Witness (John Cash) Statement 4 (Viral Inactivation)

SCHEDULE

Issue in respect of which a statement is sought

AIDS/HIV - Viral Inactivation to 1985

The implementation of heat treatment against LAV/HTLV-III by the Protein Fractionation Centre In Scotland in December 1984, and the technological background to such implementation, including the history and exploration of methods of heat inactivation by the Scottish National Blood Transfusion Service.

Sections of the Preliminary Report which may assist when preparing statement

Chapter 11: "Viral Inactivation"

Matters to be included in the statement

SNPASHOTS AND LANDMARKS

1. The SNBTS has said in its submission of October 2009 (at page 22) that it had been involved in research aimed at removing viruses from coagulation factors since 1970. As far as can be ascertained, such work as took place in the 1970s was carried out on Factor IX and related to hepatitis B. The report prepared by Mr Watt in December 1973 (SNB.001.6903 - see dvd) does not mention viral inactivation, although, according to the report of Research and Development from 1975 (SNB.010.4779 at page 11 - see dvd) there had been a paper presented at the Congress of The International Society of Thrombosis and Haemostasis, Vienna, Austria:

   "Johnson, A.J., Newman, J., Semar, M., Middleton, S. and Smith, J.K. (1973). "Removal of Hepatitis-B Antigen (HBAg) from coagulation factor II, VII, IX and X concentrates for clinical use. "

1.1 Comment: I would suggest that Dr Foster is best qualified to comment on this statement. I was not involved in this very early work.

2. The report of Research and Development from 1975 (SNB.010.4779 at page 5) also refers to what appears to have been an ongoing project relating to preparation of a Factor IX concentrate with a reduced hepatitis B activity. This project was said to have commenced in 1971 and to have about 18 months left to run. Both these references appear to relate to removal of virus, rather than steps of process designed to inactivate the virus.

2.1 Comment: As above

3. The issue of viral inactivation was discussed - briefly - at the meeting of the MRC Working Party on Post Transfusion Hepatitis on 14 February 1980. (DHF.002.4845;

paragraph 11.40). A representative of Edinburgh and South East Scotland BTS attended - was this Dr McClelland?

3.1 Answer: Dr McClelland was a member of this Working Party

4. In October 1980, Dr Cash became aware of the development of an apparently hepatitis safe Factor VIII by Behring (paragraph 11.49). Was this the first that anyone in PFC knew of the work by Behring?

4.1 Answer: Dr Foster will confirm or otherwise

5. It appears that research on pasteurisation of coagulation products began in Scotland in 1981 (SNB.007.3059; paragraph 11.51). Was this in response to the news of developments in the rest of Europe?

5.1 Answer: I do not recall, but I am certain Dr Foster will

6. It is also apparent that Dr Cash tried to assess and to some extent advance the various possibilities by establishing the Factor VIII Study Group in 1982. The report of the first meeting (see paragraph 11.56) does not describe any work in progress on the viral inactivation of Factor VIII; it is not clear why not, given the statement that research on pasteurisation had begun in 1981. Was it because this research was not a priority?

6.1 Answer: As I recall this Group was actually established in order to provide an opportunity for all SNBTS centres to feel they were involved in the task of providing safe and sufficient VIII for haemophilia patients in Scotland and to emphasise to all that this task was a top national priority. It was also intended to promote a little more transparency and objectivity in the research undertaken within PFC, and to provide an opportunity for other SNBTS scientists to give support and assistance to the PFC R&D team.

6.2 The agendas for this group were largely determined by liaison with the group members. I have no recollection of the discussions which took place on the 28 January 1982 and thus whether the note/minute of the meeting accurately reflects these discussions. But I can't imagine how, in 2010, it is possible to conclude that concern about viral contamination of VIII concentrates was in some way a low priority.

6.3 I am certain that Dr Foster would be able to add further clarification. Beyond this I suspect he would wish to remind you that at the first meeting of the Group we established small sub-groups that would bring together what we thought were the top priorities for our research in this area. One of these sub-groups was concerned with viral inactivation – which had its first preliminary meeting only 10 days after it was established!

6.4 On a more personal note I am astonished and moved to be reminded in 2010 of the quite remarkable way our small disparate team came together in the 1980s and delivered research contributions which were directed to ensuring our products were low risk, with respect to viral transmission. I also recall that SHHD officials showed little interest in this work and how dismayed, astonished and

alarmed we were when, without any consultation of the UK Blood Transfusion Services, the MRC disbanded its blood transfusion research committee in July 1982 .

7. The then current state of play appears to be summarised in the report of the Safety subgroup meeting on 9 and 10 February 1982 (paragraph 11.57). As at March 1982, (see paragraph 11.62) the intention was apparently that research would continue on the method being used by Behring, i.e. pasteurisation in the form of heating form 10 hours at 60° C. Subsequent meetings of the group and sub group are chronicled in paragraphs 11.63 to 66.

7.1 Comment: I believe the contents of my comments (6) above cover this item .

8. Dr Foster attended the International Society of Haematology and International Society of Blood Transfusion conference in Budapest in July 1982. His report is at SNB.010.4452 (see paragraph 11.69). At the conference Dr Foster seems to have procured a copy of a Behringwerke paper published on 16 July 1982 (see dvd at SNF.001.0921 and paragraph 11.74). Dr Foster also received a copy of a typewritten paper on the Behring process (s ee dvd at SNF.001.0929 and paragraphs 11.74 - 78) which he passed to Dr Cash (see acknowledgement dated 12 April 1983, SNB.007.3600).

8.1 Comment: I am not sure what point is being made, but I wonder whether you are suggesting that Dr Foster sent me an important document in April 1983, that he had first acquired in July 1982.

8.2 Perhaps it might be helpful to suggest you look again at my letter to Dr Foster of the 12 April 1983. I believe the first two lines imply that the Behring documents Dr Foster picked up in Budapest were available to all and might be classified as 'freebies'. Certainly the proposition that they were of major scientific/operational value to other plasma fractionators must, without further consultation with Dr Foster, be in some doubt. Indeed, in retrospect, the distribution of these freebies may have been the first clear signal that Behringerwerke had failed in their attempt to introduce the wet heat treatment option for viral inactivation of VIII concentrates.

9. On 14 October 1982, the Study Group met again. Heat treatment was now "the first option of the group", with high purity product to be used. Was this essentially because of the apparently promising results obtained by Behring? Behring appear to have developed their process from the wet heat treatment of albumin; presumably an existing use of similar technology will have generated savings of time and resources in research and development. Was this also an attraction for PFC, where pasteurisation of albumin had apparently begun in 1965 (see SNBTS Oct 2009 submission, App B page 7)?

9.1 Answer: Again Dr Foster is best qualified to answer this question, but as I recall Behring never marketed a product for the care of haemophiliacs, though I believe they sold their technology to Kabi. I do not recall

whether Kabi ever went to the market with it. If so, then I'm fairly certain it was never marketed by them in the UK. Moreover, my contacts with European colleagues from Sweden and Finland (whose services had contracts with Kabi) at no time mentioned they had access to wet heat treated VIII from Kabi. To the best of my knowledge, the only wet heated VIII product (Monoclate P) was produced by Armour and licensed in 1989. This product only survived for 5 years – I suspect primarily because it was not economical - very low yields. I suspect Dr Foster will have much more authoritative information.

9.2 My recollection is that despite all our optimism in 1982 and 1983, and the considerable resources used to patent some of our developments, the central and largely unresolved problem with wet heat methods remained one of the size of the VIII losses when full scale production was attempted.

9.3 It cannot be overemphasized that for a small public service plasma fractionators such as the SNBTS, which exclusively relied on a fixed indigenous voluntary unpaid donor base for its plasma source, and which in 1983 had achieved self sufficiency but was expecting major new and escalating clinical demands, we were reluctant to encourage our PFC colleagues to pursue a heat treatment programme which led to high production losses. This would have led to increased exposure of haemophilia patients in Scotland to higher risk commercial products – unless we had an assurance of funding to commence a programme of plasmapheresis which would generate source plasma to further augment our plasma intake. This difficulty must have put considerable pressure on our PFC team. Moreover, even the quantities of plasma required simply to support these heat treatment production experiments were a cause of considerable concern and tension at that time.

10. There was also correspondence between PFC and BPL in the Autumn of 1982 on these matters. This is discussed at paragraph 11.84; according to Dr Smith's letter dated 3 October 1982, which must in fact be November, (SNB.007.3267) BPL were doing "a little" on heating Factor VIII. Dr Foster wrote again to Dr Smith on 1 December 1982, dvd). How would those involved characterise the cooperation at this point? Would it be accurate to say that viral inactivation was not a priority in England at this point?

10.1 Answer: Dr Foster's and Dr Smith's responses to these questions would be much more valuable than mine.

10.2 I was never quite sure to what extent Dr Smith (who worked at PFL in Oxford in 1982) enjoyed the support of senior BPL management with regard to his collaboration with PFC. 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 (there are several documents on file which will confirm this). But prior to Mr. Watt's departure I attempted in 1980 to arrange a meeting between the PFC and BPL management teams with a view to exploring ways of getting the VIII concentrate production and associated research on a joint UK basis. BPL

management refused to agree to such a meeting – I was later to learn this had the support of DHSS.

10.3 As I recall, Dr Smith acquired much of his early training and experience in plasma fractionation at PFC. I was led to believe he fell out with Mr. Watt, resigned and went to PFL (Oxford) - which I recall was independent of BPL at that time. I always believed he had a 'soft spot' for the SNBTS and more certainly a close professional friendship with Dr Foster and other members of the PFC R&D team.

10.4 It is of interest to learn that Dr Smith advised Dr Foster in October 1982 that BPL was doing only "a little" on heating of Factor VIII. It is not clear to me whether this refers to BPL and/or PFL. However, at the UK HCD's meeting 12 months later Dr Snape of BPL advised the clinicians that BPL was close to making available a 'virus free' factor VIII concentrate for clinical trials. I do not recall what method of viral inactivation was used for this BPL product, but I wonder whether the notion that 12 months before BPL were doing 'only a little' on heating of factor VIII quite squares with Dr Snape's announcement. Dr Smith would be best able to clarify this question.

11. It appears that good progress was made in the pasteurization project: the patent claim And an optimistic memo is referred to in paragraphs 11.85 to 89. On 1 December 1982, Dr Foster wrote to Dr Smith (SNB.007.3341 - see DVD). In his letter, he details Experiments on (?)pasteurising Factor IX and also on freeze drying - apparently of Factor VIII. Is it correct that there was freeze drying of Factor VIII in PFC at this time?

11.1 Answer: In 1982 freeze drying of VIII in PFC was a routine process for the manufacturing feature of our intermediate VIII concentrate. However, freeze drying is a generic description; there are many technical variations and the one used routinely at PFC in 1982 may not have been acceptable for subsequent dry heat treatment. Dr Foster will add further detail.

12. Meanwhile, however, there was clearly a difficult meeting at BPL on 15 December 1982 (see report, paragraphs 11.90 to 92). That it was difficult is apparent from the letter dated 17 December 1982, which Dr Cash sent to Dr Lane afterwards - (SNB.004.3163, see dvd). The tension appears to have been between on the one hand, assisting commercial producers to conduct clinical trials in the UK, leading to their achievement of licences for their products, or, on the other, maintaining an "arm's length" position, without facilitating introduction of commercial products, so that the NHS bodies could have more time to develop satisfactory products of their own. What had led Professor Cash to characterise the contacts between Drs Foster and Smith as "furtive"? On its face the terms of the letter do not appear conducive to the sort of bridge building desiderated by Dr Cash. Did the content of the letter become known within PFC? If so, what was the€ effect? And is it possible that there is a "not" missing in the fourth last line on page 1?

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12.1 Answer: There is no doubt that the meeting on 15 December 1982 at BPL was a very difficult one! As I recall, my difficulties were several:

12.11 Two years before this meeting (December 1980) I had attempted to seek BPL's management support for a meeting which would explore the issue of a joint BPL/PFC approach to the manufacture and associated research of factor VIII concentrates for the whole of the UK. (see SNB:004.3163) This proposition was rejected (no meeting took place) and by 1982 I had reason to believe (briefed by Dr Harold Gunson) that DHSS had been party to this rejection, and that SHHD (not known to me) were aware of this. Thus in response to your comment about bridge building: I recall I 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.

12.12 On a number of occasions in 1980/81/82 I had sought the support of SHHD officials to use their influence to ensure the Committee on Safety of Medicines explored what could be done to enhance the safety of commercial coagulation factor concentrates imported in to the UK. These exhortations came to naught and by December 1982 I had reason to believe this proposition had also been blocked by DHSS and this was known by BPL management. I was also concerned to discover that John Holgate (MCA) and Joe Smith (NIBSC) seemed to be party to the proposition that UK clinical trials of commercial plasma products should be encouraged. Joe Smith had some senior colleagues on his staff who would have understood the consequences of supporting this development and why the Scots would oppose it.

12.13` As I recall, 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.

12.14 I totally opposed this development but later greatly regretted the way I conveyed my opposition. My initial problem was that I felt we had been ambushed and was distressed to see Professor Arthur Bloom (an old friend, a mentor of Dr Ludlam and the HCD in Cardiff) had been persuaded to Chair the meeting. My consternation was such that I felt duty bound to follow up the meeting with a letter to Dr Lane. (SNB.004.3163)). Despite his response my opposition had not changed. The reasons for this opposition were as follows:

12.141 By 1982/83 there were a very limited number of haemophilia A patients in the UK that had not been exposed to commercial concentrates (the highest percent were in Scotland). This small group of patients, (which included an even smaller sub-group –previous untransfused

patients (PUPs)) would be essential for the UK (NHS) fractionators when they wished, notwithstanding the disturbing issue of Crown immunity, to validate their viral inactivated products. If these patients 'were given away' to US commercial interests then NHS fractionators would be in serious difficulties. Whilst Scotland had the highest percent of patients which had not been exposed to commercial concentrates, in terms of total UK patients the majority would be in England and Wales (E&W). It followed that we had intentions to seek access to some of the E&W patients for the SNBTS virus inactivated products – and in due course we did.

12.142 If MCA was making clinical validation a condition for the issue of UK product licenses for these US commercial viral inactivated products, then we argued that the validation should be done in the USA under the supervision of the FDA, where the total number of patients was very much greater than in the UK and where these manufacturers were already supporting the bulk of the US patients. If MCA wished to see clinical trials of these commercial products in European countries then we argued there were several where the contribution to haemophilia care from indigenous donors was minimal – notably, as I recall, Germany, Austria and Italy - and thus in these countries there would be no significant ethical challenges.

12.143 I recall 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. Rightly or wrongly I assumed this position would have found support in all the Scandanavian countries, France and the Netherlands. It would be of interest to obtain a non redacted copy of SNB.004.9164: the list of countries (line 2) that contributed to the European haemophil T trial reported by Piero Mannucci is missing!

12.144 I recall there was understandably some doubt that the viral inactivation processes of some of these US products in 1982 were effective and thus an NHS product without viral inactivation might have been safer for our patients. By 1984 this, at least with regard to NANB hepatitis, was confirmed. (Dr Foster has details of the early heat treated commercial products which transmitted viruses). Dr Mannucci's European trial confirmed this; whilst all recipients seemed to be protected from HIV (though only 21 patients were studied and no information was given on the number of batches used) 70% of the patients developed NANB hepatitis. 12.14 (5) I recall that I took a rather simple view that the responsibility for agreeing and undertaking clinical trials of coagulation factor concentrates rested solely with the clinicians and local ethical committees. Our responsibility was to use all means to ensure that UK patients had

sufficient access to concentrates derived from unpaid donors and to protect a relatively unique but small UK patient group so that they could be used for clinicals by NHS fractionators. In 1982 I was uncertain that we had the support of DHSS, the MCA/Medicines Commission for this latter proposition nor, I regret to say, SHHD. This position changed in 1989 with the anticipated publication of the EU Directive (89/381).

12.2 There is no doubt that when I look in 2010 at the proposition that Peter Foster and Jim Smith's interactions were 'furtive', an apology is due. I'm afraid the temperature in this meeting got too high and some of us became extremely anxious that all the SNBTS had stood for was to be swept aside by market place considerations. I suspect that Jim Smith and Peter Foster were aware that in 1980 I had sought to persuade Jim's boss (Dr Lane) 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. Despite this. and at that time unknown to me, Dr Smith elected to work closely with former PFC colleagues.

12.3 I do not know whether the content of this letter was eventually conveyed to the PFC team; Dr Foster may be able to brief you on this. What I do know is that it was copied to Dr Gunson and Dr Bell (SHHD). As a consequence Dr Gunson gave his strong support for my concerns. No support or opposition came from SHHD.

12.4 There should indeed be a 'not' inserted into the fourth last line on page 1 - thank you!

13. Dr Lane replied on 21 December 1982 (SNB.004.3160 - see dvd). Dr Cash wrote back on 29 December, in more conciliatory terms (SNB.004.3159 - see dvd). It is not clear how this difference of view was ultimately resolved. Can Dr Cash and/or Dr Lane recall?

13.1 Comment/Answer: It is noteworthy that Dr Lane's response was very formal. The implication in his letter, that my position had changed, was misleading. My objections to the proposals had not changed but my view on certain tactics - notably letters in the medical media etc - had changed; I now felt there should be no media communications. Whilst you may conclude my letter of the 29 December to Dr Lane may appear conciliatory, you can be assured that this was only associated with how I expressed my opposition to the proposals rather than their substance.

13.2 To the best of my recollection the proposition in 1982 that the UK NHS fractionators should support the introduction of clinical trials of viral inactivated commercial VIII concentrates in the UK never got off the ground. I assume because the majority of the UK Haemophilia Centre Directors saw the dangers and opted to support the UK Blood

Transfusion Services. The best source of confirming or refuting this must be a HCD – such as Dr Ludlam or Professor Christine Lee and to get a non redacted copy of SNB:004.9164. On the other hand almost 2 years later (March 1984) the wider church of the UK Haemophilia Centre Directors were moved to further consider this matter (DHF.002.8963). Again Drs Ludlam and Lee would be best placed to advise on the outcome of these 1984 deliberations. Beyond this, my next best recollection is the proposal to develop clinical trails of BPL products in 1987 (see UK HDC annual meeting Minutes - 25/9/87)

13.3 The SNBTS's reaction to this confrontation in 1982 was immediate and proactive; throughout February 1983 direct contact was made with the Directors of the Haemophilia Centres in Oxford, Edinburgh and Glasgow in order to stake an SNBTS 'claim' on access to their patients. Their responses were all positive. Six months later BPL seemed to join us when it was announced at the UK Haemophilia Centre Directors, meeting in Oxford, that they had a virus inactivated VIII almost ready for clinical trials.

14. Events in the first part of 1983 are dealt with in the report at paragraphs 11.96 to 11.114. Several themes appear to have predominated: the need to maintain momentum in the attempts by the NHS bodies to produce heat-treated material because of the advent of such material from commercial producers; the need to test any heat treated Factor IX for thrombogenicity; continued reporting by Dr Foster to Dr Smith of progress in Scottish research and development (including a letter of 4 May 1983 mentioned in the report at footnote 144), and the need to organise clinical trials of such heat treated material as PFC were able to produce.

14.1 Comment: I agree. It is the perhaps appropriate to point out that the development of tests to eliminate potentially fatal thrombogenic episodes in patients receiving certain batches of factor IX concentrates were first conceived and developed by an SNBTS team. The technology associated with this development proved to be of value for regulatory authorities, worldwide and may exist even to this day.

15. Was the reporting to England reciprocal?

15.1 Answer: I regret I do not recall. Dr Foster should be of assistance.

16. It is noteworthy that both heat treatment and AIDS were discussed at the meeting of the Haemophilia and Blood Transfusion Working Group on 22 March 1983, but without any cross reference between these topics (see paragraph 11.114). It is minuted that "there was concern that AIDS might appear in the UK"; this comment appears to have come from Dr Ludlam.

16.1 Comment: I would suggest you are reading a little too much into these Minutes. Heat treatment was a process that was assumed might inactivate all viruses transmitted by plasma products. Thus in March 1983

a specific link between the two would have been taken for granted. This assumption, however, was later shown to be simplistic.

17. By 3 May however, Dr Foster was referring to the need for the heat treatment programme to deal with the threat of AIDS (paragraph 11.123). Mr Watt also wrote to Dr Cash on 5 May 1983 (11.124): both these documents appear to be arguing the case for acceleration of the heat treatment programme. Dr Foster specifically mentions AIDS, and Mr Watt is presumably also referring to it with his allusions to "news exposure" and "public opinion". Dr Foster referred to the option of beginning heat treatment of bottled fluids using the existing pasteurisation cabinets. Was he essentially advocating a swifter resort to pasteurisation using existing equipment rather than constructing new plant? Is this essentially what occurred at the end of 1984 as far as the heating step was concerned (noting that, of course, the material treated at the end of 1984 was freeze dried Factor VIII)?

17.1 Answer: As far as I recall, by May 1983 we were a little more certain that AIDS was transmitted by plasma products and that the clinical consequences were very much more serious than viral hepatitis. It follows that Dr Foster's reported efforts to accelerate our heat treatment development programmes were entirely appropriate. I no longer can recall the details of the proposed acceleration process but have no doubt Dr Foster can provide these.

18. Dr Cash responded to Mr Watt on 1 June 1983 (paragraph 11.128). The tone of this letter ("public opinion may eventually press us heavily") creates the impression that Dr Cash's view of the time frame within which acceleration would have to take place was longer than that of either of Dr Foster or Mr Watt. In connection with this, Dr Cash also considered that there were no funds available in 1983 - 84 for these proposals, citing the views of the Deputy Chief Medical Officer and the instructions from the SHHD to the CSA. It is not clear to what these comments refer - can Dr Cash recall? The Inquiry team has discovered documents relating to possible increased funding, but they appear to concern the main plan, not the "intermediate stage" contemplated by Dr Foster. Thus, it appears that Dr Foster's idea of proceeding more quickly to "an intermediate stage", Le. one using existing equipment as outlined in SNB.007.3635, was not taken forward by others. Is this correct?

18.1 Comments/Answers: I regret I now don't recall much of the detail related to these communications. But I was interested in your interpretation of my letter to Mr. Watt. As I recall I agreed that Mr. Watt had made a very good point – public opinion may one day judge us harshly if we did not react urgently with regard to expediting our heat treatment programme development. It is my understanding of this letter that as NMD I sought to support Mr. Watt and examine ways in which this acceleration might be achieved, in terms of increasing the resources PFC needed, against the background of the existing SHHD funding allocations for 1983 which had been conceived and applied for in 1982 – which I suspect relates to what you have described as 'the main plan'.

18.2 I imagine Dr Perry and Dr Foster may be able to provide you with information on whether the PFC team responded to my suggestion that

they put together a new (compared to 1982) heat treatment package for SHHD, which included a component for accelerating their programme and, if so, whether there was a positive and adequate response. I would imagine that a new request coming in the middle of the financial year would have caused some consternation to SHHD. But looking at SNB.007.4523 I conclude they did and a response, at least from the CSA, was forthcoming.

19. The next important step in the development of heat treatment in Scotland appears to have been the renewed contact with Professor Johnson of New York, described in paragraphs 11.135 and 136. Although the Preliminary Report refers to the potential for Professor Johnson's method to resolve the technical difficulties PFC were having, the letter is perhaps more indicative of a desire to share in the details of a high yielding and high purity process which was simple to perform - very attractive to fractionators. Is it possible to ascertain - at least in outline - what the particularly efficacious steps in this process were?

19.1 Answer: I'm afraid I do not have the appropriate expertise to respond to this question but have no doubt Dr Foster will be able to address it.

20. Dr Foster updated Dr Smith of PFL on the work at PFC by letter dated 23 August 1983 (see paragraph 11.139). Perhaps unsurprisingly, the intended collaboration with Professor Johnson was not mentioned.

20.1 Comment: This question should be directed to Dr Foster.

21. Meanwhile, Mr Watt had tendered his resignation as Scientific Director of PFC. We have some papers related to this, but not enough to ascertain why Mr Watt chose to leave (he says in his letter to Professor Johnson on 1 August 1983 - see paragraph 11.136 - that his decision was "multifactorial") or, more importantly, if this adversely affected the viral inactivation programme.

21.1 Comment: The reasons for Mr. Watt's departure might well be considered to be multifactorial.

21.2 I am quite certain that the departure of Mr. Watt had a profound impact on the morale of the PFC staff, but I have some doubt that it impacted adversely on the continued development of PFC's heat treatment programme. Drs Perry and Foster would be the best judge of this. It might be argued that his departure, in due course, better enabled the PFC team to make the difficult decision to switch from wet to dry heat, and institute a more constructive and sensitive internal management climate. Dr Foster would be the best judge of the former and he and Dr Perry the latter and also on the morale of PFC staff. That said, I have always believed that the departure of key PFC engineering staff to Mr. Watt's consulting company proved, in due course, to be detrimental to PFC.

22. Dr Cash and others knew of Mr Watt's resignation by 15 July 1983 (a Friday) on which date the issue was discussed at a meeting with (Dr) Graham Scott and (Dr) Bert Bell (Letter dated 19 July 1983 - SNB.005.8946 - see dvd). The issue led to postponement of a meeting with representatives of CBLA, against the background that Mr Mutch of the CSA expected that they would require to give "considerable thought to the future role of the PFC" (SGH.007.0764 - see dvd). The original plan was for Mr Watt to leave at the end of March 1984, but he left at the end of December 1983 (SNB.009.4290 - see dvd). Dr Cash described the circumstances of his departure as "unusual" in a letter of 5 January 1984 (SNB.011.1346 - see dvd) Dr Perry took over as Acting Director - and Dr Cash emphasised his view that the next Director of PFC had to be "unequivocally responsible to the National Medical Director" (Dr Cash). All of this is evident from Dr Cash's letter of 23 May 1984 (SNB.011.1688, see dvd). That the relationship between Dr Cash and Mr Watt was not in good repair can also be inferred from Dr Cash's letter to mMr Mutch of 26 August 1983 (SNB.005.8944 - see dvd).

22.1 Comment: Much of what appears here has already been addressed above. But the issue of the management accountability/reporting lines for the Scientific Director of PFC was in the 1980s, and remained throughout the 1990s and beyond, a matter of considerable concern and importance. Mr. Watt was responsible to the Secretary of the CSA (Mr. Mutch). Mr. Mutch's problem was that he had no scientific education.

22.2 Failure by SHHD officials to address this issue led to a number of avoidable management crises within PFC which could have had significant impacts on our service to SHS patients. This is well illustrated in a communication, dated 5 January 1984, between myself and Mr. Mutch. This communication in due course led me to the conclusion that there had never been any regular contact between Mr. Mutch and Mr. Watt and that despite the assurances from SHHD officials Mr. Mutch had no knowledge of any of the operational aspects of PFC. I believe this letter also reveals that there were a number of unresolved quite major management problems within PFC. Mr. Watt had been a 'free agent', and effectively accountable to no one. Mr. Watt advised me that in 1976 he had 'seen off' the NMD (General Jeffries) but in 1979, with the appointment of myself (who had been in years past a close friend) he was in some difficulty. It is my view that this single factor – a wholly inadequate management interface between CSA/NSS and PFC - was ultimately the primary cause of PFC's demise in 2005. BPL, equipped with a more appropriate management structure, continues to flourish.

23. The second half of 1983 saw progress in Scotland with trials of heat treated product and discussion of related issues.

23.1 Comment: I agree

24. Meanwhile in England, more attention appears to have been paid to dry heat treatment. This is notwithstanding a recognition, as recorded in a CBLA paper on heat treatment, that pasteurisation was "more homogeneous and efficient and to satisfy reliability in

manufacture (was) to be preferred" (paragraph 11.151). It appears from this paper that, albeit that dry heat treatment was the second choice technically, the pressure in haemophilia care was such that it had to be pursued; wet heat treatment was likely to require "a longer programme of work". (It is worth contrasting however the minutes of a meeting of the CBLA Working Group on AIDS, which noted that the dry heat treatment of Factor VIII had not been encouraging; this is presumably a reference to the knowledge that 3 chimpanzees given the product had developed hepatitis (see, for example, Dr Walford's letter to Dr Gunson of 1 July 1983, DHF.002.5668, paragraph 11.149».

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24.1 Comments: Without sight of Dr Gunson's letter of the 26 June 1983 to Dr Walford it is difficult to comment, though I note that Dr Walford is reminding Dr Gunson that with regard to concerns about safety of plasma products this remains in the hands of the CSM. We should also note that that Dr Walford (DHSS) was a member of the CSM at this most crucial time and this should give rise to questions about the influence of Ministers on the CSM's deliberations. It is also of interest that Dr Walford in June 1983 is suggesting that the introduction of clinical trials may need to be considered – to prevent what she describes as 'unjustifiable demands' by clinicians! This statement seems some distance away from the DHSS policy, in the context of defining self sufficiency, that clinicians should be free to prescribe what product they felt was in the best interest of the patient. It should also be noted that hitherto (notably in the 1970s when the importation of commercial coagulation factor concentrates began) the CSM did not consider the safety of these products, despite published concerns.

25. The Preliminary Report highlights a memorandum from Dr Smith to Dr Foster in January 1984, setting out detail of work to date on dry heat treatment of Factor VIII (see paragraph 11.156). Was this degree of disclosure new? What effect, if any, did this news have on those working at PFC?

25.1 Comment: I am unable to offer comments on these questions, but am certain Dr Foster will.

26. Also worthy of note is Dr Ludlam's letter of 11 January 1984, describing the reaction of his patient who had trialled the new heat treated product (SNB.001.5311, paragraph 11.158). Although the letter bears to be revelatory, this information had already been imparted at the meeting of 14 November 1983 (SNB.001.5188, paragraph 11.143). At that meeting, the effect had been described as a "minor adverse reaction" whereas in the letter of 11 January 1984 it is described as "significant and unacceptably adverse reactions". What is the explanation for the difference? Was the letter of 11 January 1984 written at the request of Dr Cash?

26.1 Comment: I have no recollection that I requested Dr Ludlam to change his mind and have no explanation as to why you feel this might be so.

27. The information from England was referred to at the Factor VIII Study group meeting of 12 January 1984 (paragraph 11.160), along with the information that the Hyland heat treated product was still infective. Was it the latter information which appears to have limited the perceived significance of the reports of success with dry heat treatment in England? Was there any suggestion at all of the possibility of changing tack?

27.1 Comment: These questions are important and are best directed to Dr Foster. I have reason to believe you will find that the first experimental attempt at dry heating an intermediate VIII at PFC was on 21 November 1983. The manufacture of the first batches of dry heated PFC VIII intended for clinical use commenced on 18 November 1984 (12 months later).
I have seen no documents which answer the question: why and when did PFC consider abandoning wet heat treatment of VIII and when was it decided to abandon it and who made this decision?
27.2 I do not recall who outside PFC were briefed of these events but imagine Drs Perry and Foster may be able to provide this information.

28. A costing for the production of heat treated Factor VIII was prepared in February 1984, showing a total of £90,000 (see paragraph 11.166). The date towards which PFC were aiming was April 1985 - was there any suggestion that this might be too long a timescale?

28.1 Comment: I would suggest that Dr Perry would be best placed to respond to this question.

29. By the end of March 1984, there were eight "hepatitis reduced" Factor VIII products in preparation or available for trial (DHF.002.8963, see dvd, although paraphrased in paragraph 11.175) - this document refers to the Edinburgh product being available "shortly", which appears to be over-optimistic. How did Dr Craske get this information?

29.1 Comment: I do not recall.

30. The response to the application for funds to develop the heat treatment programme appears to be illustrated by a minute from Dr Bell dated 23 May 1984; Dr Bell was very supportive of the plan (see paragraph 11.181). It is evident from his minute that the case for funds had already been approved at the BTS sub-committee on 22 February 1984. It is also apparent that the actual designation of the funds took further time - see letter of 13 August 1984 from Dr Perry to Mr Wooller of the CSA (SNB.007.4523, see dvd). This letter appears to have generated a speedy response, as SNB.007.4527 (see dvd) indicates that the expenditure is to be formally authorised within the next few days. Did issues of funding delay research?

30.1 Comment: I regret I do not recall.

31. Significant developments in viral inactivation occurred towards the end of 1984. At a meeting in Cardiff in October 1984 Dr Mannucci gave a talk which indicated that in a

group of patients given heat treated Factor VIII (Travenol - Hemofil) there had been no seroconversion after a year (see paragraph 11.190, and SNB.004.9164) The same information appears to have been imparted at a plasma fractionation conference in Groningen attended by Dr Foster. From this, Dr Foster appears to have inferred that the Hyland product would also be inactivated against HTLV III (see SNB.008.6528, paragraph 11.191).

31.1 Comment: My reading of SNB.007.9164 seems to be somewhat different to yours. Piero Mannucci's European studies signaled that Baxter's haemophil T product seemed not to transmit HIV but 70% of the recipients got hepatitis, most of which was NANB. As I recall the importance for us of the communication at Groningen was that the sensitivity of HIV to heat was confirmed and the type of product and heat treatment given (by Cutter) was very similar to ours and there did not appear to be any immediate adverse clinical reactions.

32. Also at this time - although it is not entirely clear when - it had been discovered that a group of patients treated with NHS Factor VIII at Edinburgh Royal Infirmary over the period March to May 1984 had been infected with the AIDS virus.

32.1 Comment: I am quite sure that SNBTS staff can make available the details of this event and its investigation.

33. In this context, PFC moved very quickly to introduce dry heat treatment, as narrated in 11.205 to 213.

33.1 Comment: Correct.

34. The implication in the minutes of the meeting of PFC heads of department on 26 October 1984 (SNB.010.3479 - see dvd) is that it was known, at least to Dr Perry, that there had been infection by PFC product. Is this correct? The minutes of the meeting on 13 November (SNB.010.3475 - see dvd) are similarly elliptical in their reference to the need to "render all Factor VIII free from HTLV III virus".

34.1 Comment: I have no comment to make as I did not attend this meeting

35. It appears that the swift introduction of dry heat treatment must have required equipment both for freeze drying and for heating. It is the Inquiry team's understanding that the heating took place in baths previously used to heat albumin - is this correct? And how was the equipment necessary for the freeze drying obtained? There are some references to freezers and freeze driers in the minutes of meetings around this time, but it is not entirely clear what equipment was already available, what had to be purchased and when it was all in place (see documents SNB.010.3479, SNB.010.3475, SNB.010.3483, SNB.010.3545, SNB.010.3470, SNB.010.3466 and SNB.010.3462 in dvd).

35.1 Comment: These questions should be directed to Drs Perry and Foster

36. In retrospect, the infection of the group of people known as the Edinburgh Cohort would have been prevented if PFC had moved to dry heat treated product at the beginning of 1984. It appears that the equipment necessary to do so was either already installed or easily obtained. What are the reasons why this did not take place?

36.1 Comment: I suggest it would more productive to invite Drs Perry and Foster to respond to this question.
I for my part recall:

36.11 That the first experimental dry heating of PFC VIII took place in November 1983 and that within 12 months the manufacture of the first batch of PFC VIII destined for clinical use was commenced. In the context of the pharmaceutical industry I would judge this 12 month period would be regarded as very short.

36.12 The batch we believe caused the HIV Edinburgh cohort HIV infection was processed in the first week of November 1983 – almost certainly before the first experimental dry heated batch. It follows that if my recollections are correct your proposition is a non starter.

36.13 There was great concern among many of the clinicians that any form of heating might be associated with protein denaturation which could have serious consequences for the patients. Much laboratory effort was put into this perceived problem and the move to put products in to patients had hitherto been very cautious. Faced with the reality that HIV had got into the Scottish donor population the move to put dry heat treated PFC VIII in to patients was pushed forward in late 1984 with much less caution. I and my clinical colleagues found December 1984 a very anxious time. We found ourselves alone, without active support from SHHD or the MCA. Thus, to our surprise, we found ourselves pleased with the comfort that we were operating under the cover of Crown Immunity – though it has to be said we were never sure to what extent this feeling of comfort was justified.