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."

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.

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?

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?

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?

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?

7. The then current state of play appears to be summarised in the report of the Safety sub-group 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 for 10 hours at 60° C. Subsequent meetings of the group and sub group are chronicled in paragraphs 11.63 to 66.

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 (see 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).

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)?

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, outlining PFC's work on heat treating Factor IX and freeze drying (SNB.007.3341, see 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?

11. It appears that good progress was made in the pasteurisation project: the patent claim and an optimistic memo are 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?

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?

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?

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.

15. Was the reporting to England reciprocal?

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.

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)?

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", i.e. one using existing equipment as outlined in SNB.007.3635, was not taken forward by others. Is this correct?

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?

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.

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.

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 Mr Mutch of 26 August 1983 (SNB.005.8944 – see dvd).

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

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)).

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?

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?

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?

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?

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?

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?

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).

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.

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

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".

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).

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?

Documents annexed in DVD

1. Report prepared by Mr Watt in 1973 "Development of Factor VIII Concentrates" (SNB.001.6903)
2. PFC Research & Development Report, April 1975 (SNB.010.4779)
3. Behringwerke paper – Kröniger et al, "Factor VIII Concentrates", Die Medizinische Welt, 16 July 1982 (SNF.001.0921)
4. Typewritten paper on the Behring process received during the International Society of Haematology and International Society of Blood Transfusion conference in Budapest in July 1982 (SNF.001.0929)
5. Letter from Dr Foster to Dr Smith on 1 December 1982 (SNB.007.3341)
6. Letter from Dr Cash to Dr Lane on 17 December 1982 (SNB.004.3163)
7. Letter from Dr Lane to Dr Cash on 21 December 1982 (SNB.004.3160)
8. Letter from Dr Cash to Dr Lane on 29 December 1982 (SNB.004.3159)
9. Letter from Dr Cash to Mr Mutch on 19 July 1983 (SNB.005.8946)
10. Letter from Mr Mutch to Mr Redhead on 18 August 1983 (SGH.007.0764)
11. Memorandum from Dr Perry to HODs and Section Managers dated 30 December 1983 (SNB.009.4290)
12. Letter from Dr Cash to Mr Mutch dated 5 January 1984 (SNB.011.1346)
13. Letter from Dr Cash to Mr Mutch dated 23 May 1984 (SNB.011.1688)
14. Letter from Dr Cash to Mr Mutch dated 26 August 1983 (SNB.005.8944)
15. Memorandum on trials of "hepatitis reduced" Factor VIII dated 29 March 1984 (DHF.002.8963)
16. Letter from Dr Perry to Mr Wooller on 13 August 1984 (SNB.007.4523)
17. Memo from Mr Wooller to Dr Perry on 18 August 1984 (SNB.007.4527)
18. Minutes of a meeting of PFC Heads of Department on 26 October 1984 (SNB.010.3479)
19. Minutes of a meeting of PFC Heads of Department on 13 November 1984 (SNB.010.3475)
20. Minutes of a meeting of PFC Heads of Department on 5 October 1984 (SNB.010.3483)
21. Minutes of a meeting of PFC Heads of Department on 25 April 1984 (SNB.010.3545)
22. Minutes of a meeting of PFC Heads of Department on 23 November 1984 (SNB.010.3470)

23. Minutes of a meeting of PFC Heads of Department on 29 November 1984 (SNB.010.3466)
24. Minutes of a meeting of PFC Heads of Department on 7 December 1984 (SNB.010.3462)