I, Peter Reynolds Foster say as follows:-

1. a). The covering letter concerning my witness statement on ‘AIDS/HIV – Viral Inactivation to 1985’ states:

   “While your clients may derive some assistance from the Preliminary Report, the Report may not include all material relevant to the matters in respect of which a statement is sought, in which case your client should include in the statement any material your client considers relevant to these matters, whether contained in the Preliminary Report or not.”

b). I have prepared a paper concerning virus inactivation of plasma products to assist the SNBTS in responding to enquiries from the Penrose Inquiry on this topic. This paper contains materials relevant to the matters in respect of which a statement is sought and which are not contained in the Preliminary Report. I have therefore included this document with my witness statement (Appendix A).
c). The remainder of my witness statement is set out according to each of the 36 'Snapshots and Landmarks' which have been provided to identify the 'Matters to be included in the statement'. A list of the documents which I have cited, and which have not been identified by the Inquiry, is also appended (Appendix B).

2. Snapshots and Landmarks. 1.

My Response

a). Research relating to removal of the hepatitis B virus from Factor IX and from Factor VIII concentrates was undertaken at the PFC during the 1970s, with both projects being collaborations with Dr A J Johnson at New York University Medical Center.

b). Both projects concerned removal of the hepatitis B virus, as this was the only virus known to be transmissible via plasma products at that time. In addition, a marker for the hepatitis B virus (the hepatitis B surface antigen, HBsAg) was available which enabled the distribution of the virus during plasma fractionation to be tracked.

c). Although screening of blood donors for evidence of hepatitis B infection had been introduced by the SNBTS in 1970/71, it was Dr Johnson who explained to me that the sensitivity of screening was insufficient to remove all infective donations and that coagulation factor concentrates prepared from pooled plasma donations could still be potentially infective.

Factor IX

d). The first of these projects concerned the separation of the hepatitis B virus (HBsAg) from factor IX by precipitation of the virus with polyethylene glycol (PEG) and is the project described in the 1973 abstract cited on page 11 of the 1975 R&D report [SNB.010.4779].
e). Although I was not immediately involved in this project when I joined PFC, I had studied PEG precipitation during my PhD project and I was aware that PEG could be used to precipitate viruses in general and was therefore not “related to the hepatitis B virus” only, but was also applicable in principle to other viruses. I was also aware that PEG precipitation could be used to separate large biological macromolecules from smaller biological macromolecules and I had published a paper concerning the fundamental principles on which this procedure was based (Foster et al. Biochimica Biophysica Acta 1973, 317, 505-516).

f). Factor IX prepared experimentally in the USA by this procedure, from plasma known to contain hepatitis B infectivity, was tested by Dr Johnson in chimpanzees. The chimpanzees developed hepatitis B, demonstrating that hepatitis B infectivity had not been fully removed (Johnson et al. J Lab Clin Med 1976, 88, 91-101).

g). Dr Johnson subsequently refined the precipitation parameters (the revised method being known as the mark II method) to obtain greater removal of the hepatitis B virus. However, he told me that his application for funding for another chimpanzee study, to discover if the removal of hepatitis B infectivity had been successful, was rejected by the USA National Institute of Health (NIH) because they considered that ‘hepatitis is no longer a problem’.

h). Another issue that arose with factor IX prepared by the first (mark I) version of the method was a thrombogenic reaction in dogs (Cash et al, Thromb Diath Haemorrh. 1975, 33, 632-639) [LIT.001.0959], suggesting that the product might be harmful to patients. Alternatively, this may have been a consequence of the
very high dose of factor IX that had been administered in this study, as this product was more concentrated than established Factor IX concentrates.

i). At first, this project was led at the PFC by Dr James K Smith (PFC Deputy Director) with support from Mrs Sarah Middleton (PFC research scientist). Dr Smith left PFC to take up a post at PFL (Oxford) in 1975 and Mrs Middleton left in 1976, taking a position in the Haematology Department at Glasgow Royal Infirmary. Thereafter, I led further research at PFC on this project. This primarily concerned a study of the potential thrombogenicity of the product using laboratory tests designed for this purpose. The results showed that, according to these tests, processing using the mark II procedure did not increase the product thrombogenicity but reduced it (Foster et al. Thrombosis Research 1980, 17, 273 – 279) [LIT.001.0208].

j). This finding allayed concern that the product might be thrombogenic in humans and led to the product (Supernine) being evaluated in a small number of patients. However in discussions over the licensing of Factor IX concentrates, the Medicines Control Agency advised that only one SNBTS Factor IX concentrate should be licensed, implying that if a licence was granted to Supernine, then the licence for the established SNBTS Factor IX concentrate (DEFIX) would be withdrawn.

k). There was a preference for DEX to be retained (paragraph 11.143) as this had been very successful in the treatment of haemophilia B. Research on the pasteurisation of factor IX was being undertaken at the PFC and, by November 1983, was regarded as being much more likely to eliminate the risk of hepatitis than PEG precipitation. To the best of my knowledge, no further batches of Supernine were manufactured at the PFC.
Factor VIII

i). The PEG precipitation method of Dr Johnson was not applicable to Factor VIII, as separations using PEG were based on the difference in size of the macromolecules to be separated (ie. separation of virus from protein). The factor VIII complex was much larger than the factor IX molecule and could not therefore be separated from the hepatitis B virus (or any virus) by PEG precipitation. However, knowledge of the molecular structure of the factor VIII complex was embryonic at this time and the PEG method might ultimately have been applicable to Factor VIII when the structure of the molecule was better known.

m). In his report of December 1973 (last page, paragraph (c)) Mr Watt included “Methods using specific polyelectrolytes” as a “candidate for investigation”. This method concerned a procedure for the purification of factor VIII which had been devised by Dr Johnson using a solid-phase polyelectrolyte [SNB.008.5658] (paragraphs 11.29 and 11.43) to which factor VIII could be preferentially attached, whilst other substances (including viruses) were not attached and could in theory be removed by washing the solid-phase prior to desorption (ie. detaching) of the factor VIII from the polyelectrolyte.

n). PFC scientists worked on the solid-phase polyelectrolyte method with Dr Johnson in the early 1970s, providing material and resources to support the project. At the PFC, this project was led by Dr Smith with support from Mrs Middleton. In addition to undertaking research at PFC in Edinburgh, Mrs Middleton was seconded to New York for a number of months to work on the project with Dr Johnson.

o). The specialised reagents (polyelectrolytes) were provided by Monsanto for research only. Interest in the project caused
Monsanto to consider entering the business of plasma fractionation itself, using their polyelectrolytes to obtain a proprietary advantage. The company was therefore unwilling, at this time, to confirm that they would be prepared to licence-out use of their polyelectrolytes for the manufacture of plasma products. The project was discontinued by Mr Watt, primarily, I believe, because of the uncertainty surrounding the availability of the polyelectrolyte reagents for routine production.

p). I was not directly involved with this project, but I was briefed on progress verbally by both Dr Johnson and by Mrs Middleton. However, I was advised that the agreement with Monsanto required the project to be carried out under strict confidentiality and that all written reports were held securely and either destroyed or returned to Monsanto. It is therefore unlikely that any papers relating to this project have been retained by the SNBTS.

q). Subsequently Mrs Middleton joined Speywood Laboratories where she and Dr Johnson introduced the polyelectrolyte procedure for the preparation of porcine factor VIII (named Hyate-C) for the treatment of patients with inhibitors (i.e., antibodies) to human factor VIII. The polyelectrolyte procedure was more suited to processing porcine plasma than human plasma, as the plasma of pigs has a much higher level of factor VIII than that of humans.

r). The method was examined with human plasma at the BPL (paragraph 11.42) in conjunction with Dr Johnson and Mrs Middleton at Speywood Laboratories (Tuddenham et al, Br J Haematology 1982, 52, 259-267) but was not adopted by the BPL.
s). The procedure was also used by Mrs Middleton to assist Dr Tuddenham in the preparation of monoclonal antibodies to factor VIII (Rotblat et al, J Lab Clin Med 1983, 101, 736-746) and in the purification of factor VIII (Rotblat et al. Biochemistry 1985, 24, 4294-4300), advances which contributed to the development of recombinant Factor VIII (paragraph 3.36), now the principal product used to treat people in Scotland with haemophilia A.

t). Dr Johnson utilised the knowledge gained from his work with solid-phase polyelectrolytes to devise an improved purification process which used a solid-phase (chromatography) reagent which was already commercially available. This was the subject of the collaboration with the PFC that was initiated in 1983 (paragraph 11.135).

Other Initiatives During the 1970s

u). Given the difficulties associated with removing viruses using either PEG precipitation or polyelectrolyte adsorption, I believed that fundamental research was required to discover a means of eliminating the risk of hepatitis transmission associated with coagulation factor concentrates. I therefore approached research groups at a number of UK Universities to encourage them to undertake research on this topic, but without success.

v). I particularly remember visiting the Department of Biochemistry at the University of Bristol Medical School in the late-1970s. The Department, under Dr John Holbrook, was engaged in research on human coagulation factors and was already collaborating with the PFC, which was providing him with materials for his research (for example, see acknowledgements on page 410 of Freyssinet et al. Biochem. J. 1978, 169, 403-410) and sponsoring a research student in his Department. However, my suggestion that the group might
undertake research to discover a means of eliminating the risk of hepatitis from Factor VIII concentrates was met with disbelief by his research team and I was never invited back.

w). The research student (Dr Peter Feldman), who was sponsored by the PFC, did spend some time at the PFC to complete his PhD thesis. After completing his PhD, he joined PFL (Oxford), where he worked under Dr Smith on the heat treatment of factor IX, and is currently a senior scientist at the BPL.

x). Another initiative pursued at the PFC during the late-1970s involved the concept of obtaining factor VIII from human cell culture rather than from blood donors. This concept was first proposed by Mr Watt in 1977 and led him to appoint the research scientist Dr Alex MacLeod to work on cell culture technology and coagulation factor developments. This was regarded as a long term project and depended on the site of synthesis of factor VIII being discovered and a suitable human cell line becoming available (Macleod AJ. Nature 1980, 285, 136). In the event, this approach was superseded by the development of recombinant technology in which human factor VIII was produced in animal cells (paragraph 3.36), an approach which was considered to be too complex and expensive for the PFC to pursue.

3. **Snapshots and Landmarks, 2.**

**My Response**

a). This is the project described above, which utilised PEG precipitation for the removal of hepatitis B virus from Factor IX concentrates.

b). A variety of chemical and physical procedures for inactivating the hepatitis B virus, without destroying coagulation factors, had
been explored by earlier investigators without success (see Appendix A, section 1.2 for details). These failures led to a belief that inactivation of the hepatitis virus in coagulation factors was not possible and that safety was more likely to be achieved by devising a suitable method for removing the virus by physical means. It was for this reason that "steps of processes designed to inactivate the virus" were not pursued at the PFC at this time.

c). This is essentially the situation which pertains today concerning the risk of transmission of vCJD (paragraph 5.127) as plasma products do not survive the procedures that are known to destroy the agent responsible for vCJD.

4. Snapshots and Landmarks. 3.
My Response

a). I do not know if Dr McClelland was the representative of Edinburgh and South East Scotland BTS at this meeting or not.

b). In paragraph 3.3 of the minute of the meeting [DHF.002.4845], I believe the comment on β-propiolactone concerned the work of the German company Biotest (not Bayer) which was reported at the 1982 ISBT Congress (paragraph 11.72). Research using β-propiolactone was not new. It had not previously been successful (see Appendix A, section 1.2) and is unlikely to have been pursued in the UK, because β-propiolactone was known to be a carcinogen, a fact noted in the minute. Ultimately, Biotest failed to develop a Factor VIII concentrate using this procedure. A Factor IX concentrate (PPSB) was produced by the company using this procedure, but was discontinued following the transmission of HIV (Karcher H, BMJ 1991,303,1352-3).
c). In paragraph 3.4 of the minute [DHF.002.4845], the reference to work in the USA on the removal of viruses concerned the polyelectrolyte method of Dr Johnson, with which the PFC was already familiar (see my response in 2 above).

d). I was not aware of this meeting until I read the Preliminary Report (paragraph 11.41). However, had I been aware of the minute, I do not believe that it contains any information that would have influenced our strategy at the PFC. If Mr Watt was aware of this minute, I would not have expected him to bring it to my attention for the same reason.

5. **Snapshots and Landmarks. 4.**

**My Response**

a). I believe that the symposium in Bonn that was attended by Dr Cash (paragraph 11.49) was the first public disclosure of the work of Behring on the pasteurisation of factor VIII. An abstract of this presentation was not published until 1981 (Heimburger N et al. Haemostasis 1981, 10 (Suppl.1), 204) [SNB.007.3300].

b). The 1980 paper of Heimburger [SNB.004.5880] cited the Bonn presentation (reference 12) and must therefore have been written afterwards. Therefore, Dr Cash and the other attendees of the symposium in Bonn in October 1980 would have been first to learn of this development.

c). I was informed directly by Dr Cash that Behring had claimed to be able to pasteurise factor VIII. This was the first time I had heard of this claim and was before I saw his letter of 27 October 1980 to Mr Watt [SNB.007.2646]. I am not aware that anyone at the PFC knew of this work by Behring prior to the information from Dr Cash.
d). I was quite shocked when I heard of this claim, as the notion that factor VII might be able to be heat treated under conditions that would destroy hepatitis viruses was inconceivable to me. There were a number of reasons for this.

e). I had studied Biochemical Engineering at University College London under Dr FC Webb. In his seminal textbook, Dr Webb had taught "Albumin can be pasteurised at 60°C for 10 hours but the other fractions are heat labile." (Webb FC. Biochemical Engineering. London: Van Nostrand Ltd, page 450, 1964) [PEN.012.1480].

f). My PhD project at University College London concerned the study of methods of protein fractionation. I learned that proteins could be easily damaged by heat and that it was considered good practice to work at low temperatures, especially with proteins that were labile (ie. easily damaged). According to the eminent scientist Dr EJ Cohn "the conditions that should be obtained during the purification of proteins should approach as closely as possible those of the native state, except that the temperature should be low." and "The temperature should be kept as low as possible and far lower than body temperature if the actions of the enzymes and tissue extracts are to be avoided. Even room temperature is too high for most stages in protein purification, which is best carried out as close to the freezing point as possible......." (Cohn EJ and Edsall JT. Proteins, Amino Acids and Peptides, New York: Reinhold Publishing, page 570, 1943) [PEN.012.1487].

g). During my career I had worked with a number of proteins from different sources, such as enzymes from yeast and from bacteria as well as a number of different proteins from human plasma. In my experience, factor VIII from human plasma was
considerably more sensitive and more difficult to work with than any of the other proteins that I had encountered, making it an implausible candidate for research on heat treatment.

h). The PFC process for the manufacture of Factor VIII concentrate was based on the method of Newman and Johnson [SGF.001.1913] (paragraph 1.38). One advance described by Newman and Johnson concerned the filtration of the factor VIII solution using a membrane filter to retain (ie. remove) bacterial contaminants, something which had not been possible previously. In the method described in their paper (page 8, line 16) Newman and Johnson performed this filtration at 30°C.

i) At the PFC, this filtration was performed at 20°C, but high losses of factor VIII activity were experienced at this step. Dr Johnson advised raising the temperature of the factor VIII solution to 30°C as described in his paper. This was done, only to discover that there was an even greater loss of factor VIII activity at the higher temperature. The temperature was returned to 20°C and alternative investigations were undertaken to resolve the difficulty with filtration. However, this experience confirmed to me that factor VIII was sensitive to an increase in temperature and that loss of factor VIII activity was temperature dependent.

j). I do not know who else Dr Cash informed about the reported pasteurisation of Factor VIII by Behring. I do remember a conversation with Dr Boulton, in which he indicated to me that he did not believe that it could possibly be true and that he thought it would eventually be found to be a mistake.

k). Similarly, in December 1983, the distinguished medical scientist Professor J Garrott Allen of Stanford University Medical
Center wrote to Dr Anne Welch at the PFC to express his surprise, stating “The method I developed which eradicated the activity of the hepatitis viruses B and non-B in plasma, but also inactivated the labile clotting factors, especially factor VIII, was to incubate it at 32°C for 6 months. My question is, how can Factors II, V, and VIII be sufficiently preserved at 60°C to be clinically useful, and yet be free of the hepatitis viruses B and non-B?” [SNB.007.4036] My reply to Professor Garrott Allen [SNB.007.4287] is included in the Preliminary Report, paragraph, 11.169.

I). A similar view was expressed by leading authorities from the FDA, Dr L Barker and Dr J Hoofnagle who stated “Treatment of the final product to remove infectivity would also be a satisfactory means of dealing with the problem of hepatitis associated with plasma derivatives. Unfortunately the methodology of removing hepatitis B virus without destroying desirable plasma proteins is not available except in the case of plasma protein fraction and albumin where heating apparently eliminates infectivity. Methods such as ultraviolet irradiation, treatment with beta-propiolactone and controlled heating in doses that do not denature plasma proteins have been evaluated in the past and may reduce but do not eliminate infectivity.” (Barker LF and Hoofnagle JH. Developments in biological Standardization 1974, vol. 27, page 184 of pages 178-188).

6. Snapshots and Landmarks. 5.
My Response
a). The research at the PFC on the pasteurisation of coagulation factors was a direct response to information obtained concerning the procedures being used by Behring. I was not
aware of any development "in the rest of Europe" other than the work of Behring.

b). The objective at this time, and throughout most of the period covered by this witness statement, was to inactivate agents responsible for hepatitis transmission, including agents responsible for the transmission of non-A, non-B hepatitis (NANBH). It was not until late-1984 that it was discovered that the agent responsible for transmission of AIDS could be inactivated by heat treatment procedures that were compatible with coagulation factor concentrates.

c). Information on the procedures being used by Behring was contained from the 1981 paper of Heimburger et al. [SNB.008.6794]. This paper was published in April 1981. I obtained a reprint in May 1981 from the Behring stand at a trade exhibition that was held in conjunction with a symposium in Cambridge on 'Advances in Blood Transfusion', that was organised for transfusion directors by Travenol Ltd. Mr Watt, the PFC Director, was unable to attend and had asked me to attend in his place.

d). This paper was written in German. To obtain a translation, I gave it to Dr AJ MacLeod, a research scientist in my department. Dr MacLeod was involved in a collaboration with Dr Werner Zolg, a German post-doctoral researcher at Edinburgh University, who I thought might be willing to translate the paper.

e). Shortly afterwards, I was taken ill and did not return to the PFC until mid-October 1981. On my return, I discovered that Dr MacLeod had not only obtained the translation from Dr Zolg, but had begun a set of experiments to see if he could reproduce the findings of Behring. According to his laboratory notebook, he
began his experimental work on pasteurisation of factor VIII on the 2nd September 1981. When I returned from illness, I was delighted to discover that Dr MacLeod had taken this initiative and I encouraged him to continue this research.

7. Snapshots and Landmarks, 6 and 7.

My Response

a). The early research of Dr MacLeod was essentially exploratory and aimed to confirm the findings of Behring and to establish whether or not the approach taken by Behring might be feasible and suitable for the PFC to pursue.

b). Dr MacLeod summarised his initial findings in a PFC R&D report dated 10th February 1982, entitled "Preliminary studies on the heat treatment of PFC FVIII concentrate" [PEN.012.1489] in which he concluded that further purification of the PFC Factor VIII concentrate (NY) was required if pasteurisation were to be applied.

c). The first meeting of the Factor VIII Study Group was held on the 28th January 1982, some two weeks before Dr MacLeod had completed his preliminary evaluation. I am sure that Dr Cash was aware of our work on pasteurisation when he arranged the first meeting of the Factor VIII Study Group but, as the exploratory experiments of Dr MacLeod were incomplete, it is understandable that he did not include this topic in the agenda of the first meeting of the Group.

d). Similarly the meeting of the Safety Action Group of 9-10 February 1982 (paragraph 11.57) preceded the report of Dr MacLeod.

e). I had, by 1982, obtained the abstract of the 1980 Bonn presentation by Behring (Heimburger N et al. Haemostasis
1981, 10 (Suppl.1), 204) [SNB.007.3300]. This abstract gave the yield of factor VIII as 8% (paragraph 11.57), which was less than \(\frac{1}{3}\)rd of the yield then being obtained at the PFC.

f). The immediate challenge was therefore two-fold. To discover a means of increasing purity to allow the pasteurisation process to be applied, whilst at the same time substantially increasing the yield of the overall process, including the pasteurisation stage, to enable the SNBTS to provide the quantity of factor VIII concentrate required.

g). Whether or not the pasteurisation process would be effective against hepatitis viruses was uncertain. How this might be determined became a major consideration of the Safety Action Group.

8. Snapshots and Landmarks. 8.

My Response

a). The 1982 ISBT Congress was held in Budapest on 2-5 August. I obtained all of the documents cited from the trade stand of Behring at the commercial exhibition that was held in conjunction with the Congress. These included a paper that had been published on 16 July 1982 [SNF.001.0921] as well as a typewritten version [SNF.001.0929] of the 1980 paper of Heimburger et al. [SNB.004.5880]. I am not sure when I obtained the printed version of the 1980 paper by Heimburger et al. [SNB.004.5880], but I believe that this was most probably from the Behring trade stand at either the Congress of the World Federation of Hemophilia in 1983 or the ISBT Congress in 1984.

b). It was also at the 1982 ISBT Congress that I first learned of the concept of applying heat treatment to coagulation factor concentrates in the freeze dried state (ie. dry-heat treatment).
These were listed in the programme as poster presentations at which the authors would be present to answer questions on their work. In the event, the posters were not displayed nor were the authors present at the poster session to answer questions.

c). It was also at the 1982 ISBTS Congress that Hyland/Baxter announced that they had developed a heat treated Factor VIII concentrate. The method of heat treatment was not disclosed at the Congress. Some months later, Dr Chris Prowse of the SNBTS learned from Dr Henry Kingdon, the Medical Director of Hyland/Baxter, that the procedure involved dry-heat treatment at 60°C. What had been done to enable the Hyland/Baxter Factor VIII concentrate (Hemofil) to withstand this degree of heat treatment was not disclosed and, to the best of my knowledge, has never been disclosed.

My Response
a). Although I was not a member of the Safety Action Group, I believe that there were three principal reasons why pasteurisation was, by 14 October 1982, “the first option of the group”.

b). The first reason concerned the promising results that had been presented by Behring at the ISBT Congress in August 1982.

c). The second reason was the discovery of a suitable means of reducing the fibrinogen content of Factor VIII. This discovery had been made at PFC in conjunction with Dr Milan Bier of the University of Arizona and involved the addition of zinc, which preferentially caused fibrinogen to precipitate, whilst leaving factor VIII in solution (Bier M & Foster PR. USA Patent 1983,
No. 4,406,886). This discovery enabled the purity of factor VIII to be increased prior to pasteurisation with little loss of yield and addressed the need for an increase in purity which Dr MacLeod had identified in his report of 10th February 1982. This was the "high purity product" that was noted in the minute of the meeting of the Factor VIII Study Group of 14th October 1982.

d). The third reason was the promising results that Dr MacLeod had obtained using sorbitol instead of sucrose to stabilise factor VIII during pasteurisation (paragraph 11.85), which reduced the loss of factor VIII during the heat treatment process.

e). The method discovered at Behring, that enabled coagulation factors to be pasteurised, was quite different to the method that was used for the pasteurisation of albumin, despite both procedures being performed at 60°C for 10 hours.

f). The discovery that enabled albumin to be pasteurised stemmed from a fortuitous observation by Dr J Murray Luck at Stanford University that the thermal stability of albumin was higher in the presence of acetate than in chloride. This observation led to the discovery of a series of chemicals that could dramatically increase the stability of albumin, the addition of which enabled albumin to be pasteurised for 10 hours at 60°C.

g). The pasteurisation of albumin was first introduced in the USA in 1945, but the chemical stabilisers were not able to stabilise other plasma proteins, including the coagulation factors. According to Dr J Edsall in 1984, "It is a striking fact that serum albumin remains unique in its capacity for binding anions with attached nonpolar groups and for the resulting resistance to heat denaturation. No other protein, as far as I know, has been
found to resemble it in this respect." (Edsall JT. Vox Sanguinis 1984, 46, 338-340).

h). The discovery at Behring of chemical additives which could stabilise coagulation factors to withstand heating in solution (pasteurisation) for 10 hours at 60°C was made by Dr H Schwinn. (Schwinn H. Transcript of Deposition in Corson vs Gulf Coast Regional Blood Center, et al. 1st August 1996).

i). Dr Schwinn was originally given the task of discovering a means of reducing the fibrinogen content of factor VIII. After exhausting all of the possibilities he could think of, he attempted a 'heat shock' at 56°C, a temperature at which fibrinogen was known to be denatured. To prevent the factor VIII being denatured, he explored various additives, either alone or in combination, eventually discovering that a mixture of an amino acid (glycine) and a carbohydrate (sucrose) could partially stabilise factor VIII.

j). Dr Schwinn then undertook further research to see if he could discover a formula that would enable heating for 10 hours at 60°C to be applied, presumably because this degree of heating was known to make albumin safe.

k). Ultimately his 'heat shock' procedure for removing fibrinogen was abandoned by Behring, but pasteurisation for 10 hours at 60°C was retained using the stabilisers that Dr Schwinn had discovered.

l). It can be seen from this account that it would be wrong to state that "Behring appear to have developed their process from the wet heat treatment of albumin;" and wrong to presume that
“an existing use of similar technology will have generated savings of time and resources in research and development.”

m). The attraction for the PFC centred on claims by Behring that the procedure was able to inactivate hepatitis B, as described by Dr Cash in his letter to Mr Watt of 27 October 1980 [SNB.007.2646].

n). In addition, the long history of safety associated with albumin meant that the pasteurisation of albumin represented a benchmark against which new procedures could be compared.

10. Snapshots and Landmarks. 10.
My Response
a). I had a very good relationship with Dr Smith and always found him to be extremely co-operative.

b). I first met Dr Smith in 1970 when he visited me at University College London to discuss my PhD research. After joining the PFC in January 1973, I worked closely with Dr Smith until he left in August 1975. Before leaving the PFC, Dr Smith gave a number of seminars in which he very generously shared his knowledge and expertise. I then visited Dr Smith at the PFL (Oxford) in 1976, when we agreed to maintain close communication.

c). One way of learning of progress elsewhere was to attend international conferences and symposia. As it was difficult for any one person to attend all of the conferences, Dr Smith suggested that we should share reports if one of us had attended a conference that the other had missed. Dr Smith did not attend the 1982 ISBT Congress and it was because of this arrangement that I sent my report [SNB.010.4452] to him.
d). I believe that it was on reading my report of the 1982 ISBT Congress that Dr Smith first learned that research was being undertaken on pasteurisation and dry-heat treatment of coagulation factors. It is therefore not surprising that only "a little" research on heat treatment was being undertaken at PFL (Oxford) at November 1982.

e). I do not know the degree of priority that was being given to virus inactivation research in England in late-1982.

11. Snapshots and Landmarks. 11.
   My Response
   a). Coagulation Factor concentrates have always been freeze dried products. This is because coagulation factors are especially sensitive to degradation in solution and must be stored either frozen or freeze dried to retain their activity. Freeze dried products are stored at +4°C, whereas frozen products must be stored below -20°C, making freeze drying preferable for ease of storage and for ease of reconstitution.

   b). Suitable facilities were provided at the PFC for freeze drying coagulation factors. These facilities were progressively updated to increase capacity in a planned manner, as described in my memorandum to Mr Watt of 29th December 1980 [SNB.007.2666] (paragraph 10.59).

   My Response
   a). I was not aware of the meeting at BPL on 15th December 1982, nor the subsequent correspondence from Dr Cash in which my contact with Dr Smith was described as "furtive".
b). If I had been aware of this correspondence I would have assumed that Dr Cash was making the point that the communication between myself and Dr Smith was relatively informal and that the expression "furtive" was simply an exaggeration by him to make the point more strongly, a characteristic for which Dr Cash was well known.

c). Communications that are relatively informal are more vulnerable to personal circumstances than those that are based on more formal arrangements. I believe that it was reasonable for Dr Cash to be concerned that my communications with Dr Smith might be less "sound" than a more formal arrangement, especially as I had been absent from work in 1981 for about 6 months due to illness.

d). My communication with Dr Smith was well known within the SNBTS and was not unusual. For example, Dr Duncan Pepper, Head of the SNBTS Headquarters Laboratory, who reported directly to Dr Cash, had a similar relationship with Dr Smith.

e). PFC staff had always been encouraged by the PFC Director to communicate directly with their counterparts at the BPL (Elstree) and at the PFL (Oxford). For example, shortly after joining the PFC, I was assigned by Mr Watt to lead a delegation of PFC staff to the BPL to meet their counterparts in order to promote personal communications. This visit was reciprocated by the BPL, once the new PFC facility had opened.

f). Some time after this correspondence between Dr Cash and Dr Lane, more formal arrangements were established for two projects concerning the development of heat treatment, both of which involved specific, well-defined studies: (i) a safety study of heat treated Factor IX in dogs, to which the BPL/PFL were invited to participate by Dr Cash.
(ii) a laboratory study of the degree of virus inactivation achieved in 8Y heated at 80°C, which was undertaken by PFC at the request of Dr Lane, because neither BPL(Elstree), nor PFL(Oxford) had the facilities necessary for studies of this type.

g). I had some involvement with both of these projects. In my experience the interactions between the various participants were relatively informal and similar to the communications between Dr Smith and myself, except that these specific collaborations had been initiated by Dr Cash (project i) and by Dr Lane (project ii).

h). Although a formal collaboration may be more "sound" than an informal arrangement, it is also likely to be more cumbersome due to the involvement of defined management processes and wider reporting requirements.

i). In 1979/1980, I was a member of a joint BPL/PFC technology working party, which was convened to assist the BPL in the selection of technologies for its new centre. This was a very formal arrangement, which reported to a steering group that had been established by the Department of Health and Social Security. Although the deliberations of this working party were constructive and the outcomes helpful to the BPL, I found the process more cumbersome and bureaucratic than I was used to.

j). On balance, my preference was to exchange information with Dr Smith and his staff on a less formal basis than Dr Cash may have preferred. Nevertheless, I would have been happy to accept a more formal arrangement, if this had been requested.

13. Snapshots and Landmarks, 14 and 15.

My Response
a). To the best of my knowledge the exchange of information between the SNBTS and the BPL/PFL was reciprocal, except when precluded by a requirement for confidentiality, such as the arrangements between the PFC and Dr Johnson (paragraph 11.136) and the period when BPL were planning to patent the process used to prepare 8Y (paragraph 11.245).

14. Snapshots and Landmarks. 16.
My Response
a). At this time (22nd March 1983), the cause of AIDS was not known. Even if an infectious agent was assumed to be responsible, neither the nature of the infectious agent, nor its sensitivity to heat were known. Therefore there was no basis, other than speculation, for a “cross-reference” between the topics of heat treatment and AIDS.

15. Snapshots and Landmarks. 17.
My Response
a) In my memorandum of 3rd May 1983 [SNB.007.3635], I stated “In the absence of any hard data, heat treatment (of everything) looks at the moment to be the most likely possibility that we have to face up to. If this is so……..”. This wording was more speculative than is implied by the description “Dr Foster was referring to the need for the heat treatment programme to deal with the threat of AIDS”.

b). My memo followed reports in the Lancet of 30th April 1983 concerning AIDS in 11 people with haemophilia in the USA and three in Spain, all of whom had been treated with commercial concentrates [LIT.0010403] (paragraph 8.23). These reports caused me to consider the potential implications for our strategy on the development of heat treatment, should it be found that
this syndrome was caused by an infectious agent which was susceptible to inactivation by pasteurisation.

c). The pasteurisation process involved heating large volumes of protein in a concentrated sugar solution. I had envisaged that this would be done in a single large vessel. However, early large-scale experiments demonstrated that the heating-up and cooling-down of the mixture took a very long time, during which more factor VIII was destroyed than had been experienced in small-volume laboratory experiments. To prevent this loss of factor VIII, I was considering the design of a re-circulating system, with the solution being passed through heat exchangers to accelerate heating-up and cooling-down.

d). This was not straightforward and the equipment would take some time to design, construct and install. Instead of waiting for this, it occurred to me that processing at pilot-scale could be progressed by dispensing the mixture into 1 litre bottles which could then be heat-treated in the spray cabinet that was used to pasteurise albumin.

e). This procedure was introduced and not only enabled pilot-production of pasteurised factor VIII to be accelerated but also enabled the degree of virus inactivation to be measured more accurately, as marker viruses could be added to an equivalent 1 litre container and heated in the same manner.

f). Following my meeting with Dr Johnson in June 1983 (paragraph 11.135) it was conceivable that the increased purity promised by the method of Dr Johnson would enable the volume of solution to be pasteurised to be reduced about 50-fold, making the pasteurisation in 1 litre bottles potentially feasible for full-scale manufacture as well as for pilot-scale processing.
g). However, practical work with the method of Dr Johnson did not begin at the PFC until August 1984. This was because Dr Johnson's legal advisors did not want him to disclose details of his procedure before his patent application was filed. At first this was believed to be imminent, but Dr Johnson continued to put off filing in order to add further information. Eventually it was agreed that details should be disclosed to the PFC prior to the patent being filed. This was done at a meeting with me in New York on 14th June 1984.

h). On reviewing his procedure, I calculated that the capacity of the ion exchange reagent that he was using was far from ideal for large-scale processing. I suggested that the Swedish company Pharmacia be approached to discover if they had a more suitable ion exchange matrix. I arranged a meeting between Dr Johnson and Dr John Curling, the leading expert at Pharmacia, which took place on 24th July 1984, during the 1984 ISBT Congress in Munich (paragraph 11.185). Dr Curling identified Q-Sepharose, a new ion exchange matrix that was under development at Pharmacia, as a possible candidate.

i). Following the meeting with Dr Curling, I suggested to Dr Perry that additional scientific input would be required at the PFC and I proposed that Dr Ronald McIntosh, who was working on immunoglobulin developments, be moved to work on the high-purity factor VIII project. Dr Perry agreed with my suggestion and Dr McIntosh agreed to this change when I discussed it with him on my return to the PFC. Thereafter Dr McIntosh led the project to develop high-purity factor VIII.

j). A sample of Q-Sepharose was delivered to the PFC on 22nd August 1984. Although this was found to be very promising, it became clear that further research would be required to fine-
tune the chromatography procedure before it could be integrated into the pasteurisation process.

k). I had also been present at a meeting between Dr Johnson and Dr Bernard Horowitz (of the New York Blood Center), during the ISBT Congress in Munich, at which Dr Horowitz informed us of a new virus inactivation procedure that he was developing for which a chromatographic procedure was required to remove the chemicals used. As this procedure, known as solvent-detergent treatment, could in theory be combined with the chromatographic procedure of Dr Johnson, it offered an alternative option to pasteurisation, should the pasteurisation technology prove to be unsuccessful or difficult to implement.

l). During 1983/84, a total of seven pilot batches of pasteurised Factor VIII concentrate (ZHT) were prepared at the PFC for clinical evaluation with the final batch (batch number ZHT-007) being processed on 24/25 September 1984.

m). It was on 2\textsuperscript{nd} November 1984 that I learned that HIV in Factor VIII concentrate could be inactivated either by dry-heat treatment at 68°C for 1 hour or by pasteurisation at 60°C (paragraph 11.191). I recommended that dry-heat treatment at 68°C be introduced, as this could not only be done immediately but could also be applied to existing stocks of Factor VIII concentrate.

n). Specialist ovens for dry-heat treatment (paragraph 10.129) had to be manufactured to order and could not be obtained for about 6 months. In order to avoid delay, the spray cabinet that was used to pasteurise albumin was utilised to heat vials of freeze dried Factor VIII, pending the purchase and delivery of a specialised oven.
o). Although the spray cabinet was normally operated at 60°C, it had fortuitously been designed to function up to 70°C. Successful operation of this cabinet at 68°C was confirmed in a validation run on 14th November 1984, enabling routine dry-heat treatment of Factor VIII to begin on 18th November 1984.

   My Response
   a). My proposal to use the spray cabinet for pasteurisation in SNB.007.3635 was taken forward as described in 15 above.

17. Snapshots and Landmarks. 19.
   My Response
   a). The process devised by Dr Johnson involved the chromatographic purification of factor VIII, in which chemicals were added to subtly modify the conformation of the factor VIII molecule to promote its attachment to a conventional ion exchange matrix. A patent for this process was filed by Dr Johnson on 1st February 1985 (Matthews R and Johnson AJ. USA Patent 1988, No. 4,743,680) and included experimental data supplied by the PFC.
   
   b). I had been advised by Dr Johnson that this process would be very easy to scale-up, that it could be integrated easily into the new process being devised at the PFC and would be compatible with pasteurisation, as well as being high yielding and providing a product at least 50x more pure than any available Factor VIII concentrate.
   
   c). My interest was also in resolving the technical difficulties already described in 15 above. Subsequently, an adverse reaction to the first pilot batch of pasteurised Factor VIII
(paragraph 11.158) emphasised the potential value of substantially increasing purity, to eliminate any harmful material that might be present.

18. **Snapshots and Landmarks. 20.**

**My Response**

a). The formal agreement with Dr Johnson required complete confidentiality. Subsequently I encouraged him to offer the procedure to the BPL and helped to arrange a meeting between him and the BPL to discuss this option. Unfortunately correspondence between the BPL and New York University (NYU) resulted in the Dean of NYU requesting that Dr Johnson collaborate with a US company rather than organisations in Europe. This led to a temporary breakdown in relations between the PFC and NYU, but did not interfere with research at PFC.

19. **Snapshots and Landmarks. 21.**

**My Response**

a). Mr Watt did not discuss his reasons for leaving with me.

b). I do not believe the resignation of Mr Watt adversely affected the virus inactivation programme or influenced the SNBTS strategy. According to his CV [PEN.012.1491], Mr Watt continued to be a member of the Biologicals sub-committee of the Committee on Safety of Medicines until 1986. In March 1984 this committee approved an application from Behring for a licence for its pasteurised Factor VIII and, in July 1984, rejected an application for a licence from Armour for its dry-heat treated Factor VIII. I do not know the advice, if any, that Mr Watt offered at these meetings, but the fact that the SNBTS strategy was consistent with both of these decisions does not suggest that Mr Watt would have encouraged the SNBTS to take a different position if he had remained in post.
20. Snapshots and Landmarks. 22.

My Response
a). I learned that Mr Watt had resigned on Monday 11th July 1983 on my return from the meetings of the WFH and the ISTH in Stockholm (paragraph 8.37).

b). Subsequently I was informed by a colleague that Mr Watt was planning to establish a company to fractionate animal plasma and that he was seeking to recruit staff from the PFC.

c). Shortly after this, I was called to meet Dr Cash. He too had heard that Mr Watt was planning to recruit staff from the PFC and he wanted to know if I would be leaving with Mr Watt. I told him that Mr Watt had not asked me to join him and that, if he did so, I had no intention of leaving the PFC. Dr Cash then asked me if I knew who had been approached by Mr Watt. I gave him the names of four people whom I had heard about.

d). It was evident to me that Dr Cash was worried that the PFC might be damaged by the loss of key staff. Later, he told me that he had discussed the matter with Mr Watt, who had indicated that he intended to recruit only a small number of staff from the PFC to avoid any damage to the PFC. Nevertheless, I believe that it was concern over the potential loss of key PFC staff that led to Mr Watt leaving at the end of December 1983, rather than at the end of March 1984.


My Response
a). In addition to hepatitis being transmitted to chimpanzees by a dry heat treated Factor VIII concentrate [DHF.002.5668], it became generally known in September 1983 that hepatitis was still being transmitted to patients by a Factor VIII concentrate
that had been dry-heat treated at 60°C for 72 hours (Mannucci PM. J Thrombosis Haemostasis 2003, 1, 2065-2069)

[LOT.002.8635] That the SNBTS was aware of this is confirmed by the minute of the meeting of the Factor VIII Study Group of 12th January 1984 [SNB.007.4059].

b). Further evidence against the dry-heat treatment was obtained by the SNBTS in late-1983, from a study using marker viruses in which virus inactivation by dry heat treatment at 60°C was compared with that obtained by pasteurisation. A much greater degree of virus inactivation was observed with pasteurisation, using either the method of Behring or the modified method of the PFC. This study was performed by Dr Cuthbertson and Dr Pepper and the results were mentioned in my report of 20th December 1983 [PEN.012.1500] that I prepared for the meeting of the Factor VIII Study Group of 12th January 1984 (paragraph 11.160).

c). The memorandum from Dr Smith to myself, of 5th January 1984 (paragraph 11.156), concerned the ability of the current BPL Factor VIII concentrate to withstand dry heat treatment under different conditions. Although these data were more extensive than those that had been obtained by the SNBTS, the results were consistent with those of Dr Cuthbertson and Dr Pepper and were not regarded as representing new findings.

d). The absence of any data from BPL concerning the inactivation of any viral markers, meant that the data from Dr Smith were of limited value. Virus inactivation data were available for pasteurisation, from laboratory studies with marker viruses by the SNBTS, as well studies in animals and in patients by Behring, all pointing to pasteurisation being more likely to succeed in making coagulation factor concentrates safe with
respect to non-A, non-B hepatitis than dry-heat treatment. Consequently the information from Dr Smith did not alter the opinion in Scotland that pasteurisation should continue to be the main focus of research on virus inactivation.

e). As well as undertaking studies on dry-heat treatment, interest in pasteurisation was maintained by BPL/PFL. For example, Dr Smith led a group of staff from PFL/BPL to the PFC on 25-26 June 1984 to observe the preparation of a pilot-scale batch of the SNBTS pasteurised factor VIII concentrate (ZHT). During the visit, Dr Smith photographed the different stages of the ZHT process and copies of the photographs that he took are available.

f). I believe that the decision in England to give priority to research on dry-heat treatment was driven by the recognition that a pasteurisation process would be very difficult to accommodate at the already overcrowded BPL facility.

22. **Snapshots and Landmarks. 26.**

My Response

a). I do not know why the description of the adverse reaction given by Dr Ludlam in his letter of 11\(^{th}\) January 1984 [SNB.001.5311] was different to that given in the minute of 14\(^{th}\) November 1983 [SNB.001.5188].

b). I do not know if the letter of 11\(^{th}\) January was written at the request of Dr Cash or not.

23. **Snapshots and Landmarks. 28.**

My Response

a). The target date of April 1985 was extremely ambitious for the installation and commissioning of such a large and complex
manufacturing process. That is why the focus shifted in August 1984 to the incorporation of Dr Johnson’s purification procedure in order to substantially reduce the volume of solution to be pasteurised (see response 15).

b). It is also why it was decided to introduce dry-heat treatment in November 1984, as soon as there was evidence that HIV could be inactivated by this procedure. Dry-heat treatment at 60°C-68°C was technically straightforward and did not require a completely new process to be devised or new equipment to be installed and could therefore be introduced much sooner than pasteurisation.

24. Snapshots and Landmarks. 29.

My Response
a). I do not know how Dr Craske obtained his information.

b). By the end of March 1984, five pilot-scale batches of pasteurised factor VIII concentrate (ZHT) had been prepared at the PFC for clinical evaluation.


My Response
a). Issues of funding did not delay research at the PFC.


My Response
a). The results of the study reported in Cardiff by Dr Mannucci were published on 2nd February 1985 (Rouzioux C et al. Lancet 1985, I, 271-272) [LIT.001.0436]. Although these data were consistent with HIV having been inactivated by dry-heat treatment at 60°C for 72 hours (ie. the conditions used to treat
Hemofil T of Hyland/Baxter) the study did not provide definitive proof, as there was no evidence that the batches of Hemofil T that were used in this study had contained infective virus.

b). Experimental proof that HIV could be inactivated by the dry-heat treatment of Hemofil T was first published by Hyland/Baxter in 1987 (Piszkiewicz et al. Thrombosis Research 1987, 47, 235-241) [LIT.001.0633].

c). A claim by the Haemophilia Society, to the Archer Inquiry, that the dry-heat treatment process of Hyland/Baxter was known to inactivate the virus responsible for AIDS in May 1983 (paragraph 11.124, footnote 180) has been refuted in a paper written by myself (Foster PR. Response to Questions Raised at the Inquiry into Contaminated Blood and Blood Plasma Products 3. The Discovery of Heat-Treatment Conditions for the Inactivation of HIV in Coagulation Factor Concentrates, SNBTS, September 2007) [PEN.012.1506].

d). The report of the meeting in Cardiff was received at the PFC on 6th November 1984 (paragraph 11.190) four days after the same information had been presented to the symposium in Groningen (paragraph 11.191) which was attended by Dr Perry and Dr McIntosh (PFC) and Dr Prowse (SEBTS) as well as myself.

e). The data on the inactivation of HIV that were presented at Groningen by Dr Jason of the USA Centers for Disease Control concerned pasteurisation at 60°C (not 68°C as written in my report [SNB.008.6528]) and dry-heat at 68°C. This was the first evidence available to me that HIV could be inactivated in Factor VIII either by dry-heat treatment (at 68°C) or by pasteurisation (at 60°C).
f). Prior to leaving for Groningen I had received results from Mr Thomas McQuillan (Manager of the PFC Quality Control Laboratory) that indicated that PFC's Factor VIII concentrate (NY) could withstand dry-heat treatment at either 60°C for 24 hours or at 68°C for about 3 hours.

g). These data were discussed by Dr Perry, Dr McIntosh and myself on our return journey from Groningen to Edinburgh and we agreed to propose to Dr Cash that the SNBTS should immediately adopt dry heat treatment at 68°C.

27. Snapshots and Landmarks. 32, 33 and 34.

My Response

a). As far as I can remember, I first learned of these infections in late October 1984, when Dr Bruce Cuthbertson received a telephone call about this, most probably from Dr Brian McClelland. Dr Cuthbertson's office was adjacent to mine and, as both doors were open, I overheard his conversation.

b). I immediately called Dr MacLeod to my office to ask him to identify all R&D samples of Factor VIII concentrate that were already available and which could be used for heat treatment experiments, including samples which I had previously formulated with different additives and which were being monitored for long term stability. It was necessary to use samples that had been prepared previously, as production of Factor VIII had ceased whilst modifications to the production building were being carried out and there was therefore no immediate possibility of obtaining suitable fresh material for research.
c). I was aware of a publication in the Lancet of 29th September 1984 (Levy J et al. Lancet, 2, 722-723) which reported substantial inactivation, after several hours of dry-heat treatment at 68°C, of a murine (ie. mouse) retrovirus that had been added to Factor VIII concentrate. As the AIDS virus was also known to be a retrovirus (paragraph 8.84) these data suggested that HIV might be destroyed by dry-heat treatment at 68°C.

d). I also knew that the study reported by Levy et al. had been undertaken by Cutter Laboratories (also known as Bayer) and concerned their Factor VIII concentrate, Koate HT, which was dry-heat treated at 68°C for 72 hours (paragraph 11.200). What had been done to enable Koate HT to withstand this degree of dry-heat was not disclosed nor, to the best of my knowledge, has this ever been disclosed.

e). When Dr Macleod returned with a list of available samples, we drew up a plan of investigation to obtain as much information as possible on the impact that the various additives might have on the ability of the PFC Factor VIII concentrate (NY) to withstand dry-heat treatment at 68°C. I believe that it was from this investigation that I was able to discover that dry heat treatment of Factor VIII concentrate (NY) at 68°C could be extended from 2 hours to 24 hours by the addition of 2% sucrose (paragraph 11.221).

f). I had attended the scheduled meeting of the PFC Heads of Department [SNB.010.3479] on 26 October 1984. During the meeting it was agreed that dry-heat treatment of the existing PFC Factor VIII concentrate (NY) should also be examined further.
g). Results from this study were available on Tuesday 30th October 1984 and included data on factor VIII activity and reconstitution time after dry-heating for different periods of time at either 60°C or at 68°C. I had specified that heating at 68°C be included, not only because of the publication of Levy et al. of 29th September 1984, but also because this was the highest temperature to which a Factor VIII concentrate (Koate HT of Cutter/Bayer) had been dry-heat treated, in addition to having obtained regulatory approval in the USA (paragraph 11.200).

h). On the following day, Wednesday 31st October 1984, I travelled to Groningen in the Netherlands (paragraph 11.191), with Dr Perry and Dr McIntosh, where we were to learn that HIV could be substantially inactivated by dry-heat treatment at 68°C for 1 hour, conditions which I already knew could be tolerated by the existing PFC Factor VIII concentrate (NY).

i). The actual presentation that was given by Dr Jason at Groningen on 2nd November 1984 was not published, nor was the finding that HIV could be a substantially inactivated after dry-heating at 68 degree for 1 hour. However, these data were included in a commercial brochure distributed by Cutter Laboratories (Cutter Biological. Inactivation of AIDS-associated viruses in antihemophilic factor products: the effectiveness of heat treatment. Commercial Brochure CB671, September 1985. Elkhart, Indiana: Miles Laboratories Inc.) [SNB.004.7753] I believe that I most probably obtained this brochure from the Cutter commercial stand at the 1986 ISBT Congress in Sydney, Australia.

28. Snapshots and Landmarks. 35.
   My Response
a). Dry-heat treatment was at first carried out using the spray cabinet that was used to pasteurise albumin (see my response 15 above). This procedure was replaced in mid-1985 by using a specialist oven that was based on the specification that had been obtained from BPL on 16\textsuperscript{th} January 1985.

b). Coagulation factor concentrates are freeze dried products (see my response 11 above); therefore no additional equipment was required to undertake dry-heat treatment at 68°C.

29. Snapshots and Landmarks. 36.

My Response

a). In my opinion, dry-heat treatment was not introduced by the SNBTS in January 1984 for the following reasons:

- the cause of AIDS was not known (paragraph 8.84),
- the virus responsible for AIDS had not been discovered (paragraph 8.84),
- that the virus responsible for AIDS could be inactivated by heat treatment was not known,
- that the virus responsible for AIDS could be inactivated by dry-heat treatment, under conditions that SNBTS Factor VIII concentrate could withstand, was not known,
- the SNBTS was already preparing pilot batches of a heat treated product (ZHT) for clinical evaluation, similar to a number of other manufacturers,
- no manufacturer in the world had switched from unheated to heat treated Factor VIII concentrate, although some manufacturers were heat treating a small proportion of their Factor VIII,
- it was known that dry-heat treatment had not inactivated agent(s) responsible for non-A, non-B hepatitis (paragraph 11.160),
• there was concern that patients might react adversely to heat treated products [SNB.007.3625].

b). The concern that patients might react adversely to heat treated Factor VIII resulted in the SNBTS being strongly criticised by Dr Ian Hann (of the Royal Hospital for Sick Children, Glasgow) for the introduction of dry-heat treatment (Hann I. Letter to Dr J D Cash. National Medical Director SNBTS, 19th December 1984. Glasgow, Royal Hospital for Sick Children) [SNB.007.4689]

c). A similar concern was published by Bird et al. in the Lancet on the 19th January 1985 [SNB.008.5887] (paragraphs 8.111 and 11.247) when the authors stated that the "switch completely to heat treated factor VIII.....would be based on inadequate evidence. Moreover, the policy would expose all haemophiliacs to a new series of risks and difficulties." After expressing concern that "Even mild heat treatment will......... enhance the immunogenicity of native factor VIII and therefore the propensity to antibody formation" the authors went on to warn "There is, therefore, a considerable danger that the unproven benefits of heat treatment will be offset by potential risks – one of which, antibody, (inhibitor) formation, would be irreversible."

d). To the best of my knowledge Scotland was the first country in the world to "switch completely to heat treated factor VIII" and the only country to re-call unheated Factor VIII concentrate at this time.

e). It was not until 26th January 1985, that a peer-reviewed paper was published which reported that HIV was relatively heat sensitive. Even then, the authors warned "The data cannot,
however, be extrapolated to lyophilised products since our experiments were conducted in liquid medium”. (Spire B et al. Lancet 1985, I, 188-189) [SNB.007.4724].

f). A UK survey undertaken in May 1985 found that unheated domestic Factor VIII concentrate was still being used in over half of the Haemophilia Centres that replied (Bloom et al. British Medical Journal 1985, 290, 1901) [LIT.001.0333].

g). Although the BPL issued some batches of dry-heated Factor VIII in early 1985, unheated factor VIII concentrate continued to be issued until 1st May 1985, then the issue of Factor VIII concentrate by the BPL ceased until 19th September 1985. (Snape T. Hep C. Facsimile Transmission to Dr R J Perry, Director SNBTS Protein Fractionation Centre, 26 August 1999. London, BioProducts Laboratory) [PEN.012.1511]. When the issue of Factor VIII concentrate was resumed by the BPL, all of its Factor VIII concentrate was dry-heat treated, but was only about 30% of the amount required for England & Wales. By contrast, the SNBTS supplied 100% of Scotland’s requirement for heat treated Factor VIII concentrate from 10th December 1984.

h). In addition to being first in the world to switch to heat treatment, the SNBTS applied this treatment to all of its stock of unheated Factor VIII concentrate (NY), which amounted to almost 12 months supply (paragraph 10.127). Therefore heat treatment was actually applied to SNBTS Factor VIII concentrates that had been prepared from donations obtained almost 12 months earlier.

i). It was discovered subsequently that a number of HIV-positive donations from this period had contributed to batches of SNBTS Factor VIII concentrate that were subsequently dry-heat treated,
one HIV-positive donation having been collected as early as 24th March 1984, a date which preceded the discovery of the AIDS virus (paragraph 8.84).

j). This heating of a 12 month stock of Factor VIII concentrate did not extend back to the batch of Factor VIII concentrate that was implicated in the transmission of HIV to “the group of people known as the Edinburgh Cohort” (paragraph 8.102) as this batch had been prepared in early November 1983.

k). Therefore, “In retrospect, the infection of the group of people known as the Edinburgh Cohort” would not “have been prevented if PFC had moved to dry heated product at the beginning of 1984”, unless stocks of Factor VIII concentrate, which had been prepared earlier, had also been subjected to a speculative heat treatment procedure, despite the concern that heat treated Factor VIII concentrate might harm patients.

l). Subsequently, two heat treated Factor VIII concentrates produced in Europe did harm patients by causing the formation of inhibitors (Peerlinck K et al. Thromb Haemost. 1993, 69, 115-118) [PEN.012.1518] (Peerlinck K et al. Thromb Haemost. 1997, 77, 80-86) [PEN.012.1522]. Both of these products were withdrawn from use, demonstrating that the earlier concern that heat treatment might do more harm than good was not unreasonable.
30. **Appendices**


B). List of New Documents Cited.

**Statement of Truth**

I believe that the facts stated in this witness statement are true.

Signed .................................................................

Dated .................................................................