation.**

(i) When I joined PFC, I became aware that Mr Watt had established relationships with plasma fractionation organisations around the world, including commercial companies. This involved correspondence and visits to other fractionation facilities for the exchange of scientific and technical information.

(ii) The Director of PFC, Mr Watt was a member of the following bodies:

- The Blood Products Sub-Committee of the European Pharmacopoeia, which established the specifications required for plasma products.

- The Biologicals Sub-Committee of the Committee on Safety of Medicines, which determined applications for product licences.

- The WHO Group of Experts on Requirements for Processing Blood and Blood Products, which laid down international guidelines on the design and operation of facilities for the preparation of plasma products.

(iii) Membership of these committees enabled Mr Watt to meet and share information with other committee members, all of whom were experts in the field.

(iv) I am not aware of any policies concerning communications with commercial companies, except that from April 1974 all travel and its purpose had to be approved by the CSA Blood Transfusion Sub-Committee, see my answer to question 18.

(v) To the best of my knowledge the purpose of communications with commercial companies was for mutual scientific benefit.

(vi) Communications with commercial companies reduced considerably following the replacement of Mr Watt with Dr Perry as PFC Director, as Mr Watt had been very assiduous in establishing contacts within commercial companies.

(vii) In my experience most companies maintained strict confidentiality over critical information, for commercial reasons. I do not believe that information or co-operation which PFC might reasonably have expected to obtain was withheld.

(viii) The most important information relating to advances in virus inactivation was evidence that a particular technology was either ineffective or effective in inactivating viruses of concern. Data of this type were usually reported promptly by the investigators, whether the studies were commercial or non-commercial. For example:

- Failure of Baxter's Hemofil HT (dry heat at 60°C for 72 hours) to inactivate NANBH was reported promptly at a conference by the lead investigator, Dr Mannucci (see my response to question 43).

- Evidence that HIV could be inactivated by dry heat treatment of PFC's existing product was reported promptly in November 1984 at an international symposium by a spokesperson for the US Centers for Disease Control (see my response to question 43).

- Preliminary data suggesting that BPL's 8Y (dry heat treated at 80°C for 72 hours) might be safe from transmission of NANBH were reported promptly to UK HCDO in October 1986 (see my response to question 43).

- Application of dry heat at 80°C for 72 hours to FVIII concentrate depended on the formation of a specific ice crystal structure during freeze drying. The importance of this was identified at PFC, where a specific method for achieving the necessary ice structure was devised. This information was reported to an International Congress in July 1987 (see my response to question 43).

(ix) Concerns about patents vis-à-vis BPL were never a consideration, as I assumed that PFC, being a part of the NHS, would be granted free access.

(x) Concerns about patents held by commercial companies were not an issue as I believed that the cost of access, if available, would be met by SHHD. For example, when PFC adopted solvent-detergent technology for virus inactivation, a licence for this purpose was obtained from the New York Blood Center.

In Dr Cash's Second Penrose Statement (§12.13) he states that the "*main reason why we met at BPL on 15 December 1982 was for BPL and MCA/DHSS to ascertain whether the SNBTS would support the introduction of clinical trials on UK haemophilia patients of US sourced commercial VIII concentrates that had been subject to some form of viral inactivation. I had the feeling throughout this meeting that a decision in favour of this development would somehow be an advantage to BPL and DHSS.*"

Dr Cash further states that (§12.143) "*I viewed this development in the UK was actually a sophisticated marketing exercise by US commercial fractionators rather than one directed to product safety. I believed it was primarily designed to once and for all 'take out' those irritating Scots with their pious public sermons proclaiming the sanctity of national self sufficiency! It followed that I believed in 1982 that the NHS fractionators should do nothing to support our commercial rivals.*"

a. **To what extent, if at all, did you share Dr Cash's view of the motives of US fractionators in seeking UK clinical trials and his view that the NHS fractionators "*should do nothing to support our commercial rivals.*'?**
b. **To what extent, if at all, would such an approach, if implemented in Scotland, have affected the development of methods of viral inactivation of blood products by the PFC?**
c. **Why would a decision in favour of the proposal have been an advantage to BPL and DHSS as Dr Cash suggests?**

28.1 <u>Background Information</u>

(i) Medicinal products for use in the UK, including plasma products, had to be approved by the Committee on Safety of Medicines (CSM) before they could be entered into general use. See paragraph 3.6 of the Witness Statement of Lord Fowler (WITN0771001).

(ii) Manufacturers who were seeking approval of a new or revised medicinal product were normally required to provide clinical trial data to demonstrate that their clinical objectives had been achieved.

(iii). To obtain the clinical data needed for the CSM approval of a factor concentrate that had been treated to eliminate transmission of no-A, non-B hepatitis (NANBH) it was necessary to

demonstrate that the concentrate in question was both clinically effective in treating haemophilia and that NANBH was not transmitted.

(iv) By 1982, it was becoming known that all recipients of coagulation factor concentrates may have been infected with NANBH. Therefore, the only patients suitable for the clinical evaluation of coagulation factor concentrates that had been treated to inactivate agent(s) responsible for NANBH, were those who had not already been treated with coagulation factors.

(v) As haemophilia is a genetic disorder (either inherited or newly formed ie. *de novo*) new cases continue to be diagnosed. In the UK, about 80 new cases of haemophilia are diagnosed each year. This means that the number of patients in the UK who were suitable for the clinical evaluation of factor concentrates that had been treated to eliminate infection with NANBH was limited to a maximum of about 80 per year.

(vi) I believe that Dr Cash was concerned that if UK patients were entered into clinical trials of commercial products, there may not be enough patients for BPL and PFC/SNBTS to carry out the clinical trials needed for their products to be approved by CSM.

28.2 <u>Response to Question 28</u>

(i) I am not familiar with issues surrounding clinical trials, as it was SNBTS policy that this was the responsibility of its medically qualified staff, with Dr Cash taking the lead in this respect.

(ii) According to relevant publications, the clinical trials by US commercial companies, to which Dr Cash referred, were carried out in a number of countries; including Italy, France, West Germany and the USA, as well as the UK.

(iii) To the best of my knowledge, no patients in Scotland were entered into clinical trials of US sourced commercial FVIII.

(iv) I am not sure that this is consistent with Dr Cash's opinion that the motive of US commercial companies was to target the UK in general, and Scotland in particular, to undermine UK state fractionators.

(v) Dr Cash did ask me, in 1985, if I thought a NANBH clinical safety study should be carried out with PFC's FVIII that was dry heat treated at 68°C for 24 hours. I advised him against this,

as I did not believe that this product was safe from NANBH transmission. Dr Cash agreed with my advice.

(vi) I do not know if the fact that some UK patients were entered into commercial clinical trials delayed completion of the 8Y safety study. However, this did not affect the development of virus inactivation at PFC, as the decision to develop a product comparable to 8Y was based on increasing the margin of safety against HIV and was taken well before completion of the 8Y clinical NANBH safety study

(vii) I do appreciate the concerns being expressed by Dr Cash, as only about 8 patients per year were potentially available in Scotland for SNBTS to complete the necessary clinical trials.

Section 5 - Knowledge of risk associated with blood products

In general terms, how would you characterise and describe the state of scientific knowledge of the risk of infection associated with blood products amongst fractionators from the mid 1970s to the mid 1980s concerning:

a. **Hepatitis B ("HBV");**
b. **Non-A Non-B hepatitis ("NANB");**
c. **HIV/AIDS**

Please identify the key issues, in particular, the risk from imported blood products from the USA, and how the state of scientific knowledge evolved and the consequent response to emerging and known risks.

Please identify or refer to relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

29.a Hepatitis B

(i) I believe that all fractionators were well aware that certain products (e.g. coagulation factor concentrates) carried a risk of hepatitis transmission because a number of reports of hepatitis transmission had been published (see [WITN6914003] for references).

(ii) Regulatory authorities, such as the UK Committee of Safety of Medicines (CSM) and the USA Food and Drug Administration (FDA) were also well aware of this risk because a number of reports of hepatitis transmission had been published (see [WITN6914003].

(iii) In the UK, the CSM required that warnings by Fractionators be approved by them for issue with the products. Some examples of these are available [PRSE0002726].

(iv) For example, a warning issued by Cutter Biologicals in 1978 was especially clear:
"***Warning*** *Koate concentrate is a purified dried fraction of plasma obtained from many paid donors. The presence of hepatitis virus should be assumed and the hazard of administering Koate concentrate should be weighed against the medical consequences of withholding it, particularly in persons with few previous transfusions of blood and plasma products".*
(v) Commercial Factor VIII concentrates were licensed by the UK regulatory authority from February 1973 and would have included approved warnings of hepatitis (see PEN.013.1125, pages 46-47) [PRSE0001083].

29.b Non-A, Non-B Hepatitis

(i) I believe that fractionators would have been generally aware of the risk of non-A, non-B hepatitis from about the mid-1970s from publications in the medical literature.

(ii) For example, in March 1976, an FDA symposium was held in the USA entitled "*Unsolved Therapeutic Problems in Hemophilia*".

(iii) The proceedings of the symposium were published in 1977 (Fratantoni JC et al. (eds) Unresolved Therapeutic Problems in Hemophilia (US Dept. of Health, Education and Welfare) 1976).

(iv) In a paper on pages 45-50, FDA authors R Gerety and L Barker wrote [BAYP0000020_004]:
"*recent studies have provided considerable evidence for a third category, termed non-A, non-B hepatitis, which is presumably caused by an as yet unidentified agent or agents".*

(v) A copy of these proceedings was available in the PFC library, and I believe would probably have been known to fractionators in general, especially as the symposium was organised by the USA FDA.

(vi) The warnings of risk issued with factor concentrates by fractionators usually referred to hepatitis in general without differentiating between hepatitis B and/or hepatitis non-A, non-B.

(vii) Although generally aware of non-A, non-B hepatitis, I believe that fractionators may have been more concerned about hepatitis B because, at the time, hepatitis B was generally

considered to be more serious than NANBH and donor screening methods for hepatitis B infection were imperfect.

(viii) I believe that the concern of fractionators moved more towards non-A, non-B hepatitis after a vaccine for hepatitis B became available in the early 1980s.

29.c HIV/AIDS

(i) I believe that fractionators would have known from the 16th July 1982 issue of MMWR that three people with haemophilia in the USA had been diagnosed with Pneumocystis carinii pneumonia, two of whom had died (Penrose Inquiry document, LIT.001.0559) [PRSE0000523].

(ii) The state of knowledge of commercial companies is evidenced in a letter of August 1983 from The Lord Glenarthur, who wrote *"in March this year the US Food and Drugs Administration (FDA) initiated new regulations for the collection of plasma designed to exclude donors from high risk groups"* and *"some of the American manufacturers had, well in advance of the FDA, instituted their own precautions which were at best as demanding as those later contained in the new regulation."* (Penrose Inquiry document, PEN.013.1240) [PRSE0001258] & (Penrose Inquiry Preliminary Report, 8.21) [PRSE0007003].

(iii) In Scotland, Dr Brian McClelland, Director of the Edinburgh Transfusion Centre, led moves to cease taking blood from donors considered to be at risk from AIDS (Penrose Inquiry Preliminary Report, 8.28) [PRSE0007003] with a leaflet for blood donors being issued in Edinburgh from 30th June 1983 (Penrose Inquiry Preliminary Report, 8.39) [PRSE0007003].

(iv) The actions described in (ii) & (iii) indicate the extent to which the risk of AIDS was becoming appreciated by fractionators and transfusion services and the actions that were being taken by them.

(v) Further information is available in section 8 of the Preliminary Report of the Penrose Inquiry [PRSE0007003].

> **At §34 of Dr Smith's Proof he states that: "Most Haemophilia Centre Directors (Dr F.E. Preston … a notable exception) seemed to think that hepatitis Non-A Non-B was not a very serious disease, rarely causing death, hardly ever giving clinical jaundice, and without the late sequelae of liver cancer or cirrhosis. Fractionators were much more concerned, believing the worst possible case, as usual and subsequent events showed their instincts were right."**

You may be assisted further by reference to Dr Smith's Penrose Statement (§6), and Dr Smith's Transcript, p.25 (4).

a. **Do you agree that fractionators were more concerned about NANB than haemophilia physicians? If so, please explain why.**

b. **In your experience, and in general terms, were the opinions of fractionators given sufficient weight and prominence by clinicians, scientists and policy makers involved in this field in the late 1970s and early 1980s?**

(i) I had much less interaction with haemophilia doctors than Dr Smith. PFC was a part of SNBTS and it was the policy of SNBTS that SNBTS medical staff should interact with clinicians rather than PFC staff, who were not medically qualified.

(ii) I never attended meetings of UK HCDO and did not read the minutes of their meetings, as these were held in confidence in PFC and were not available to me.

(iii) Therefore, I was not as familiar as Dr Smith with the views of haemophilia physicians on NANBH and I cannot say if fractionators were more concerned about NANBH than physicians.

(iv) I can confirm that senior staff at PFC were well aware of NANBH and took it extremely seriously.

(v) PFC was represented at annual policy meetings with haemophilia doctors that were held under the auspices of SHHD. I do not remember there being any disagreement in general terms with policies or plans being proposed by SNBTS/PFC.

(vi) Other than my attending the annual meeting with Scotland's haemophilia directors, I was not involved with policy makers at this time, either in Scotland or in the UK. I am not therefore in a position to say how much weight was given by them to the views of fractionators.

(vii) see also my response to question 66.

In Dr Smith's First Penrose Statement [§16] he states that: "*There was some resistance among haemophilia clinicians to the idea that AIDS was caused by a blood-borne virus*."

a. **From your experience, do you agree with Dr Smith on this point?**

(i) From my answer to question 30, I had much less knowledge than Dr Smith of the views of haemophilia doctors at the time. I am now aware that The Penrose Inquiry examined this

matter and agreed with Dr Smith on this point (Penrose Inquiry Final Report, para 11.183) [PRSE0007002].

b. From your experience, how did the attitudes of the haemophilia clinicians on this matter compare to those of contemporary fractionators at the time?

(i) See my answer to a.

c. What weight was given to the voices of fractionators in discussions on this matter in the late 1970s and early 1980s?

(i) I do not know how much weight was given to the voices of fractionators, other than from my own experience concerning correspondence in 1983/84 between The Lord Glenarthur and Mr Clive Jenkins of ASTMS, in which the only views cited by The Lord Glenarthur were those of the Haemophilia Society (see Question 34).

The Inquiry is investigating the proposition that if NANB had been identified as a serious chronic condition at an earlier stage, this would have led to a greater interest in viral deactivation of blood products in the late 1970s and early 1980s, and the successful heat treatment of such products at an earlier stage than was in fact achieved. What is your view on this proposition:

a. Generally;
b. By reference to work undertaken by PFC;
c. By reference to work undertaken by BPL;
d. By reference to work undertaken by commercial fractionators both in the UK and abroad?

(i) I believe that all manufacturers wanted to make their products safe with respect to both hepatitis B and NANBH. Research aimed at eliminating hepatitis infection from blood products had been underway since 1944 (see page 13 of cited document 1, PEN.013.1309) [PRSE0002291] and WITN6914003 pages 270 & 275). Early studies that were unsuccessful include:

- treatment of plasma with phenol and ether (1944)
- treatment of plasma by irradiation with ultraviolet light (1946)
- pasteurisation of plasma for 4 hours at 60ºC (1953)
- storage of plasma for 6 months at 30-32ºC (1954)

• the chemical treatment of human blood, with 550 chemicals being evaluated (1955)
• treatment of Factor VIII concentrate with ultraviolet light (1957)
• irradiation of plasma using cathode rays (1957)
• irradiation of plasma using gamma rays (1957)
• treatment of Factor VIII concentrate with nitrogen mustard (1957)
• treatment of Factor VIII concentrate with beta-propiolactone and uv-irradiation (1969)

(ii) I do not believe that it was a lack of desire that prevented effective heat treatment being developed earlier, it was a lack of knowledge about how this could be done in a manner that would destroy the infectious agent(s) of concern without also destroying the blood product.

(iii) Investigators who were undertaking research to eliminate the risk of hepatitis infections associated with coagulation factor concentrates were limited by:

• the inability of hepatitis viruses to be cultured
• uncertainty over the nature of the infective agent(s) responsible for NANBH
• the failure of studies in chimpanzees to predict NANBH infection in humans
• that surrogate markers for hepatitis infection were not specific for hepatitis C
• that a serological marker for hepatitis C infection was not available until 1989.

(iv) When I joined PFC in 1973, research was already underway to try to eliminate the risk of viral infections associated with coagulation factor concentrates, including:
• Removal of viruses from Factor IX concentrate by a method of precipitation (in conjunction with Dr A J Johnson of New York University Medical Center).
See cited document no. 5 (PEN.012.1438) pages 2-4. [PRSE0003349]

• Removal of hepatitis B virus from Factor VIII concentrate using solid-phase adsorption (in conjunction with Dr A J Johnson, NYU).
See cited document no. 5 (PEN.012.1438) pages 5-7.[PRSE0003349]

(v) Later approaches undertaken or considered at PFC included:
• Obtaining factor VIII from human cell culture instead of donated blood.
See cited document no.5 (PEN.012.1438) page 8.[PRSE0003349]

• Using a high-speed centrifuge to remove viruses.
The PFC Director, Mr Watt, was interested in determining if viruses could be removed from factor VIII solutions using a high-speed centrifuge, known as the K-rotor, which had been

developed at the Oak Ridge Laboratory, California. The centrifuge was too large for the R&D lab at PFC and could not be located in the Production area before its effectiveness had been established. Therefore, purchase of a K-rotor was added to the equipment list for the R&D pilot plant that was included in the proposed Microbiology Extension to PFC (see para 19.4 above). By the time the Microbiology Extension had been built, interest had moved from hepatitis B virus to NANBH. As the agent(s) responsible for NANBH had not been discovered, it was impossible to physically measure the extent to which NANBH might be separated from factor VIII by the K-rotor. Therefore, I proposed that the funding that had been set aside for the K-rotor be used instead to purchase a pilot-scale, steam sterilisable freeze drier. This freeze drier was not only able to simulate the behaviour of the industrial freeze driers used in production, but could also be used for dry heat treatment studies using live viruses, including HIV (see para 22.2(iii)).

(vi) Research on heat treatment (pasteurisation) was begun at PFC as soon as it became known that this might be feasible.
See cited document no.5 (PEN.012.1438) pages 10-20 [PRSE0003349] and (PEN.013.1309) pages 32-36 [PRSE0002291].

(vii) In considering the published research on this topic, it should be appreciated that scientists tend not to publish negative results and even if they do try, editors may be reluctant to accept negative results for publication. Therefore, published studies probably underestimate the amount of research on this subject. For example:
• It is now known, that following the discovery of how to pasteurise Albumin in 1945, Edwin Cohn attempted to pasteurise other blood products, but failed to achieve this and abandoned this research (Surgenor DM, *Edwin J Cohn and the Development of Protein Chemistry*, Centre for Blood Research, Boston, 2002, page 223) [WITN6914055].

• In a meeting at PFC on 4th December 1986, Mr John Lundblad of Bayer admitted that Bayer had attempted to develop BPL's 8Y dry heat treatment, but had failed to be able to do this and had abandoned the project (see PEN.013.1309 page 63) [PRSE0002291].

• Following my involvement in the MDL litigation (see 14.1 above), I received a final phone call from Dr Johnson of NYU before he retired. I asked him if he had ever considered heat treating Factor VIII. He said he had attempted both dry heat treatment and heating in solution and had failed with both. That is why he had begun research on physical methods of removing viruses instead (see 32.iv above).

(viii) Few commercial fractionators mastered heat treatment that was effective against both HBV and NANBH, as well as HIV, and most turned instead to the use of solvent-detergent technology once it had been found to be effective against HIV and NANBH (see PEN.013.1309, page 22) [PRSE0002291].

It was argued during the course of previous litigation that, (i) by the mid-1970s, fractionators were aware both of the risk of HBV infection and of relevant methods of viral deactivation (such as heat treatment, detergent treatment and lipid solvent treatment), and (ii) that had a "reasonable research effort" taken place in the mid-1970s, with sufficient resources invested in appropriate areas, then this would have established methods of deactivating HBV and, consequently, the hepatitis C virus ("HCV") and the human immunodeficiency virus ("HIV"). What is your view of that argument:

a. **Generally;**
b. **By reference to work undertaken by UK state fractionators; and**
c. **By reference to work undertaken by commercial fractionators both in the UK and abroad?**

In this regard, you may be assisted by reference to §2.2 of the Heat Treatment Briefing Paper: "Obstacles to the Development of Heat Treatment for Coagulation Factors" and p8 and p10 of the Archer Statement dealing with issues such as the state of scientific knowledge in the 1970s.

Please identify or refer to relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

33.1 Heat Treatment (Pasteurisation)

(i) I first learned from Dr Cash in October 1980 that pasteurisation (heating in solution) was being applied to factor VIII by the German company Behringwerke, as he had heard about this at a symposium in Bonn. I was shocked to hear of this. In my 6-year experience of working with factor VIII, the idea that it could be pasteurised in a manner that would destroy hepatitis viruses without also destroying the factor VIII was literally inconceivable, due to the sensitivity and instability of the proteins concerned.

(ii) I first came across the claim that pasteurisation of factor VIII could have been developed much earlier during my involvement with the USA Multi-District Litigation, MDL-986 (see para 14.1).

(iii) This claim was made by the main expert witness for the Plaintiffs in the MDL Litigation, Dr Frank Putnam, Distinguished Professor Emeritus of the University of Indiana. In his evidence circa 1995, Dr Putnam described a series of simple experiments which he believed would have identified conditions that enabled factor VIII to be pasteurised. These experiments were based on the approach taken by Dr E J Cohn in the 1940s which Dr Putnam claimed could have been applied to factor VIII by 1970.

(iv) Dr Putnam was a very eminent academic protein chemist who was taken seriously. In particular, he was the editor of a series of textbooks entitled 'The Plasma Proteins', in which he and invited authors provided detailed accounts of the biochemistry of various plasma proteins, including factor VIII.

(v) These books were available in the PFC library. I read them very carefully, especially two volumes that had been published in 1975, but could find no mention of the idea that heat treatment of factor VIII should be investigated, either by Dr Putnam or any of his contributing authors.

(vi) In his evidence to the MDL litigation, the method for stabilising factor VIII proposed by Dr Putnam was identical to that discovered by Dr Schwinn of Beringwerke, that he had published in 1981.

(vii) It appeared to me that Dr Putnam's claim was based on hindsight ie. knowing how Berhringwerke had stabilised their factor VIII, he had outlined a set of experiments to produce the same answer.

(viii)The approach taken by Beringwerke was extremely limited. As their yield of factor VIII at 8% was so low that they had continued to supply most of their Factor VIII unheated.

(ix) Mr Eric Weinberg, a lead attorney for the US Plaintiffs, published his account of the MDL litigation in conjunction with Professor of Journalism, Donna Shaw, (Weinberg E, Shaw D. Blood on Their Hands, Rutgers University Press, 2017) [WITN6914057].

(x) I can find no mention in this book of Dr Putnam, or the set of experiments that he

claimed should have been done by 1970.

(xi) The main expert cited in the book is Dr Edward Shanbrom who, according to Weinberg and Shaw "*ridiculed the heat-treatment theory*" (page 230).

(xii) The exclusion of Dr Putnam from his account of the MDL litigation, suggests that Mr Weinberg no longer has confidence in his evidence.

(xiii) I believe that the exclusion of Dr Putnam from the account of the MDL-litigation published by Mr Weinberg and Ms Shaw is consistent with my opinion that pasteurisation of coagulation factors could not have been developed earlier.

(xiv) To the best of my knowledge, the difficulty of the technology associated with the pasteurisation of factor VIII restricted the output of pasteurised factor VIII by Bayer, with solvent-detergent treatment subsequently being adopted by Bayer instead of pasteurisation.

(xv) Similarly, to the best of my knowledge, pasteurisation was at first only applied by Behringwerke to a very small proportion of its Factor VIII concentrate production, with most of Behringwerke's Factor VIII being unheated until mid-1985. It was only after further process advances had been achieved that the company was able to apply pasteurisation technology to all of its factor VIII production (see WITN6914003, pages 270-271).

33.2 Heat Treatment (Dry Heat Treatment)

(i) Early dry heat treatment procedures failed to prevent transmission of NANBH in people with haemophilia, including heat treatment at:

- 60ºC for 30 hours (Preston FE. et al Lancet 1985,2, 213) [RLIT0000186]
- 60ºC for 72 hours (Colombo M et al. Lancet 1985, 2, 1-4) [BAYP0000007_139]
- 60ºC for 24 hours, with the dried powder suspended in an organic solvent (Kernoff PBA et al. Br J Haematol. 1987, 67, 207-211) [WITN6914056].

33.3 Solvent-Detergent Treatment

(i) In June 1982, Dr Duncan Pepper of the SNBTS Headquarters Laboratory suggested that research should be undertaken on the use of detergents for virus inactivation.

(ii) At a meeting of the SNBTS Coagulation Factor Study Group of 14th October 1982, chaired by Dr Cash, it was decided that treatment with detergent should "*not be pursued at expense of heat treatment, which was considered a better option.*" [PRSE0002206]

(iii) The concept of using a detergent in combination with a solvent was published by the New York Blood Center in 1985 (Horowitz B et al. Transfusion 1985, 25, 516- 522 [BAYP0000024_063]). This followed the discovery that AIDS was caused by a lipid-enveloped virus that might be inactivated by chemicals able to disrupt the lipid envelope.

(iv) Impediments that prevented this development being achieved sooner are described in my submission associated with the MDL litigation (para 14.1, WITN6914010). These included:
• S/D-treatment being effective only against viruses with a lipid-envelope
• the infective agent of AIDS not being known to be a lipid-enveloped virus until 1984
• the infective agent for hepatitis C not being known to be a lipid-enveloped virus until 1989
• that the chemical reagents used in S/D-treatment are potentially toxic and must be removed from the final product.
• manufacturing technologies suitable for removing the S/D chemical reagents from coagulation factors not being fully developed until the late-1980s.

(v) In their book concerning the MDL litigation, see para 33.1(ix), Weinberg and Shaw note that Dr Shanbrom had submitted a patent application in 1980 for the use of detergents (page 95) which would inactivate "*hepatitis and HIV*" (page 99).

(vi) In his patent application, Dr Shanbrom had shown that factor VIII could be treated with detergents without obvious damage. However, he did not provide data to show that his detergent treatment could inactivate any viruses [BAYP0000018_021].

(vii) If Dr Shanbrom had examined the effect of detergent treatment on viruses he would have found that it did not work. Another chemical was needed, a solvent to open the virus coat to enable the detergent to be effective. This was the discovery made at the New York Blood Center (para iii above).

(viii) In their book, Weinberg and Shaw change the description of Dr Shanbrom's invention from "*detergent*" (pages 95 and 99) to "*solvent detergent*" (page 118) indicating that they were aware that a solvent was required in addition to a detergent.

(ix) The solvent-detergent method of NYBC was approved by the FDA in 1985 because of its effectiveness against HIV, a lipid-enveloped virus that was therefore susceptible to inactivation by solvent-detergent treatment.

(x) It was not until 1988 that limited data were published by NYBC on an absence of NANBH in recipients of solvent-detergent treated Factor VIII (Horowitz MS, et al. Lancet 1988, 2, 186) [PRSE0001913].

(xi) It was not until 1989 that the infectious agent responsible for NANBH was found to be a lipid-enveloped virus, designated the hepatitis C virus. This confirmed that the infectious agent responsible for NANBH should be inactivated by solvent-detergent treatment [PRSE0000246].

(xii) Therefore, I believe that claims that either pasteurisation, or solvent-detergent treatment, of factor VIII could have been developed sooner are incorrect.

In your First Penrose Statement [§ B3(iv)] you refer to certain correspondence with the Association of Scientific, Technical and Managerial Staffs (ASTMS) and TUC in 1983 in which you stated you expressed your "*concern over the continued importation of blood products from the USA in light of AIDS and the extent to which the PFC facility was underused.*"

a. **Can you produce a copy of that correspondence (as Appendix VI to your First Penrose Statement said to contain the correspondence is not included in the statement)?**
b. **Please describe what you meant by PFC being "*underused*".**

34.1 Background

(i) In early June 1983, I attended a meeting of the Edinburgh Health Service Branch of the trades union, the Association of Scientific, Technical & Managerial Staff (ASTMS) at which the secretary read from a note of a meeting of the ASTMS National Executive Council that had been held on 4th May 1983 [WITN6914016].

(ii) I was especially interested in concern being expressed over *"the importation of contaminated blood supplies into Britain and the resultant spread of AIDS into this country"* [WITN6914016].

(iii) I was aware that little or no imported Factor VIII was being used in Scotland and believed that importation was required in England because BPL did not have the capacity to produce more Factor VIII.

(iv) I therefore wrote to Mr Gordon Craig, the full-time ASTMS official for the NHS in Scotland to point out that PFC had unused capacity.

(v) Mr Craig forwarded my letter to Ms Sheila McKechnie, Health & Safety Officer at ASTMS Head Office.

(vi) Ms McKechnie invited me to comment on various documents, including:
• a letter of 4th May 1983 from The Revd. Alan J Tanner of the Haemophilia Society advising patients to continue to use imported Factor VIII concentrates,

• correspondence between Mr Clive Jenkins, General Secretary of ASTMS and The Lord Glenarthur, Joint Parliamentary Under Secretary of State at the DHSS.

(vii) I included this material in a written statement to the Penrose Inquiry (document 3, PEN.015.0101) [PRSE0000545] attaching the correspondence as appendix VI (PEN.013.1231) [WITN6914017] Original copies are in my possession if required.

(viii). The correspondence was examined in the oral proceedings of the Penrose Inquiry, with myself (Penrose Inquiry transcript 11th May 2011, pages 17-34 [RLIT0001069]) and with Mr David Watters of the Haemophilia Society (Penrose Inquiry transcript, 19th January 2012, pages 97-103 [RLIT0001070]), and in the Final Report of the Penrose Inquiry, sections 9.109-9.113. [PRSE0007002]

34.2 Comments

(i) In the letter received by Mr Jenkins on 26th August 1983, The Lord Glenarthur wrote that the "*Haemophilia Society is aware of the situation and has in fact made known to me its opposition to any move to ban American F VIII.*"[MACK0001404_003].

(ii) I was somewhat bemused by the position that the Haemophilia Society had taken, as much of my knowledge had been obtained at the Congress of the World Federation of Hemophilia (WFH) that had taken place in Stockholm from 27th June – 1st July 1983. The WFH was an organisation that represented patients and the UK Haemophilia Society was a founder member. I therefore assumed that the Haemophilia Society would have had the same knowledge that I had obtained from the WFH Congress, namely, that AIDS was caused by a blood borne infectious agent that could be transmitted by Factor VIII concentrates.

(iii) That is why in my letter to Ms McKechnie of 29th September 1983, I wondered if

the Haemophilia Society might have been influenced by commercial interests.

(iv) I did not know that the Haemophilia Society was receiving funding from commercial companies (Penrose Inquiry document, PEN.018.1396) [PRSE0003929].

(v) In a letter received by Mr Jenkins on 10th January 1984, The Lord Glenarthur explained, contrary to my belief (at 34.1.iii) "*the existing laboratory at Elstree is capable of fractionating all the plasma currently available.*" [PRSE0001727].

(vi) This led me to ask in my letter to Ms McKechnie of 23rd January 1984, *"Why is England so short of plasma? What can be done about it? What would it take to achieve more plasma? What would it take to bring PFC capacity up? Surely the DHSS should be investigating and costing these options with some urgency."*

(vii) I did not know that on 9th January 1984 the Haemophilia Society had advised the DHSS "*…there are no grounds for favouring NHS Factor VIII over commercial materials in the respect that we have in the past considered relevant. In addition, of course, the marginal factors of stability and more convenient presentation favour commercial material.*" (Penrose Inquiry document, DHF.001.5151) [PRSE0002290].

(viii) In taking decisions at this time, it is important to appreciate that the cause of AIDS had not been discovered [WITN6914018], nor was it known that the virus responsible (HIV) would turn out to be both relatively heat sensitive and inactivated by treatment with solvent-detergent. Therefore, it was possible that the risk of AIDS being transmitted to people with haemophilia could have continued indefinitely.

34.3 Underuse of PFC

(i) See my response to Question 66.

In your First Penrose Statement you also refer to the fact [§B3 (iv)] that you were aware "*that in May 1983 Dr F Boulton, Deputy Director of the Edinburgh Regional Transfusion Centre, engaged in communication with Professor Bloom concerning the position of the UK Haemophilia Centre Directors Organisation on this topic [continued importation of blood products from the USA in light of AIDS*]" (§8.29 of the Penrose Report).

In his reply to Dr Boulton [§8.29, footnote 38] dated 23 May 1983, Professor Bloom comments that "*I think we all agree that it would be counter-productive to ban the importation of blood products [from the USA] at this moment*".

a. **In your opinion, to what extent was this view representative of the scientific consensus at that time as Professor Bloom asserts?**
b. **Did you agree that it would be "*counter-productive to ban the importation of blood products*" from the USA at that time? Please explain your answer, and state whether your view changed over time.**
c. **Did you share your view on whether or not the importation of blood products from the USA should be banned? Was your view on this matter sought by anyone (and if so, please provide details)?**

35. Response

(i) When I wrote my First Penrose Statement, I indicated that I was aware that Dr Boulton had written to Professor Bloom in May 1983, as I had read about this in the Preliminary Report of the Penrose Inquiry, para 8.29 [PRSE0007003]. I had not known about this correspondence until I read of it in the Preliminary Report of the Penrose Inquiry.

(ii) I do not know if the view of Professor Bloom represented the scientific consensus at that time, as I am not sure that there was a scientific consensus given that the state of knowledge was changing rapidly.

(iii) My opinion by June 1983 was that action should be taken to minimise the use of coagulation factor concentrates from the USA as much as possible. See my response to Question 34.

(iv) I did not know if it would be "*counter-productive to ban the importation of blood products*", as I did not know either the treatment needs of patients or if sufficient essential haemophilia treatment products could be obtained from UK plasma.

(v) I did believe that action was required on two fronts: increasing supplies of UK plasma and reducing levels of treatment of people with haemophilia, if that was medically appropriate.

(vi) I made the first point in my correspondence to ASTMS on 23rd January 1984 (see 34.2.vi above). I did not submit the second point, as I was not medically qualified to comment on the treatment of patients.

(vii) Given that the output of Factor VIII by BPL was limited by the availability of plasma, I believed that an increase in the preparation of cryoprecipitate, without a commensurate increase in the supply of plasma, would have reduced the supply of plasma to BPL and therefore the provision of UK derived Factor VIII concentrate.

(viii) I believe that such a move would have been counter-productive, if it had resulted in more Factor VIII concentrate being imported from the USA to compensate for a reduced output of Factor VIII concentrate by BPL.

(ix) My views on this matter were sought by ASTMS (see 34 above). I told Dr Perry, PFC Head of Quality, about my correspondence with ASTMS, as he was the only other senior member of staff at PFC who was a member of ASTMS at that time.

(x) I did not share my views with either the PFC Director (Mr Watt) or the SNBTS National Medical Director (Dr Cash). I already knew that they were both strong advocates of UK self-sufficiency and that both believed that PFC should be utilised to process plasma from England & Wales.

In July 1983, you wrote two memorandums to Mr Watt concerning your attendance at recent meetings of the WFH and ICTH. The memorandum of 13 July 1983 was on the subject of "*T Cell Abnormalities & Haemophilia*". Please explain the significance of this issue, and your views on it, and consider the following matters:

a. **Why you had attended these conferences?**

b. **The difference in view between the US and European delegates, and the reasons for that difference in view.**

c. **Your position, at the time, and subsequently, on that debate; in particular what you meant when you wrote that: "*My own feeling was that there was something of an attempt to suppress AIDS 'hysteria' but, as an uninformed observer, some of the more scientific criticism of the T cell situation did appear to make sense.*"**

36.1 <u>Personal Narrative</u>

(i) I attended the World Federation of Hemophilia Congress in Stockholm (27th June – 1st July 1983) because I was an invited speaker. I had been invited by the session chair, Dr Mannucci, to give a presentation on increasing the yield of factor VIII [PRSE0004094]. I was aware that Dr Cash had recommended me to Dr Mannucci.

(ii) I attended the Congress of the International Society of Haemostasis & Thrombosis in Stockholm (2nd – 8th July 1983) because I wanted to present our work and to have an opportunity to learn of scientific progress. It was also easier to obtain permission from the CSA, as my travel expenses were being met by WFH.I displayed three poster presentations, with abstracts published in the volume of Thrombosis & Haemostasis that was issued in conjunction with the Congress:

• the use of zinc to precipitate fibrinogen and increase the purity of factor VIII.
• the addition of calcium to increase the stability of factor VIII.
• studies on the pasteurisation of coagulation factor concentrates.

(iii) T-cell abnormalities had been detected in people with AIDS and were being used as a diagnostic tool to monitor their condition. Similar T-cell abnormalities were being observed in people with haemophilia and was the subject of presentations at WFH.

(iv) Although this was not my area of expertise, I observed that some of the data points presented graphically were widely scattered, with lines of 'best fit' being drawn to try to demonstrate a trend. I doubted that this was meaningful, hence my comment that some of the scientific criticism did appear to make sense.

(v) In my memo on T-Cell Abnormalities (SNF.001.3714) [PRSE0002014] I wrote in para 4: *"A number of speakers pointed out that T cell abnormalities can result from viral infections (CMV, EBV, hepatitis)."* As the majority of people with haemophilia were known to be infected with non-A, non-B hepatitis, this infection could well have been a cause of T-cell abnormalities in people with haemophilia in addition to AIDS.

(vi) Given the uncertainty at this time, and the seriousness of the issues being discussed, it was inevitable that there would be differences of opinion which would sometimes be expressed strongly.

(vii) There seemed to me to be a major difference between those who thought that T-cell abnormalities in people with haemophilia were independent of AIDS and those who were concerned that they might indicate an AIDS or pre-AIDS condition. I did not know the people involved, but I observed that the former tended to have American accents and the latter European accents.

In your memorandum of 15 July 1983, entitled "AIDS", you set out the "key points concerning AIDS" from the conferences. You concluded by noting that "*With the*

***1st haemophiliac case only 12 months ago and a possible incubation period from 1-3 years a number of delegates (mainly European) were clearly uneasy and felt that we may be still only seeing the tip of an iceberg.*"**

a. **What were your views, following the conference, on whether AIDS was, or was likely to be, caused by a transmissible agent spread by blood products? How did this compare with your views in March 1983, as summarised at paragraph 11.82 of the Final Penrose Report (i.e. that you perceived the risk to be between possible and probable)?**
b. **What were your views, following the conference, on the degree of risk to patients who had used commercial blood products?**
c. **What were your views, following the conference, on the risk that factor concentrates produced at the PFC may lead to the transmission of AIDS?**
d. **Please explain what, if any, differences there were between European and American delegates on these issues at the conference, and the reasons for those differences.**

37.1 Personal Narrative

(i) The presentation by Dr Evatt at the WFH Congress was the point at which I became convinced that AIDS was caused by a blood borne infection.

(ii) Prior to this, I believe that there was an implied assumption that haemophiliacs who had been diagnosed with AIDS could be gay men who had hidden their sexuality.

(iii) This belief was no longer tenable after the presentation of Dr Evatt, who addressed the issue of male sexuality, making it very clear that none of the haemophiliacs who had been diagnosed with AIDS were gay.

(iv) Unfortunately, there was no abstract of his presentation in the book of abstracts – just a blank page. Meaning that people who had not attended his presentation might continue to think that haemophiliacs who had been diagnosed with AIDS were gay men who had hidden their sexuality.

(v) I believed that the greatest risk was associated with concentrates from the USA, not because they were commercial, but because they had been prepared from plasma collected at the epicentre of the AIDS epidemic, from both commercial and non-commercial sources.

(vi) It may not have been appreciated that plasma recovered from donated blood was sold for fractionation by Community Blood Banks in the USA. Nor, that at the outset of the AIDS epidemic, gay men queued at Blood Banks to give blood to help their stricken community. According to David France (How to Survive a Plague, Vintage Books 2016, p 59 [WITN6914058]): "*Gay men, he learned, were extremely avid blood donors. In fact, in recent months an unnoticed and massive blood drive had been underway in LA's gay neighborhoods in response to the mounting GRID crisis there. Week after week, long lines of men rolled up their sleeves to donate blood, dutifully offering up pint after pint of harm they never dreamed of.*"

(vii) I did not believe that AIDS would be confined to the USA, but I hoped that a time-lag between the USA and UK, combined with the voluntary exclusion of gay men from giving blood, might buy time for scientific advances, such as the discovery of the infectious agent responsible, the testing of blood donors and a means of eliminating infectivity from blood products. All of which occurred, with effective heat treatment of FVIII concentrates being applied by PFC from late-1984.

The Medical Board of the WFH subsequently recommended that there was "*insufficient evidence to recommend, at present, any change in treatment; therefore present treatment of haemophilia should continue with whatever blood products are available, according to the judgement of the individual physician*". The Medical Board also called for urgent longitudinal studies. Were you aware of these recommendations at the time, and if so, what were your views of them in light of the discussion you had heard at the conferences?

38.1 I was not aware of these recommendations at the time.

Did the information that you learned and conveyed at these two conferences alter the approach taken at PFC to the production of factor concentrates (including issues concerning heat treatment)? If not, should it have done?

39. Response

(i) The development of heat treatment had begun at PFC in 1981. This was aimed at removing the risks of hepatitis infection and was being pursued as rapidly as possible at the time that these conferences took place

(ii) Although, by the time of the WFH Congress in June 1983, it was increasingly assumed that AIDS was caused by a blood borne infection, the infective agent had not been discovered and neither its sensitivity nor its resistance to heat were known.

(iii) In these circumstances, the main objective at PFC was to provide sufficient Factor VIII concentrate for Scotland to enable FVIII from the USA to be avoided.

What role did PFC play in advising the Government, haemophilia doctors and patients on the risks associated with (i) its own products and (ii) with commercial blood products? In each instance, please indicate:

a. **Which individuals within PFC had responsibility in this area?**
b. **What role, if any, did you play in this area?**
c. **How significant was PFC's role when compared to that of other bodies, committees and organisations?**

40. <u>Response</u>

(i) Plasma products are prescription only medicines, as such they had to be approved by the Committee on Safety of Medicines (CSM).

(ii) Applications to CSM for Product Licences had to include an account of the risks associated with a product.

(iii) As 'PFC' did not treat patients, information concerning the transmission of infections was obtained by medical doctors responsible for patient care. It was expected that this information would be passed to SNBTS/PFC.

(iv) Whenever PFC was informed of a patient having been infected by a PFC product, an investigation would be carried out and an incident report prepared by the Head of Quality. To the best of my knowledge this incident report would then be sent to the UK regulatory authority, the Medicines Control Agency (MCA), now MHRA.

(v) Accounts of infections in people with haemophilia were often published by the treating physician and therefore available to fractionators, such as PFC, and regulatory authorities such as the MCA (see WITN6914003).

(vi) PFC did not supply commercial products, so had no knowledge of their infectivity, other than via the published literature, or reports to HCDO.

(vii) PFC supplied warning literature with its products. This was aimed at the treating physician, not the patients. However, warning labels were attached to each vial and would have been accessible to patients on home therapy. For examples, see [PRSE0002726].

(viii). The responsibility for providing warnings relating to PFC products lay with the PFC Director and the PFC Head of Quality.

(ix) I had no responsibilities in this area within PFC and had no role in advising Government, haemophilia doctors, or patients. Therefore, I do not know how significant PFC's role was compared to that of other bodies, committees and organisations.

What information was provided with PFC products to explain the risks associated with them? In particular, what information was provided about the risks of (i) HBV, (ii) HCV/NANB hepatitis, and (iii) HIV? Was that information designed to be read by clinicians and/or patients.

a. **In respect of warnings on HIV, you may be assisted by paragraphs 33.75 to 33.92 of the Penrose Final Report. Please identify any additional points, or points of correction, that you wish to add to your previous evidence on this issue.**

41. (i) & (ii) <u>Hepatitis Warnings</u>

(i) General warnings of hepatitis were issued by PFC with its coagulation factor concentrates [PRSE0002726], including:

- A leaflet, issued with each carton of product, that contained two warnings of hepatitis,
- Two warnings of hepatitis printed on each carton of product.
- A label attached to each vial of product with a printed warning of hepatitis.

(ii) These warnings were designed to be read by clinicians.

(iii) The wording of each warning was approved by the Committee on the Safety of Medicines.

(iv) See also my response to question 40.

41.(iii) Warnings on HIV

(i) In the account published in the Penrose Final Report, para 33.80 [PRSE0007002], I do not agree with the memory of Dr Cash, who believed that the discussion on 14th November 1983 concerned the inclusion of warnings about hepatitis. The discussion could not have concerned warnings of hepatitis, as these had already been provided by PFC for a number of years.

(ii) I remember the meeting of the Working Group of 14th November 1983, as it was the first meeting that Dr Perry had attended as he was covering for Mr Watt [PRSE0002581].

(iii) I believe that Mr Watt had asked Dr Perry to attend on his behalf to specifically raise the question of adding a warning of a possible risk of HIV infection with PFC coagulation factor concentrates, as the responsibility for this lay jointly with Mr Watt and Dr Perry, as Head of Quality.

(iv) I remember being disappointed that Dr Cash had acceded to the concern of haemophilia doctors that this would cause "*unnecessary anxiety to patients*".

(v) I had expected that Dr Perry would report back to Mr Watt and that Mr Watt would then insist on the HIV warning being added, as I knew that he took the need for warnings very seriously.

(vi) As I was not involved in the design or the distribution of product leaflets, I did not know when warnings concerning HIV were issued with PFC products and only learned of this from paragraphs 33.81 of the Final Report of the Penrose Inquiry:

33.81 Dr Perry explained that the PFC did revise its product leaflets in April 1985 when FVIII NY (Factor VIII heat-treated at 68°C for 24 hours) was introduced. The revised leaflet and package label stated: 'the freeze dried product has been heat treated but cannot be assumed to be non-infective'. He explained that the term 'non-infective' was intended to encompass all potential blood-borne infections, including HIV/AIDS. In addition, when the new heat-treated Factor IX product, DEFIX, was issued in October 1985 it stated:

> In addition, product, plasma pools and individual donations are tested for the presence of antibody to HTLVIII. The product has been heat treated at 80Â°C for 72 hours in the freeze dried state. This treatment is expected to inactivate viruses associated with the Acquired Immune Deficiency Syndrome.[137] [PRSE0007002]

How, when and in what circumstances did you become aware that Scottish patients may have been infected with HTLVIII/HIV through the use of blood products produced at PFC? Explain the role you played in responding to such news. In particular, please comment on the following:

a. **The circumstances in which you became aware that Dr Gallo had identified patients from the Glasgow Haemophilia Centre as having HTLVIII antibodies in or before October 1984.**

b. **The circumstances in which you became aware that Professor Tedder had identified patients from the Edinburgh Haemophilia Centre as having HTLVIII antibodies in November 1984. (You may be assisted by your Third Penrose Statement, p.25, §27).**

c. **What role, if any, did you play in providing information of the infections to any relevant agency in Scotland, the UK or elsewhere? If you did not play any such role, please identify who within PFC may have done so.**

d. **What role, if any, did you play in providing information of the infections to patients? If you did not play any such role, please identify who within PFC may have done so.**

e. **You attended a BTS seminar held by Dr Froebal at Glasgow Royal Infirmary in October 1984 (see the letter sent from Dr Perry to Dr Froebal on 15 October 1984). During this seminar, discussions took place about 18 Glasgow patients who had HTLVIIII antibodies (see Dr Froebal's letter to Dr Perry on 29 October 1984). An article was subsequently prepared and published in the Lancet (December 22/20, 1984, p.1444-1446). These events took place before many of the patients themselves were informed that they had been infected. Were you aware of this sequence of events, and if so, what were your views on it? Did you, or anyone else, raise concerns about the delay in providing the patients with this information? Please also provide what evidence you can of what took place at the seminar at the Glasgow Royal Infirmary in October 1984.**

f. **What role did you play in recalling blood products, or otherwise seeking to minimise exposure to the infected batches? If you did not play any such role, please identify who within PFC may have done so.**

g. **What role did you play in seeking to identify any batches of PFC blood products that may have been infected with HTLVIII/HIV? If you did not play any such role, please identify who within PFC may have done so.**

42. 1 Response

(i) According to the letter from Dr Perry to Dr Froebel of 15th October 1984, I attended a seminar by Dr Froebel on 14th October 1984 concerning patients in Glasgow testing positive for antibodies to HIV [MACK0001839_002].

(ii) I am afraid that I have no memory of attending this seminar and I am therefore unable to comment on it.

(iii) I learned that patients treated at the Edinburgh Haemophilia Centre had tested positive for antibodies to HIV from overhearing Dr Cuthbertson being informed of this by telephone, as his office was adjacent to mine and we both had our doors open.

(iv) I believe that this phone call took place during the morning of Monday 29th October 1984, because:

• I remember the phone call being in the morning.

• A meeting of the PFC Heads of Department took place on the afternoon of Friday 26th October 1984. If we had known of these data then, it would have been discussed at our meeting – it was not discussed.

• I travelled to the Netherlands on Wednesday 31st October 1984, to attend a symposium on plasma Fractionation in Groningen – I knew about these data when I left for Groningen.

• That points to Monday 29th October as being the date on which Dr Cuthbertson was informed of these data.

(v) I had no role in providing information of infections to any relevant agency. This was the responsibility of the PFC Head of Quality (Dr Cuthbertson) and the PFC Director (Dr Perry).

(vi) I played no role in providing information of the infections to patients, nor to the best of my knowledge did anyone from PFC. This task was the responsibility of the prescribing physician. To the best of my knowledge, PFC staff were not authorised to provide information to patients directly.

(vii). I played no role in recalling blood products. That was the responsibility of the PFC Head of Quality, Dr Cuthbertson, and the PFC Director, Dr Perry.

(viii) I played no role in identifying any batches of PFC blood products that may have been infected with HTLVIII/HIV. That was the responsibility of the PFC Head of Quality, Dr Cuthbertson, who, I believe, did this in conjunction with Regional Transfusion Directors, in particular Dr Brian McClelland, Director of the Edinburgh Regional Blood Transfusion Centre.

Section 5: Heat treatment at PFC

By way of background, please give an outline of the following topics, insofar as it is within your knowledge and expertise to do so:

a. How heat treatment affects (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products;

b. The challenges for fractionators in heat treating (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products;

c. The manufacturing processes and equipment required in large scale production of heat treated (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products, and when these processes and equipment became available;

d. How knowledge of heat treatment of blood products developed in the 1970s and 1980s;

e. The way in which the PFC developed heat treated blood products in the 1980s, and how effective the different methods proved to be in terms of viral inactivation;

f. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by pharmaceutical companies in order to inactivate viruses in blood products.

g. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by BPL in order to inactivate viruses in blood products (in particular, how and when you learned of the success of 8Y in inactivating HCV/NANB hepatitis).
h. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by other state fractionators in order to inactivate viruses in blood products.

Please identify or refer to relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

Response to Question 43 - Overview

(i) During the 1970s, PFC was engaged in R&D aimed at removing viruses from coagulation factor concentrates. R&D on heat treatment was begun in 1981, as soon as information on this approach became available.

(ii) This focussed on applying the technique of pasteurisation to coagulation factor concentrates, with process improvements aimed at increasing yield to a point where manufacture would be viable. Eleven pilot-scale batches of pasteurised FVIII (ZHT) were prepared between February 1983 and September 1984, with clinical evaluation beginning in late-1983. R&D on substantially increasing factor VIII purity was begun in conjunction with scientists at New York University Medical Center in August 1984.

(iii) In November 1984 it became known that HIV could be inactivated by dry heat treatment at a temperature (68ºC) which PFC FVIII could withstand. PFC immediately changed its approach to dry heating its existing FVIII concentrate, as this could be introduced more quickly than pasteurisation, despite the heating conditions being known to be ineffective against NANBH. Some 12 months stock of FVIII was heated in this manner, not only filling the supply chain to allow unheated FVIII to be recalled, but also enabling batches of FVIII prepared as early as October 1983 to be heat treated.

(iv) It was known by late-1984 that BPL/PFL had developed a Factor VIII concentrate (8Y) that could withstand dry heating at 80ºC. It was not known if this would inactivate NANBH, therefore PFC continued its research on increasing FVIII purity as this would assist the development of pasteurisation (for which there was some evidence that NANBH was inactivated).

(v) It was believed that it was the higher purity of 8Y that had enabled it to withstand heating at 80ºC and the research at PFC on increasing purity was therefore also believed to be consistent with dry heating at 80ºC, or higher if required. However, when R&D samples of PFC's high-purity FVIII were subjected to dry heat treatment, it was discovered that it was not the increased purity that had enabled 8Y to withstand dry heat at 80ºC, but the way in which it had been freeze dried.

(vi) In December 1985, PFC obtained a pre-publication copy of a report which questioned the effectiveness of dry heat of FVIII at 60ºC against HIV. It was therefore decided to suspend work on a high-purity FVIII in order to produce a product comparable to 8Y as quickly as possible, to increase the margin of safety with respect to HIV.

(vii) It was believed that the quickest way of doing this was to apply a revised method of freeze drying by modifying the process that had been designed for pasteurisation, as PFC production staff were already familiar with the technologies involved.

(viii) It was subsequently discovered that the aspect of freeze drying that was critical to achieving dry heating at 80ºC was the crystalline structure that formed when the factor VIII solution was frozen within the freeze drier.

(ix) A method was devised to obtain the precise crystal structure throughout every vial of every batch. As a consequence, PFC's FVIII concentrate Z8, equivalent to 8Y, was available from PFC from 2nd December 1986.

Question 43a

a. How heat treatment affects (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products;

Response to Question 43a

Plasma products must comply with in-process specifications and with final product specifications. Minimum final product specifications are established by relevant national bodies ([NHBT0000236_013], pages 1012-3). Products used in the UK had to comply with final product specifications set out in the European Pharmacopoeia.

Key criteria relating to heat treatment in the mid-1980s were:

43.a.(i) Albumin

• The liquid should be colourless to amber,
• Molecular aggregates (eg. as measured by gel filtration chromatography) should be not more than 5%,
• The optical density, measured by spectrophotometry at 403 nanometers, should be not more than 0.15.

Heat treatment could affect any of these parameters such that a batch of Albumin would fail to meet the necessary specification and be discarded.

43.a.(ii) FVIII Concentrate

- The product should be a white or pale yellow powder,
- The reconstitution time at 20-25ºC should be not more than 30 minutes,
- The residual moisture should be not more than 2%,
- The factor VIII potency should be not less than 3 IU/ml,
- The factor VIII purity should be not less than 100 IU/gram protein,
- The product should be free from coagulation for not less than 3 hours at 20-25ºC,
- The vial content should be within 80-125 % of the value on the label.

Many fractionators had in-house specifications that were higher than the minimum set by the European Pharmacopoeia, particularly in relation to reconstitution time, potency and purity.

Heat treatment could affect any of these parameters such that a batch of Factor VIII concentrate would fail to meet the necessary specification and be discarded.

Although not specified by the European Pharmacopoeia, product yield was also a key issue as a very low yield of factor VIII would result in a considerable reduction in the amount of FVIII concentrate that could be produced from a given quantity of plasma, making a process either practically or commercially non-viable.

A major clinical concern was that heat treatment might modify the factor VIII molecule in a way that would stimulate recipients to produce antibodies (inhibitors) against factor VIII.

43.a(iii) <u>Factor IX Concentrate</u>

- The product should be a white powder, but could be colourless, blue, yellow or green on reconstitution,
- The reconstitution time at 20-25ºC should be no more than 10 minutes,
- The residual moisture should be no more than 2%,
- The factor IX potency should be not less than 20 IU/ml,
- The factor IX purity should be not less than 600 IU/ gram protein,
- The vial content should be within 80-125 % of the value on the label,
- The thrombin-fibrinogen time test (a measure of potential thrombogenicity) should be not less than 24 hours at room temperature and greater than 6 hours at 37ºC,
- The nonactivated partial thromboplastin time (a measure of potential thrombogenicity) should be not less than 150 seconds.

Heat treatment could affect any of these parameters such that a batch of Factor IX concentrate would fail to meet the necessary specification and be discarded.

A major clinical concern was that heat treatment might modify the factor IX in a way that would cause a thrombogenic (thrombosis) reaction in recipients.

Question 43b

b. The challenges for fractionators in heat treating (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products;

Response to Question 43b

The challenges for fractionators in heat treating plasma products were two-fold; (1) Obtaining evidence that a particular heat treatment process would be effective in inactivating the infectious agent (s) of concern, and (2) Obtaining the technical and scientific knowledge needed to apply the effective heat treatment without compromising in-process or final product specifications, including yield (see **a** above), or causing adverse reactions in recipients.

43.b (i) Albumin

A technique for heat treatment of Albumin by pasteurisation (heating in solution) was devised during the early 1940s. The technique involved the addition of chemical stabilisers that were specific to Albumin and which did not need to be removed from the final product, as they were physiologically acceptable for infusion in recipients [PRSE0000345]. Pasteurisation for 10 hours at 60ºC was applied to the final product from 1945, with the aim of destroying bacterial contaminants. Confirmation that these heating conditions inactivated the infectious agent responsible for serum hepatitis (hepatitis B) was not obtained until the mid-1950s. (see WITN6914003, pages 264-265).

The method which enabled Albumin to be pasteurised was published in the 1940s and was required by Regulatory Authorities to be used by all fractionators.

43.b (ii) Factor VIII Products

Heat treatment techniques applied to factor VIII mainly concerned either pasteurisation (heating in solution) or dry heat treatment (heating the freeze dried product in its final container).

Pasteurisation: A technique for pasteurising factor VIII for 10 hours at 60°C was devised in the late 1970's by scientists at the German commercial company Behringwerk. This was first reported orally in October 1980, with technical details being published (in German) in 1981. Limited clinical data suggested that the product might be free from transmitting hepatitis. Unlike Albumin, the chemical stabilisers had to be removed after pasteurisation as they were not physiologically acceptable. The loss of factor VIII activity by heat treatment (50%), combined with losses of factor VIII during additional processing, resulted in a final product yield of 8%. Only a very small proportion of the Factor VIII produced by Behringwerke at this time was pasteurised, presumably because of the very low yield. Subsequent process modifications enabled Behringwerke to apply pasteurisation to all of their factor VIII. Evidence that this new product did not transmit HIV or NANBH was first published in 1987 (see cited document 1, page 22 and WITN6914003 pages 270-271).

A pasteurised Factor VIII concentrate was also developed by Bayer, but to the best of my knowledge it was only produced in limited amounts and was subsequently replaced with a solvent-detergent treated Factor VIII concentrate.

Subsequently a pasteurised Factor VIII concentrate produced at the Central Laboratory of the Netherlands Red Cross was withdrawn following the observation of an enhanced incidence of inhibitors to factor VIII in recipients (see cited document no. 7 (PEN.018.0623) [PRSE0000553]).

Dry Heat Treatment: A technique of heating freeze dried Factor VIII concentrate in its final container was first applied by the commercial company Hyland/Baxter, with its product Hemofil HT being heated for 72 hours at 60°C in 1982. A clinical study found in 1983 that the product continued to transmit NANBH. Similar heat treatment applied by other commercial companies (e.g. Alpha Therapeutics, Armour Pharmaceuticals) also failed to prevent transmission of NANBH. The heating conditions employed (up to 72 hours at 68°C by Bayer) were presumably the most severe that these products could tolerate. To the best of my knowledge, failure to prevent transmission of NANBH meant that the companies concerned had not applied dry heat treatment to most of the factor VIII that they manufactured, and continued to issue most of their Factor VIII concentrates unheated.

In late 1984, it was reported by the USA Centers for Disease Control (CDC) that dry heat treatment, comparable to that which had failed to inactivate agent(s) responsible for NANBH, had been found in laboratory experimental studies, to be effective in inactivating HIV. This type of dry heat treatment was introduced almost immediately by most fractionators, including PFC, even though it was known that agent(s) responsible for NANBH would not be inactivated.

Despite the data from CDC concerning inactivation of HIV, a Factor VIII concentrate from Armour Pharmaceuticals, that was dry heated for 30 hours at 60°C, transmitted HIV to patients in a number of countries (see para 43.8).

Subsequently two fractionators, BPL at Elstree followed by PFC Edinburgh, were able to prepare Factor VIII concentrates that could withstand dry heat treatment at a much higher temperature (80°C for 72 hours). Preliminary clinical data from BPL in 1986 found no transmissions of NANBH, with results from the study being published in 1988.

This approach was also taken by the Australian state fractionator CSL (Commonwealth Serum Laboratories – later privatised) which introduced a dry heat treated FVIII concentrate comparable to 8Y in 1990.

43.b (iii) Factor IX Products

Heat treatment techniques applied to factor IX mainly concerned either pasteurisation (heating in solution) or dry heat treatment (heating the freeze dried product in its final container).

Pasteurisation: The technique devised at Behringwerke for the pasteurisation of factor VIII was also applied in the preparation of their Factor IX. Concentrate. However, the product (Beriplex HS) infected over 30 patients with hepatitis B. The German regulatory authority concluded that the effectiveness of Behringwerke's method of pasteurisation was subject to fluctuation and advised that an additional virus inactivation step be included (see WITN6914003, page 271).

Dry Heat Treatment: The technique of heat treating the freeze dried product that had been studied with Factor VIII concentrate was equally applicable to Factor IX concentrates.

The failure of the technique to prevent transmission of NANBH meant that it was introduced only following evidence in late-1984 that HIV could be inactivated by dry heat treatment at 68°C.

Two fractionators, BPL (Elstree) and PFC (Edinburgh), modified the formulation of their Factor IX concentrates to enable dry heat treatment to be applied for 72 hours at 80ºC (see para 43.6). Preliminary clinical data from BPL in 1986 found no transmissions of NANBH, with results from their study being published in 1988.

Question 43c

c. The manufacturing processes and equipment required in large scale production of heat treated (i) albumin, (ii) Factor VIII products, and (iii) Factor IX products, and when these processes and equipment became available;

Response to Question 43c

43.c (i) Albumin

Pasteurisation of Albumin is done either by heating each batch of final containers in a temperature controlled water tank, or in a temperature controlled spray cabinet or in a temperature controlled hot air oven.

An alternative approach of heating the albumin solution in a batch vessel prior to dispensing into bottles was used by Armour Pharmaceutical Co. This method was discontinued in 1974 following transmission of hepatitis which was believed to have been due to inadequate heat treatment in the batch vessel. This incident resulted in the regulatory requirement that pasteurisation of Albumin be carried out only by heating the product sealed in its final container (see WITN6914003, page 265).

At PFC, Albumin was introduced in 1965 and the bottles of the final product were pasteurised in a large tank of heated water. This was replaced by a spray cabinet after PFC moved to its new Centre in 1975. The spray cabinet was of a more hygienic design and was engineered to provide more precise control of temperature.

43.c (ii) Factor VIII Products

Pasteurisation: I do not know how pasteurisation of factor VIII was carried out by the fractionators (Berhingwereke, Bayer, Armour) who used this technique.

In undertaking research on pasteurisation of factor VIII at PFC, pasteurisation of product intended for clinical evaluation was carried out by utilising the spray cabinet that had been designed for the pasteurisation of Albumin. Unlike Albumin, pasteurisation was carried out at an intermediate stage of processing and required the part-processed factor VIII solution to be filled into bottles from which the factor VIII solution was removed for further processing after pasteurisation was complete.

Dry Heat Treatment: I do not know how dry heat treatment was carried out by fractionators who used this technique.

At PFC, dry heat treatment of Factor VIII was begun in November 1984 using the spray cabinets that had been designed for the pasteurisation of Albumin. Although Albumin is pasteurised at 60ºC, it was possible to heat PFC's Factor VIII concentrate at the desired temperature of 68ºC, as the PFC spray cabinets had fortuitously been designed to operate up to 70ºC.

A specialist hot air oven was used for this purpose from mid-1985, as soon as the equipment could be obtained. This oven had been designed by BPL/PFL in conjunction with a company that specialised in the construction of equipment of this type. It was not therefore generally available, and each oven had to be specified and ordered some 6 months in advance of delivery.

Although dry heating of PFC Factor VIII was begun in November 1984, the heating conditions (2 hours at 68ºC) were chosen to be compatible with product already manufactured so that heat treatment could be applied immediately (ie. without waiting for new batches of FVIII to be manufactured, which could have taken several months). This also enabled a stock of some 12 months of PFC Factor VIII concentrate to be heat treated. Consequently, batches of PFC Factor VIII concentrate that had been manufactured as early as October 1983 were able to be heat treated for 2 hours at 68ºC.

Research on the formulation of factor VIII enabled PFC's Factor VIII concentrate to be modified from January 1985 to tolerate dry heating for 24 hours at 68ºC.

Further research resulted in the development of a new PFC Factor VIII concentrate (Z8) that could be dry heat treated for 72 hours at 80ºC. The specialist hot air oven that had been obtained in mid-1985 was designed to operate at this temperature. Heat treatment of Factor VIII under these conditions was begun at PFC in late-1986.

43.c (iii) Factor IX Products:

Pasteurisation: I do not know how pasteurisation was carried out by fractionators who used this technique.

Dry Heat Treatment: I do not know how dry heat treatment was carried out by fractionators who used this technique.

At PFC, Factor IX Concentrate was dry heated for 72 hours at 80ºC following a modification to the product formulation to bring results of a test of potential thrombogenicity within the specification of the European Pharmacopoeia.

The dry heat treated product was only approved for clinical use after freedom from thrombogenicity had been confirmed in an animal model (see section 43.7). Delivery of the specialist hot air oven designed by BPL/PFL, which operated at 80ºC (see dry heat treatment of FVIII above) coincided with completion of the animal thrombogenicity study and enabled Factor IX concentrate for clinical use to be immediately dry heated for 72 hours at 80ºC.

Question 43d

d. How knowledge of heat treatment of blood products developed in the 1970s and 1980s;

Response to Question 43d

See cited document no. 1 (PEN.013.1309, pages 14-22) [PRSE0002291] and WITN6914003 (pages 270-272).

Question 43e

e. The way in which the PFC developed heat treated blood products in the 1980s, and how effective the different methods proved to be in terms of viral inactivation;

Response to Question 43e

See cited document no. 1 (PEN.013.1309, pages 32-49) [PRSE0002291] and my personal narrative of events below, especially para 43.11.

Question 43f

f. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by pharmaceutical companies in order to inactivate viruses in blood products.

Response to Question 43f

See cited document no. 1 (PEN.013.1309, pages 14-15) [PRSE0002291] and personal narrative below.

Question 43g

g. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by BPL in order to inactivate viruses in blood products (in particular, how and when you learned of the success of 8Y in inactivating HCV/NANB hepatitis).

Response to Question 43g

See my personal narrative of events below and the detailed chronology of events in cited document 1 (PEN.013.1309, pages 55-67) [PRSE0002291].

Question 43h

h. What (and when) you, and others at PFC, knew of the heat treatment processes introduced by other state fractionators in order to inactivate viruses in blood products.

Response to Question 43h

(i) Dr Robert (Bob) Herrington of CSL Australia visited me at PFC on 17th December 1985 to discuss virus inactivation (heat treatment). I cannot remember his account of what CSL were doing at this time. However, according to a 1999 textbook (Feldman EA, Bayer R. Blood Feuds, Oxford Univ Press 1999, pages 251- 252) [WITN6914059], CSL Australia had begun to dry heat treat its FVIII for 12 hours at 60ºC from November 1984, but unheated Factor VIII had continued to be used in Australia until March or April 1985.

(ii) I learned in April 1987 that scientists at CSL Australia were attempting to develop a FVIII concentrate comparable to 8Y (see para 43.10). It was only following a Commission of Inquiry by the Australian Senate that I learned that this was introduced into clinical use in about 1990.

Please identify or refer to relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

Question 43 - Additional Comments

Personal Narrative of Events (Key Points)

43.1 1973-1980

(i) Before I joined PFC, I had been taught in, my MSc course in Biochemical Engineering at University College, that Albumin was pasteurised for 10 hours at 60ºC to make it safe from transmission of serum hepatitis and that this was the only plasma protein that could withstand pasteurisation. A view that continued to be held in 1984 by Dr John Edsall, one of the scientists involved [PRSE0000345].

(ii) When I was appointed Head of R&D at PFC, I learned that research was underway at PFC aimed at physically removing the hepatitis B virus from coagulation factor concentrates.

(iii) At the same time, I became involved in research aimed at increasing the yield of factor VIII. I read how factor VIII activity decayed progressively and observed this myself. I particularly observed a greater loss of factor VIII activity at higher temperatures.

(iv) I undertook a study in conjunction with Dr Christopher Prowse, of the Edinburgh Regional Transfusion Centre, to determine the mechanisms by which factor VIII was being lost in production. This included the use of a new means of detecting the factor VIII molecule immunologically, which had been developed by Dr Ian Peak of the Department of Haematology, University Hospital of Wales, Cardiff [WITN6914019].

(v) As a result of this research, I identified that factor VIII activity began to reduce progressively only after an anti-coagulant had been added to the process to prevent coagulation.

(vi) In October 1980 I was informed by Dr John Cash that the German company Behringwerke had announced at a symposium in Bonn that it was pasteurising factor VIII, something that had been inconceivable to me.

43.2 1981

(i) At the beginning of 1981, the full-scale version of a device for thawing plasma continuously, that I had designed to increase the yield of factor VIII in cryoprecipitate, began to be used in Production at PFC, resulting in the yield of factor VIII being increased by about 50% in comparison with batch thawing [PRSE0003156]. I filed a patent application on 2nd April 1981.

(ii) In May 1981, I attended a one-day symposium in Cambridge for Blood Transfusion Directors, where I was deputising for Mr Watt. I noticed that a commercial exhibition was being held in an adjacent room and spent the lunch break gathering literature from company stands.

(iii) On my return to PFC, I discovered an article in my bundle of literature that concerned Behringwerke's pasteurisation process (Penrose Inquiry document SNB.008.6794) [PRSE0001863]. This was written in German, so I gave it to my colleague Dr Alex MacLeod to see if he could have it translated by a German post-doctoral researcher at Edinburgh University with whom he was collaborating.

(iv) Shortly after this, I was taken ill and was absent from work for a number of months
On my return, I was pleased to discover that Dr MacLeod had not only obtained a translation of the paper (Penrose Inquiry document SNF.001.0881) [PRSE0001335] but had himself begun experiments to see if the pasteurisation method could be applied to PFC's Factor VIII.

(v) I also discovered that the abstract of the presentation by Behringwerke, that Dr Cash had heard in Bonn, had been published (Penrose Inquiry document SNB.007.3300) [PRSE0003591], giving the overall yield of factor VIII as 8%, ie. 80 iu per litre of plasma. This compared with a yield of over 250 iu per litre plasma (ie. over 25%) that was being achieved at PFC. The yield of factor VIII obtained by Behringwerke was so low because 50% of the factor VIII activity was destroyed by pasteurisation, with further losses during the processing used to remove the stabilisers from the final product.

43.3 1982

(i) Dr MacLeod completed his preliminary experiments in early 1982, finding that although promising, the approach was not immediately applicable to PFC's Factor VIII. The reason for this was that PFC''s Factor VIII concentrate was not sufficiently purified, having a relatively high fibrinogen content that was unsuited to pasteurisation.

(ii) It was shortly after this that Dr Milan Bier from the University of Arizona came to PFC to demonstrate his new equipment for preparative scale electro-dialysis, which he had designed for the separation of immunoglobulins. Dr Bier was also interested in applying zinc as a protein

precipitant and was seeking possible applications. I suggested that he examine its behaviour on cryoprecipitate extract to see if fibrinogen might be separated from factor VIII, as it was a poorly soluble protein which co-purified with factor VIII. We were surprised not only to see a heavy precipitate form, but also to discover that factor VIII had remained in solution. I then found that the precipitation of fibrinogen by zinc could be enhanced by the addition of heparin, which I examined to the maximum concentration possible before it interfered with the PFC assay of factor VIII activity.

(iii) Meanwhile, Dr MacLeod had continued to study variations to the Behringwerke pasteurisation process to try to reduce the loss of factor VIII over pasteurisation, which was about 50%. In particular, he replaced the high concentration of sucrose with another carbohydrate, sorbitol, based on its better thermodynamic properties that had been published in an academic study (Gekko K. et al. J Biochem. 1981, 90, 39-60) [PRSE0000619].

(iv) I attended a Congress of the International Society of Blood Transfusion in Budapest in August 1982. Although there were a number of presentations on potential methods of virus inactivation, there was no presentation on pasteurisation. However, I did obtain information on the clinical evaluation of Behringwerke's pasteurised Factor VIII from their commercial stand (Penrose Inquiry document SNF.001.0929) [PRSE0002249] which reported an absence of hepatitis transmission by their pasteurised factor VIII.

(v) There was also a poster presentation listed in the book of abstracts concerning the concept of heating Factor VIII in its final freeze dried state. Unfortunately, the poster was not presented, as the authors did not attend the Congress. According to the abstract, the heated factor VIII had to be diluted beyond the recommended level before it would dissolve, making it unsuitable for clinical use. There was no information on the ability of the dry heat treatment to inactivate any viruses.

(vi) Near the end of the Congress it was announced that Baxter had developed a heat treated factor VIII but the method of heat treatment was not disclosed. Dr Christopher Prowse of Edinburgh BTS was friendly with the recently appointed Medical Director of Baxter, Dr Henry Kingdon, as they shared an interest in thrombogenicity of Factor IX concentrates. Dr Prowse subsequently learned from him that Baxter's method was dry heat treatment at 60°c for 72 hours.

(vii) I was also exploring how the instability of factor VIII could be prevented (see 41.3 (v) above) and had studied the addition of calcium to factor VIII solutions to try to achieve this. I

first presented this at a British Society of Haematology symposium in London in November 1982.

43.4 1983

(i) By early 1983, the following laboratory studies had reached a stage where they could be combined to form the basis of a manufacturing process:

• optimisation of zinc/heparin precipitation of fibrinogen to increase the purity of factor VIII, with a patent application being filed jointly with Dr Bier on 14th January 1983.

• optimisation of the addition of calcium to stabilise factor VIII, and

• optimisation of the addition of a carbohydrate, together with an amino acid, to stabilise factor VIII during pasteurisation,

A process scheme based on these developments was first applied at larger volumes in the PFC R&D pilot plant, which had recently been constructed in the new PFC Microbiology Extension. This was done in full compliance with PFC manufacturing protocols, including the completion of a detailed batch record and the full analysis that would be applied to a standard production batch of Factor VIII. Samples were also provided to scientists at the SNBTS Headquarters Laboratory, Dr Duncan Pepper and Dr Joan Dawes, to examine the product for evidence of biochemical changes that might cause antibodies (inhibitors) to be formed against the heated factor VIII molecule. A total of four small batches of the product (named ZHT) were prepared in this manner during 1983.Vials from these batches were issued for preliminary clinical evaluation, with the first clinical grade batch being given to Dr Ludlam in Edinburgh and the second clinical grade batch to Dr Forbes in Glasgow.

(ii) By early 1983, Dr MacLeod had also optimised conditions for the pasteurisation of factor IX. The possibility that heat treatment might make Factor IX concentrates thrombogenic (ie. cause thrombosis in recipients) was of major concern and it was proposed that study in animals should be undertaken to rule this out. This was agreed with Scotland's Haemophilia Directors at the annual planning meeting in January 1983 [PRSE0001736]. Dr Smith (PFL) was approached by Dr Cash. He agreed with the need for this study and accepted an invitation to participate. The study was directed by Dr Cash and managed by Dr Prowse of Edinburgh BTS, with a new assay to detect an early marker of a thrombogenic reaction being developed specifically for this purpose by Dr Joan Dawes of the SNBTS Headquarters Laboratory.

(iii) During 1983, I attended the Congresses of the World Federation of Hemophilia (WFH) and the International Society of Thrombosis & Haemostasis in Stockholm (ISTH) (see question 36). At the WFH Congress I learned from the authors of an unscheduled poster that Armour Pharmaceuticals were developing a dry heat treated Factor VIII concentrate.

(iv) At the meeting of the ISTH Factor VIII sub-committee, there was considerable discussion over protocols to determine if a heat treated concentrate was safe from transmitting NANBH. The claims of safety from NANBH that had been published by Behringwerke were heavily criticised, especially by the chair of the committee, Dr Mannucci, who believed that patient monitoring was inadequate. Dr Mannucci proposed that suitable guidelines be established for this purpose by the ISTH subcommittee. In his memoirs [PRSE0002333], Dr Mannucci indicates that this protocol was first applied to the clinical evaluation of Baxter's dry heat treated Factor VIII concentrate and that failure of this product to prevent NANBH was generally known by late-1983. According to a minute of the SNBTS Factor VIII study Group [PRSE0000428], this was known by Dr Bruce Cuthbertson of PFC by January 1984.

(v) In December 1983, experiments on dry heat treatment were undertaken by Dr Bruce Cuthbertson (PFC) and Dr Duncan Pepper (SNBTS Headquarters Laboratory). They found that PFC factor VIII was insoluble after heating at 60ºC for 72 hours, the conditions used by Baxter that had failed to prevent transmission of NANBH. They also observed that the degree of inactivation of an added marker virus was lower with dry heating at 60ºC for 72 hours than with the pasteurisation method that was being applied to factor VIII, consistent with pasteurisation being more effective in inactivating the agent(s) of NANBH (see para 43.3 (iv)).

43.5 <u>1984</u>

(i) In January 1984, Dr Ludlam advised that one of his patients had suffered "*an unacceptable*" adverse reaction to the PFC's pasteurised Factor VIII. By contrast two patients treated in Glasgow by Dr Forbes had tolerated the product well. Why this had happened was the subject of speculation, but was not resolved.

(ii) The plan to supply PFC pasteurised Factor VIII (ZHT) remained in place with an estimate that limited amounts would be available by September 1984 and full-scale production by April 1985 [WITN6914020]. The avoidance of NANBH in susceptible patients remained the objective at this time, as the cause of AIDS had not been discovered [WITN6914018].

(iii) A total of seven small volume batches of ZHT Factor VIII were produced during 1984, with the final batch being processed at the end of September 1984.The purpose of preparing these batches of ZHT was to:

- increase the experience of PFC production staff in operating the process.
- provide samples for laboratory investigations of virus inactivation

• provide clinical grade product for further clinical evaluation. The further clinical evaluation of ZHT was being managed by Dr Cash.

(iv) I had provided Dr Smith with details of our research, including the zinc/heparin precipitation of fibrinogen, addition of calcium to stabilise factor VIII and the amino acid/carbohydrate additives for pasteurisation. In May 1984, I was informed by Dr Smith that "*we have stumbled (literally) on an intriguing alternative to zinc*". It transpired that in performing PFC's zinc/heparin method for the precipitation of fibrinogen, too much heparin had been added accidentally. More precipitation had occurred, to the extent that Dr Smith decided to continue using a higher concentration of heparin without zinc. He was able to do this because, unlike PFC, BPL/PFL used a method for measuring factor VIII activity that high concentrations of heparin did not interfere with. This was the origin of the 8Y process in which zinc/heparin was replaced by a higher concentration of heparin, the addition of calcium was retained but pasteurisation was replaced by dry heat treatment because, according to Dr Smith, BPL did not have enough space to accommodate pasteurisation.

(iii) Whilst small batches of pasteurised Factor VIII (ZHT) were being produced at PFC, R&D continued into a number of issues during 1984, including:
• possible changes to the temperature and time of pasteurisation of factor VIII to bring the degree of virus inactivation closer to that of Albumin pasteurisation.
• studies on increasing the degree of purification substantially, in conjunction with Dr A J Johnson of New York University Medical Center.

(iv) In July 1984 control infusions were begun in the SNBTS animal model that was designed to measure if heat treated factor IX might be thrombogenic.

(v) I attended the Congress of the International Society of Blood Transfusion in Munich in July 1984, where I gave an invited presentation on PFCs research concerning the marked reduction in virus inactivation during 60ºC/10 hour pasteurisation of factor VIII in comparison with the pasteurisation of Albumin at 60ºC for 10 hours. This demonstrated that the long-term safety record of pasteurised Albumin could not be extrapolated to the pasteurisation of factor VIII. I have no memory of there being any other presentations on heat treatment at this Congress.

(vi) Laboratory research aimed at substantially increasing factor VIII purity was begun at PFC in August 1984, with Dr Ronald McIntosh (PFC R&D) being assigned by me to lead the project

which was being undertaken in conjunction with Dr A J Johnson of New York University Medical Center.

(vii) Following the discovery of the virus responsible for AIDS in May 1984 and the knowledge that it was a type of virus known as a retrovirus, a study of the effect of dry heat treatment on a mouse retrovirus was published in the 29th September edition of Lancet, by scientists from Bayer [CBLA0001898]. This suggested that dry heat treatment might be more effective at inactivating retroviruses than it had been with agent(s) of NANBH.

(viii) At the meeting of PFC Heads of Department on Friday 26th October 1984 [PRSE0001048], Dr Perry asked me to provide him with an update of our virus inactivation studies. Dr Cuthbertson had found, in December 1983, that PFC's Factor VIII concentrate did not withstand dry heating at 60ºC for 72 hours, the heating conditions that Baxter had used that had failed to prevent infection with NANBH. However, the degree of dry heat treatment, if any, that PFC's Factor VIII concentrate could withstand had not been determined, as we had focussed our work on the more promising technique of pasteurisation. The findings of Bayer (para vii above) suggested the possibility that dry heat treatment might be effective against the AIDS virus, despite having failed to destroy the agent(s) responsible for NANBH. I therefore asked the QC Laboratory Manager, Mr Tom McQuillan, to determine how long PFC Factor VIII might withstand dry heating at 68ºC. I chose 68ºC because it was the temperature used by Bayer ([CBLA0001898], which I assumed had been specified by them as the maximum dry heat temperature that the factor VIII molecule would tolerate. (Years later I discovered from Dr Cuthbertson that 68ºC had been a typographical error and that Bayer had originally intended its research on dry heat treatment to be done at 60ºC).

(ix) On Monday 29th October 1984, I learned from Dr Cuthbertson that a number of Edinburgh patients who had only ever received PFC Factor VIII had been found to have antibodies to HIV. I had been studying potential additives to factor VIII to improve its stability and some freeze dried samples were still available. I therefore arranged with Dr MacLeod to determine if any of these additives might extend the time that factor VIII could withstand dry heating at 68ºC.

(x) Just before leaving work on Tuesday 30th October 1984, Mr McQuillan gave me his initial results of dry heating at 68ºC. He had found that samples of PFC's existing Factor VIII could withstand dry heating at 68ºC for up to three hours.

(xi) The next day, Dr Perry, Dr McIntosh and I travelled to Groningen in the Netherlands to attend a two-day symposium on plasma fractionation. On Friday 2nd November 1984, Dr Jason from the USA Centers for Disease Control gave a presentation on AIDS. She announced that she had just received some results that were *"hot from the press"*. She reported that more than 100,000 particles of HIV had been added per ml of Factor VIII and that less than 10 particles per ml remained after dry heat treatment at 68ºC for 1 hour, with all of the added HIV destroyed by 24 hours at 68ºC.

(xii) I discussed these findings with Dr Perry and Dr McIntosh and we agreed to propose that PFC should immediately dry heat its existing Factor VIII concentrate at 68ºC. We also agreed that I would begin this process, while Dr Perry obtained agreement from Dr Cash. I also spoke with Dr Prowse who was attending the symposium and asked him to give me an update of the schedule for the animal thrombogenicity study that was being undertaken for heat treated factor IX.

(xiii) On Monday 5th November 1984 I initiated a 68ºC dry heat treatment study of samples from a large number of Factor VIII batches to determine the final heating conditions. Dr Perry returned from seeing Dr Cash, having obtained his approval to consider dry heat our existing Factor VIII at 68 ºC as quickly as possible. I also received a handwritten note from Dr Prowse with the latest schedule of animal infusions for the factor IX thrombogenicity project that he had drawn up with Dr Smith, which I reviewed to see if the timescale could be shortened.

(xiv) It was found that all batches of Factor VIII could withstand 68ºC dry heating for 2 hours, but not all batches could tolerate heating for 3 hours. Therefore, 68ºC for 2 hours was chosen for dry heat treatment. The spray cabinets used for pasteurisation had been designed in-house by former head of Engineering Mr Barry White who had set an upper control limit of 70ºC, meaning that the cabinets that were normally used for pasteurisation at 60ºC could also be used for dry heat treatment at 68ºC.

(xv) I met with Dr Smith at the end of November where I learned that he was aiming to dry heat Factor IX at 80ºC as he had already had success heating 8Y at 80ºC. As PFC used the same method as PFL for preparing Factor IX concentrate, we decided to explore dry heat treating PFC's Factor IX concentrate at 80ºC as this would be quicker for inactivating HIV than the development of pasteurisation.

(xvi) PFC's Factor VIII, dry heat treated at 68ºC for 2 hours, was distributed throughout Scotland and Northern Ireland on 10th December 1984 and unheated Factor VIII recalled.

(xvii) On 21st December 1984, Dr Cash received a letter from Dr Ian Hann, Haemophilia Director at Yorkhill Hospital, Glasgow, in which Dr Hann expressed doubt about the rapid introduction of heat treatment, because of concern over the possible formation of inhibitors (antibodies) in recipients of heat treated Factor VIII concentrate (Penrose Inquiry document, SNB.007.4689) [PRSE0003840].

(xviii) One benefit of selecting dry heat conditions that could be applied to the existing PFC Factor VIII concentrate was that over 12 months supply was available, enabling heat treatment to be applied immediately and providing a stock of heated treated Factor VIII to fill the national supply chain. Although I discovered that dry heating of PFC's Factor VIII at 68ºC could be extended from 2 hours to 24 hours by adding sucrose before freeze drying, this could only be applied to batches of product that were newly manufactured. As PFC was in the middle of a 3-month closure, a delay would have been incurred if only newly manufactured Factor VIII had been heat treated. By heat treating its existing 12-month stock, Factor VIII batches manufactured at PFC from as early as October 1983 were heat treated. As a result, the heat treatment of Factor VIII concentrate undertaken at PFC was effectively 'back-dated' to plasma donated at an earlier point in the AIDS epidemic, when the risk of infection was lower.

43.6 <u>1985</u>

(i) As BPL/PFL had begun research on dry heat treatment earlier, they had designed a precision oven for this purpose in conjunction with the company Pickstone Ltd who specialised in the manufacture of precision ovens. I was sent a copy of the specification by BPL, which I received on 16th January 1985. An order for an oven was placed immediately by PFC. Unlike PFC's pasteurising cabinet, this oven was specified to operate at 80ºC and higher. It was delivered in July-1985 and enabled Factor IX concentrate to be dry heat treated at 80ºC.

(ii) On 19th January 1985, a letter by Dr Graham Bird and colleagues was published in the Lancet which questioned the heat treatment of Factor VIII because of concerns over the possible formation of inhibitors (antibodies) in recipients. (Penrose Inquiry document, SNB.008.5887) [PRSE0003980].

(iii) After examining various formulations of Factor VIII, I had discovered that 68ºC dry heating could be extended to 24 hours by adding 2% sucrose to the product. This change was made as soon as processing at PFC re-started on 20th January.

(iv) As there was no evidence that the agent(s) of NANBH could be inactivated by dry heat treatment, pasteurisation continued to be our option for achieving this, but now aligned with a much higher degree of purification to eliminate substances being implicated as a cause of the immune disturbances being observed in patients. Our research on developing a highly purified Factor VIII was advancing well and contributed substantially to a patent application filed by Dr Johnson on 1st February 1985 [WITN6914021].

(v) As a result of the concern of Dr Bird over the possibility that heat treated Factor VIII might result in the formation of inhibitors (see ii above), Dr Cash invited Dr Bird to a meeting to discuss his concerns further. This meeting was held at SNBTS on 9th May 1985. I was unable to attend, and Dr Ronald McIntosh attended in my place. As Dr McIntosh had a PhD in immunology, he was able to re-assure both Dr Cash and Dr Bird that heat treating Factor VIII had been the right thing to do (Penrose Inquiry document SNB.007.5113) [PRSE0002506].

(vi) During the initial study of dry heating Factor IX at 80°C it was found that both PFC and PFL products failed one of the in vitro tests of thrombogenicity. Further research was undertaken to discover if this could be avoided by re-formulating the product with PFC and PFL agreeing a suitable change to the formulation.

(vii) The re-formulated Factor IX concentrates dry heated at 80°C for 72 hours were then examined in the animal model that had been developed to measure any potential thrombogenicity. No potential thrombogenicity was observed [WITN6914022].

(viiii) Dry heat treated Factor IX concentrate, approved by Dr Cash, was issued to Dr Ludlam on 15th July for clinical evaluation, with the first infusion on 17th July 1985. The clinical evaluation was completed satisfactorily on 9th August and dry heat treated Factor IX was issued to the Edinburgh RTC for routine use on 12th August, with routine issue throughout Scotland and Northern Ireland on 1st October, as soon as supplies were available.

(ix) By October, our research to develop a very high-purity Factor VIII had reached a point where equipment for production could be specified. This was done by Dr McIntosh in conjunction with the specialist chromatography company Pharmacia. A 2-stage automated chromatographic process was specified and an order placed to purchase the equipment. This was the most complex design undertaken by Pharmacia resulting in delivery being scheduled for mid-1986 at the earliest.

(x) Also in October, our research on developing a very high-purity factor VIII had reached the point where sufficient material could be prepared in the R&D laboratory for freeze drying. Surprisingly, the samples were destroyed using the standard method employed for freeze drying Factor VIII at PFC. Dr McIntosh and I re-designed the method of freeze drying from first principles, following which Dr McIntosh dry heated the samples at 80ºC.

(xi) It was believed that it was the higher-purity of 8Y that enabled it to withstand heating at 80ºC and we had therefore expected that our much more highly purified factor VIII would not only withstand 80ºC, but even higher temperatures, if this became necessary, to inactivate agent(s) responsible for NANBH.

(xii) There were two further surprises, our very-high purity factor VIII, which was about 20-times more pure than 8Y, did not withstand dry heating at 80ºC, but a sample of our existing low-purity factor VIII concentrate, which Dr McIntosh had included as a 'control', did survive heating at 80ºC.This suggested that the ability of 8Y to withstand heating at 80ºC might be due to the method of freeze drying, rather than to its increased purity.

(xiii) Therefore, I wrote to Dr Smith on 13th November 1985 [PRSE0000668] to ask him for details of the method used to freeze dry 8Y. His response of 17th December 1985 described conditions similar to the method that we had designed for our samples of high-purity factor VIII, strongly suggesting that it was the method of freeze drying that enabled both our lower purity factor VIII and 8Y to be dry heated at 80ºC. Why our much more highly purified samples had failed to survive heating at 80ºC remained to be determined.

(xiv) On 17th December, Dr Robert (Bob) Herrington of CSL Australia visited PFC to discuss virus inactivation. He was organising presentations for the Congress of the International Society of Blood Transfusion that was due to be held in Sydney in May 1986. He invited me to give a presentation on PFC's research on dry heat treatment. Dr Herrington was a close friend of Dr Smith and was staying with him during his UK visit. I therefore assumed that Dr Smith had also been invited to give a presentation concerning 8Y.

(xv) It seemed to me that we needed to review our strategy, so I drew up a list of options for discussion and arranged a meeting for this for 23rd December 1985 (see Penrose Inquiry document SNB.013.6680) [PRSE0004009].

(xvi) Present at the meeting were Dr Perry, Dr Cuthbertson, Dr McIntosh, Dr MacLeod and myself. In addition to my memo, a pre-publication copy of a paper by Dr Alfred Prince of the

New York Blood Center was tabled by Dr Perry, which he had been given by Dr McClelland. In his paper [PRSE0004828], Dr Prince found that dry heat treatment at 60ºC for 30 hours was less effective in destroying HIV than had been reported in previous studies of dry heat treatment. Although the earlier data from Bayer had involved dry heat at 68ºC and PFC's current FVIII was heated at 68ºC for 24 hours, we were concerned that the findings of Dr Prince might result in a loss of confidence in current dry heat procedures.

(xvii) We agreed that we should increase the margin of safety in respect of HIV as soon as possible. To produce all factor VIII by pasteurisation (i.e. ZHT) would be very challenging without further purification. However, the complexity of the chromatographic process, already on order, meant that its introduction might be delayed, not only by the time needed to complete delivery, installation and validation of the chromatographic equipment, but also because the longer processing time required extended working arrangements (e.g. shift-working), provision of which was out-with our control.

(xviii) Having discovered what we believed to be the importance of freeze drying to BPL's 8Y, we agreed that modifying our current product to be able to tolerate dry heating at 80ºC would be the fastest route to achieving a greater margin of safety against HIV.

43.7 <u>1986 -The Development of Z8</u>

(i). Dr Perry obtained agreement from Dr Cash for our proposed change of strategy and Dr McIntosh began to plan how to obtain factor VIII in which the final dose (ie. potency and volume per vial) would be compatible with the newly designed freeze drying cycle.

(ii) The new freeze drying cycle was not directly applicable to our existing Factor VIII concentrate as it would have taken too long to dry the volume of product involved. It was therefore necessary to concentrate the factor VIII into a smaller volume. To achieve this dose form as quickly as possible, Dr McIntosh based his new process on the already established ZHT process, but excluding pasteurisation. This new product was named Z8. A detailed description of the Z8 process is available (Penrose Inquiry document PEN.012.1852) [PRSE0000814].

The main steps were:

- thawing plasma and recovering cryoprecipitate by centrifugation
- washing cryoprecipitate in a solution of ethanol to remove soluble contaminants
- dissolving cryoprecipitate, using modified conditions
- adjusting the pH of the factor VIII solution
- treating the factor VIII solution with aluminium hydroxide to remove specific contaminants

• adding zinc acetate plus heparin to precipitate fibrinogen and removing the precipitate by centrifugation
• formulating the resultant factor VIII solution with 4 specific chemicals
• adjusting the pH of the factor VIII solution
• clarifying the factor VIII solution by membrane filtration to 0.45µm
• concentrating the factor VIII solution using membrane ultrafiltration
• re-formulating the factor VIII solution by membrane dia-filtration against 5 specific chemicals
• removing bacteria from the final factor VIII solution by membrane filtration to 0.22µm
• automatic dispensing of the factor VIII solution into vials aseptically
• freezing the vials of solution within the freeze dryer with a shelf temperature of -50ºC
• primary freeze drying for 4 hours at 0.1 millibar pressure and -25ºC
• secondary freeze drying for 24 hours at 0.06 millibar pressure and +35ºC
• introducing sterile nitrogen to bring the freeze drier chamber to atmospheric pressure
• sealing the vials under atmospheric pressure within the freeze drier
• heat treatment of the freeze dried product in a specialist oven for 72 hours at 80ºC

(iii) At a meeting of the SNBTS Coagulation Factor Study Group on 27th February 1986, Dr Perry estimated that Z8 would be "*manufactured from April 1986*" and be available for "*issue from January 1987*" (SNB.007.5596) [PRSE0003078]. I believed that this meant that from April 1986 he expected small quantities, prepared at clinical grade, to be available for clinical evaluation, as this was the procedure that had been followed in the development of ZHT, with full-scale production by late-1986.

(iv) Three unexpected problems were encountered during the development of Z8.

• Replacing a Pump:
During the scale-up of a procedure known as ultrafiltration, it was found that standard pumps used for this purpose were unsuitable because they either damaged factor VIII or did not give the velocity of fluid needed to avoid membrane blockage (known as concentration polarisation). Dr McIntosh approached specialist companies to find a suitable pump. He tested a number before a suitable one was found. Although mechanically suitable, this was intended for food-grade processing not pharmaceutical-grade. Dr McIntosh had to have all contact parts replaced with pharmaceutical grade materials. I believe that all of this took about two months to achieve.

• Processing Time:

Trials at pilot-scale demonstrated that the processing time required would exceed the normal working day according to the staffing arrangements in place at PFC. As establishing new terms and conditions of employment was out-with PFC's control, it was decided to reduce the volume of the process by dissolving the cryoprecipitate in a smaller volume of solution. This change required all of the process parameters to be re-optimised. Despite these delays, a small clinical grade batch of Z8 began production on 23rd June 1986. However, unlike ZHT, this was not issued for clinical evaluation, as the Head of Quality, Dr Cuthbertson wanted to wait for production to be achieved at full-scale before he authorised product for clinical trial.

• Ice Crystal Structure:

Following successful completion of two small production batches of Z8, preparation of a full-scale batch was begun on 4th August. Surprisingly many of the vials did not tolerate dry heating at 80ºC, with the colour and reconstitution time being out-with specification. The batch was inspected carefully and it was observed that vials composed of fine dried crystals tolerated dry heating at 80ºC but vials containing either large crystals or a mixture of fine and large crystals did not survive heating. The crystal structure is determined when the vials are frozen prior to drying, with fast freezing giving a finer crystal structure. This is normally done by placing the vials on refrigerated shelves inside the freeze drier, with shelves set at -50ºC to cool and freeze the factor VIII solution as rapidly as possible.

We suspected that there was enough refrigeration capacity to achieve this when the freeze drier was only part full, but not with a full load. To obtain fine crystals throughout a full load, I suggested that we should try to supercool the vials. Supercooling is a process where water is cooled below its freezing point without any ice formation. The formation of ice crystals is then triggered, causing fine crystals to form instantaneously throughout the liquid volume.

Dr McIntosh carried out a series of experiments in the production freeze dryer to determine how this could be achieved with the Z8 factor VIII solution. He established a two-stage freezing process, whereby all vials of solution were cooled slowly to -5ºC, then the shelf temperature control was set to -50ºC, causing the compressor to start-up and vibrations from the compressor triggering instantaneous freezing. Fine crystals formed instantaneously in all vials, with all vials being able to withstand heat treatment [WITN6914023]. The first batch of Z8 heated at 80ºC for 72 hours was placed at issue on 2nd December 1986; within the timescale that Dr Perry had estimated on 27th February 1986.

(v) I attended the Congress of the International Society of Blood Transfusion in Sydney, Australia in May 1986, where I gave an invited presentation on the importance of freeze drying to dry heat treatment. I was surprised that there was no presentation on 8Y. It was about 18

months later that I found out that there had been a presentation on 8Y at a symposium in Melbourne immediately prior to the ISBT Congress, that I had not known about.

(vi) A Congress of the World Federation of Hemophilia took place in Milan from 8-13 June 1986. As I did not attend, Dr Smith sent me a copy of his report. There was nothing about 8Y in his report. The apparent absence of information concerning 8Y at either of these major conferences caused me to wonder if a problem might have arisen in the 8Y clinical trial. It was only much later that I discovered that there had been a presentation concerning 8Y at the WFH Congress in Milan [WITN6914024], which Dr Smith had presumably omitted from his report as this was written for colleagues at BPL/PFL who would have already known about the 8Y presentation. This was similar to the information that Dr Smith had presented in Melbourne in May, which Dr Smith may have assumed I had attended.

(vii) At the end of June 1986, Dr Boulton inquired on behalf of Dr Ludlam if a small amount of 8Y could be obtained for the treatment of patients in Scotland who were susceptible to infection with NANBH. Why Dr Ludlam had made this request at this time could not be established by the Penrose Inquiry. I believe that it could have been a result of the presentation concerning 8Y at the WFH Congress in Milan on 13th June 1986, that Dr Ludlam may have attended or learned about subsequently.

(viii) On 9th October 1986, I met with Dr Smith and he gave me his interim report on the BPL surveillance study of 8Y and 9A, both dry heated at 80ºC for 72 hours (SNF.001.1123) [CBLA0002348]. There were data on 10 recipients of 8Y and 6 recipients of 9A, with Dr Smith combining the data from both products to estimate a residual risk from NANBH in the range 0-14%. If the data for 8Y are taken separately the residual risk from NANBH was 0-30%. These were the first data that I had seen on the safety of 8Y.

(ix) On 4th December 1986, Mr John Lundblad, a senior R&D scientist from Bayer, visited PFC. He explained that Bayer had attempted to develop a product comparable to 8Y, but had abandoned their research as they had been unable to resolve a problem with vial-to-vial variability within the freeze drier.

43.8 <u>1986 – HIV Infections from Dry Heat Treated Factor VIII</u>

(i) On 11-12 February 1986, I attended a conference on AIDS in Newcastle at which Dr Peter Jones announced that there was a case of HIV infection in the UK from a dry heat treated Factor VIII concentrate.

(ii) The article by Dr Prince, whose draft manuscript had caused us to change our strategy (para 43.6 (xv)), was published in the Lancet on 31st May 1986 [PRSE0002534].

(iii) It transpired that the HIV infection announced by Dr Jones was associated with a dry heat treated Factor VIII from Armour Pharmaceuticals and that the study of Dr Prince was based on the method of Armour [MDUN0000020_250].

(iv) HIV infections from Armour's dry heat treated Factor VIII were reported for patients treated in the USA, Canada, The Netherlands and the UK with the product being voluntarily withdrawn from the UK in October 1986 [WITN6914003, page 272).

(v) It has generally been assumed that Armour's factor VIII was infectious because their dry heat treatment was carried out at 60°C for 30 hours. However, there is an important manufacturing detail that has been overlooked. In describing the manufacturing method, Prince states "*Vials were stoppered under vacuum*" [PRSE0002534].

(vi) When freeze drying ends, vials of coagulation factors are sealed by automatic stoppering within the freeze drier. As freeze drying is carried out in a vacuum, manufacturers could either release the vacuum, with a sterile inert gas, before stoppering the vials or they could stopper the vials under vacuum. The advantage of stoppering under vacuum is that the negative pressure within the vial would 'suck-in' the water used for reconstitution, causing the dried plug to re-dissolve more quickly.

(vii). In her evidence to the Infected Blood Inquiry, Dr Anna Pettigrew (formerly of Yorkhill Hospital, Glasgow), noted that one reason for preferring Factor VIII from Armour over that of PFC/SNBTS was that it dissolved more quickly (IBI transcript, 7 December 2020, pages 38-39). PFC did not seal its vials under vacuum to avoid any risk of outside air leaking into a vial. Therefore, the evidence of Dr Pettigrew is consistent with Armour's vials being stoppered under vacuum as described by Dr Prince.

(viii). With dry heat treatment, stoppering vials under vacuum has two implications. First the vacuum will provide a barrier to heat transfer, Secondly, it is not possible to monitor the temperature inside the vial with a vacuum present. At PFC, dry heating was monitored and controlled by placing temperature sensors within 'dummy' vials spread throughout the load. Consequently, the temperature cited by PFC was the actual temperature within the vial of product. By contrast manufacturers who sealed their vials under vacuum could not do this, so

presumably the temperature cited by them was the temperature of the oven, not the temperature within the vials of product being heated.

(ix) For Armour Pharmaceuticals this means that although 60°C was cited as the temperature of heat treatment, this was most probably the temperature of the oven rather than the temperature within the vial.

(x) The other company whose dry heat treatment data were especially important was Bayer, as it was their procedure of dry heating at 68°C that was first reported to be effective against HIV. On 19th December 2020, I contacted the senior Bayer scientist involved in this work, Dr Milton Mozen, to ask if they had sealed their vials under vacuum or under atmospheric pressure. He replied on 29th December 2020 – "atmospheric pressure", implying that the temperature of 68°C quoted by Bayer was most probably the temperature measured within vials of Factor VIII during heat treatment.

43.9 1987

(i) PFC's new FVIII concentrate (Z8) was issued routinely from 15th April 1987 (see question 53).

(ii) Meetings were held with scientists from BPL/PFL on 22nd April 1987, 19th October 1987 and 2nd December 1987 to discuss dry heat treatment.

(iii) Drs McIntosh, Cuthbertson and Perry attended the Congress of the International Society of Thrombosis and Haemostasis in Brussels from 6-10 July 1987. Dr McIntosh gave a presentation on the development of Z8, of which I was a co-author [WITN6914023].

(iv) Following his presentation, Dr McIntosh was approached by Dr Adrian Oats of CSL Australia who explained that they had been unable to develop 8Y, but that the information provided by Dr McIntosh should now enable them to do this.

43.10 1988 – Z8 Unable to Withstand Dry Heat Treatment at 80°C

(i) During 1988, a number of batches of Z8 were unexpectedly found to be unable to withstand dry heat treatment at 80°C (ie. the product would not dissolve within the specified reconstitution time). Production of Z8 was suspended pending an investigation to discover the cause and Haemophilia Directors advised to purchase commercial Factor VIII, if necessary. Although these commercial products were heat treated to inactivate HIV, they still carried a risk of infection with NANBH as commercial products were not yet free from a risk of

transmission of NANBH/HCV (see cited document no. 1, PEN 013.1309, page 22 [PRSE0002139]).

(ii) The investigation was conducted by Dr Ronald McIntosh who found that the failed batches of Z8 were associated with plasma that had been stored frozen off-site.

(iii) Plasma was separated from whole blood at Regional Transfusion Centres after which it was immediately frozen. The frozen plasma would then be transported to PFC in a refrigerated vehicle at -20°C. On arrival at PFC the frozen plasma would be transferred to a large cold-store which operated at -35°C and was held there until taken for processing.

(iv) By 1988, the PFC plasma cold-store had been operating continually for about 14 years and repairs were required. To enable the refrigeration to be turned off so that the necessary repairs could be carried out, all of the plasma was transferred to commercial cold storage. The coldest facility available off-site operated at -20°C.

(v) Dr McIntosh discovered that the failed batches of Z8 were all associated with plasma that had been stored frozen off-site, with virtually all PFC's plasma implicated.

(vi). He also found that the change in frozen storage had resulted in a small increase in the amount of cryoprecipitate produced per litre of plasma and that this cryoprecipitate was less soluble than that obtained previously and on which the Z8 process was based (WITN6914025).

(vii) To recover the situation, Dr McIntosh revised the operating parameters of the Z8 process, to make it compatible with the cryoprecipitate now being obtained from the plasma that had been stored off-site.

(viii) This experience demonstrates how sensitive the dry heat treatment process was to the conditions under which plasma was stored. It may also explain why Dr Johnson did not succeed in applying dry heat treatment to factor VIII (para 32(vi)), as the collection and storage of plasma would have been much less refined at that time.

43.11 <u>Summary - Key Dates in the Development of Heat Treatment at PFC</u>

<u>1980</u>

- Oct: Learned that FVIII had been pasteurised by Behringwerke, Germany.
- Dec: Discovered that addition of sodium citrate made FVIII unstable in production process

1981

• May: Obtained details of Behringwerke's pasteurisation process (in German)

• Sep: Experiments begun at PFC on pasteurisation of FVIII

• Oct: Studies begun on addition of calcium to prevent citrate-induced instability of FVIII

1982

• Feb: Preliminary study of pasteurisation completed. Removal of fibrinogen required.

• May: Discovered that fibrinogen can be removed by precipitation with zinc chloride

• Aug: Obtained Behringwerke clinical data with no NANBH from pasteurised FVIII

• Nov: First PFC presentation on the use of calcium to stabilise factor VIII activity

1983

• Feb: First non-clinical, pilot-scale preparation of pasteurised factor VIII (ZHT) at PFC.

• Jun: Invited by Dr Johnson (NYU) to collaborate on developing a very high purity FVIII

• Aug: First clinical-grade, pilot-scale preparation of pasteurised factor VIII (ZHT) at PFC

• Dec: First experiments on dry heating; PFC FVIII did not survive 60°C for 72 hours.

1984:

• Jan: Known that Baxter's FVIII, dry heat treated at 60°C for 72 hours, had transmitted NANBH

• Jan: Informed of an "unacceptable" adverse reaction to PFC's 1st pilot batch of ZHT

• Jun: Given details of new US (NYU) method for preparing very high purity FVIII

• Jul: Presented findings from PFC lab virus inactivation studies comparing FVIII with Albumin

• Aug: Research begun at PFC on development of a very high-purity FVIII

• Sep: Ninth pilot batch of ZHT prepared for clinical evaluation

• Sep: Bayer publication on inactivation of a murine (mouse) retrovirus by dry heat at 68°C

• Oct: Discovered that samples of PFC FVIII could tolerate dry heat at 68°C for 3 hours.

• Nov: Obtained first US data that dry heat at 68°C for 1 hour destroyed most HIV added.

• Nov: Dry heating of PFC FVIII at 68°C for 2 hours begun

• Dec: PFC FVIII dry heated at 68°C for 2 hours issued for clinical evaluation

• Dec: Distribution of PFC FVIII dry heated at 68°c for 2 hours to all Scotland/NI.

• Dec: Found change to FVIII formulation for dry heat at 68°C to be increased to 24 hours

1985

• Jan: All newly prepared PFC FVIII dry heated for 24 hours at 68°C

• Jan: Specification of oven for dry heat treatment provided by BPL; PFC order placed

• Mar: PFC FIX dry heated at 80°C for 72 hours for animal safety study – failed QC test

• Mar: PFC FVIII dry heated for 24 hours at 68°C issued for clinical evaluation

• Apr: Preparation of re-formulated FIX for animal safety study, dry heated at 80°C for 72 hr

• May: Scottish HCDs agree to continue use of 68°C/2hr FVIII to retain batch dedication

• July: Reformulated FIX dry heated for 72 hours at 80°C issued for clinical evaluation

• Aug: Routine issue to Edinburgh BTS of FIX dry heated for 72 hours at 80°C.

• Sep: Routine issue of FVIII dry heated for 24 hours at 68ºC, with batch dedication
• Oct: Equipment specified and ordered for production of very high purity FVIII
• Oct: Discovered new freeze drying allowed 80ºC/72h dry heating of sample of existing FVIII
• Dec: Learned that 8Y was freeze dried using similar operating conditions
• Dec: Obtained copy of Prince report questioning the effectiveness of dry heat against HIV
• Dec: Agreed to develop FVIII comparable to 8Y to provide greater assurance of HIV safety

1986

• Feb: Heard from Dr Jones that HIV had been transmitted by heat treated commercial FVIII
• Mar: New PFC FVIII (Z8) at lab scale gave 80% recovery over 80ºC/72hr dry heat
• Jun: First pilot-scale preparation of Z8 in PFC production department
• Aug: First full-scale preparation of Z8 in PFC production department, some vials fail to survive dry heating at 80º/72hrs
• Sep: New method of freezing Z8 devised to obtain fine crystals throughout all vials
• Oct: First batch of Z8 prepared using new freezing technique
• Oct: PFC given first interim report of BPL NANBH safety study re. dry heating at 80ºC/72hrs
• Dec: First batch of Z8 released for issue.

43.12 Evidence for the Effectiveness of Heat Treatment.

(i) In addition to discovering technically how to heat treat a plasma protein in a manner that retains the chemical, biochemical and biological specifications set by the relevant regulatory authority, at a viable yield, it is necessary to have evidence that the treatment is effective in destroying the infective agent(s) of concern.

(ii) Science is evidence based. Modern medicine is evidence based. When responding to a question on the ethics of medical research, Professor Farsides commented "*although it has long been appreciated that this is an area where potential for ethical wrongs is very real, we wouldn't want that to undermine our attempts to ensure that as broad a range of the population as possible benefits from scientifically sound evidence-based medical practice.*" (Infected Blood Inquiry transcript 27th January 2021, page 58 [INQY1000091]). Her opinion implies that a requirement for evidence is not only scientifically sound, but is also an ethical requirement of medical practice.

(iii) **Pasteurisation of Albumin**

• Background

Accounts of the development of pasteurised Albumin are available (WITN6914003 and PRSE0000345). Albumin was produced from 1941-1945 without being pasteurised. It included

a high concentration of sodium chloride to make it stable for storage in North Africa and a mercury-based preservative to prevent bacterial growth. Following a chance observation by Dr J Murray Luck of Stanford University, chemicals were discovered that could stabilise Albumin and allow the sodium chloride concentration to be reduced to a physiological level. Dr George Scatchard of The Massachusetts Institute of Technology (MIT), a close friend of Dr EJ Cohn, suggested that it might be possible to heat the Albumin to destroy bacterial contaminants and enable the mercury-based preservative to be omitted. Consequently Albumin, pasteurised for 10 hours at 60°C was introduced in June 1945.

• Hepatitis

It was in 1948 that a preliminary study first indicated that the agent responsible for serum hepatitis might be inactivated (Gellis SS, et al. J Clin Invest 1948, 27, 239-44) [PRSE0004131] and in 1955 that substantive proof was obtained (Murray R, Bull NY Acad Med 1955, 31, 341-58 [WITN6914061]; Murray R et al. N Y State J Med 1955, 55, 1145-60 [SBTS0003649_046]). The studies of Gellis and Murray both being undertaken in prison volunteers in the USA.

Following the discovery of the virus believed to be responsible for serum hepatitis (designated hepatitis B in 1947) and the development of serological assays, samples retained from the study by Murray were analysed for the presence of hepatitis B surface antigen. It was found that most virus had been removed by cold-ethanol fractionation, with pasteurisation being responsible for the inactivation of residual virus (Hoofnagle JH, Barker LF, Proc Workshop on Albumin 1976, pp. 305-14. DHEW Publ No. (NIH) 76-925) [DHSC0003621_026]. The implication of this analysis was that the hepatitis safety of Albumin was due not only to pasteurisation but also to virus being removed by the fractionation process. It is for this reason that cold-ethanol fractionation remained the established method of plasma fractionation.

• HIV

Evidence that HIV could be inactivated during pasteurisation of Albumin was first reported in 1987 by PFC (Cuthbertson B et al. Lancet 1987, 2, 41) [BAYP0000010_136].

(iv) **Pasteurisation of Coagulation Factors**

• Hepatitis

The first evidence that the pasteurised Factor VIII concentrate developed by Beringweke, Germany might be free from transmitting hepatitis was published in 1980 (Penrose Inquiry document SNB.004.5880) [PRSE0004058]. It was these data that were the subject of criticism by the factor VIII Sub-Committee of the International Society of Thrombosis & Haemostasis at its meeting in Stockholm in July 1983 (see para 43.4 (iv)).

A study compliant with the ISTH guidance was published in 1987 (Schimpf K et al. N Eng J Med 1987, 316, 918-22) [NHBT0000037_016] with no NANBH transmissions, but had to be repeated, as Beringwerke had modified their production process (Manucci PM, et al. Ann Int Med 1990, 113, 24-32 [WITN6914060]) with no transmissions of NANBH, HCV.

A pasteurised Factor IX concentrate produced by Beringwerke infected over 30 patients with hepatitis B, causing the effectiveness of the pasteurisation process to be questioned (WITN6914003, page 271).

• HIV

Evidence that HIV could be inactivated by the pasteurisation of coagulation factors was first reported in November 1984, By Dr Jason of the Centers for Disease Control at a symposium in Gronigen.

The first publication providing clinical evidence of an absence of HIV infection in recipients of pasteurised FVIII was in 1987 (Schimpf K et a. N Engl J Med 1987, 316, 918-22).

• Inhibitors (Antibodies) to Factor VIII

A pasteurised Factor VIII concentrate developed by the Netherlands Red Cross was associated with the formation of inhibitors to factor VIII in people with haemophilia A (Peerlinck K, et al. Thromb Haemost 1993, 69, 115-8 [WITN6914065]; Rosendaal FR, et al. Blood 1993, 81, 2180-6 [DHSC0020815_094]) and was discontinued.

A pasteurised Factor VIII concentrate developed by Octapharma was also associated with the formation of inhibitors to factor VIII in people with haemophilia A (Laub R, et al. Thromb Haemost 1997, 77 (suppl), 590 [WITN6914062]; Peerlinck K et al. Thromb Haemost 1997, 77, 80-6 [PRSE0003191]) and was discontinued.

(v) **Dry Heat treatment of Coagulation Factors**

• Hepatitis

Early dry heat treatment procedures failed to prevent transmission of NANBH in people with haemophilia, including heat treatment at:

• 60ºC for 30 hours (Preston FE. et al Lancet 1985,2, 213) [RLIT0000186],

• 60ºC for 72 hours (Colombo M et al. Lancet 1985, 2, 1-4) [BAYP0000007_139]

• 60ºC for 24 hours, with the dried powder suspended in an organic solvent (Kernoff PBA et al. Br J Haematol. 1987, 67, 207-211) [WITN6914056].

For 8Y of BPL/PFL, dry heated at 80ºC for 72 hours:

• At a symposium in Melbourne on 9th May 1986, Dr Smith reported *"It is too early to know whether NANBH transmission has been eliminated by severe dry heating".* The proceeding of the symposium were published in 1987 (Smith JK et al. Dev Biol Standardization 1987, 67, 323-5) [WITN6914063].

• At the Congress of the World Federation of Hemophilia in Milan, Dr Fletcher reported *"the results suggested that transfusion with FVIII produced by this method may reduce the incidence on non-A, non-B hepatitis".* (Conference book of abstracts, 13th June, page 243) (WITN6914024).

• In a report to the UK HCDO dated 30th Sept 1986, Dr Smith concluded, in respect of NANBH, that his combined data for 8Y and 9A were *"compatible with an infectivity rate of 0-14%".* (SNF.001.1123) [CBLA0002348].

• A final report of the 8Y study was published in 1988 (Colvin B et al. Lancet 1988, 2,814-6 [WITN6914064]) with no cases of NANBH. The study did not comply fully with the protocol that was devised for this purpose by the International Society of Thrombosis & Haemostasis (ISTH), PRSE0002333.

• A second study of 8Y was undertaken to be compliant with ISTH guidance and was published in 1993 (Rizza CR et al. Br J Haematol 1993, 84, 269-72) [PRSE0000192], with no cases of either NANBH, nor HCV recorded.

• <u>HIV</u>

On 26 October 1984, CDC reported inactivation of HIV by dry heat treatment at 68ºC for 24 hours (Penrose Inquiry document LIT.001.0460) [BART0002308]. On 2nd November 1984, it was reported by Dr Jason of CDC at a symposium in Groningen that HIV could be substantially inactivated by dry heat treatment at 68ºC for 1 hour. Additional data were published in 1985 (Levy JA et al. Lancet 1985, 1, 1456-7 [PRSE0000008]; McDougal JS et al. J Clin Invest 1985, 76, 875-7 [PRSE0001941]). In February 1985, no cases of HIV transmission were observed in a clinical study of FVIII from Baxter that had been dry heat treated for 72 hours at 60ºC (Rouzioux C et al et al. Lancet 1985, 1, 271-2) [SHPL0000371_036].

(vi) **Conclusions**

• Evidence that infective agent(s) in coagulation factor concentrates, that were responsible for NANBH infection, might be destroyed by pasteurisation was published in 1980.

• Evidence that HIV might be destroyed by dry heat treatment at 68°C was available to PFC in November 1984 and published in 1985.

• Evidence that infective agent(s) in coagulation factors, that were responsible for NANBH infection, might be destroyed by dry heat at 80°C was available to PFC in October 1986 and published in 1988.

For further information on heat treatment see cited documents:

• 1 (PEN.013.1309) [PRSE0002291],

• 5 (PEN.012.1438) [PRSE0003349],

• 6 (PEN.017.1556) [PRSE0000256]

• and (PEN.012.1797) [PRSE0001478], my revised response to the Penrose Inquiry on Topic B3.

For information on the heat treatment procedures employed by different USA companies, see Kasper CK et al. Transfusion 1993, 33, 422-434 (Penrose Inquiry document).

Who were the most significant figures in the development of heat treated plasma products at PFC and what roles did they play? Please also set out your role and responsibilities as Development Manager, Head of R & D and Senior Research Scientist at various times.

a. Other than Dr James Smith and Dr Terence Snape, are there any living individuals with knowledge of how heat treatment was developed at PFC or BPL who you think would be able to assist the Inquiry further?

44.1 The Most Significant Figures in the Development of Heat Treatment at PFC

(i) Dr Peter R Foster: Obtaining information on the pasteurisation method of Behringwereke; leading the necessary platform studies on the purification and stabilisation of factor VIII; leading the scale-up studies of pasteurisation; leading the introduction of dry heating treatment of FVIII at 68°C; leading PFC's application of 80°C dry heating of factor IX; collaborated with Dr McIntosh on the development of a factor VIII concentrate (Z8) that could be dry heated at 80°C.

(ii) Dr Alexander J MacLeod: Undertaking a preliminary study of the pasteurisation method of Behringwerke; developing and optimising new formulations for pasteurisation, based on the method of Behringwereke, for application to factor VIII and to factor IX.

(iii) Dr Ronald V McIntosh: Discovering that relatively low purity FVIII could withstand 80°C dry heat treatment and subsequently leading the development of the Factor VIII concentrate, Z8, that was PFC's equivalent to 8Y.

(iv) Dr Bruce M Cuthbertson: A virologist who provided information on viral infections/virus inactivation and who undertook studies on the inactivation of marker viruses as well as being Head of Quality at PFC from 1984. Dr Cuthbertson was a member of the SNBTS Safety Action Group that was established by Dr Cash in January 1982 to consider virus inactivation technologies.

(v) Significant Figures from the wider SNBTS who assisted PFC were:

• Dr Duncan S Pepper: Head of the SNBTS Headquarters Laboratory, who chaired the SNBTS Safety Action Group from January 1982. Dr Pepper carried out PFCs first dry heat treatment experiments in December 1983 in conjunction with Dr Cuthbertson. He also examined a number of alternative methods of virus inactivation.

• Dr Christopher V Prowse: A specialist in the biochemistry of coagulation factors who co-ordinated studies to ensure that heat treated Factor IX concentrates were free from thrombogenic side effects.

• Dr Joan Dawes: An analytical biochemist at the SNBTS Headquarters Laboratory who developed a new method for measuring an early marker of thrombogenic reactions on which the Factor IX safety study was based. Dr Dawes also examined samples of heat treated factor VIII for any evidence of molecular damage that might cause the formation of inhibitors in patients.

44.2 My Roles and Responsibilities

See my responses to question 2 (at 2.3) and 16 (at16.1).

44.3 Staff of BPL and PFL

I am not aware of any individuals with knowledge of how heat treatment was developed at PFL or BPL who could assist the Inquiry more than Dr James K Smith and Dr Terence Snape.

Was there any discussion of alternatives or resistance to PFC pursuing heat treatment (as opposed to other methods of viral inactivation) of Factor VIII and Factor IX products? If so, please provide details and, if there was resistance, from whom did it come, when and why?

(i) Research on alternatives to heat treatment was undertaken by Dr Duncan Pepper of the SNBTS Headquarters Laboratory in from 1982-1986 [PRSE0000428] (Penrose Inquiry documents SNB.001.3932; SNB.007.5596) [PRSE0002206; PRSE0003078]. None of this research was successful. These alternatives included:

- treatment with detergents
- gamma-irradiation
- treatment with hydrogen peroxide

(ii) There was no resistance by SNBTS to heat treatment being pursued at PFC. There was full agreement that this was the preferred option.

How were decisions taken on which research and development projects concerning viral inactivation should be taken forwards at PFC, both generally and in respect of heat treatment, both wet and dry?

(i) Decisions on which R&D projects were undertaken at PFC concerning virus inactivation were taken by PFC Director Mr John G Watt, in consultation with myself, until January 1982.

(ii) From January 1982 decisions concerning PFC R&D projects on virus inactivation were taken by Dr John D Cash, who created and chaired a SNBTS Coagulation Factor Study Group for this purpose. He obtained advice on virus inactivation via a sub-group known as the Safety Action Group, which comprised Dr Duncan Pepper (SNBTS Headquarters Laboratory), Dr Bruce Cuthbertson (PFC) and Dr Robert Somerville, Consultant Virologist at Ruchill Hospital.

(iii) Between meetings of the SNBTS Coagulation Factor Study Group, decisions were taken by Dr John D Cash in consultation with the PFC Director, Mr Watt, until 31st December 1983, then Dr Robert J Perry from January 1984.

See also my answer to question 17.c.

§4.4 of the Heat Treatment Briefing Paper records that experimental research into heat treatment of coagulation factor concentrates was begun by the SNBTS in

September 1981 when it became aware of the method of pasteurising Factor VIII devised by Behringwerke (60C/10hr).

Can you expand on the factors relevant to the origins of research into heat treatment at PFC, including:

a. **The relative importance of those factors;**
b. **The chronological sequence in which they developed;**
c. **How the factors interacted with one another.**

See my response to question 43 at 43.1 (vi) and 43.2 (iii).

What resources were available for research and development at PFC (including personnel, laboratory space and equipment)? In particular:

a. **What resources were available to pursue work on heat treatment?**
b. **To what extent, if resources were limited, were those resources mitigated by co-operation with BPL/PFL?**
c. **How did those resources compare to those available at BPL/ PFL (to the best of your knowledge)?**
d. **How did those resources compare to those available in commercial fractionators (to the best of your knowledge)?**
e. **Did you ever request additional resources for research and development, and if so what was the response**

(i) See response to question 44.

(ii) When I was assigned Head of R&D in April 1974, I became responsible for a small laboratory and 7 members of staff (4 scientists, 2 technicians and 1 ancillary worker).

(iii) The laboratory was a basic biochemistry laboratory capable of handling volumes up to about 250ml. Equipment included standard refrigerated laboratory centrifuges and analytical equipment such as a spectrophotometer (many analytical measurements were made in the adjacent PFC Quality Control Laboratory, which had a much wider range of analytical equipment).

(iv) An R&D pilot plant became available in late-1982 which included vessels, pumps and refrigerated centrifuges capable of handling volumes of up to about 100 litres. A steam sterilisable pilot-scale freeze drier was also installed and a technician employed and trained to operate it.

(v) The original scientific staff were:
• Mrs Sarah Middleton, who specialised in coagulation factor R&D.
• Ms Moira Patterson, who specialised in immunoglobulin R&D.
• Mr Christie Turnbull, who specialised in Albumin R&D.
• Mr Alistair Ross, who specialised in computing and process control.

(vi) Mrs Middleton left in 1976, after which I led coagulation factor R&D in conjunction with an experienced technician Mrs Ida Dickson. Dr MacLeod was appointed to replace Mrs Middleton and was assigned to carry out research on the potential use of cell culture for the preparation of factor VIII, as well as research concerning plasma derived Factor IX concentrates.

(vii) The development of heat treatment for application to coagulation factors was given top priority at PFC once it became conceivable. Dr Macleod and Mrs Dickson were involved from the outset and Mr Turnbull assisted with studies at pilot-scale.

(viii) Ms Moira Patterson left PFC R&D in 1975 and was replaced by Dr Anne Welch, who assisted Dr MacLeod in optimising conditions for pasteurisation with a view to apply the technology to immunoglobulins as well as to coagulation factor concentrates.

(ix) Mr Alister Ross left in 1980 and was replaced by Dr Ronald V McIntosh, who was initially assigned to work on the development of intravenous immunoglobulin, but was subsequently transferred, at my request, to work on Factor VIII.

(x) In order to undertake R&D as efficiently as possible, PFC practiced the following measures:
• materials for research would be obtained from the relevant stage of a production process. This meant that R&D staff did not have to work from plasma directly and that the outcome of the studies would be applicable to production material.
• standard assays were done by the PFC QC laboratory.
• new research assays were developed by staff of the SNBTS Headquarters Laboratory.
• staff from the PFC Production Department would assist with pilot-scale development studies where appropriate.

(xi) In my opinion, hiring additional staff would have been counter-productive, as the training and supervision required would have taken resources away from on-going research into virus inactivation.

(xii) In my experience the most important resource in the development of heat treatment was the quality of the staff available, the most important qualities being:
• an aptitude and ability to work in research and in production environments,
• intelligence, especially an ability to solve problems,
• dedication, including determination and perseverance in addressing problems.

(xiii) I do not know the resources available for R&D at either BPL or at commercial companies, so I cannot make comparisons with PFC.

Was the speed at which effective heat treatment of Factor VIII and Factor IX products was achieved at PFC affected by:

a. **Any limitations on the personnel, equipment, infrastructure and financial resources available to those working on heat treatment?**
b. **Decision making on research and development?**
c. **Funding limitations?**
d. **The relationship between PFC and BPL/PFL?**
e. **The suspension of production between October 1984 and January 1985 to introduce changes to facilities required by the Medicines Inspectorate?**
f. **Any other factors?**
   In this respect, you may be assisted by the Fourth Penrose Statement (§ 10 (d)(v)) where you refer to the time taken to perform assays being usually the rate limiting factor in research of coagulation factor concentrates and necessary automated equipment being subject to *"NHS financial procedures"* (presumably having a negative impact).

49 **General Response**

(i) Research on heat treatment began at PFC in 1981 when it became conceivable that factor VIII might be able to be heat treated in a manner that would destroy hepatitis viruses without the factor VIII being destroyed.

(ii) Information was obtained from publications and from discoveries made at PFC.

(iii) The speed of progress was determined by the time taken to discover how to modify and scale-up the preparation of coagulation factors at PFC to enable heat treatment, such as pasteurisation, to be applied in a manner consistent with the objectives of SNBTS/PFC.

(iv) Once basic discoveries had been made in the research laboratory, it was necessary to evaluate and modify (fine-tune) these at a pilot-scale. This was done in a manner that mirrored production operations, with the timing determined by:

- the time required to plan and organise an appropriate study,
- the time required to carry out the practical work
- the time required to obtain all necessary analytical results,
- the time required to analyse and interpret the resultant data,
- the time required to determine how best to proceed,
- the time required to plan and organise the next study.

(v) There were no staffing or funding limitations as far as I was concerned. I did propose in July 1984 that Dr McIntosh be transferred from the development of intravenous immunoglobulin to work on FVIII developments. My proposal was accepted by Dr Perry and by Dr McIntosh.

(vi) I was not involved with factor VIII assays, but I believe that one limitation was the supply of haemophilic plasma required as a substrate for the assay. I also understand that the assay was at first a manual assay, which was very laborious, and for which additional staff were employed to cope with the increased volume of work. I remember that automated equipment was developed by an equipment supplier and was purchased by PFC. To the best of my knowledge, the cost of this equipment meant that it had to be purchased as a capital item under the standing financial instructions for the NHS, which usually involved a delay of several months.

(vii) The relationship with BPL/PFL was beneficial, especially the sharing of information on the purchase of a specialist oven for dry heat treatment and on the sharing of information on freeze drying cycles.

(viii) The suspension of PFC Production from October 1984 to January 1985 was beneficial (see my answer to Question 19).

(ix) Progress in relation to the implementation of a heat treated product was dependent on satisfactory clinical evaluation. This was led by Dr Cash in conjunction with Haemophilia Directors and was out-with the control of PFC.

On 3 May 1983 you wrote a memorandum to Mr Watt and the Heads of Department at the PFC on the subject of "*Heat Treatment of FVIII. A Strategy*". In this, you proposed a change of strategy away from heating only 30% of PFC factor VIII concentrates (to provide to those who had not previously been exposed to factor concentrate), to heat treating all PFC factor VIII on the basis that, "*In the absence of any hard data, heat treatment (of everything) looks at this moment to be the most likely possibility that we have to face up to*", given the "*possibility that another more serious infectious agent (AIDS) is now involved.*" Please explain why you wrote this memorandum, and the reception that it received, including commenting on the following:

a. **Why you considered that heat treatment was "the most likely possibility" to respond to the risk posed by AIDS.**
b. **The confidence you had, at that time, in the effectiveness of heat treatment to address the risk of AIDS transmission through blood products.**
c. **What, if anything, was known about the length of time or the temperatures that would be required to reduce the risk of AIDS transmission.**
d. **Whether any thought was given, at this time, to alternatives to pasteurisation to achieve heat treatment of all PFC factor VIII more rapidly.**
e. **How the memorandum was received by those to whom it was sent.**
f. **What steps were taken in response to the memorandum. (You may be assisted by the letter from Dr Cash to Mr Watt dated 1 June 1983 [SNB0073708] and §18 - 18.2 of Dr Cash's Second Penrose Statement, and by the summary contained in the Final Penrose Report at §23.123)**
g. **What steps were not taken that you felt, at the time, should have been taken.**
h. **Whether, in your view, there was a failure to respond appropriately to this memorandum, which slowed the production of heat treated factor VIII at PFC.**
i. **Were you "*essentially advocating a swifter resort to pasteurisation using existing equipment [pasteurisation cabinets] rather than constructing new plant*" (see §17 of Dr Cash's Second Penrose Statement). If so, why?**

(i) The strategy and timing that we had adopted for the development of pasteurised FVIII was based on preventing transmission of NANBH in the relatively small number of patients who

were not already infected (i.e. those who were untreated or who had received little treatment) as it was known by the early 1980s that most people with haemophilia who had been treated repeatedly were probably already infected with NANBH.

(ii) By contrast, if AIDS was due to a blood borne infection, those most at risk would be patients who required most treatment.

(iii) The main purpose of my memo was to point out that as our current strategy was based on NANBH "*The possibility that another more serious infectious agent (AIDS) is now involved suggests that we may need to review this strategy"* and *"we will have to plan to pasteurise all of the FVIII (rather than 30%) and we may also want to review the timescales...There may therefore be a case for accelerating our heat treatment programme"*.

(iv) I then set out a technical approach for "*accelerating our heat treatment programme"* which involved carrying out the pasteurisation of FVIII in the spray cabinets that were used to pasteurise albumin, instead of designing and purchasing separate equipment for pasteurising FVIII.

(v) As far as I remember the technical approach that I proposed was welcomed by Mr Watt and formed the basis for the preparation of some ten small pilot batches of pasteurised FVIII (called ZHT) from May 1983 to September 1984.

(vi) The purpose of these small pilot batches was to familiarise PFC Production staff with the process, provide samples for laboratory virus inactivation studies at PFC and to provide product for preliminary clinical evaluation under the direction of Dr Cash.

(vii). My comment that "*heat treatment (of everything) looks at the moment to be the most likely possibility that we have to face up to"* was speculation.

(viii). The focus at PFC remained on pasteurisation as it was the only heat treatment procedure for which there was evidence that it was effective in inactivating agent(s) of NANBH.

(ix) I became aware of the concept of dry heat treatment in 1982, but no data were available on its effectiveness in destroying viruses. By late 1983 it became known from a clinical study that dry heat treatment for 72 hours at 60ºC had failed to inactivate the agent(s) of NANBH (see para 43.11 (v)).

(x) In December 1983, dry heat experiments by Dr Cuthbertson (PFC) and Dr Pepper (SNBTS HQ Lab) found that PFC's FVIII was insoluble after dry heat treatment at 60ºC for 72 hours, the heating conditions which had failed to inactivate NANBH. This added support to the SNBTS/PFC strategy of continuing to focus on pasteurisation as the most promising candidate for inactivating the agent(s) responsible for NANBH.

(xi) It was not until evidence that HIV could be inactivated by dry heat treatment became available in November 1984 that the SNBTS/PFC changed its strategy to introduce dry heat treatment for the inactivation of HIV in the short term.

(xii) Ultimately, all FVIII concentrate prepared at PFC from October 1983 was subjected to dry heat treatment, as a 12 month stock of FVIII was heated from November 1984, as soon as the effectiveness of dry heat treatment in inactivating HIV became known.

(xiii) I do not believe there were any steps that could have been taken by SNBTS that would have enabled heat treatment of Factor VIII to have been introduced earlier at PFC.

In Dr Smith's Penrose Statement [p.30, response to §11.191 to 11.193; see also p.14, §29] he referred to the Groningen Symposium which you attended on 2 November 1984 (referred to (at §10(iv) et seq) of the Fourth Penrose Statement). Dr Smith refers to the Symposium as the "*turning-point in priorities (for both PFC and PFL) from a 'cautiously implemented programme to kill NANBH' to 'something quick against Aids.' Nobody was happy about it, but failure to react to the news from CDC could have been considered negligent (in my view, then and now).*"

a. **Do you share this view? If not, what is your view on the significance of the Symposium?**
b. **If, indeed, this was the "turning point" how did that affect the production of heat treated products in PFC (and, insofar as it is within your knowledge), BPL/PFL?**
c. **Do you have a view on what Dr Smith means by the phrase, "Nobody was happy about it"?**
d. **How does the approach to heat treatment identified by Dr Smith in his evidence about the changes in position in November 1984 differ from the approach you had advocated in your May 1983 memorandum?**
e. **In the Third Penrose statement, you wrote that Dr Jason's presentation at the Groningen Conference, and the finding that HIV could be substantially inactivated**

after dry hearing at 68 degrees for 1 hour, was not published at the time. Do you know why it was not published? Did the lack of publication cause any delay to the PFC's efforts to inactivate HIV in blood products? Are you aware of the lack of publication causing such a delay in any other countries or companies?

(i) I agree with Dr Smith that the Symposium was a "*turning point in priorities ... from a cautiously implemented programme to kill NANBH….to something quick against AIDS".*

(ii) This was the first time evidence had been presented that HIV added to FVIII could be inactivated by heat treatment, both dry heat at 68ºC and pasteurisation at 60ºC.

(iii) PFC acted on this evidence immediately (see para 43.5 (xii-xvi) changing its approach from pasteurisation (May 1983 memo) to dry heat treatment, as the latter could not only be introduced more quickly but could also be applied to PFC's existing stock of FVIII (ie with no need to wait for new batches of FVIII to be manufactured).

(iv) I do not know what Dr Smith meant when he wrote "*Nobody was happy about it".*

(v) The situation at PFC was different to that at BPL/PFL. In Scotland we had 12 months supply of FVIII available for heat treatment under conditions expected to inactivate HIV, due to the success of our drive for self-sufficiency. By contrast BPL was supplying less than 50% of the amount used in England & Wales. It was therefore unlikely that BPL/PFL would have any stocks in reserve that could be used to 'kick-start' heat treatment. Dr Smith also had the dilemma of choosing between heating the existing BPL FVIII (8A) or fast-tracking the development of 8Y.

(vi) To expedite publication of the proceedings, it was the policy of the organisers of Groningen symposia that invited speakers should hand in their manuscript on arrival or they would not receive their expenses. Hence, Dr Jason's paper that is published in the proceedings would be the manuscript that she handed over on her arrival. During her presentation she described the results concerning the inactivation of HIV by heat treatment as "*hot from the press".*

(vii) A Cutter/Bayer internal memorandum of 5th December 1984 (BAYP0005509) states:
We have supplied the Office of Biologics, Dr.Aronson, a solution of AHF and reagents which allow him to introduce HTLV-III virus then do wet and dry heat treatment per Cutter procedures. He has finished the biochemical part of the work and has sent to the CDC samples for virus cultivation."

(viii) It would appear therefore that the data presented at Gronigen by Dr Jason of CDC were the first results of the study undertaken between Dr Aronson (FDA) and CDC, based on Cutter/Bayer procedures.

(ix) The lack of publication did not delay PFC's efforts as we had already obtained the key information verbally. I do not know if lack of publication caused a delay in any other countries or companies.

(x). The change that I proposed in my memo of May 1983 was aimed at being able to pasteurise all of PFC's factor VIII, instead of only 30%, and to be able to do this quickly if evidence emerged that the infectious agent responsible for AIDS was heat sensitive. In the event, the evidence from CDC that was presented at the Groningen symposium made dry heat treatment the faster option, something that PFC was able to introduce immediately because of the quantity of FVIII in stock and its choice of heating conditions.

In the Fourth Penrose Statement (§10 (xiv)) you refer to the discovery, in late 1985, of the importance of the method of freeze drying (rather than the degree of purity) that enabled 8Y to tolerate severe dry heat treatment at 80C and that led PFC "*to judge that increased heat treatment could be achieved most quickly by developing a new Factor VIII concentrate, using procedures that would, as far as possible, be compatible with PFC's existing operation.*" At §10 (xv) you list the steps needed in order to apply severe heat treatment to Factor VIII and the fact that a new manufacturing process was devised to achieve this (i.e. Z8). You state that the new Z8 process took about 12 months to develop and implement, with clinical trials taking a further 4 ½ months.

a. **Could/should SNBTS-PFC have introduced Factor VIII concentrate, which was sufficiently heat treated to inactivate NANB, prior to May 1987 in particular against the background that BPL was able to make such a concentrate (8Y) available from October 1985?**

This question is addressed directly in Prof van Aken's First Penrose Statement. The Inquiry would be assisted by your observations on that statement, in particular whether PFC should have changed its policy at an earlier stage, i.e. before December 1985 when PFC decided that an intermediate purity Factor VIII concentrate that could be treated at 80°C should be developed, rather than pursue pasteurisation of Factor

VIII concentrate with the objective to inactivate the agent(s) responsible for the transmission of NANBH.

b. **To what extent were the following factors relevant (as identified in Prof van Aken's Second Penrose Statement, Conclusion):**
   i) **the procedure to inactivate blood borne viruses, in particular those present in plasma, by dry heating were not known until the later part of 1984;**
   ii) **the characteristics of the viruses to be inactivated (HIV and HCV) were not known until respectively the beginning of 1984 (HIV) and 1989 (HCV);**
   iii) **cell lines producing sufficient quantities of HIV and HCV to perform validation studies (virus spiking experiments) in the laboratory were not available until mid 1984;**
   iv) **methods to improve the yield of factor VIII and to determine that the structure of Factor VIII (or other clotting factors) after heating was still intact were not yet available.**

c. **At §11(b)(iii) of the Fourth Penrose Statement you explain why it was decided to develop an entirely new process to produce Z8 rather than adopting/adapting the BPL method for 8Y (presumably under licence from BPL) centred around the use of a two-stage assay devised by BPL which was incompatible with PFC's one-stage method.**

   Does it still remain your view that the difficulties and delay likely to be caused by adopting the 8Y process outweighed the time it took to develop and implement the Z8 process, leading to routine supply of Z8 some 18 months later than 8Y? You may be assisted in this respect by Transcript, 26 October 2011, p126 (7 et seq).

d. **In the Fourth Penrose Statement (§4(ii)) you refer to the importance of the freeze-drying method not being appreciated at PFL/BPL. Why, in your opinion, did BPL not recognise the crucial importance of the freeze-drying procedure (to the extent that it was not mentioned in their initial patent application) when, in your view (at §11 (vi)) "*It is conceivable that the manufacture of 8Y at BPL would have been much less successful, or have failed altogether, without this recognition of the important role played by the freeze drying process.*"**

e. **Had that importance been appreciated at an early stage (by, for example, inclusion in BPL's original patent application for 8Y), what might have been the implications in**

terms of the development and earlier introduction of Z8 by PFC and the ability of other manufacturers to reproduce the process?

(i) PFC had introduced dry heat treatment to inactivate HIV in November 1984, as there was evidence available that this would be effective. By contrast, PFC had decided not to pursue dry heat treatment to inactivate NANBH because there was no clinical evidence that it would inactivate agents(s) of NANBH. On the contrary, dry heat treated FVIII had continued to transmit NANBH (see para 43.11(v) above).

(ii) During 1985, PFC's research focussed on developing a high-purity FVIII to assist in developing pasteurisation, for which clinical evidence was available that the agent(s) responsible for NANBH could be inactivated (see para 43.11 (iv)).

(iii) We were aware that BPL had introduced 8Y but there was, as yet, no evidence that agent(s) of NANBH would be inactivated.

(iv) It was believed that 8Y was able to tolerate dry heat at 80°C because of its increased purity. Therefore, PFC's research on increasing purity to a much greater extent was expected to enable its FVIII to be dry heated at 80°C or even higher if that was needed to inactivate the agent(s) of NANBH.

(v) The decision taken at PFC in December 1985, to further develop dry heat treatment, was aimed at increasing the margin of safety against HIV in view of the findings due to be published by Dr Alfred Prince of NYBC (see para 43.6 (xv)).

(vi) This decision was also taken at this time because we had discovered that it was not factor VIII purity that had enabled 8Y to withstand 80°C dry heat treatment, but the way in which it was freeze dried (see para 43.6 (xiii)).

(vii). I believe that if PFC had attempted to adopt the 8Y process it would have taken longer and would probably have failed altogether. This view is based in part on the experience of those who attempted to do this:

- we learned in December 1986 that Bayer had attempted to develop 8Y, but had failed to achieve it and had abandoned their attempt.
- we learned in July 1987 that CSL Australia had been unable to develop 8Y. Dr McIntosh (PFC) provided advice which enabled CSL to proceed, but it was not until 1990 that CSL were able

to issue 8Y (despite the lead scientist at CSL Dr Robert (Bob) Herrington being a very close friend of Dr Smith).

- I am not aware of any other fractionator who was able to develop 8Y.

(viii) Patent applications are almost always filed very early in the discovery process. The patent application filed by BPL on 5th March 1985 (SNF.001.1091) [PRSE0000770] did not include any information on freeze drying, presumably because its relevance had not yet been appreciated. The BPL patent application also stated that 8Y was suitable for heat treatment either by pasteurisation at 60ºC for 10 hours or by dry heat treatment at 70ºC for 24 hours. As PFC had been dry heating its FVIII at 68ºC for 24 hours since January 1985, this patent application offered little or no advance.

(ix) The importance of freeze drying was subsequently appreciated by BPL. For example, a PFL report of March 1987 (that was shared with PFC) explained "*The freeze drying (FD) cycle established for our previous intermediate purity concentrate, which was not heated, had been satisfactory and had provided a stable, soluble product with good post-dry recovery of factor VIII activity. Adaptation of this FD programme for high purity 8Y appeared at first to be satisfactory and it proved possible to heat the final product very severely (80º, 72h). During early 1986 two problems arose which gave an indication of the fragility of the lyophilisation process and pointed up our complete lack of knowledge about the important FD parameters."* The authors concluded "*We have obviously only scratched the surface of the extremely complicated process of freeze drying."* [PRSE0003416]

(x) In Professor van Aken's Second Penrose Statement (cited document 22) Prof van Aken did not make the statement given in Question 52.b(iii). In section IIB (page 5) headed "*With regard to HCV*", Prof van Aken wrote "*As is described above it took till 1989 before the first part of the genomic structure of HCV was published and during the following years the complete genomic structure of HCV was elucidated"* and "*As with HIV, the virus material for validation studies was not available in 1984 (or before) and only when the genome of the virus was determined, it was possible to decide which viruses resembled and could be used as model viruses for HCV."* Meaning that cell lines producing HCV for validation studies were not available until after 1989 (not mid-1984 as stated in Question 52.b(iii)).

(xi) Professor van Aken was head of the Netherland's Red Cross (NRC), including its fractionation centre. The NRC first issued a heat treated FVIII concentrate in June 1985. This was dry heated at 60ºC for 72 hours, conditions that were expected to inactivate HIV but not NANBH/HCV [HSOC0001563]. The NRC continued to issue its FVIII concentrate dry heat

treated at 60ºC/72hr until 1990, when dry heat was replaced by pasteurisation at 60ºC for 72 hours. This latter product was discontinued in 1992 following a higher than expected incidence of inhibitors (antibodies to factor VIII) in recipients. It was not until 1995 (eight years after PFC) that NRC was able to provide a suitable FVIII concentrate that was free from transmission of HCV. With respect to FIX concentrate, the NRC issued a Factor IX concentrate dry heated at 60ºC for 72 hours from 1985 to 1992. It was not until 1992 (seven years after PFC) that NRC provided patients with a Factor IX concentrate that was free from transmission of HCV. (see cited document no. 7 (PEN.018.0623) [PRSE0000553].

(xii) According to the Report of The Lindsay Tribunal of Inquiry (page 93) the dry heat treatment of Factor VIII concentrate at 80ºC for 72 hours was "*viewed with some astonishment by other fractionators at the time.*"

In the Fourth Penrose Statement (§ 5 (v)) you state that "*clinical evaluation of Z8 had not been progressed because of the issue of compensation / indemnity.*" You further refer to Dr Ludlam's concern that suitable arrangements for compensation should be in place due to the degree of heat treatment to which Z8 was being subjected.

Whilst (at §5(i)) you state that you were not involved in the topic of compensation/indemnity, please provide what further evidence you can about why this delay occurred, and what effect it had on the time at which Z8 became available for use by patients.

(i) Z8 was first placed at issue by PFC on 2nd December 1986.

(ii) Z8 was issued by PFC to Edinburgh BTS on 22nd December 1986, being intended for distribution to the Edinburgh Haemophilia Centre for clinical evaluation.

(iii) At the annual meeting of SNBTS Directors and Haemophilia Directors on 9th February 1987 I learned that the clinical evaluation of Z8 had not begun because of a question about compensation to patients who might be harmed during clinical trials. This issue had been raised by Dr Ludlam, who was supported by all of Scotland's haemophilia doctors.

(iv) Dr Ludlam had previously raised this issue at annual meetings with SNBTS, HCDs & SHHD held on 2nd February 1984, 7th March 1985 and 5th March 1986. According to the minute of the meeting held on 5th March 1986 "*Dr Forrester said that the question of compensation*

for clinical trials is a UK issue which the Department is pursuing with DHSS colleagues." (Penrose Inquiry document SNB.001.5448) [PRSE0001081].

(v) According to the Final Report of the Penrose Inquiry (para 24.214) :
"*When the SHHD finally did take responsibility for resolving Professor Ludlam's concerns (following Professor Cash's telephone conversation with Dr McIntyre on 30 December 1986), and consulted with the DHSS and the Treasury, they were able to obtain agreement on a compensation scheme by early February 1987 which, in turn, resulted in clinical trials of Z8 being carried out." [PRSE0007002]*

(v) The first results from the clinical evaluation were provided to PFC on 31st March 1987 (Penrose Inquiry document SNB.006.5609) [PRSE0001162] and authorisation to issue Z8 for routine clinical use was provided to PFC by Dr Cash on 14th April 1987. Routine distribution of Z8 by PFC began on 16th April 1987.

Please identify any further factors that delayed the provision of Z8 to patients in Scotland and Northern Ireland.

(i) At the annual meeting of SNBTS, HCDs & SHHD held on 5th March 1986 (Penrose Inquiry document SNB.001.5448) [PRSE0001081] it was agreed that the batch dedication system in place should continue for another 12 months. Batch dedication involved each patient being allocated a specific batch of Factor VIII concentrate, which they would continue to use until it was finished, thereby reducing the number of donations to which they were exposed.

(ii) This decision meant that the provision of Z8 to patients in Scotland and Northern Ireland was delayed until their current batch of SNBTS FVIII (dry heat treated at 68ºC/12 hrs) had been used up.

(iii) My memory is that this decision was taken because of continued uncertainty over Z8 (and 8Y) being free from transmission of NANBH and there being greater confidence in the merit of batch dedication. As there was insufficient Z8 available to support a batch dedication system immediately, the previous PFC product continued to be supplied temporarily.

Are you aware of any NHS patient becoming infected with HIV or HCV through the use of severe dry heat treated Factor VIII and IX products; namely Z8 and HTDEFIX produced by PFC and 8Y and 9A produced by BPL?

If you are aware, please provide as many details as you can as to when and how this infection took place, and what steps were taken in response to it.

I am not aware of any NHS patients becoming infected with HIV or HCV through Z8 or HTDEFIX of PFC or 8Y or 9A of BPL.

On 5 November 1991 you wrote a letter to Professor Cash about a meeting you had attended a week earlier at the Edinburgh HIV discussion group. In the letter, you raised various criticisms made by Dr Christopher Ludlam of PFC's product. Please explain the context of this letter, and your view of the criticisms and comments it contains. In particular, please address:

a. **Who was in the audience?**
b. **What was "*the party line*" that Dr Ludlam said he would have to "toe" in light of SNBTS staff being present?**
c. **Why, in your understanding, Dr Ludlam described SNBTS Factor VIII as "crud", and to which product he was referring?**
d. **Your views, at the time and in retrospect, on Dr Ludlam's thesis about the alloantigenic protein.**
e. **Your views, at the time and in retrospect, on Dr Ludlam's claim that PFC's early heat treatment programme was "*a complete waste of time*". Please explain why, in your understanding, Dr Ludlam expressed that view.**
f. **What steps, if any, were taken by you, Professor Cash, or SNBTS to respond to the comments made by Dr Ludlam?**

(i) I am afraid that I have very little recollection of the meeting in question.

(ii) I appreciated that Professor Cash always did his utmost to please haemophilia doctors. This was because he was acutely aware that SNBTS had only one 'customer', the NHS in Scotland; whereas haemophilia doctors were able to obtain haemophilia treatment products from sources other than SNBTS.

(iii) I was concerned by the negative comments that Dr Ludlam had made about SNBTS and PFC and believed that Professor Cash would want to address any concerns that Dr Ludlam might have.

(iv) Given the date of the meeting, I believe that Dr Ludlam may have been disappointed that PFC/SNBTS had delayed its earlier development of a high-purity FVIII concentrate in December 1985, in favour of the more rapid introduction of the severely dry heat treated FVIII concentrate (Z8), followed by a plan to introduce a higher yielding form of Z8, known as S8, the development of which had been delayed due to the demand for Z8 being so high that it had not been possible to schedule the necessary trial batches of S8 in Production.

(v) I was open minded about Dr Ludlam's view that a biological component of plasma, that co-purified with factor VIII, might be responsible for a disorder of immunity observed in people with haemophilia who were not infected with HIV. That is one of the reasons why I had initiated PFC's research on the development of a high-purity Factor VIII concentrate in 1984.

(vi) I was also aware of other explanations. For example, my memo of 13th July 1983 on T-Cell Abnormalities (see Question 36) included infection with hepatitis amongst the possible causes. Similarly in her paper of October 1983 (Penrose Inquiry document LIT.001.0215) [PRSE0001121] Dr Froebel noted *"In terms of lymphocyte abnormalities, Scottish patients with haemophilia yield results that are consistent with those seen in the acquired immune deficiency syndrome and in acute viral infections."*

(vii) As virtually all people with haemophilia were infected with HCV, their infection with HCV was a plausible hypothesis for the cause of the observed abnormalities of immunity. If this hypothesis were correct, then these abnormalities would be prevented by removing the risk of NANBH/HCV infection from factor concentrates. The development of suitable virus inactivation technology was the most secure way of achieving this.

(viii) Technology used for the preparation of high-purity FVIII was devised primarily to remove reagents that had been added either to inactivate viruses (eg. solvent-detergent) or to protect coagulation factors during pasteurisation which (unlike Albumin) had to be removed from the final product.

(ix) Consequently, high-purity concentrates were treated to be safe with respect to HIV and HCV transmission (but not necessarily from transmission of hepatitis A).

(x) Therefore, the only way to determine if HCV infection was responsible for disorders of immunity would be to monitor hepatitis negative patients for abnormalities of immunity after treatment with low purity, but hepatitis safe, FVIII concentrates.

(xi) The only low purity FVIII concentrates that were HCV safe were PFC's Z8, BPL's 8Y and the 8Y from CSL Australia (issued from 1990).

(xii) I am not aware of any studies of this type being undertaken with recipients of Z8 or CSL's 8Y.

(xiii) One study in recipients of BPL's 8Y found no T-cell abnormalities in 15 previously untreated people with haemophilia. I believe that this was consistent with HCV infection being the cause of the immune abnormalities in people with haemophilia who were not infected with HIV. Although this was published in 1991 [BPLL0005719], I do not know if Dr Ludlam was aware of this when he gave the presentation to which this question refers.

(xiv) My view of PFC's early heat treatment programme in retrospect is that:
• PFC was the first fractionator in the world to provide all of the patient population that it served with a FVIII concentrate that was safe from transmission of HIV,
• PFC was the first fractionator in the world to provide all of the patient population that it served with a Factor VIII concentrate that was safe from transmission of HCV.

(xv) My letter to Professor Cash was copied to Dr Perry (PFC Director) and to Mr David McIntosh (National Director of SNBTS). I do not know if any of them responded to the comments made by Dr Ludlam.

On the same day, you wrote to Dr Ludlam to confirm that four batches of SNBTS heat treated Factor VIII had been found to contain an HIV positive donation. Two had been heated for two hours at 68°C, and two for 24 hours at 68°C. Did these batches result in the infection of any patients with HIV? Please state the confidence with which you can answer that question, and the reasons for your confidence.

(i) I was surprised that Dr Ludlam should have described the PFC's early heat treatment as "*gentle warming*" and that he did not believe that this heat treatment had prevented patients from being infected with HIV for two reasons:
• Water at 68°C will result in 3rd degree burns in a matter of seconds; not something that I would have described as "*gentle warming*".
• Dr Ludlam had co-authored a paper in 1988 concerning two batches of heat treated FVIII for which an HIV infected donation had been included in their manufacture. The authors had concluded that "*heat treatment applied to these batches prevented transmission of HIV infection*" [STHB0000159].

(ii) According to cited document no. 1 (PEN.013.1309, page 53) [PRSE0002291], a total of five SNBTS donors were found to have contributed HIV infected donations, plasma from which was used in the preparation of seven batches of 68ºC dry heat treated FVIII concentrate and two batches of unheated FIX concentrate. According to the haemophilia doctors responsible for their treatment, no HIV negative patients who were treated with these batches became HIV positive.

(iii) The determination of the HIV status of patients was carried out by haemophilia doctors and was accepted by SNBTS/PFC as being correct.

(iv) PFC did not have access to patient records to verify these findings, as these records were confidential. Similarly, PFC did not know the identity of the patients involved as this was also confidential.

(v) Of the seven batches of 68ºC dry heated FVIII, four had been heated for 2 hours and three had been heated for 24 hours. I believe that Incident Reports were prepared for each of these batches by PFC's Head of Quality Dr Bruce Cuthbertson.

(vi) Details of the four batches of FVIII heated at 68ºC for 2 hours are:

Batch	**Date Plasma Processed**	**Date Product Heat Treated**	**Issue Date (heat treated product)**
1	April 1984	November 1984	December 1984
2	July 1984	November 1984	December 1984
3	April 1984	February 1985	March 1985
4	November 1984	January 1985	March 1985

(vii) This information only concerns returning donors who tested positive for antibodies to HIV after donor screening had been introduced in October 1985. The number of HIV positive donors who did not return to donate after donor screening was introduced is not known.

(viii). Seven batches of PFC FVIII were found retrospectively to have been prepared from HIV-infected plasma. Four of these batches were prepared before the introduction of heat

treatment and, as they were still in stock when heat treatment was begun, they were able to be heat treated before being issued. This demonstrates that PFC's decision to immediately dry heat its stock of FVIII concentrate for 2 hours at 68ºC almost certainly prevented additional transmissions of HIV.

Section 5: Small / panel pools and cryoprecipitate

Please explain the arrangements that were in place in Scotland in the 1970s and 1980s for the production of cryoprecipitate. In particular, please consider the following matters:

a. **Which organisations were responsible for producing cryoprecipitate in Scotland, including the role (if any) played by PFC.**
b. **Which organisations were responsible for producing cryoprecipitate for the use in Northern Ireland, including the role (if any) played by PFC.**
c. **How (and by whom) decisions were made about the proportion of plasma donations in Scotland to be used in the production of cryoprecipitate in the 1970s and 1980s.**
d. **How (and by whom) decisions were made about the proportion of plasma donations in Northern Ireland to be used in the production of cryoprecipitate in the 1970s and 1980s.**
e. **The approach of the management of the PFC to the role of cryoprecipitate in meeting the demands of patients in Scotland for treatment of haemophilia and other bleeding disorders (including any concerns about how this would affect the ability of PFC to produce factor concentrates).**
f. **The approach of the management of the PFC to the role of cryoprecipitate in meeting the demands of patients in Northern Ireland for treatment of haemophilia and other bleeding disorders (including any concerns about how this would affect the ability of PFC to produce factor concentrates).**

(i) Although the CSA was legally responsible for SNBTS, for all practical purposes responsibility for the preparation of cryoprecipitate in Scotland lay with SNBTS.

(ii) Single donor cryoprecipitate was not produced at PFC. It was produced only at Regional Blood Transfusion Centres.

(iii) In the 1970s's and 1980's, to the best of my knowledge, SNBTS produced cryoprecipitate at its Regional Transfusion Centres in Edinburgh (Edinburgh Royal Infirmary), Glasgow (Law

Hospital, Carluke), Dundee (Ninewells Hospital), Inverness (Raigmore Hospital) and Aberdeen (Forresterhill Hospital).

(iv) It is my understanding that the SNBTS, PFC included, did its utmost to provide haemophilia doctors with the haemophilia treatment products that they sought. It was not appropriate for PFC to influence or to try to influence medical decisions.

(v) Annual meetings were held with SNBTS Directors and Haemophilia Directors to review the needs of haemophilia doctors and to put suitable plans in place concerning the future provision of Factor VIII concentrate and cryoprecipitate.

(vi) SNBTS Directors held regular 'Supply and Demand' meetings to forward plan the supply of products according to clinical need. To the best of my knowledge, decisions on whether fresh frozen plasma should be used for the preparation of cryoprecipitate or Factor VIII concentrate were made by Regional Transfusion Directors.

(vii) PFC did its best to provide the amounts of coagulation factor concentrates agreed at the annual meetings with haemophilia directors and at the 'Supply and Demand' meetings of SNBTS Directors.

(viii) The pressure on PFC in relation to government policy of January 1975, that the UK should become self-sufficient, and the demands of haemophilia doctors, was to produce as much Factor VIII concentrate as possible.

(ix) I believe that there were two reasons for this:

• to make importation of Factor VIII concentrate unnecessary, as commercial FVIII was considered to carry a greater risk of transmitting blood borne infections

• to replace the use of cryoprecipitate, which was inconvenient to use and less effective for the treatment of haemophilia A. For example, in an article published in 1977, Drs Forbes and Prentice of Glasgow Royal Infirmary examined the mortality of people with haemophilia in the UK from 1955-1972 and reported *"Slightly surprising is the fact that the mortality in haemophilia showed no tendency to reduction over this period, even with the advent of cryoprecipitate from 1966 onwards."* (Fratantoni JC et al. (eds) Unresolved Therapeutic Problems in Hemophilia (US Dept. of Health, Education and Welfare) 1977).

(x) I was never involved in either the preparation or distribution of cryoprecipitate as this was done directly from Regional Transfusion Centres. However, to the best of my knowledge,

SNBTS cryoprecipitate was always available on demand. I am not aware of any situation where a request for cryoprecipitate was not met.

(xi) Information on the amounts of cryoprecipitate and Factor VIII concentrate issued by SNBTS from 1975/76 to 1989/90 are available in cited document no. 2, pages 58-59 (PEN.013.1125) [PRSE0001083].

(xi) I have no knowledge of the production of cryoprecipitate in Northern Ireland. Dr Maurice McClelland, Director of the Northern Ireland BTS, either attended or was invited to attend the annual meeting between SNBTS Directors and Haemophilia Directors and was therefore engaged with the processes of review and future planning that was taking place.

One proposition that the Inquiry will consider is the suggestion that there should have been a return to the use of cryoprecipitate and a foregoing of the use of Factor VIII concentrate in the early to mid-1980s in response to the growing knowledge of the risk of AIDS to those using blood products. What is your view on this matter? In particular:

a. **What was (i) your position, and (ii) the position of the management of PFC at the time to proposals to return to the use of cryoprecipitate? In particular, please comment on your observation in your memorandum of 3 May 1983 that, "*There are some who would find a move back to cryo attractive and if this gathers momentum (it would only need 1 suspected case from NHS FVIII) we could see our FFP disappear overnight.*"**
b. **Was a return to the use of cryoprecipitate rather than blood products a practical possibility in the period c.1982 to 1985 given the infrastructure, equipment and personnel available at PFC/SNBTS and, to your knowledge, BPL/PFL/SNBTS?**
c. **What would the effect on overall levels of production of blood products at PFC and, to your knowledge, BPL/PFL have been given the economies of scale involved in producing cryoprecipitate?**
d. **What would the effect have been on the work being undertaken on viral inactivation of blood products?**
e. **What would have been required (in terms of plant, training, plasma supply etc.) to allow for an expansion of production of cryoprecipitate in order to meet the demands of those who had been using blood products in (i) Scotland, and (ii) Northern Ireland?**
f. **To what extent would other measures have been required in order to facilitate such a change in policy (for example, ceasing prophylactic treatment, limiting or ceasing elective surgery)?**

g. To what extent, if at all, would a reversion to cryoprecipitate have provided greater protection for individuals requiring treatment for haemophilia and other bleeding disorders?

h. Were you aware of consideration being given to a reversion to cryoprecipitate in (i) PFC, (ii) Scotland, (iii) Northern Ireland and (iv) the rest of the UK in this period? If so, what was said, and why was it rejected or not implemented more widely?

(i) The comments in my memo of 3rd May 1983 demonstrate that I was aware that patients or haemophilia doctors might suddenly want to use cryoprecipitate instead of FVIII concentrate.

(ii) As both Factor VIII concentrate and cryoprecipitate were prepared from Fresh Frozen Plasma (FFP), I believed that the PFC Director might want to draw up contingency plans so that essential products could continue to be supplied by PFC in the event that the supply of Fresh Frozen Plasma (FFP) to PFC was reduced.

(iii) As well as fractionating FFP, PFC also fractionated the plasma that remained following the preparation of cryoprecipitate at Regional Transfusion Centres, known as cryo-supernatant. Therefore, with the exception of coagulation factor concentrates, all PFC products could have continued to be supplied by fractionating cryo-supernatant.

(iv) As people with haemophilia B cannot be treated with cryoprecipitate, a supply of FFP for the preparation of Factor IX concentrate would have to have been retained, or people with haemophilia B would have had to revert to treatment with plasma, which was much less effective than Factor IX concentrate.

(v) When plasma was in short supply, the provision of plasma for R&D was usually considered less important than meeting patients' needs. Therefore, a switch to cryoprecipitate would probably have had a negative impact on the development of virus inactivation.

(vi) SNBTS & PFC were public sector bodies who were required to adhere to Government policy. If Government had decided that there should have been a switch to cryoprecipitate, SNBTS and PFC would have done their best to comply.

(vii) A move to cryoprecipitate would have required support from haemophilia doctors and their patients, otherwise extra supplies of cryoprecipitate produced by SNBTS could have remained unused, with commercial Factor VII concentrate being imported from the USA to make up for any reduction in supply of FVIII concentrate from PFC.

(viii) At the annual meeting between SNBTS Directors and Haemophilia Directors on 2nd February 1984, I clearly remember Dr Cash offering to increase supplies of cryoprecipitate because of concerns over AIDS and that his offer was declined by haemophilia directors. This is not fully recorded in the minute, which only states *"It was agreed that a certain minimal amount of cryo was required and Dr Cash pointed out that TDs could produce it in emergencies."* (Penrose Inquiry document, SNB.001.5252) [PRSE0001556].

(ix) I do not know enough about the preparation of cryoprecipitate at Regional Transfusion Centres to say what would have been required to expand production. However, for the period 1983/84 SNBTS prepared cryoprecipitate from 2,520 kg FFP and coagulation factor concentrates from 42,423 kg FFP (see cited document no. 2, PEN.013.1125, page 35) [PRSE0001083]. If 10% of fractionation FFP was reserved for the preparation of Factor IX concentrate, then 38,180 kg FFP would have been potentially available for the preparation of additional single donor cryoprecipitate, a 15-fold increase.

(x) Scotland's Regional Blood Transfusion Centres were subjected to inspection by the Medicines Inspectorate in the early 1980s. The inspection reports of the Glasgow RTC at Law Hospital [SBTS0000407_006] and the Edinburgh RTC (IBI document BNOR0000573) were extremely critical of the facilities, making it difficult to see how a significant increase in the preparation of cryoprecipitate would have been authorised at these Centres by the Medicines Inspectorate.

(xi) The preparation of cryoprecipitate did not comply with DHSS Guide to Good Pharmaceutical Manufacturing Practice (see question 19, response 19.2), and was not required to do so, as it was classified as a blood component not a plasma product which, for regulatory purposes, were classified as pharmaceutical products.

(xii) Following the 1980 inspection of PFC, a programme of remedial actions had been agreed between the Medicines Inspectorate, SNBTS and SHHD. The purpose of these remedial actions was to bring PFC into compliance with the DHSS Guide to Good Pharmaceutical Manufacturing Practice (see para 19.1). These remedial actions were still underway during the early to mid-1980s. As the preparation of cryoprecipitate did not comply with the GMP standards to which PFC was required to operate, I do not believe that single donor cryoprecipitate could have been prepared at PFC unless the Government (SHHD) had over-ruled the standards required by the Medicines Inspectorate. Similar considerations would have

applied to a proposal to prepare cryoprecipitate at BPL/PFL.(see also my response to question 61).

(xiii) With regard to BPL/PFL and the supply of haemophilia treatment products to England & Wales; if the objective was to reduce the need to import commercial FVIII concentrate from the USA, this could not have been achieved by increasing the production of cryoprecipitate without also increasing the supply of fresh frozen plasma (FFP), as supply of Factor VIII concentrate from BPL was limited by the supply of FFP for fractionation. FFP was also required for the preparation of cryoprecipitate. Therefore, a move to cryoprecipitate without an increase in the supply of FFP would have reduced the output of FVIII concentrate by BPL. This may even have resulted in greater importation of FVIII concentrate from the USA, if haemophilia doctors and/or patients did not want to return to cryoprecipitate.

(xiv) If the supply of FFP for England & Wales had been increased substantially, and cryoprecipitate had been acceptable to haemophilia doctors and their patients, I believe that provision of cryoprecipitate from the extra FFP (rather than the provision of extra Factor VIII concentrate) would have been the quickest route to reduce the need for FVIII imports, as cryoprecipitate can be produced much more quickly than FVIII concentrate.

(xv) I am not qualified to say what impact a move back to cryoprecipitate would have had on the treatment of people with haemophilia.

(xvi) I am not aware of any consideration being given to a reversion to cryoprecipitate in Scotland, other than the offer by Dr Cash to increase the production of cryoprecipitate (see viii. above).

During the early 1980s, the possibility of producing freeze-dried cryoprecipitate in Scotland was explored, including through a project in the west of Scotland: see:

- ***"Report on the Production of Lyophilised Cryoprecipitate", G. Gabra, January 1980.***
- **Letter from Prof Bloom to Dr Ludlam, 8 September 1980, concerning freeze-dried cryoprecipitate.**
- **Letter from Dr Ludlam to Dr Rizza, 16 September 1980, proposing a discussion of freeze-dried cryoprecipitate at the next meeting of the Regional Haemophilia Centre Directors meeting, which refers to consideration of this topic in Scotland, including at the PFC.**

- Minutes of the Regional Haemophilia Centre Directors, 22 September 1980, at which the issue was discussed, and at which reference was made to work being undertaken on this matter in Scotland.
- Letter by G S Gabra, Robert Crawford and Ruthven Mitchell to the British Medical Journal, vol. 281, p.1006 (11 October 1980).
- Note of a meeting of Haemophilia and Blood Transfusion Working Group, 4 March 1981 (see item 7).
- Note of a meeting of Haemophilia and Blood Transfusion Working Group, 4 November 1981 (see item 1).
- Letter from Dr Watt to Dr Cash, 2 December 1981.
- "*Liver disease complicating severe haemophilia in childhood*", McGrath et al, Archives of Disease in Childhood, 1980, 55, 537-540 (as referred to in Dr Watt's letter of 2 December 1981).
- Minutes of the meeting of the Directors of the SNBTS and Haemophilia Directors, 21 January 1983 (see item 4(b)).
- Milligan G, Graham R, Hanratty S, Muir W and Mitchell R, (1981) *"Production of freeze- dried human antihaemophilc cryoprecipitate*", Journal of Clinical Pathology, 34, 1091- 1093.

Please explain your understanding of the discussions over the production of freeze-dried cryoprecipitate in this period. In particular, please consider:

a. The role PFC played in exploring this possibility, and the extent to which that role was limited by resource issues (You may be assisted by the note of the Haemophilia and Blood Transfusion Working Group meeting, 4 March 1981).
b. The other organisations or individuals involved in exploring this matter.
c. The perceived advantages and disadvantages of freeze-dried cryoprecipitate.
d. The views of those within management positions within SNBTS and PFC on whether freeze-dried cryoprecipitate should be pursued further.
e. The views, insofar as you were aware of them, of haemophilia clinicians in Scotland and Northern Ireland to this debate.
f. The knowledge those involved in the debate had of freeze-dried cryoprecipitate programmes in Europe at that time.
g. The reasons why, ultimately, freeze-dried cryoprecipitate was not explored further, and in particular the significance of the Medicines Inspectorate.
   In this respect, you may be assisted by your evidence recorded in Transcript, 10 May 2011, p64-68.

(i) Freeze dried cryoprecipitate was under development at the Law Hospital facility of the Glasgow & West of Scotland BTS from about late 1979. The freeze drying facility at Law Hospital had previously been used to manufacture freeze dried plasma which, by the late-1970s, had been largely replaced by Albumin manufactured at PFC.

(ii) PFC was first inspected by the Medicines Inspectors in December 1979/January 1980, during which I was designated to accompany the inspectors to take notes on their behalf (see my response to Question 19).

(iii) In conjunction with the PFC inspection, the Inspectors decided to inspect an animal facility at Law Hospital that was used for testing PFC products for the presence of pyrogens (a by-product of bacteria). This took place on 17th January 1980. After inspecting the animal facility, the lead inspector (Mr John Flint) decided that there was sufficient time to inspect the freeze drying plant used for the preparation of dried plasma at Law Hospital.

(iv) The inspectors were extremely critical of this facility, as neither the spin freezer (used to obtain a thin film of frozen plasma at the bottle wall) nor the bottle freeze drier could be sterilised, nor were they operated in a sterile environment, nor was it possible to close the bottles within the freeze drier.

(v) I was familiar with these criticisms, as equivalent equipment at PFC had just been condemned by the inspectors on similar grounds, despite PFC using its equipment only at an intermediate stage of manufacture rather than for the preparation of a final product.

(vi) Dr Cash subsequently arranged for freeze dried cryoprecipitate to be considered at an SNBTS HQ Workshop on 17th October 1980, at which I was invited to present "A view from PFC', presumably because of my involvement in the inspection that had been held at Law Hospital on 17th January 1980.

(vii) In my presentation I pointed out the deficiencies of the facility at Law and its operation, including GMP weaknesses inherent with freeze dried cryoprecipitate. I provided a preliminary sketch of a possible floor plan for a new facility, into which new equipment would be required to be installed. Despite this, I noted that it "*may be impossible to meet GMP requirements*". [WITN6914026].

(viii) I also listed the advantages and disadvantages of freeze dried cryoprecipitate (FDC), with the advantages being "*High Yield*", which I described as "*Doubtful*", and "*Lower Hepatitis Risk*", which I described as "*Not Now*".

(ix) I described the claim of higher yield of FDC as "*doubtful*" as I had increased the yield of FVIII as PFC concentrate from 153 iu/l in 1977/78 to 220 iu/l in 1979/80 and went on to increase it to 264 iu/l in 1980/81 (see cited 2nd document, PEN.013.1125, page 51, table 13) [PRSE0001083].

(x) I believe that my characterisation of a lower hepatitis risk as "*Not Now*" was based on my understanding that freeze dried cryoprecipitate was more convenient to administer than standard (frozen) cryoprecipitate and therefore aimed at patients requiring repeated treatment (including home therapy). I also believe that I was aware that the prevalence of NANBH in the general population was such that infection with NANBH was likely to occur in patients who were treated repeatedly with cryoprecipitate (see also my response at 10.2(iii)). I also knew that a vaccine against hepatitis B would be available soon.

(xi) At the meeting of the Haemophilia and Blood Transfusion working group of 4th March 1981 (Penrose Inquiry document SNB.001.5064) [PRSE0000181], I indicated that PFC did not have the resources to undertake R&D on freeze dried cryoprecipitate. This was because the priority assigned by Mr Watt was to increase the output of FVIII concentrate to minimise the need to import commercial FVIII concentrate from the USA. PFC staff were also fully occupied in responding to points concerning PFC that had been raised by the Inspectorate. I also believed that a new facility was required for the preparation of freeze dried cryoprecipitate and that this would not be consistent with the GMP guidelines under which PFC was required to operate.

(xii) That the preparation of freeze dried cryoprecipitate was out-with the GMP guidelines under which PFC was required to operate was made clear by PFC Director Mr Watt in his letter to Dr Cash of 2nd December 1981, in which he wrote "*Such a product is not possible within GMP guidelines but can be produced. Such production would have to be carried out on the basis of named patient dispensing, outside the control of the medicines inspectorate but subject to legislation such as the Pharmacies Act. It would be possible for the PFC to support such an endeavour by lending such laboratory and general services facility as may be necessary but separate premises (which could be attached to the existing buildings) with separate equipment would be required.*"

(xiii) The preparation of freeze dried cryoprecipitate at Law Hospital was the subject of a subsequent Medicines Inspection on 8th-9th March 1982. In their report [SBTS0000407_006], the inspectors noted:

• "*the product is freeze dried in a totally unsuitable environment*" (para 50)

• The "*Remedial action required" was "Purchase of a modern freeze drier which could be located with its chamber opening into an aseptic area*" (para 53).

They concluded:

• "*A period of 12 months should be sufficient for detailed proposals to be made by the Service (and SHHD). These should rectify the deficiencies in processing facilities and storage areas (By 11th June 1983)".*

• *"The absence of such proposals should result in a drastic reduction of processing activity at this Centre including cessation of freeze drying."*

(xiv) At the meeting of the Directors of SNBTS and Haemophilia Directors held on 21st January 1983, Dr Cash reported "*it had been decided to abandon production of FDC meantime, having regard to the closure of the plasma freeze drying plant at Law and the cost of meeting the standards demanded by the Medicines Inspectorate."*

(xv) I was not present at this meeting, but note that there is no dissent recorded in the minute (Penrose Inquiry document SNB.001.5160) [PRSE0001736].

(xvi) SNBTS continued to provide standard (frozen) cryoprecipitate on demand for patients for whom it was requested by their treating physician, such as those who had had little or no previous treatment and were likely to be free from infection with NANBH.

(xvii) From my experience at PFC, purchase and installation of a suitable freeze drier would typically take about 18 months. Therefore, construction of a new facility for the preparation of freeze dried cryoprecipitate would probably have taken at least two years. Heat treatment of FVIII was begun at PFC on 18th November 1984. As freeze dried cryoprecipitate could not withstand heat treatment, a new facility would have soon become redundant.

(xviii) I am not sure when I became aware that Red Cross fractionators in Europe were producing cryoprecipitate rather than FVIII concentrate. I do remember attending a symposium at the Blood Transfusion Centre in Groningen, The Netherlands, in November 1981 when, during a tour of his Centre, the Director Dr Smit Sibinga expressed considerable concern over what he saw as a failure of European Red Cross fractionators to produce FVIII concentrate.

He was concerned that patients were receiving inadequate treatment and that haemophilia doctors were looking to import commercial concentrates from the USA.

(xixi) A similar situation existed in the Republic of Ireland. According to the Report of the Lindsay Tribunal of Inquiry (pages 52-53):

• *"The freeze-dried cryoprecipitate produced by the BTSB...never gained general acceptance among the treating doctors as a product suitable for use for home treatment"* (page 52).

• "*It would have been difficult for doctors and persons with haemophilia who had become used to the advantages of using concentrates to revert to the more awkward freeze-dried cryoprecipitate"* (page 53).

(xx) I also became aware, from a publication in 1982, that the use of freeze dried cryoprecipitate in Finland had clinical limitations, especially in the treatment of people with haemophilia who had developed inhibitors (antibodies) to factor VIII [PRSE0003666].

(xxi) I remember that a delegation from SNBTS visited Belgium. I was not a member of the delegation and do not remember seeing their report. I note that relevant information is included in a June 1981 report by an NBTS Working Party (DHSC0002207_040). According to this report, freeze dried cryoprecipitate was prepared in Belgium and in France from pools of 1000 donations. Compliance with UK standards of GMP was identified as an issue, consistent with the position of the Medicines Inspectorate concerning the preparation of freeze dried cryoprecipitate in Glasgow.

The Inquiry will examine the proposition that very small donation pools (e.g. 6-12 donations, such as are referred to in Dr Smith's Draft Proof (§36(a)) should have been used in the early or mid-1980s in order to provide better protection against HIV. What are your views on this matter? In particular:

a. **Do you think that such an approach would have provided greater protection for individuals using products produced from such pools?**
b. **Were such pools a practical possibility in the period c.1982 to 1985 given the infrastructure, equipment and personnel available at PFC?**
c. **What would the effect on overall levels of production of blood products at PFC have been given the economies of scale involved in producing small donation pools?**
d. **Was this approach considered in (i) Scotland, and (ii) the wider UK? If so, why was it rejected or not implemented more widely?**

61.1 General Comments

(i), PFC was required to operate in accordance with the DHSS Guide to Good Pharmaceutical Manufacturing Practice (GMP) (see para 19.1). The manufacture of FVIII and Factor IX concentrates from pools of 6-12 donations at PFC could not have complied with the DHSS Guide to GMP in respect of aseptic dispensing, freeze drying, and Quality Control testing.

(ii) As plasma is used for the preparation of multiple products, the impact on other plasma products prepared from the same plasma also needs to be considered.

61.2 Aseptic Dispensing

(i) It is a requirement of GMP that all products are dispensed within a contained aseptic facility (sometimes known as a sterile room) and that each batch of product be dispensed in one working session by one team of operators.

(ii) Before a new working session could begin, it was necessary to ensure that specified environmental standards were being met by suitably sanitising the area, including overnight fumigation as required. Materials necessary for a new work session would also have to be provided, including the preparation and sterile filtration of the final bulk solution as well as provision of sterilised equipment, containers and components.

(iii) With only one aseptic dispensing suite at PFC and the constraints outlined in (ii) above, I believe that only one batch of one product could be dispensed each day.

(iv) During the early to mid-1980s, 13 different types of plasma product were manufactured at PFC. They included albumin, normal immunoglobulin (two products) and specific immunoglobulins (eight products), as well Factor VIII concentrate and Factor IX concentrate for the treatment of haemophilia A and haemophilia B respectively.

(v) I was not involved in scheduling of product dispensing, but I believe that it was standard practice to schedule the dispensing of two batches of Factor VIII concentrate each week.

(vi) PFC's objective (set by Government), was to increase the production of Factor VIII concentrate to eliminate the need for Factor VIII concentrate to be imported (ie. to achieve self-sufficiency).

(vii) The only way output of Factor VIII concentrate could be increased in compliance with GMP guidelines was to increase batch size.

61.3 Freeze Drying

(i) As Factor VIII and Factor IX concentrates are freeze dried product, facilities for freeze drying need to be considered. The process for freeze drying Coagulation Factor Concentrates lasted about 1 week.

(ii) According to GMP guidance, products should be freeze dried as individual batches ie. multiple batches should not be dried together in the same freeze drier.

(iii) To maximise output, the batch size of FVIII concentrate was chosen to virtually fill a freeze drier, with a typical batch of Factor VIII concentrate at the time comprising about 800 vials. This would be equivalent to about 3,000 donations of plasma.

(iv) Twelve standard donations of plasma would have produced about 3 vials of Factor VIII concentrate. To freeze dry 3 vials in equipment designed to dry 1000 vials would have been inefficient and would have resulted in a reduction of FVIII output.

(v) To the best of my knowledge, freeze driers suitable for processing such a small number of vials were not sterilisable, nor were they capable of sealing vials within the chamber and would not therefore have been compliant with GMP.

(vi) Therefore, freeze drying of Factor Concentrate from very small donation pools would have required operation out-with GMP guidelines

61.4 Quality Control Testing

(i) Samples for Quality Control are taken during the manufacturing process and by consuming vials of final product. Each batch of product must be subjected to specified biochemical and biological tests and to sterility testing to ensure freedom from bacterial contamination.

(ii) The test for sterility is done by consuming whole containers of product. The number of containers required varies according to batch size. The smallest number allowed (for a batch of less than 100 containers) is 10% or 4 containers, whichever is the greatest.

(iii) The number of vials of FVIII concentrate that could be produced from very small donation pools (e.g. 12 donations) was about 3. Therefore, the number of vials of Factor VIII concentrate that could be produced from a small donation pool was insufficient to comply with GMP requirements for sterility testing.

61.5 Impact on Other Plasma Products

(i) Regulatory guidance specifies that normal immunoglobulin should be prepared from plasma pools containing plasma from at least 1000 donors (NHBT0000236_013, page 1013). This number of donors was required to ensure the provision of the full spectrum of antibodies needed to treat people with disorders of immunity. The quantity of plasma obtained from 1000 standard blood donations in the UK was equivalent to a plasma pool size of about 250 litres.

61.6 Conclusions

(i) In my opinion the production of Factor Concentrates from very small pools of plasma was not a practical possibility at PFC.

(ii) In terms of 'providing better protection against HIV', it is my opinion that such an approach would have been counter-productive. It would have reduced the output of UK-donor derived FVIII concentrate and have led, most probably, to an increase in importation of USA-donor derived Factor VIII concentrate which, in my opinion, carried a greater risk of HIV infection.

It may be suggested that in the same period blood products should have been fractionated from pools comprising plasma from a panel of selected donors.

a. **Do you think that such an approach would have provided greater protection for individuals using products produced from such pools?**
b. **Were such pools a practical possibility in the period c.1982 to 1985 given the infrastructure, equipment and personnel available at PFC/SNBTS?**
c. **What would the effect on overall levels of production of blood products at PFC and, to your knowledge, BPL/PFL have been given the economies of scale involved in producing small donation pools?**
d. **Was this approach considered in (i) Scotland and (ii) the wider UK? If so, why was it rejected or not implemented more widely?**

(i) I was not involved in donor selection, or plasma collection, and do not know how much plasma could have been obtained in this manner, given that UK blood donors were restricted to about 2 donations per annum and UK plasma donors to about 12 litres per annum.

(ii) The manufacture of factor concentrates from relatively small pools would have involved the same considerations described in my response to question 61 and I believe would have reduced output of Factor VIII concentrate from PFC.

(iii) I do not believe that patients who required repeated treatment would have avoided infection with NANBH, as the risk of infection would have been similar to repeated treatment with cryoprecipitate [WITN6914005], given that no effective donor screening test for NANBH was available.

(iv) I believe that recipients of small pool factor concentrates obtained from selected UK donors would have had a reduced risk of being infected with HIV, but the consequent reduction in output of Factor VIII concentrate from PFC could have resulted in more commercial Factor VIII concentrate being imported from the USA, with a greater risk of HIV infection.

(v) I do not know if this approach was considered in Scotland. I do know that Dr Smith began a study of this approach, but did not implement it routinely.

Section 6: Self-sufficiency in Scotland and the UK

The inquiry will examine the meaning of the term "*self-sufficiency*" and how it came to be interpreted:

a. **What did the term "*self-sufficiency*" come to mean to you?**
b. **In your opinion, to what extent, if at all, did its meaning change over time and its interpretation differ between:**
   i. Scotland, and the rest of the United Kingdom; and
   ii. Individual fractionators?
c. **What were the key factors at issue in any change of meaning or difference in interpretation of the term?**
d. **What was the consequence of any change of meaning or difference in interpretation of the term, in particular:**
   i. in influencing estimates of demand for factor products;
   ii. in the definition of what constituted "treatment" (for example, whether prophylactic and home treatment were included);
   iii. in the extent to which the concept of "clinical freedom" was or was not a consideration.

e. **To what extent, if at all, did the impetus behind the concept of "self-sufficiency" change over time (taking into account such factors as cost control and risk reduction strategy)?**

Please feel free to identify relevant sections of your evidence to the Penrose Inquiry and other inquiries in answer to these questions. If you do so, please indicate where you have further evidence to add to that which you have already provided.

63.1 <u>Policy of Self-Sufficiency - Chronology</u>

(i) In 1973, the DHSS established an Expert Group "*To advise the Department on trends in methods of treatment of haemophilia and allied conditions; and to consider possible future requirements for the treatment of the condition and the consequences for the supply of therapeutic agents"* [PRSE0004706].

(ii) The DHSS Expert Group met on 20th March 1973 under the chairmanship of Dr Rosemary Biggs and confirmed that freeze-dried intermediate-purity concentrates were the product of choice for the treatment of haemophilia, despite *"the theoretically increased risk of acquiring hepatitis".* They also recommended:

• "*the UK should aim to become self-sufficient as soon as possible by increasing home production of freeze dried AHG concentrate."* [PRSE0004706]

(iii) On 22nd January 1975 the recommendation of the Expert Group that the UK should aim to become self-sufficient was accepted in a parliamentary statement by the Minister of State for Health, Dr David Owen

(iv) On 29th May 1975, the World Health Assembly adopted resolution WHA 28.72 on the utilization and supply of blood and blood products which urged member states:

• to "*promote the development of national blood services based on voluntary nonremunerated donation of blood;"*

• to *"enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and of recipients of blood and blood products;"*

• and requested *"cooperation between countries to secure adequate supply of blood products based on voluntary donations;"*

(v) On 30th April 1980, the Council of Europe Committee of Ministers to Member States adopted Recommendation R (80) 5 [PRSE0002575] concerning blood products for the treatment of haemophilia, which advised Governments of Member States:

• to inform *"all concerned in hemophilia therapy of the problems arising from the procurement and rational use of blood components concerned in order to balance the needs and resources;"*

• to reach "*as far as possible, self-sufficiency of member states...both in respect of antihaemophilia products and blood plasma required for their preparation."*

• to use *"frozen cryoprecipitate only when other preparations of Factor VIII of controlled potency are not available with satisfactory conditions of efficiency, safety and cost."*

• to follow *"the recommendations of WHO and of the League of Red Cross Societies concerning the promotion of voluntary non-remunerated blood and plasma donations"*

• to make "*special efforts... to reduce the risk of transmission of hepatitis…"*

• to achieve "*a balance …between the available resources and the justified needs of haemophiliacs."*

(vi) On 15th December 1980, the Under-Secretary of State for Health & Social Security, Sir George Young, endorsed the UK Government's objective of achieving national self-sufficiency in a speech to the House of Commons.

(vii) On 30th January 1981, a meeting of Directors of SNBTS, Scotland's Haemophilia Directors and officials of SHHD considered the Council of Europe Recommendation R (80) 5 and "*agreed that policy and practice in Scotland were consistent with this document, subject to further consideration of the recommendation on the setting up of a haemophilia register."* (Penrose Inquiry document SNB.001.5055) [PRSE0000144].

(viii) On 23rd June 1983, The Council of Europe Committee of Ministers to Member States adopted Recommendation R (83) 8 [MACK0000307] concerning the prevention of the possible transmission of AIDS to patients receiving blood or blood products in which governments of member states were advised:

• to "*achieve national self-sufficiency in the production of coagulation factor products from voluntary, non-remunerated donors,"*

• to "*avoid importation of blood plasma and coagulation factor products from countries with risk populations and from paid donors;"*

• to "*avoid wherever possible the use of coagulation factor products prepared from large plasma pools; this is especially important for those countries where self-sufficiency in the production of such products has not yet been achieved;"*

(ix) On 7th March 1988, The Council of Europe Committee of Ministers to Member States adopted Resolution R (88) 4 [WITN6914027] on the responsibilities of health authorities in the field of blood transfusion, in which governments of member states were advised:

• "*self-sufficiency with respect to blood products is one of the basic conditions for minimising the hazard of the transmission of infectious diseases by blood transfusion;"*

• "*A programme of self-sufficiency should be organised for blood and plasma."*

• "*Pending the achievement of self-sufficiency, HAs may decide to authorise the importation of blood products. For ethical and security reasons, it is recommended that blood products are imported from countries where the legislation and practice governing the protection of donors and recipients meet the criteria laid down."*

(x) On 29th March 1990, The Council of Europe Committee of Ministers to Member States adopted Resolution R (90) 9 [WITN6914028] on plasma products and European self-sufficiency, in which governments of member states were advised:

• to "*promote self-sufficiency for plasma products on the basis of voluntary non-remunerated donation;"*

• "*Health Authorities of countries not having achieved self-sufficiency of source plasma should take the necessary measures to reach this goal as soon as possible*."

• "*For the collection of source plasma a country should rely exclusively on voluntary, non-remunerated donation."*

• "*where sufficient plasma to meet fractionation needs cannot be recovered from whole blood donation, plasmapheresis should be promoted within the framework of blood transfusion services;"*

• *"research to increase Factor VIII yields should be promoted, with investment where appropriate, since essential steps to ensure safety of products have significantly reduced yields."*

(xi) On the 1st of November 1990, Dr Donald Acheson, UK Chief Medical Officer, wrote on behalf of the Department of Health to Mr David Watters of the Haemophilia Society [DHSC0030028] in respect of Council of Europe Resolution R (90) 9:

• "*Ministers accord great importance to the principle of clinical freedom."*

• "*Where therefore a doctor decides in the light of the available clinical information, that a particular product is indicated for a particular patient, we believe that this decision should be respected even if that product has to be imported from outside the EC."*

• *"The principle of self-sufficiency therefore means that the supplies of domestically sourced blood products should be sufficient, both in range and quantity, to meet the needs of all patients whose clinicians prefer these to other available products."*

As this interpretation of the principle of 'self-sufficiency' had not been formally announced, its date of implementation by the UK Government and its Department of Health is not known.

(xii) On 26th February 1998, Mr Frank Dobson, Minister of State for Health authorised the importation of plasma into the UK as a precaution against the theoretical risk that vCJD might be transmitted via plasma products manufactured from plasma obtained from UK-donors (Department of Health Press Release 98/076).

(xiii) On 13th May 1998, The Department of Health announced [DHSC0004790_065] that the Committee on Safety of Medicines had completed its review of the use of UK-sourced plasma in the manufacture of blood products and had advised:

- "*manufactured blood products should not be sourced from UK plasma for the present time*"
- *"The Secretary of State for Health has accepted this advice."*
- *"the Government is allowing the NHS's Bio Products Laboratory and the Scottish National Blood Transfusion Service's Protein Fractionation Centre to import plasma from outside the UK until such time as a test is developed to screen for the possibility of infection, or it is proven that the manufacturing process destroys any infective agent."*

This statement ended the UK policy of aiming for self-sufficiency.

(xiv) PFC responded to the ban on UK plasma by importing plasma from 1998 that derived from unpaid volunteer donors in Germany and in the USA, to remain in accordance with the 1975 Resolution of the World Health Assembly WHA 28.72, which advised:

- *"cooperation between countries to secure adequate supply of blood products based on voluntary donations;"*

(xv) PFC was unable to obtain hyper-immune plasma from unpaid donors and purchased paid donor plasma for this purpose. PFC also had to purchase normal plasma from paid donors occasionally, when it was unable to obtain sufficient plasma from unpaid donors.

(xvi) On 18th December 2002, Lord Hunt announced, under 'Plasma Supplies', that the Department of Health had purchased the USA plasma collection company Life Resources Inc to secure long-term supplies of plasma for the NHS-owned Bio Products Laboratory. Life Resources Inc obtained its plasma from USA paid donors.

(xvii) On 15th February 2021, the UK Government removed its ban on the use of UK sourced plasma for the manufacture of immunoglobulins [RLIT0001063].

(xviii) For additional documents, see section 80.4, page 159.

63.2 <u>The Meaning of 'Self-Sufficiency'</u>

(i) In the summer of 1968 I sold my blood at a Blood Centre in Athens to 'earn' money to support my student holiday. I was pleased to be able to obtain much needed money and thought nothing of the wider implications.

(ii) I began to change my mind when I read 'The Gift Relationship' by Richard Titmus, that was published by George Allen & Unwin Ltd, 1970.

(iii) I went on to interpret 'self-sufficiency' as meaning that each country should provide its medical needs for blood and blood products from its own population, using unpaid volunteer donors.

(iv) In December 1989, Dr Harold Gunson had pointed out in an article in the British Medical Journal [DHSC0002003] that England & Wales had not achieved self-sufficiency, despite the construction of a new facility at BPL, due to insufficient plasma being collected. Dr Gunson explained that the additional plasma required would have to be obtained by plasmapheresis which would require investment.

(v) In a letter to the British Medical Journal published on 6th April 1991 [SBTS0000209_007], Professor J D Cash disagreed with the definition of self-sufficiency that had been communicated by Dr Acheson (see para 63.1 (xi)), proposing instead:

- *"The principle of self-sufficiency in the UK means that supplies of domestically sourced blood products will be sufficient, both in range, quantity, and quality, to meet the needs of all patients."*
- *"Where this is not possible, preference should be given to sources using unpaid donors,"*

(vi) In 1993, in a report prepared for the Council of Europe, Professor Dr W G van Aken, Medical Director of the Central Laboratory of the Netherland Red Cross, defined self-sufficiency as:

- *"Provision of human blood and blood products from within a population to satisfy the clinical needs of that population"*

He gave the origin of this definition as a Meeting of European Experts that had been held in Brussels on 9-10 January 1990.

In a footnote he stated:

• "*In one country (UK) this definition was slightly reworded and extended in the following way: the principle of self-sufficiency means that supplies of domestically sourced blood products should be sufficient, both in range and in quantity, to meet the needs of all patients whose clinicians prefer these to other products."*

(vii) I believe that the change in the definition of self-sufficiency by the UK Government was made to be able to claim that UK self-sufficiency had been achieved to avoid meeting the costs of plasmapheresis, which Dr Gunson sought (para 63.2 (iv)) According to van Aken (para 63.2 (vi)) "*the United Kingdom …. reported self-sufficiency in plasma products on the basis of unpaid donations...According to the definition for self-sufficient used by the UK."*

63.3 <u>Estimates of Demand (Chronology)</u>

(i) On 20th March 1973 the DHSS Expert Group on the Treatment of Haemophilia [PRSE0004706] advised that treatment of haemophilia in the UK would require 400,000 donations per annum, equating to 32 million international units (miu) FVIII per annum (Penrose Inquiry document PEN.013.1125, pages 22-23) [PRSE0001083].

(ii) In 1974, a Medical Research Council working party concluded "*An assessment of the total amount of factor VIII likely to be required for all types of treatment puts the total in excess of 500,000 blood donations or 40 million units of factor VIII"* (Biggs R et al. Br J Haematol 1974, 27, 391 [WITN6914066]).

(iii) On 13th July 1977, a DHSS working group on trends in the demand for blood products, advised "*the commonly accepted target figure was 1000 iu per 1000 population"* and that this "*should be increased by 25% to meet sudden demands"* [WITN6914054].

(iv) In December 1979, the same DHSS working group advised "*We accept the estimate that to meet the needs of haemophiliacs in the foreseeable future the amount of FVIII produced will have to be about 1000 iu per 1000 population per annum.*

(v) On 11th December 1979, at a meeting of SNBTS Directors an estimate of 1.8 iu factor VIII per head of population was agreed.

(vi) In January 1981, in his notes for a meeting with Scotland's Haemophilia Directors, Dr J D Cash proposed a target within the next 5 years of 2.75 iu per head of population. In doing this he estimated requirements for home therapy, the treatment of patients with mild/moderate

haemophilia A, the treatment of inhibitors, elective surgery and the effects of increasing age. (Penrose Inquiry document SNB.001.5076) [PRSE0004724].

(vii) In June 1981, a DHHS working party to advise on plasma supplies for self-sufficiency noted "*Representatives of the Haemophilia Directors estimate by the mid-1980's the annual requirement for FVIII will reach 100 M.i.u. for the United Kingdom. Forecasting beyond that time could not be accurate but it was considered that by the 1990's the need for FVIII could reach 150 M.i.u. per year*".

(viii) As the HCDO collected data on the amounts of FVIII used in the UK, it is possible to determine the accuracy of these different estimates and to compare the amounts of UK-derived factor VIII (concentrate & cryoprecipitate) with that of commercial FVIII concentrate [WITN6914029].

(ix) Not only had the early estimates of the amount of factor VIII required been exceeded by 1977, but the experts appointed by DHSS had failed to anticipate the year on year increase in use.

(x) It should be appreciated that the data on the amount of factor VIII used to treat people with haemophilia A was collected retrospectively by HCDO on an annual basis. Consequently, forward planning was based on information that was inevitably out-of-date.

63.4 <u>Estimates of the Amount of Plasma Needed</u>

(i) Having estimated the amounts of factor VIII required, the amount of plasma needed to provide this can be calculated. This calculation requires an estimate of the amount of factor VIII than can be obtained from a donation of plasma, expressed as the yield per litre of plasma.

(ii) The MRC working party of 1974 (see 63.3(ii)) used a yield estimate of 37%. ie. 370 iu factor VIII per litre of plasma, based on data from the Plasma Fractionation Laboratory in Oxford.

(iii) I believe this figure was too high for planning purposes for two reasons. First, batch sizes were increased to produce more Factor VIII concentrate. The larger volumes took longer to process and because factor VIII was unstable, more factor VIII activity was lost during processing. Second was a change by The National Institute of Biological Standards & Control (NIBSC) in December 1976 to the way factor VIII activity was measured [WITN6914030] which resulted in an apparent loss of yield of 22% [WITN6914031].

(iv) The combination of the under-estimate of the amounts of FVIII needed for treatment, with the over-estimate of yield, meant that the amounts of plasma required were greatly underestimated, with significant consequences in planning for the collection and the processing of plasma.

(v) In 1973, The DHSS Expert Group had estimated that UK self-sufficiency would require the collection and processing of 400,000 donations per annum; equivalent to 100,000 kg plasma per annum.

(vi) By 1982, it was estimated that 435,000 kg plasma per annum were needed to enable England & Wales to achieve self-sufficiency [GFYF0000127], with this estimate rising to 550,000 kg per annum in 1989 due to the impact of heat treatment on factor VIII yield [DHSC0002003].

(vii) According to the Department of Health, the output of Factor VIII concentrate from BPL was limited by insufficient plasma until 1985, at which point the plasma capacity of BPL of 150,000kg per annum was reached [GFYF0000127].

63.5 <u>The Collection of Plasma</u>

(i) Plasma was obtained primarily by recovery from whole blood. Obtaining plasma from whole blood donations required hospital doctors to change their practice from administering whole blood to administering red cell concentrates.

(ii) Hospital doctors throughout the country had to be persuaded to make this change. As this was not done to benefit their patients, it is possible that some hospital doctors could have been reluctant to make the change to red cell concentrates, considering it to be unethical according to their obligation under the Geneva Convention that "*The health of my patient will be my first consideration"* (Infected Blood Inquiry transcript 27th January 2021, page 75) [INQY1000091].

(iii) The amounts of plasma collected in England & Wales and in Scotland per million population are available for the period 1982/83 to 1988/89 (Penrose Inquiry document PEN.013.1125, page 67) [PRSE0001083].

Year	Amount of Fresh Frozen Plasma (Kg per million population)	
	England & Wales	Scotland
1982/83	3,000	7,446
1983/84	3,800	8,717

Year	Amount of Fresh Frozen Plasma (Kg per million population)	
	England & Wales	Scotland
1984/85	4,850	8,593
1985/86	6,100	8,653
1986/87	6,200	9,142
1987/88	7,250	8,913
1988/89	7,550	10,650

(v) Although I was not involved in the collection of plasma, I believe that differences between Scotland and England & Wales could have involved:

• the different sizes of the populations served,

• the number of hospital doctors required to change their medical practice,

• the reluctance of hospital doctors to change practice,

• differences in organisation; Scotland's Transfusion Centres being administered centrally by SNBTS and NBTS Transfusion Centres via Regional Health Authorities,

• the proportion of each population donating blood,

• the proportion of blood donations converted to red cell concentrates,

• the use of additives (optimal additives solutions) to enable the amount of plasma that could be removed to be increased, without compromising red cell concentrates,

• the facilities available for separating plasma from red cells,

• the use of plasma frozen within 6-24 hours of donation, in addition to plasma frozen within 6 hours of donation,

• concern over the wastage of red cells,

• the development and application of plasmapheresis,

• the availability of finance,

• the drive and determination of the leadership.

63.6 <u>Clinical Freedom</u>

(i) On 29th June 1974 a letter from Dr Biggs of the Oxford Haemophilia Centre was published in the Lancet [OXUH0000651]. In her letter Dr Biggs wrote:

• *"Factor VIII to a haemophilic patient is literally his expectation of life",*

• *"Without treatment...few patients reached adult life and those who did were helpless cripples",*

• "*90% of haemophilic patients in the United Kingdom receive less (and in some cases much less) than optimum treatment of their complaint",*

• *The consequences of this undertreatment included… unnecessary, painful, and destructive bleeding into joints and muscles...loss of education time and inability to hold continuous employment,"*

• *"The question that arises is for how long should this shortage of factor VIII be considered to be a reasonable feature of haemophilia treatment?"*
• *"Two things, in my view, make continued limitation both unnecessary and unethical."*
• *"three commercial companies are now licensed to sell good quality human factor VIII",*
• "*Some immediate solution should be found for the ridiculous impasse of large available stocks of therapeutic materials locked up in stores because no one will buy them and, on the other hand, patients in dire need of this same material."*

(ii) The request by Dr Biggs that commercial Factor VIII be purchased for the treatment of haemophilia A in the UK was supported by the Directors of the Haemophilia Centres at St Thomas's Hospital, London on 6th July 1974 [WITN6914032], Sheffield Royal Infirmary on 13th July 1974 [WITN6914033], The Royal Free Hospital, London on 20th July 1974 [DHSC0030028], The Royal Victoria Infirmary Newcastle on 20th July 1974 [WITN6914034] and by the UK Haemophilia Society on 3rd August 1974 [WITN6914035].

(iii) Authority to purchase commercial Factor VIII concentrate was issued by the Department of Health on 4th November 1974 [WITN6914036].

63.7 <u>Impact of Clinical Freedom on Self-Sufficiency</u>

(i) I do not believe that the authority given by DHSS to Haemophilia Directors to purchase commercial FVIII concentrates (see para 63.6(iii)) had any impact on the UK policy on self-sufficiency, until the definition of self-sufficiency was changed by the Department of Health circa 1990 (see para 63.1(ix) above).

(ii) I do not believe that the authority that was given to Haemophilia Directors to purchase commercial FVIII concentrates had any impact on the failure to achieve self-sufficiency. I believe that this failure was primarily due to planning being based on incorrect advice from UK experts, such as Dr Biggs. The amount of Factor VIII concentrate needed to treat haemophilia A was underestimated by Dr Biggs by at least a factor of two, whilst the yield of factor VIII was overestimated by about a factor of two, the net effect on the amount of plasma to be collected and processed being underestimated by a factor of four at least (see para 63.3 & 63.4 and cited document no. 2, PEN.013.1125, pages 22-29) [PRSE0001083].

(iii) I do not believe that the authority given to Haemophilia Directors to purchase commercial FVIII prevented the use of local FVIII concentrate in England & Wales, as the supply of local Factor VIII concentrate was never sufficient to treat haemophilia A adequately.

(iv) I do believe that the authority given to Haemophilia Directors to purchase commercial FVIII prevented the use of local FVIII concentrate in Scotland, due to a preference for commercial products by some clinicians in some instances (eg. evidence of Dr Pettigrew, 7th December 2020, transcript page 26).

In the Archer Statement, you refer to Scotland being "*one of the few countries ever to have achieved self-sufficiency using donations from unpaid volunteers and, as far as I am aware, the first country to do so*". In the First Penrose Supplementary Statement (summary, p60) you provide a further analysis of whether Scotland had achieved self- sufficiency, noting the different interpretation of the figures of Factor VIII production that result if cryoprecipitate is included in the calculation.

a. **In your opinion, when was self-sufficiency achieved in Scotland in the terms described in the preceding question, both including and excluding cryoprecipitate as a suitable alternative?**
b. **Please explain on what basis the assumption was made that the situation in Scotland regarding use of Factor VIII was the same, or not materially different to, *"average UK clinical practice"*.**

64.1 <u>Assumptions for Clinical Practice in Scotland</u>

(i) I used *"average UK clinical practice"* as a benchmark for self-sufficiency in Scotland for the following reasons:

• annual data were available for the whole UK from HCDO for the period covered by the Penrose Inquiry,

• data from a population much larger than that of Scotland avoided potential distortion by individual patients whose treatment needs were particularly high,

• data from a much larger population avoided potential distortion from treatment given by a haemophilia doctor that was atypical,

• Scotland's haemophilia doctors attended meetings of UK HCDO, which I believe was a forum for establishing best practice,

• treatment of people with haemophilia A in the UK was not limited by supply of concentrate per se, as UK Haemophilia Directors were authorised to purchase commercial Factor VIII from November 1974 [WITN6914036].

64.2 <u>Outcome in Scotland Compared with UK Clinical Practice</u>

(i) If cryoprecipitate is included, then the amount of treatment for haemophilia A available from SNBTS exceeded average UK treatment throughout the period 1975/76 to 1987/88 (Penrose Inquiry document PEN.013.1125, table 18, page 60) [PRSE0001083].

(ii) If cryoprecipitate is excluded, then the amount of Factor VIII concentrate available from SNBTS in the period 1975/76 to 1987/88 either matched or exceeded average UK treatment, except for 1978/79 and 1979/80 when the availability of FVIII concentrate was below average UK treatment by 30% and 11% respectively.

64.3 Self-Sufficiency for Scotland

(i) Based on average UK treatment of haemophilia A, and excluding cryoprecipitate, Scotland was self-sufficient in the supply of SNBTS FVIII concentrate from 1980/81 to 1987/88.

(ii) Commercial FVIII concentrate was purchased for use in Scotland:

- For the period 1977/78 to 1982/83: the purchase of commercial FVIII concentrate averaged about 25% of the FVIII concentrate and 15% of the total factor VIII (including cryoprecipitate) for use in Scotland.
- For the period 1983/84 to 1987/88: the purchase of commercial FVIII concentrate averaged about 1.5% of the Factor VIII concentrate and 1.2% of the total factor VIII (including cryoprecipitate) for use in Scotland.
- For the period 1988/89 to 1989/90: purchase of commercial FVIII concentrate averaged about 16% of the total Factor VIII concentrate for Scotland, due to a manufacturing failure at PFC (see para 43.10).
- For the period 1990/91 to 1999/2000: purchase of Commercial FVIII concentrate averaged about 7.4% of the total FVIII concentrate for Scotland.

(see Penrose Inquiry document PEN.013.1125, page 61, table 19) [PRSE0001083]:

Was there ever a period in which PFC lacked the capacity to fractionate the plasma supplied by the Regional Transfusion Centres? Alternatively, was there ever a period when efforts to increase the supply of plasma were suspended or limited as a result of a lack of capacity to process the plasma at PFC?

65 PFC Capacity

(i) In general PFC never lacked the capacity to fractionate the plasma supplied by Regional Transfusion Centres, except for planned short periods when building modifications were carried out to comply with the requirements of Medicines Inspectors.

(ii) To the best of my knowledge efforts to increase the supply of plasma from Regional Transfusion Centres to PFC were never limited by PFC's capacity to process plasma.

It may be suggested that the production of blood products from plasma would have been achieved with more efficiency within the UK had a decision been taken to concentrate production at PFC. How would you respond to this suggestion? In particular:

a. **To the best of your knowledge, did PFC have unused capacity to fractionate additional large quantities of plasma and thereby produce, store and supply additional blood products?**
b. **What, if any, effect would concentration of efforts at PFC have had on the development of heat treated products in the early/mid-1980s?**
c. **In Dr Lane's Proof (§152) he refers to "*exaggerated claims made by the Director of PFC Liberton [Mr Watt] for its operational capacity*" in connection with the decision to redevelop BPL. In §407 of Dr Lane's Proof, he refers to "*grandiose claims made for [PFC] by those responsible for its administration*" and the "*belief that there was any spare capacity immediately available for fractionating English and Welsh plasma at PFC was, I believe, a myth.*"**

In the light of your evidence to the Penrose Inquiry and the Lindsay Tribunal as referred to at questions 65 and 68 please comment on Dr Lane's evidence.

Overview

66.1 Differences in the Fractionation Technology used at BPL and PFC.

(i) The capacities of the plasma fractionation centres at BPL and PFC were determined by the volume of plasma that could be manufactured to produce Albumin using the established method of cold-ethanol (Cohn) fractionation [PRSE0002176]/

(ii) Although the manufacture of FVIII concentrate was limited by freeze drying capacity, I believe that it was the ability to fractionate the plasma that remained after removal of cryoprecipitate that determined overall plant capacity.

(iii) BPL used batch tanks for cold-ethanol fractionation, which was the universal technology at the time. BPL's capacity was limited to about 150,000 kg plasma per annum (prior to its new centre becoming available in 1987/88).

(iv). PFC developed continuous-flow processing for this purpose, instead of batch processing. The equipment for each cold-ethanol fractionation step was fitted into a continuous-flow, computer- controlled module, with a sequence of three precipitation steps (ie. three modules) being used to obtain the albumin rich precipitate.

(v) According to the original design by PFC Director Mr John G Watt, each continuous-flow module operated at a flowrate of 15 litres per hour, with an expectation that operation would take place on a 24-hour basis [WITN6914037].

(vi) The new PFC centre was designed on this basis with space and services being allocated for the operation of up to 15 continuous-flow modules [WITN6914037 & WITN6914038]

(vii) When I joined PFC in January 1973, I was assigned to work on Mr Watt's continuous-flow process, as results were variable. I re-designed most of the elements of the process and increased the flow-rate from 15 litres per hour to up to 45 litres per hour. It was estimated that with 9 modules operating fully continuously, 9,000 litres of plasma could be processed weekly, equivalent to about 400,000 litres per annum [WITN6914039].

(viii) Although the design capacity of the PFC facility had incorporated processing of plasma for England as well as for Scotland, equipment and staffing were provided for Scotland's needs only in the first instance. This included 6 continuous-flow modules.

(ix) Scotland's needs were met at first by operating only 3-modules on a 9am to 5pm basis. In 1984, 3 additional modules were brought into use to meet Scotland's increased needs, still operating on a 9am to 5pm basis.

(x) The continuous-flow modules were re-designed in 1985, with a number of features upgraded, including the replacement of a main-frame computer by local micro-processor controls [WITN6914040].

(xi) In conclusion. Cold-ethanol fractionation of plasma at PFC was carried out using continuous-flow technology as opposed to the standard batch technology used at BPL. This was only operated at PFC on a 9am to 5pm basis, as this was sufficient for Scotland's needs. The staffing arrangements needed to operate on a 24 hour basis (as designed), in order to process plasma from England, were not provided.

66.2 Policy - Chronology

(i) In the late 1960s a series of meetings were held between senior staff of BPL and SNBTS/PFC, together with officials from SHHD/DHHS, to consider the future plasma fractionation strategy for the UK.

(ii) At a meeting held on 14th March 1969, it was proposed by the Director of BPL, Dr W d'Maycock, that one third of the plasma from England & Wales should be processed at the new PFC centre [PRSE0002199].

(iii) When I applied for a position at PFC in August 1972, the job description stated "*New premises are under construction….The Centre has the prime function of processing human plasma collected in regional transfusion centres in Scotland and, later, in North England to provide materials for clinical use."* [WITN6914041].

(iv) To accommodate plasma from England, Mr Watt envisaged the introduction of shift-working to allow the continuous-flow ethanol fractionation process to be operated on a 24-hour basis rather than an 8-hour basis.

(v) I was present at a meeting in 1976 that Mr Watt held with full-time trades union officials to discuss how changes to conditions of employment should be negotiated to enable shift-working to be introduced.

(vi) On 11th March 1977, a joint meeting was held between DHSS and SHHD on "*Mutual Problems".* It was noted [WITN6914042]:

- "*PFC Edinburgh's effective capacity was however much lower than its potential capacity, due to a problem in the present phase of Incomes Policy of entering into an agreement with the trades unions on shift working."*
- *"…the PTB Whitley Council Management Side were unable to make an acceptable offer because of current pay policy. The Chairman agreed that it was essential to try to break the existing deadlock and to raise the matter again within DHSS,"*
- *"Armed with the information that SHHD would provide, [name redacted] would bring to the notice of the Whitley Division concerned the problem which the inability to introduce shift working at Liberton was causing, the regrettable underusage of production capacity and the dire consequences for the NBTS."*

(vii) On 11th August 1977, another joint meeting was held between DHSS and SHHD on "*Mutual Problems*". It was noted [WITN6914043]:

• "*Dr Lane, who was to succeed Dr Maycock in about 12 months time said that it was his intention to concentrate on the production of Factor VIII at BPL….it would be wrong, in his view, to send plasma from Regional Transfusion Centres in England to the PFC, if this had the effect of leaving spare capacity at Elstree …He envisaged that only time expired plasma would be sent to the PFC and was unwilling to enter into any long term agreement to have regular quantities of plasma fractionated in Edinburgh.*"
• *"It was, however, pointed out that any fundamental departure from what had already been agreed about the fractionation by the PFC of plasma from England...could raise questions about the need to introduce shift working."*
• "*SHHD said that after discussion with all parties concerned, it had been agreed that, in view of the failure to reach agreement on the introduction of shift working through the Whitley machinery, a case should be prepared for the PFC to be accepted as a pharmaceutical factory type development with a staffing structure out with Whitley arrangements. The case had now been prepared and would be sent in the next day or two.*"
• "*Should the approach to CSD be successful Mr Watt did not anticipate any particular resistance from staff at PFC to the introduction of shift working.*"
• "*The next meeting would be in London but the date would depend on the rate of progress in resolving the problems of shift working arrangements on which the future progress on co-operation depended.*"

To the best of my knowledge, no further meetings were held.

(viii) In 1981, 24-hour operation of the continuous-flow process was undertaken at PFC for a 2-week period to demonstrate that the estimated capacity could be achieved in practice. I was absent from PFC due to illness, but I understand that a 2-shift system was employed with the agreement of trades unions. In a January 1982 report [SBTS0000612_026], the SNBTS National Medical Director Dr John Cash concluded:
• PFC had a capacity to process up to 350,000 kg plasma per year, but extended finishing capacities would be needed to support this level of operation;
• On an interim basis PFC could accommodate 100,000 kg plasma per year from NBTS, with outdated plasma being processed initially;
• Processing fresh frozen plasma to recover FVIII would require a new freeze drier, which would take 15 months to install after purchase;
• In the longer term PFC could process 270,000 kg plasma per year for NBTS and 80,000 kg per year for Scotland + N. Ireland;

• The cost of upgrading PFC to meet requirements of the Medicines Inspectors was estimated to be £5.8m for Scotland/N.Ireland, with an additional £1.2m to accommodate plasma from NBTS.

(ix) In the September/October 1981 issue of Medical World, Mr GRO-C, an ASTMS trades union official for Scotland, described a visit of the ASTMS Parliamentary Committee to PFC, [SBTS0001455_012]:

• *"…it was pointed out by the Centre's Director that there was capacity in the Plant to increase production considerably without high scale new investment."*

• *"It was stressed however that the Plant was considerably under utilised and could process blood to serve a population of 25 million."*

• *"Of course such an increase would require running the plant for longer periods and would lead inevitably to the introduction of a shift system."*

(x) In an undated briefing note for Ministers entitled "*Blood Products Laboratory Redevelopment"* [WITN6914044], a number of options were identified, including:

• Building a BPL to process 400,000 kg per year (estimated capital cost £21.03m).

• Building a BPL to process 200,000 kg plasma per year (estimated to cost £18.6m), with 200,000 kg per year being processed at PFC (estimated cost £4m), at a combined cost of £22.6m.

• The less expensive option of building BPL to process 400,000 kg at a cost of £21.03m was recommended.

• it was also noted "*in the view of DHSS officials, it remains highly doubtful whether a shift-working agreement can be negotiated with staff at PFC without serious repercussions on pay of other groups in the NHS and the Industrial Civil Service."*

(xi) In a letter to DHSS of 2nd September 1982 [DHSC0002333_018] an SHHD official wrote:

• *"The impression is given ...that the capital investment of £6-7millions would be required solely for the processing of English plasma. In fact about half of this sum will have to be spent in any case to fractionate plasma for Scotland and Northern Ireland to Medicines Inspectorate standards."*

• *"I note also that you have expressed a pretty firm line on the shiftworking issue. As I said in my letter of 16 July, we here take the view in light of the known attitude of the main Scottish union official involved that an acceptable agreement can be negotiated, though not without difficulty."*

• "*I am a little unhappy about the decision on this topic being based to any material extent on the concept of shift working being too difficult for the NHS."*

(xii) On 18th January 1984, The Lord Glenarthur wrote to Mr GRO-C (ASTMS) [PRSE0001727] to explain:

• *"the existing laboratory at Elstree is capable of fractionating all the plasma currently available. Should the situation arise where the plasma supply builds up beyond the capacity of the existing laboratory, we should need to examine whether any surplus capacity at the Protein Fractionation Centre could be used."*

(xiii) On 14th May 1984, John J Mackay, Minister for Health and Social Work at the Scottish Office wrote to Mr GRO-C (ASTMS) [MACK0002271_012] to explain:

• "*The function of PFC is to concentrate on the needs of Scotland and Northern Ireland."*

• *"...the needs of England and Wales are to be met by a new production unit being built at BPL Elstree, and not by looking to any expansion of production at PFC."*

• *"There is thus no need to consider your interesting suggestion whereby this could be achieved."*

(xiv) In June 1991, following negotiations with trades unions, a new staffing structure was introduced at PFC which included a shift working system. This was needed to support the production of a high-purity FVIII concentrate which entailed processing over-night.

66.3 Comments

(i) The first impediment to processing plasma from England at PFC was a claim in 1977 that the staffing arrangements (a shift system) were not compatible with the Government's Incomes Policy (see 66.2 (vi-vii)).

(ii) The Incomes Policy of the Government (known as the Social Contract) concerned annual pay awards, which provided an increase in pay for the same job.

(iii) PFC was seeking to introduce new terms and conditions of employment (to encompass shift working) with a suitable rate of pay. As this new rate of pay was for a new job, it should not, in my opinion, have contravened the Government's incomes policy.

(iv) At the joint meeting between DHSS and SHHD held on 11 August 1977 (para 66.2(vii)), the BPL Director designate opposed the processing of Fresh Frozen Plasma (needed for FVIII) at PFC. This implies that he believed that BPL could fractionate all of the available plasma with sufficient capacity to meet the needs of England & Wales for FVIII concentrate.

(v) That meant that the issue being addressed at this meeting was only the processing of outdated plasma from England & Wales at PFC. The relevant product obtained from outdated plasma was Albumin. As Albumin was pasteurised to eliminate the risk of hepatitis transmission, the consideration facing the civil servants (and government) was the cost of importing Albumin, rather than the risk of disease transmission.

(vi) The opposition of Dr Lane to a long term agreement for English plasma to be processed at PFC, together with his opinion that only time-expired plasma for the preparation of Albumin would be sent to Scotland, may have reduced the pressure on civil servants to resolve the apparent conflict between the governments incomes policy and the staffing needs of PFC.

(vii) Subsequently in 1982, some three years after the end of the previous government's incomes policy, a second impediment was raised when it was claimed that shift working at PFC could have "*serious repercussions on pay of other groups in the NHS and the Industrial Civil Service.*" (para 66.2 (ix)).

(viii) It should be appreciated that to operate shift-working, PFC needed to hire additional staff. It is difficult to see how people of a suitable quality would have applied for positions involving shift-work, without a shift premium.

(ix) The third impediment to utilising PFC to process plasma from England concerned the estimated costs of the different options in which the cost for utilising PFC was estimated as £4m (para 66.2(ix)), despite the figure from Dr Cash being £1.2m (para 66.2(viii)).

(x) If Dr Cash's figure had been used, the estimated cost of building BPL to process 200,000kg, with 200,000 kg being processed at PFC, would have been £19.8m and would have been less expensive than the chosen option of building a 400,000kg facility at BPL at an estimated cost of £21.03m.

(xi) Despite the marginal differences in these cost estimates, the time taken to complete the different options does not seem to have been taken into consideration, despite the option to utilise PFC and to build a much smaller BPL obviously being much quicker to achieve than constructing a much larger BPL.

(xii) Construction of the new BPL took about 5 years to complete, at a capital cost of £59m (GFYF0000127 , page 25), almost 3x greater than the cost estimate on which this option was chosen.

(xiii) A small northern extension to PFC was built in the early 1990s for Scotland's needs, with shift working also being introduced in 1991 to support the production of high-purity Factor VIII concentrate.

(xiv) The NHS land to the north of PFC, that had been earmarked for a larger extension, remained vacant when PFC was closed in 2008.

(xv) Dr Lane's claim at Question 66 (c) that operational capacity of PFC was exaggerated by PFC Director Mr Watt is incorrect. PFC's continuous-flow fractionation process was designed to operate continuously, not intermittently. That it functioned well with intermittent (ie. 9am - 5pm) operation [WITN6914039] demonstrated its success in a more difficult circumstance than it had been designed for.

(xvi) As the routine fractionation of plasma from England required increased staffing at PFC, with new terms and conditions of employment, Dr Lane's comment in Question 66(c), that this could not have been done "*immediately*" is correct. Similar considerations applied to the production of Factor VIII concentrate, which would have required PFC to install additional freeze drying capacity before significant quantities of Factor VIII concentrate could have been produced for England. This would have taken about 18 months.

In your First Penrose Supplementary Statement [§5.1.2] you stated that: "*Although production trials using plasma from England & Wales were completed successfully at the PFC (Cash, 1982: ['Notes on "An Interim Report on a Study of Continuous Fractionation of Plasma*" by JG Watt, November 1981, Edinburgh SNBTS']), the DHSS decided not to utilise the PFC for the fractionation of plasma from England & Wales as this was judged, wrongly, to be more expensive than the construction of a larger new facility at the BPL (Department of Health & Social Security, 198243). 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.

a. **Why, in your opinion, did the DHSS judge this issue "wrongly"?**
b. **Was cost the sole factor or were other factors relevant, in particular agreement with the Trade Unions on the introduction of shift-working?**
c. **What evidence, if any, is available to support your view?**
d. **What action, if any, was taken at the time by you or the PFC in respect of this decision?**

e. What communications, if any, in whatever form can you direct the Inquiry to in respect of this matter?

In this respect, you may be assisted by your evidence in Transcript, 10 May 2011, p80/22 and the Policy Steering Group Minutes (§6).
You may also be assisted by a letter written by Mr Cash to Mr J Hammill of the Scottish Home and Health Department, dated 11 January 1990n. Please provide what evidence you are able to on Mr Cash's observation that the PFC management repeatedly requested shift working facilities over many years, but that these requests were rejected by the SHHD, something that he considered as "*dictated by London*" and *"influenced by the Union ASTMS".*

(i) I do not know why DHSS judged this issue wrongly (see paragraph 66.3).

(ii) The opposition of DHSS to shift-working at this time concerned the view of DHSS officials that, *"….. it remains highly doubtful whether a shift-working agreement can be negotiated with staff at PFC without serious repercussions on pay of other groups in the NHS and the Industrial Civil Service."* [WITN6914044], a view rejected by SHHD [DHSC0002333_018] (see para 66.2(x)).

(iii). I wrote to my trades union on 9th June 1983 to complain about the underuse of PFC (see 34.1(iv)).

(iv). PFC Director Mr John G Watt resigned from his post in July 1983. Although he did not give me a reason for his resignation, I believe that decisions not to send plasma from England to be processed at PFC played a part.

(v) The possibility of plasma from England being processed at PFC ended on 14th May 1984, when John J MacKay, Scottish Office Minister for Health and Social Work, wrote "*The function of PFC is to concentrate on the needs of Scotland and Northern Ireland."* [MACK0002271_012].

(vi) See also my response to question 66

Please explain, insofar as it is within your knowledge, how and why the decision was taken to fractionate plasma from Northern Ireland at the PFC. In doing so, please consider:

a. **The person or organisation, originally proposed this step, and why,**
b. **Whether there was any opposition to the proposal.**
c. **The attitude of the PFC management to this proposal.**
d. **Whether the decision to fractionate plasma from Northern Ireland caused any difficulties within PFC, and if so, what effect this had on wider production of blood products.**
e. **How the plasma from Northern Ireland was used in the production of blood products, including whether Northern Irish plasma was reserved to be used only in the blood products provided to Northern Ireland, or whether it was pooled with other plasma.**
f. **How, if at all, the arrangements for Northern Irish plasma differed from the arrangements made for plasma obtained from Scottish donors.**

68 <u>General Comments</u>

(i) I was not involved in decisions concerning the processing of plasma from Northern Ireland at PFC.

(ii) To the best of my knowledge there was no opposition to this proposal, which was welcomed by the staff and management of PFC as it enabled them to make a greater contribution to health care.

(iii) To the best of my knowledge plasma from Northern Ireland was treated no differently to plasma from Scotland once it had been validated as suitable for the production of FVIII concentrate.

(iv) I am not aware of any difference in arrangements between plasma from Northern Ireland and plasma obtained from donors in Scotland.

> **At §290 of Dr Lane's proof he says that trial of 24 hour continuous fractionation "*ultimately proved unsuccessful and ultimately led to the expressed view by the SHHD that the redevelopment plans for BPL should not take Scottish requirements into consideration.*"**

Do you know why Dr Lane took a different view on the outcome of the trial and its repercussions?

69. <u>Comment</u>

(i) I do not know why Dr Lane took a different view on the outcome of the trial, except to note that it was consistent with his reluctance for plasma from England to be processed at PFC (see para 66.2 (vii)).

The Lindsay Tribunal Report at p56 states: *"From the outset [PFC] had a capacity to process more plasma than was collected in Scotland and to supply more concentrate than was necessary to meet Scotland's requirement. The Protein Fractionation Centre was anxious to utilise this surplus capacity to improve its economic efficiency. It had originally been that plasma collected in England would be sent to the Edinburgh Centre for fractionation. This did not in fact occur. From 1983 onwards plasma collected in Northern Ireland was fractionated in the Edinburgh centre. The evidence of Dr. Foster was, however, that the [PFC] had surplus capacity at all stages from 1975 to 1985."*

a. **Is this statement a true and accurate summary of the position in terms of the PFC's "*surplus capacity*"?**
b. **To what extent would that "surplus capacity' have been sufficient to fractionate plasma collected in England and Wales?**
c. **Why did the sending of plasma collected in England and Wales to the PFC not "*occur*"?**

In this respect you may be assisted:

i) by your comments regarding capacity and the failure of plans to process English and Welsh plasma in the Archer Statement (p9):

ii) by your comments in the Transcript, 11 May 2011: (p25/16) referring to a letter to Sheila McKechnie at the ASTMS dated 29 September 1983 [Appendix 6, p50] in which you refer to: "*the true capacity of the Scottish Fractionation Centre and the reasons for its neglect (in my opinion) this is scandal which deserves an inquiry in its own right.*" And (p30/18) in the comments referred to in a letter assumed to be from Clive Jenkins to Lord Glenarthur dated 27 October 1983 [Appendix 6, p55] in which Mr Jenkins states: "[*PFC] is substantially underused and this seems to be being ignored by your Department. I am advised by my members that [PFC] could increase its capacity to a level where we could manufacture over two-thirds of the Factor VIII currently purchased from the U.S.A. This in no way would affect the plans to build further facilities at Elstree as we must take into account that the level of Factor VIII in the U.K is still well below the level considered appropriate for proper clinical treatment*".

See my response to question 66.

§291 of Dr Lane's Proof refers to Mr Watt's view on PFC's potential, and refers to (i) a letter to the Times dated 2 January 1981 from Brain Meakin of the School of Pharmacy and Pharmacology at the University of Bath, and (ii) a reply from Dr E Harris, Deputy chief Medical Officer dated 7 January 1981. Mr Meakin refers to PFC being *"seriously under utilised, working at less than a third of its current capacity...this state of affairs [being] nothing less than scandalous."*

At §292, Dr Lane describes this view as "incorrect" for the reasons he gives. On the assumption that you do not share Dr Lane's opinion, please set out your views on this issue, including the assertions regarding the requirement for 24 hour operation to achieve the stated capacity and misrepresentation of the plasma supply position at the relevant time.

71.1 <u>PFC Capacity</u>

(i) In January 1982, Dr Cash estimated that PFC had the capacity to process 350,000 kg of plasma per annum (para 66.2 (viii) and SBTS0000612_026).

(ii) The largest quantity of plasma processed at PFC per annum was 73,585 kg in 1991/92 (cited document no.2, PEN.013.1125 page 35) [PRSE0001083].

(iii) This is consistent with Dr Meakin's advice to Dr Harris that PFC was "*seriously under utilised, working at less than a third of its current capacity..*"

71.2 <u>Brian Meakin</u>

(i) Brian Meakin was senior lecturer in Pharmaceutics at the University of Bath School of Pharmacy and Pharmacology.

(ii) The UK Medicines Inspectors held their internal training sessions at the University of Bath School of Pharmacy.

(iii) The Medicines Inspectors were intrigued by the different approaches to plasma fractionation being taken at BPL and PFC and both centres were invited to make a presentation to the Inspectors.

(iv) I gave the presentation concerning PFC on 25th September 1980. Mr Watt attended the training session with me.

(v) I believe that he made contact with Brian Meakin at this point and engaged in a dialogue with him to explain that PFC was being "*seriously under utilised.*"

(vi) Dr Lane is incorrect when he claims that shift working at PFC was never accepted by the workforce. In 1977, it was the management side of the Whitley Council that had ruled against shift working at PFC, not the staff side. My evidence to the Penrose Inquiry on this (Penrose Inquiry transcript 10th May 2011, pages 82-83 [RLIT0001068]) was not included in the Final Report of The Penrose Inquiry, which instead repeated an incorrect statement from the Preliminary Report.

(vii) Staff at PFC knew that shift-working was intended, but they were not consulted, nor were they aware that the matter was being considered at national level in 1977, other than from brief reports of these meetings being given to the PFC Heads of Department by Mr Watt.

(viii) In 1981, the staff of PFC welcomed the opportunity of carrying out a shift working experiment, despite having to work two-12 hour shifts due to there being insufficient staff to operate 3-shifts.

(ix) Following the 1981 PFC shift working experiment, the relevant trades union official for Scotland acknowledged that shift working at PFC was inevitable (see para 66.2 (ix)) [SBTS0001455_012].

(ix) Dr Lane's statement is consistent with his opposition to plasma from England being processed at PFC (see para 66.2 (vii)) [SBTS0001455_012].

§338 of Dr Lane's Proof refers to a letter from the SHHD to the DHSS dated 11 January 1982 which Dr Lane states "*concluded that PFC would not be considered in the future planning of self-sufficiency in England and Wales.*"

a. Do you agree that this is the conclusion of the letter? If not, please provide your reasons. Dr Lane then attempts to summarise the letter and at §340 effectively dismisses the prospect of PFC fractionating sufficient amounts of English plasma.

b. Please set out your opinion on Dr Lane's views.

See my responses to question 66 ,69 and 71.

In your First Penrose Statement [§9.2] you refer to the transfer of 2.1 million iu of SNBTS Factor VIII concentrate to BPL in 1984. Please explain the circumstances in which that transfer was made, including:

a. Who proposed that this be done, and why.

b. What use was made by BPL of the Factor VIII concentrate (insofar as this is within your knowledge).

c. Whether there were any other such transfers, and if not, why not.

73 Comments

(i) I was not involved in this transfer, but can comment from my general knowledge of what took place.

(ii) Factor VIII concentrate had a shelf-life of two years, with stocks being held at Regional Transfusion Centres as well as at PFC.

(iii) Following the annual stock take circa March 1984, PFC Director Dr Perry realised that the SNBTS stock of FVIII concentrate was so high that batches would begin to outdate at the present rate of use.

(iv) Therefore, to avoid SNBTS FVIII outdating Dr Perry offered to provide some to BPL, to reduce the amount of commercial FVIII from the USA being used in England & Wales, which was considered to have a higher risk of transmitting AIDS.

(v) I do not know how BPL used this product.

(vi) Subsequently the application of heat treatment and planned closures for building modifications reduced the amount of FVIII concentrate in the SNBTS stock, such that the risk of out-dating ceased and there were no further transfers of Factor VIII to BPL.

What, in your opinion, were the principal reasons why the UK as a whole did not become self-sufficient in blood products? Please interpret "*self-sufficiency*" in this question to mean the production of sufficient blood products to allow all NHS patients to elect to use an NHS blood product on request, including for prophylactic use.

See my response to question 63 for details.

74. Summary

(i) Experts advising government in the early to mid-1970s failed to predict the amount of FVIII concentrate needed to treat people with haemophilia A.

(ii) Experts advising government made incorrect assumptions concerning the amount of factor VIII (yield) that could be obtained from plasma.

(iii) These errors combined meant that the amount of plasma required and the facilities needed to process it were greatly underestimated.

(iv) To the best of my knowledge, it was not until about 1981 that it was appreciated that the collection and processing of some 400,000 kg of fresh frozen plasma (FFP) per year would be required to achieve self-sufficiency for England & Wales [WITN6914044].

(v) At the same time, Dr Cash estimated that 57,000 litres of plasma were needed to treat people with haemophilia A in Scotland, using intermediate-purity Factor VIII concentrate (Penrose Inquiry document SNB.001.5076) [PRSE0004724].

(vi) Prior to the opening of the new BPL in 1987/88, the maximum capacity of BPL was about 150,000 kg plasma per year.

(vii) According to the Lord Glenarthur, in January 1984, output of FVIII concentrate from BPL was limited by plasma supply (see para 66.2 (xii) and PRSE0001727)

(viii) According to the Department of Health, BPL was able to process all of the plasma supplied until January 1985 (GFYF0000127 , page 25), thereafter it was the capacity of BPL that was limiting rather than the supply of plasma, until the new BPL facility opened.

What difference, in your opinion, would have been made to rates of HBV, HCV and HIV infection among NHS patients had self-sufficiency in blood products been achieved throughout the UK, or achieved earlier?

75.1 General

(i) To the best of my knowledge self-sufficiency (as generally defined, see my response to question 63) was never achieved in the UK as a whole.

75.2 Viral Infections

(i) To the best of my knowledge, according to data presented to UK HCDO, the incidence of infection with HBV was lower with Factor concentrates produced by NHS fractionators than with commercial concentrates, but was not zero.

(ii) To the best of my knowledge the incidence of infection with HCV was the same with Factor concentrates produced by NHS fractionators as with commercial concentrates, but the viral load was greater with commercial concentrates because of a higher prevalence of NANBH amongst commercial USA donors. I do not know if this had any impact on the disease or its progression in people with haemophilia.

(iii) To the best of my knowledge, the sub-types of HCV generally transmitted by products derived from UK-donors were different to HCV sub-types transmitted by products derived from USA donors, because of population differences in HCV sub-type distribution. I do not know if this had any impact on the disease or its progression.

(iv) To the best of my knowledge the incidence of infection with HIV was lower with Factor concentrates produced by NHS fractionators than commercial Factor concentrates from the USA, because HIV infection was more prevalent amongst USA donors as the USA was the epicentre of the AIDS epidemic.

Section 7: Commercial blood products and pharmaceutical companies

How well did commercial fractionators communicate with UK fractionators, regulators and haemophilia clinicians about the risks of using their products, including findings from clinical trials (published and unpublished)?

76.1 UK Fractionators

(i) To the best of my knowledge, commercial fractionators did not communicate the risks of using their products to UK fractionators directly as UK fractionators did not use or distribute their products.

(ii) UK fractionators obtained knowledge of the risks associated with commercial products indirectly; from the published literature, from presentations at conferences and symposia, from attending HCDO meetings and from leaflets issued with commercial products that were available from commercial sales booths present at conferences.

(iii) Similarly, UK fractionators learned of findings of clinical trials of commercial products from the published literature and from attending meetings, symposia and conferences.

76.2 Regulators

(i) To the best of my knowledge, commercial companies were required to inform the UK regulator of any risks associated with their products when applying for a product licence (marketing authorisation).

(ii) To the best of my knowledge, commercial companies were required to inform the UK regulator of any new risks concerning a licensed product.

(iii) I do not know how well this was done.

(iv) To the best of my knowledge clinical trials of commercial products had to be approved by the UK regulator under the CTX scheme (note: CTX is sometimes referred to as 'clinical trial exemption'. This does not mean 'exempt from clinical trial', it means 'exempt from the more onerous Clinical Trial scheme (CT) that had been established for new drug substances).

(v) I do not know if commercial companies were required to inform regulators of the results of their clinical trials.

76.3 Haemophilia Clinicians

(i) I do not know how well commercial companies communicated the risks associated with their products to haemophilia clinicians.

Did you have any concerns about commercial fractionators in respect of:

a. **Using NHS patients in clinical trials? Please comment on how, if at all, this affected the development of blood products produced at PFC and what, if any, steps were taken in response to any perceived issues.**
b. **Exerting undue influence over NHS haemophilia clinicians?**

77. Concerns over Commercial Fractionators

(i) I do not believe that the use of NHS patients in clinical trials by commercial fractionators affected the development of blood products produced by PFC.

(ii) Commercial products were licensed for use in the UK by the Committee on Safety of Medicines. Consequently, commercial companies were engaged in selling their products to their customers, with a sales force and product literature typical of commercial pharmaceutical companies.

(iii) I do not know if commercial fractionators exerted any "*undue*" influence over NHS haemophilia clinicians.

Section 8: HIV infections with PFC products

The Penrose Final Report analysed the numbers of patients infected with HIV in Scotland as a result of the use of blood products, including the number whose infections were attributed to PFC products [§3.263 to 3.315]. Lord Penrose accepted, with some caution, Dr Bruce Cuthbertson's evidence that it was likely that 25 people were infected with HIV through the use of PFC products, 19 in Edinburgh, four in Glasgow and two in Aberdeen [§3.308]. Please comment on those findings, in particular stating whether you consider them to be accurate. If you do not, please identify where and why you consider them to be inaccurate or potentially inaccurate.

(i) I had no involvement in collecting or processing data on the number of patients whose HIV infection was attributed to PFC products.

(ii) I am therefore unable to say if I consider them to be accurate or potentially inaccurate, with one exception.

(iii) During the Penrose Inquiry, SNBTS was given details of batches of Factor IX concentrate that had been used by a haemophilia B patient (given the pseudonym 'David') who was infected with HIV and who believed that he had only ever received Factor IX concentrate from PFC. The purpose of this request from the Penrose Inquiry was to see if SNBTS could identify the batch responsible for his HIV infection.

(iv) I remember Dr Cuthbertson pointing out that according to the information provided by the Penrose Inquiry, the last batch of FIX administered before the patient was found to be HIV+ve was not a PFC product. This was evident to Dr Cuthbertson because the style of the batch number was not one used by PFC.

79. Are you aware of any Northern Ireland patients who were infected with HIV as a result of blood products produced by the PFC? Please explain what steps, if any, were taken by the PFC to try to identify any such infections.

(i) I am not aware that any Northern Ireland patients were infected with HIV as a result of products produced by PFC.

(ii) The possible source of any HIV infection was determined by the treating physician.

(iii) PFC could not do this, as patient treatment records and their identity were confidential and not available to PFC.

(iv) If a treating physician believed that a PFC product might be implicated, it was their responsibility to notify PFC.

(v) To the best of my knowledge, if PFC believed that a batch of a PFC product was implicated in an HIV transmission it was recalled immediately and the centres to which it had been dispatched notified.

(vi) Any further information should be obtained from Dr Cuthbertson, as this was his area of responsibility at PFC

Section 9: Other issues

80.Can you direct the Inquiry to other evidence, or possible sources of evidence, in support of your answers and views to the above questions?

80.1 BPL History

(i) A history of BPL is available (Gunson H et al, Transf Med 1996, 6, (suppl.1) 37-58) [NHBT0000028].

80.2 USA Multi-District Litigation

(i) Additional documents available (see para 14.1 (xi)):

• A deposition by Dr H Schwinn who developed Beringwerke's method of pasteurisation [WITN6914045].

• An Expert Report by Dr Carol Kasper MD [WITN6914046].

• A Canadian legal judgement [MDUN0000020_250].

80.3 Personal Contributions

(i) I am the author or joint author of invited reviews of:

• Plasma Fractionation (NHBT0000236_013, WITN6914047 and WITN6914048)

• Freezing and Thawing Plasma (PRSE0000232], MDUN0000020_250)

• Protein Precipitation (WITN6914049)

• Formulation of Factor VIII solutions (WITN6914050)

• Virus Inactivation (PRSE0001156, WITN6914051, WITN6914052 and WITN6914053)

80.4 Section 6, Self-Sufficiency in Scotland and the UK

(i) To assist in responding to the questions in this section, I compiled a list of potentially relevant documents in chronological order in which the key points of each document are summarised, see WITN6914053.

81.Please explain, in as much detail as you are able to, any other matters that you believe may be of relevance to the Infected Blood Inquiry, having regard to its Terms of Reference and to the current List of Issues.

81.1 The Proposed Privatisation of BPL

81.1.1 Background

(i) BPL underwent its first Medicines Inspection in 1979, when it was concluded that it was not capable of complying with the DHSS Guide to Good Pharmaceutical Manufacturing Practice and that a new centre was required.

(ii) To address this issue, the incoming Government of Mrs Thatcher decided to explore the option of privatising BPL.

(iii) This was opposed by the Trades Union ASTMS and by investigative reporters from World in Action.

(iv) I was involved with the activities of both ASTMS and World in Action in this respect.

(v) Information on this was included in my evidence to the Penrose Inquiry (cited document 3, PEN.015.0101, pages 3-6) [PRSE0000545] .

(vi) The issue was not examined by the Penrose Inquiry.

81.1.2 ASTMS

(i) When I first learned of the plan to privatise BPL, I wrote to the full-time NHS ASTMS official for Scotland, Mr GRO-C to inform him of this.

(ii) Mr GRO-C notified ASTMS Head Office, resulting in Parliamentary Questions being submitted by Dr Maurice Miller MP in July 1980.

(iii) An ASTMS MP, Mr GRO-C sponsored a debate on the Blood Transfusion Service which was held in the House of Commons on 15th December 1980.

81.1.3 World in Action

(i) I attended a meeting at BPL in September 1980, where staff from PFC were met by the Director Dr Richard Lane who told us that Beecham's Ltd had visited BPL and were "*about to sign on the dotted line.*"

(ii) He appeared extremely depressed and resigned to BPL being sold to Beecham's.

(iii) Before returning to Edinburgh, I visited a friend in London and mentioned that BPL was about to be sold to Beecham's Ltd.

(iv) About two days later I received a phone call from Mr Laurie Flynn, a reporter from World in Action, who wanted to investigate the proposed sale of BPL to Beecham's.

(v) I told him everything that I knew and gave him the names of people who might be able to assist him further.

(vi) Mr Flynn subsequently visited PFC to speak to the Director Mr John G Watt.

(vii) Around late October 1980, I received a phone call from Mr Flynn at about 11pm to ask if he could come to my flat. I agreed and he arrived a few minutes later with his colleague Mr Michael Gillard.

(viii) Mr Flynn had with him a copy of the Medicines Inspection report of BPL. He refused to tell me how he had obtained it, but wanted my assistance in identifying and explaining the key issues.

(ix) Although I was aware of the report, I had not seen it before, but did my best to assist Mr Flynn and Mr Gillard.

(x) On 25th November 1980, Mr Flynn phoned to tell me that Mr Gillard had made an important discovery which they planned to feature in a World in Action programme scheduled for transmission on Monday 29th October 1980.

(xi) He explained that it was the policy of Granada Television that where a government minister was involved, they should be informed before transmission. He intended to do this the next morning.

(xii) Mr Flynn phoned back the following evening, to inform me that after hearing from World in Action, the minister had arranged for a Parliamentary Question to be tabled to which he replied "*...we have concluded that there is no place for a commercial company in the management of a service, which depends on volunteer donors.*" (Hansard, 26 November 1980, Written Answers, column 102 [PRSE0000063]).

(xiii) The World in Action programme that had been scheduled for transmission on Monday 29th October was withdrawn and a revised version was broadcast on 22nd December 1980.

81.1.4 <u>Possible Implications</u>

(i) Although I was not aware at the time, the plan of the Government was to allow Beecham's to import commercial plasma, which would inevitably have been obtained from the USA.

(ii) According to a memo from Dr Diana Walford of 15th September 1980 [WITN0282008]:
"... *the principal medical worry is presented by Beecham's intention to import plasma for fractionation. Unless it were Beecham's intention to process such plasma in an entirely separate plant or with complete duplication of facilities in a single plant, it would be impossible to prevent contamination of the UK material with imported hepatitis viruses.*"

(iii) As the output of FVIII from BPL was limited by its supply of plasma, it is conceivable that if the sale to Beecham's had gone ahead commercial plasma would have been imported to maximise output of FVIII concentrate by BPL, prior to the construction of a new facility.

(iv) This could have begun in 1981, with plasma being obtained from the USA co-incident with the emergence of the AIDS epidemic.

(v) Given the comment from Dr Walford that *"it would be impossible to prevent contamination of the UK material…",* it is conceivable that many more UK haemophiliacs could have been infected with HIV if the sale had gone ahead.

81.2 Clarification of Evidence to The Infected Blood Inquiry

81.2.1 The Inquiry Hearing of 9th June 2021.

(i) The report of the October 1981 Inspection of PFC (BNOR0000572) was considered at the Inquiry hearing held on 9th June 2021, with Counsel to The Inquiry reading from paragraphs 4.3 and 4.4 of the report (Inquiry transcript, 9th June 2021, page 151) [INQY1000126].

(ii) In respect of paragraph 4.3, Counsel to The Inquiry read *"a licence would not be recommended for an industrial equivalent unless agreed upgradings were instituted as a matter for urgency"* (transcript, page 151, lines 17-20).

(iii) I believe that this wording was designed to set out the authority held by the inspectors and that a statement of this type was probably included in all inspection reports. For example, if a commercial company was inspected, a statement of the inspector's authority would probably have been along the lines *"a licence would not be recommended unless agreed upgradings were instituted as a matter of urgency*". The inspectors were not able to use this particular form of wording with NHS facilities at this time due to Crown Immunity, hence the wording used in para 4.3.

(iv) I would also like to point out that during the oral evidence at the Infected Blood Inquiry on 9th June 2021, findings were quoted from a 1982 inspection report (BNOR0000573), without it being clarified that this report did not concern PFC, but a unit of the Edinburgh Regional Transfusion Centre at Edinburgh Royal Infirmary, a Victorian building some 4 miles from PFC (9th June 2021 transcript, page 152). The witness responded as though it were a report of PFC (9th June 2021 transcript, pages 153-157) making a specific reference to PFC, without being corrected (9th June transcript, page 156, line 13).

81.2.2 William Wright (Witness Statement)

(i) In his Witness Statement Mr William (Bill) Wright wrote that there was *"surprise expressed by SNBTS representatives that someone could be infected as late as 1986*" (Witness

Statement WITN2287019, paragraph 2.6).

(ii) I gave the presentation to which Mr Wright is referring and do not believe that the account given by Mr Wright is consistent with my presentation [WITN6914011], which explained that the Factor VIII concentrate supplied by SNBTS/PFC during 1986 was not free from a risk of transmission of HCV.

81.2.3 The Inquiry Hearing of 2nd November 2021

(i) In considering knowledge of the risk of AIDS and the actions taken by pharmaceutical companies, information was presented from a memoir published by Dr Bruce Evatt in 2006 (Journal of Thrombosis and Haemostasis 2006, 4, 2295-2301).

(ii) It may assist the Inquiry to know that some of the views of Dr Evatt were disputed by Dr Aledort (Aledort LM. Journal of Thrombosis and Haemostasis 2007, 5, 607-608; with a reply from Dr Evatt at pages 608-609).

81.2.4 The Inquiry Hearing of 10th November 2021

(i) During the presentation on Professor Cash, a letter written by him (PRSE0000462) that was critical of PFC was considered (transcript pages 41-44).

(ii) It may assist the Inquiry to know that The Penrose Inquiry asked SNBTS to comment on this letter. A response was prepared jointly by Dr Cuthbertson, Dr Perry and myself in which we refuted the comments made by Professor Cash and explained why we believed he had written them (PRSE0001919).

81.2.5 Addendum: Comments on The Fractionation Expert Group Report

I have had an opportunity to consider the Report of the Expert Group on Fractionation following notification by the Infected Blood Inquiry that the Report had been published on its document sharing platform, Relativity.

I would like to offer some comments on this Expert Report which may be helpful to the Infected Blood Inquiry.

A1. Page 20, lines 12-13.

"Cohn and colleagues developed a continuous system for separating plasma proteins into five major fractions."

Comment:

This statement is not correct.
Dr Cohn fractionated plasma via a sequence of steps using batch processing. Batch vessels used by Cohn for this purpose can be seen in photographs of Cohn's Harvard pilot plant facility and that of an industrial collaborator (WITN6914067).
(Note: These photographs were copied from 'A Collection of Pamphlets prepared for Publication by Edwin J Cohn, 1952' and 'Edwin J Cohn, A History of Plasma Fractionation, in Advances in Military Medicine, 1948').

The successful application of continuous-flow processing to plasma fractionation was first achieved in 1975 at PFC in Scotland, which, to the best of my knowledge, has been the only successful application of this approach to the fractionation of plasma using Cohn's cold-ethanol system.

See my Witness Statement, page 151, sections 66.1(iv) to 66.1 (xi).

A2. Page 55, lines 30-31.

"...strict compliance with Good Manufacturing Practice, quality assurance guidelines and regulations is required."

Comment:

For completeness, GMP regulations for the UK were published from 1971 by the Department of Health and Social Security, the Scottish Home and Health Department and the Department of Health and Social Services for Northern Ireland (Sharp JR, Editor. Guide to Good Pharmaceutical Manufacturing Practice, HMSO London).

See my Witness Statement, page 28 sections 19.1 (i) to 19.1(iii).

A3. Page 56, lines 12-15.

"Since the late -1980s, materials and equipment have improved considerably, with introduction of pressured self-cooling stainless steel closed tanks, large-scale continuous low-speed centrifugation, and refrigerated multi-chamber centrifuges, usually of the Westphalia type."

Comment:

For completeness., the refrigerated Westphalia multi-chamber centrifuge was developed by Westphalia AG in conjunction with PFC in 1973/74 and used routinely at PFC from 1975.

See my Witness Statement page 21, section 16.2 (i).

A4. Page 61, lines 19-20 and page 79, lines 13-14.

"In 1983, dry heat treatments were introduced in coagulation factor products to protect against HIV." **(page 61, lines 19-20)**

"Initially, dry heating at 60 to 68ºC for up to 72 or 96 h was applied to coagulation factor concentrates to inactivate HIV." **(page 79, lines 13-14).**

Comment:

It is important to note that both of these assertions are incorrect.

Limited clinical studies of dry heat treated Factor VIII concentrates were initiated in June 1983, to determine if infection with non-A, non-B hepatitis could be prevented. To the best of my knowledge, these studies were undertaken in the USA, the UK, Italy, West Germany and France (see my Witness Statement page 43 section 28.2(ii).

These dry heat treatments failed to prevent NANBH infection in previously untreated patients. Consequently, Factor VIII concentrates that had been dry heat treated were not licensed for general use in the UK at this time.

Evidence that HIV could be inactivated by similar dry heat treatments became available in late-1984 and dry heat treated Factor VIII concentrates were licensed for general use in the UK in 1985.

For a correct account, with supporting references, see my Witness Statement, page 98, section 43.12 (v).

A5. Page 61, lines 20-21.

"In 1987, solvent-detergent treatment became available against HIV, HBV and HCV in almost all products."

Comment:

For completeness, data demonstrating absence of HCV infection in previously untreated patients who had been treated with solvent-detergent treated Factor VIII concentrate were first published in 1989 (Noel L, et al. Lancet 1989, ii, 560; [WITN6914068])

See also my Witness Statement, page 55 sections 33.3 (x) to (xi).

A6. Page 87, line 20.

"Between 1994-1998, treatment at low pH (eg. pH 4) in the presence or absence of pepsin was originally developed to disaggregate immunoglobulin polymers."

Comment:

For completeness, pH 4 treatment was introduced at PFC in 1983. Although this process was used to disaggregate immunoglobulin polymers, it was done in the knowledge that pH 4 treatment also represented a virus inactivation step.
(Welch A, et al. Lancet 1983, ii,1198; [WITN6914069]; Reid KG et al. Vox Sang 1988,55,75-80: [WITN6914070]).

Statement of Truth

I believe that the facts stated in this witness statement are true.

Signed GRO-C

Dated 7 March 2022

Table of exhibits:

Date	Notes/Description	Exhibit number
August 2021	Curriculum Vitae of Peter Reynolds Foster	WITN6914002
November 2010	Foster PR, *SNBTS Briefing Paper on the Development of Heat Treatment of Coagulation Factors*	PRSE0002291
October 2009	SNBTS, Events Concerning the Safety of Blood and Blood Products with Special Reference to the Treatment of Haemophilia	PRSE0003480
2008	Foster PR et al. *Fractionated Products.* In: Transfusion Microbiology, (eds Barbara JAJ, Regan FAM, Contreras MC) Cambridge Univ Press. 2008, pp 259-303.	WITN6914003
2 July 2011	Foster PR, Revised Response to a Request of 28 April 2011 from Mr A Evans of the Penrose Inquiry Concerning Topic B3	PRSE0001478
8 November 2011	Foster PR, Addendum to Self-Sufficiency and the Supply of Blood Products in Scotland	PRSE0003147
September 2007	Foster PR. Submission to the Archer Inquiry. Examples of warnings issued with coagulation factor concentrates	PRSE0002726
September 2007	Foster PR. Submission to the Archer Inquiry. Testing Coagulation Factor concentrates for HIV-Contamination	WITN6914004

September 2007	Foster PR. Submission to the Archer Inquiry. The Discovery that HIV could be destroyed by Dry-Heat Treatment	PRSE0001214
27 September 2007	Franklin IM, Foster PR, SNBTS Submission to the Archer Inquiry. Cryoprecipitate and Hepatitis.	WITN6914005
	Foster PR. Submission intended for the Archer Inquiry. Failure to use PFC.	WITN6914006
2011	Penrose Inquiry transcript 10th May 2011, pages 82-83	RLIT0001068
19 July 2001	Foster PR. Transcript of Evidence to the Lindsay Tribunal of Inquiry. LIND0000320	LIND0000320
11 November 1975	Letter from JG Watt to J O'Riordan proposing that plasma from ROI be processed at PFC.	WITN6914007
12 August 1997.	Foster PR. Transcript of evidence in the USA Multi-District Litigation, MDL-986.	WITN6914008
1986	Cheinsong- Popov et al. *Retrovirus infections among patients treated in Britain with various clotting factors* Br Med J 1986, 293, 168-9	BAYP0000008_303
15 Sept 2005.	Foster PR. Response to questions from US attorney D Barr concerning HIV in the UK.	WITN6914009
21 November 2005	Foster PR. Response to questions from US attorney D Barr concerning impediments to the development of solvent-detergent technology.	WITN6914010
1995	Meisel et al, *Transmission of hepatitis C virus to children and husbands by women infected with contaminated anti-D immunoglobulin*, Lancet 1995, 345, 1209-11	DHSC0002549_067

August 1995	Foster PR et al, *Hepatitis C infection from anti-D immunoglobulin*, Lancet 346	HSOC0010138_003
25 November 1999.	Foster PR. Presentation to the Haemophilia Society on the Development of Heat Treatment by SNBTS.	WITN6914011
9 December 1999.	Foster PR, McIntosh RV. Report to the Scottish Executive Investigation on the Development of Heat Treatment at PFC.	PRSE0000131
February 2000	Additional Information from SNBTS to the Scottish Executive Investigation.	PRSE0001249
October 2000	Scottish Executive. Report of the Investigation into hepatitis C and Heat Treatment of Blood Products.	GGCL0000010
14 March 2001	Health & Community Care Committee (HCCC) of the Scottish Parliament. Transcript of Evidence to an Inquiry on Hepatitis C and the Treatment of Blood Products.	WITN6914012
May 2001.	SNBTS. Follow up submission to HCCC Inquiry on Hepatitis C and the Treatment of Blood Products.	WITN6914013
26 September 2001	HCCC. Final Report of an Inquiry on Hepatitis C. SP Paper 398.	WITN6914014
February 2016	Foster PR. *The Manufacture of blood plasma products in Scotland: a brief history.* Scot Med J 2016, 61, 34-41.	WITN3530032
15 December 2005	Answer to Scottish Parliamentary Question, SPQ A2W-20899.	WITN6914015
1977	Guide to Good Pharmaceutical Manufacturing Practice 1977	PRSE0002339

1983	The Guide to Good Pharmaceutical Manufacturing Practice (Third Edition)	SBTS0000423_004
26 October 1981	Medicines Inspectorate report on the current status at the Protein Fractionation Centre, Edinburgh	BNOR0000572
1 October 2011	McIntosh, RV (2011) The regulation of the manufacture of medicinal products derived from blood plasma and the preparation of blood and blood components by the SNBTS	PRSE0002556
1979	DHSS. *Standards for Collection & Processing of Blood and Blood Components and the Manufacture of Associated Sterile Fluids.*	PRSE0003128
17 July 2021	Written statement of Norman Fowler	WITN0771001
1977	Gerety R J, Barker LF. *Viral antigens and antibodies in hemophilia*. In: Proc Unsolved Therapeutic Problems in Haemophilia (eds Fratantoni JC, Aronson DL) DHEW Publ No. (NIH) 77-1089, pp. 45-50	BAYP0000020_004
16 July 1982	MMWR Weekly, "Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among persons with Hemophilia A"	PRSE0000523
2 September 2011	Witness statement of Dr Perry regarding Hepatitis C - Viral inactivation 1985-1987 to Penrose Inquiry	PRSE0001258
1 September 2010	Penrose Preliminary Report	PRSE0007003
1 March 2015	Penrose Final Report	PRSE0007002
2002	Surgenor DM, Edwin J Cohn and the Development of Protein Chemistry, Centre for Blood Research, Boston, 2002, page 223	WITN6914055

2017	Weinberg E, Shaw D. Blood on Their Hands, Rutgers University Press, 2017, pages 95, 118	WITN6914057
28 September 1985	Wet heating for safer factor VIII concentrate?". P. B. A. Kernoff, E. J. Miller, G. F. Savidge, S. J. Machin, M. S. Dewar and F. E. Preston	RLIT0000186
2 November 1985	Lancet article "NANB Hepatitis after Factor VIII Concentrate treated by heating and chloroform' by P.M Mannucci, M. Colombo and F. Rodeghiero	BAYP0000007_139
1987	Kernoff PBA et al. Br J Haematol. 1987, 67, 207-211	WITN6914056
14 October 1982	Minutes of Factor VIII Study Group meeting	PRSE0002206
1 January 1985	Transfusion: "Inactivation of viruses in liable blood derivatives, I. Disruption of lipid-eveloped viruses by tri(n-butyl)phosphate detergernt combinations", by B. Horowitz et al, 1985.	BAYP0000024_063
9 February 1982	Shanbrom E. *Purification of plasma protein products.* USP 4,324,997.	BAYP0000018_021
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