Written Statement in relation to viral inactivation in the period to 1985 – Dr.J.K.Smith

In the course of making these Notes, I found it impossible to consider HIV/AIDS without explaining some of the historical and technical background, especially in relation to NANBH. I have strayed occasionally beyond 1985, but only where necessary to tie up reflections on the main period. I also plead guilty of as much interpretation as confirmation of "facts". My heavy involvement at the time may justify that. There is an opportunity to minimise that element of the draft if I am so guided by the Inquiry.

My draft statement is in three parts:

1. **" Snapshots and Landmarks" .**

These have been overwritten in red with brief comments in their most natural positions. Where it is unclear whether a question is being addressed to me, I have erred on the positive side. Unsought remarks may of course be ignored.

2. **JKS Notes 1-5.**

These arose in several ways:

- A specific Question seemed to need a longer, more informative answer.
- A thematic narrative seemed to be helpful in bringing together related facts which have become dispersed in the chronological account adopted by the Preliminary Report (PR).
- An important issue appeared to me to be accorded too little or too much weight in Questions or PR .
- It seemed helpful to respond frankly (see especially JKS Notes 3 and 4) to some questions not put directly in Snapshots or the PR, but which nevertheless I see hovering over the text .

3. **Comments on specific paragraphs of the PR**

These were not actually requested, but have been included in the spirit of correcting any conclusions or inferences in the PR which seemed to be misleading. Other comments are intended to enrich the Inquiry's understanding of some event whose significance may be unclear at a distance of 25-30 years.

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.

   That is correct.

   The report prepared by Mr Watt in December 1973 (SNB.001.6903 – see compressed file) does not mention viral inactivation,

   That report (which appears to have been assembled by me), concerned solely F.VIII

   although, according to the report of Research and Development from 1975 (SNB.010.4779 at page 11 – see compressed file) there had been a paper presented at the Congress of The International Society of Thrombosis and Haemostasis, Vienna, Austria:

   I do not have a copy of this paper, which was probably given by Dr.Johnson – a fuller version was published in 1976. The Newman&Johnson mentioned here are indeed the same authors on whose F.VIII methods we were building in the early 1970s, but the Factor IX/HBsAg project was quite distinct.

   a. *"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 - compressed file) 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.

   That is exactly right – we now use the term "virus reduction" to cover both partitioning of the virus and its inactivation.

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?

(Throughout this written statement, my interpretation of PFC's activities during this period is not based on inside knowledge, but on the collection of evidence in the Preliminary Report and my fallible reconstruction of ideas current at the time.)

The text says "learned of" which could mean almost anything but almost certainly not a repeatable process description. Dr.Foster may have seen the first evidence of this, also in 1980, in a very brief notice of a patent application, in Chemical Abstracts; he would almost certainly have waited for fuller publication in 1981 [Arzneimittel Forschung 1981; 31:619-22] [see SNB.008.6794 and paragraph 11.44 of the Preliminary Report] before taking a view. To be pedantic, some details had been "published" in Behringwerke's house journal [Die gelben Hefte 1980; 20: 165] but this un-refereed journal was scarcely available in UK and certainly not on any fractionator's regular reading list.

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?

Almost certainly, in view of the fact that Behringwerke had started clinical trials. However, there was a patent application from Cutter (US) at about this time, which Dr.Foster may have found out about, at least in general terms. It is significant that PFC already believed that pasteurisation would be successful only if F.VIII could be substantially purified first. It was probably in 1981 that Hyland began to reveal experiments on "heat treatment" of F.VIII. The actual treatment and process conditions were not published for some years, and more than one person was misled into guessing that this, too, was pasteurisation (heating in solution) [See SNB.007.3342].

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?

   I could adduce two main threads.

   It is not sufficiently realised, even in the PR, how little pressure there was from the haemophilia treaters and patients to take NANBH seriously in this period before 1983. Most clinicians would have assumed that "NHS" concentrates were much safer from NANBH than commercial concentrates because of the unpaid donor source. The view that NANBH could have severe long-term sequelae was not widely held. Hepatitis B was thought to have been tamed by donation testing, and there was a vaccine on the near horizon (1984). It really took AIDS in 1983-4 to get the attention of the majority on to blood-borne viruses.

   Fractionators were much more concerned about NANBH but this was always a very recalcitrant virus, with no convincing markers until right at the end of the decade. We had very few tools at our disposal, especially for proving whether any attempt at inactivation had succeeded. We were also misled by persistent claims that there might be more than one NANBH virus. The work begun at PFC in 1981 would have been exploratory and may not have acquired much in the way of data or priority by January 1982. Alternative methods were being considered with at least equal care and apparently greater prospects of success. Some impediments to embracing pasteurisation are discussed in JKS Note 1.

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 compressed file at SNF.001.0921 and paragraph 11.74).

   That 1982 paper is about detailed characterisation of F.VIII products and is not helpful in providing process details.

   Dr Foster also received a copy of a typewritten paper on the Behring process (see compressed file at SNF.001.0929 and paragraphs 11.74 - 78) which he passed to Dr Cash (see acknowledgement dated 12 April 1983, SNB.007.3600).

   That paper, too, has no real process detail. It simply holds out some promise of successful preliminary studies in chimpanzees and in patients. It would have served to increase interest in the pasteurisation approach and perhaps increase its priority.

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)?

   This overplays the similarities between the pasteurisation of albumin and that of any other protein. See JKS Note 2.

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 Correct, (SNB.007.3267) BPL were doing "a little" on heating Factor VIII.

    <u>Brief</u> heating at temperatures around 60ºC, without stabilisers, was being considered as a means of precipitating fibrinogen as a solid while leaving most

F.VIII in solution – by no means an original idea, but we were ready to try almost anything short of voodoo. There was no intention to inactivate NANBH. The letter goes on to say that BPL was in no shape to start serious work on pasteurisation (anticipating a very long haul) and that I would be very pleased if PFC's work might offer some encouragement.

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 compressed file). How would those involved characterise the cooperation at this point?

I would characterise it as decidedly lopsided at this point, insofar as virus inactivation in F.VIII was concerned. BPL was in a delicate transitional condition and had few resources to tackle the problem seriously.

It was a correspondence between scientists with a clear sense of their responsibilities. We were both well aware of a degree of tension between the upper layers of our respective organisations but agreed (without as I recall having to discuss the question) that this must not be an obstacle to pooling what information we could each gather

It will also be evident from SNB.007.3342 that, during my tenure at BPL Elstree, PFC visitors were welcomed and technical information shared openly. My colleagues and I invariably received an equally warm welcome from everyone at PFC and the rest of SNBTS. I had quite frequent correspondence also with Dr.Pepper, and less frequently with Dr.Prowse, though not in the mainstream of heat treatment.

What degree of importance did viral inactivation have in the R&D priorities of BPL at this point?

In the wake of an unfortunate transmission of NANBH by intravenous immunoglobulin in England, the Director (and Medical Director) of BPL, Dr RS Lane, was among the earliest to realise that NANBH was becoming a very serious problem in recipients of plasma products, and therefore a threat to broader perceptions of the safety of large-pool fractionation. There were many obstacles to tackling the problem, other than the local ones of resources in a difficult period at Elstree (See JKS Note 1). A measure of our frustration and desperation is that, in designing the Coagulation section of the new BPL, I

planned (April 1981) an area in which uneconomically small pools of 10-20 donations could be fractionated to F.VIII and F.IX, either aseptically or under tight environmental control. This idea, which thankfully never had to be played out, envisaged only sufficient product to protect infants and other previously-untreated patients from NANBH, until a solution was "arrived at by someone" – buying time until the cavalry appeared.

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 compressed file). In his letter, he details experiments on (?)pasteurising Factor IX

Yes, this refers to pasteurisation of our respective F.IX products – I had forgotten that work on F.IX at Oxford PFL had advanced even so far.

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?

All F.VIII products (other than cryo) have been freeze-dried since the earliest crude fractions in the 1960s. It's really a sine qua non.

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 compressed file). 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"?

It may be kinder not to pursue Dr.Cash about a momentary misjudgement - certainly of Dr.Foster's probity. Dr.Lane did not offer any support for the term in his crisp reply [SNB.004.3160]. I received no rebuke, or discouragement from proceeding as we were. Dr.Foster appeared to remain serene.

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 compressed file). Dr Cash wrote back on 29 December, in more conciliatory terms (SNB.004.3159 – see compressed file). 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?

I would have continued to inform PFC without constraint of anything notable coming out of our still very tentative work on pasteurisation, and later dry-heating, in 1983. But I cannot document that.

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.

There was some resistance among haemophilia clinicians to the idea that AIDS was caused by a blood-borne virus. I do not think that this affected the urgency felt by SNBTS.

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).

I believe that most fractionators thought it likely that AIDS was caused by a blood-borne virus, even before the seminal publication by Montagnier's group [Barre-Sinoussi ...Science 1983;220: 868]. My recollection is that this was published in March or April 1983, and was taken by transfusionists as strong support for their working hypothesis.

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?

Yes, in my reading. Very resourceful.

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)?

Yes, in my reading.

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?

There was no undue delay between these energetic moves in 1983 and the costing and schedule developed in February 1984 for national roll-out in April 1985 (See Q.26 and 11.166). It seems that during the autumn of 1983, pilot-scale batches were prepared successfully and put into clinical trials. However, work on purification in conjunction with Alan Johnson was going so well that it was thought likely the next generation of pasteurised F.VIII would be based on chromatographic purification rather than on the less pure product of zinc-heparin precipitation. (See JKS Note 3.)

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?

This may have been a chromatographic process using a new ion-exchanger. The process was not finally adopted, partly because of difficulty in getting repeatable results using different batches of the proprietary adsorbent. There followed discussions with Pharmacia and there was slow progress towards a reproducible ion-exchanger. This did not bear fruit within the period up to the end of 1985. Development may have been accorded less priority than dry-heating to defeat HIV - still seen in 1984 as a stop-gap measure unlikely to deal with NANBH. I guess that at this point PFC was not convinced of the necessity of high purification for physiological reasons, but was following its experience that prior purification facilitated pasteurisation (JKS Note 2).

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.

Proprietary information released under a Confidentiality Agreement never featured in our exchanges. In fact, during the early 1980s we communicated almost exclusively on technical aspects of virus inactivation and did not seek to stay abreast of our respective national policies.

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

22. Meanwhile in England, more attention appears to have been paid to dry heat treatment.

This paragraph is correct in its inferences but requires some exposition (JKS Notes 4.2 and 4.3).

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).

This paper is not by my hand, and contains several misconceptions, including the date by which dry-heated products might be sufficiently developed for release.

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;

I would have concurred (JKS Note 4.5)

wet heat treatment was likely to require "a longer programme of work".

I would have concurred.

(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).

I see no contrast here. There is no inference in 11.151 that NANBH would be inactivated by dry heating.

23. 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?

There does appear to be some gap in technical correspondence, but Dr Foster and I both understood perfectly well that we were pursuing different approaches in the short term, for our respective pressing reasons. For example, during this period PFC was greatly preoccupied with preparing a pasteurised product for clinical trial. My letter would not be intended in any sense to divert PFC from pasteurisation (JKS Notes 4.3 and 4.5), simply to show that the Oxford and larger-scale Elstree products were capable of withstanding heat treatment, as Rubinstein predicted. I had no information (and at the time little hope) that this treatment would inactivate NANBH, which remained the goal of pasteurisation.

What effect, if any, did this news have on those working at PFC?

See JKS Note 4.5.

24. 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?

See JKS Note 3.

25. 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?

See JKS Notes 4.5 and 5.

26. 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?

27. By the end of March 1984, there were eight "hepatitis reduced" Factor VIII products in preparation or available for trial (DHF.002.8963, see compressed file, 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?

28. 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 compressed file). This letter appears to have generated a speedy response, as SNB.007.4527 (see compressed file) indicates that the expenditure is to be formally authorised within the next few days. Did issues of funding delay research?

This was fast-tracking indeed. Nor were we at the sharp end in England ever flatly refused any resource which could be bought, during this first surge of concern about AIDS – I'm fairly sure NANBH was far from most minds by the end of 1984.

29. 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

i.e. infection with AIDS/HIV – there was little or no protection from NANBH

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.

This para may be conflating two separate notions. The crucial information was from the Groningen meeting, at which the US Centres for Disease Control reported the first solid laboratory evidence that "HTLV III" grown in lab culture and spiked into F.VIII was inactivated fairly rapidly by dry-heating at 60-70ºC. At PFC, this did appear to swing the balance, possibly for the first time, towards doing something quickly about AIDS and coming back to NANBH and pasteurisation when resources permitted. That something was done with remarkable speed. The Groningen news precipitated rapid decisions and action at BPL/PFL also (See JKS Notes 3 and 4.4). The speed with which PFC reacted is all the more remarkable in view of the fact that these efforts coincided with a major plant shut-down (see refs in Q.32)

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).

30. 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.

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

32. The implication in the minutes of the meeting of PFC heads of department on 26 October 1984 (SNB.010.3479 – see compressed file) 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 compressed file) are similarly elliptical in their reference to the need to "render all Factor VIII free from HTLV III virus".

There is no reason to read into either of these minutes prior knowledge of infections described in Q.30. Dr.Perry was simply confirming the natural sequelae to Groningen, Cardiff etc.

33. 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?

That is my reading. The temperature of these baths was controlled sufficiently precisely for consistent dry-heating.

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 compressed file).

34. 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?

May I be allowed to speculate, since I was not party to PFC's decision-making but was swimming in the same soup at the time? (See JKS Note 4.5):

- ***Prior to November 1984, there was no reason to believe that dry-heating would succeed in preventing transmission of AIDS, and in fact almost all the early dry-heated (commercial) concentrates caused confirmed transmissions of HIV at later dates. In the wake of Hyland's experience, there was no likelihood that NANBH would be inactivated if dry-heating were applied to PFC's F.VIII at that time.***
- ***I am not sure that, in early 1984, it was generally perceived that AIDS had entered the UK donor population. No test was generally available, validated for application to large populations of donors.***
- ***In about May 1984, three patients in England were given mildly-heated (60ºC, 72h) Factor VIII, and by the end of 1984 had contracted neither AIDS nor NANBH. For reasons discussed in JKS Note 5, this anecdotal experience***

had no impact on BPL's policy. If in fact the information was considered significant enough for me to share with SNBTS, I would not have expected it to affect PFC policy.

- ***At the beginning of 1984, clinical trial of PFC's pilot-scale batches of pasteurised F.VIII was still being considered successful (11.143) and there were detailed plans for scale-up and national issue in a credible time-scale (11.166). There was reason to expect that this pasteurised F.VIII would transmit neither AIDS nor NANBH. For several reasons, it is extremely difficult to envisage running two candidate products full-pelt in a unit with limited resources, so a choice had to be made (England did not have the luxury of choice [JKS Note 4.4] and was perhaps lucky in that – but only with hindsight). It should not be inferred that PFC made the "wrong" choice at that period, or that PFC was slow to modify its position when the evidence moved on, later in the year.***

JKS Note 1. Impediments to the development of heat treatment against NANBH

The intention here is simply to assemble in one place the obstacles perceived in, say,1980, to sterilising Factor VIII etc. by heating. Most of them are explained further in the PR, in Snapshots and my responses, or elsewhere in these Notes.

- NANBH was widely perceived as a mild, transient illness with only very rare serious sequelae.
- It was widely believed that NANBH was transmitted by unpaid donations (as in UK) much less frequently than by plasma from paid donors (predominant in large pools used in "commercial" fractionation).
- There was no credible marker or screening test for NANBH, at donation or concentrate level.
- There was no means of culturing NANBH, e.g. for "spiking" and detection of residual virus in model virus-inactivation studies.
- The only way to confirm infectivity of a concentrate was to inject it into three previously-untreated chimpanzees, an endangered species. Even this could not prove non-infectivity. (The chimp model, developed for Hepatitis B, proved later to be unreliable for NANBH).
- It was thought by some that there were two variants of NANBH virus, whose properties differed in important ways.
- No protein concentrate survives classical heat sterilisation (autoclaving, pasteurisation, boiling). A simple protectant allowed albumin to be pasteurised, but this "quick fix" was known to be unique to that protein [JKS Note 2].
- It was thought that any protectants "strong enough" to protect super-sensitive Factor VIII would also protect any virus from inactivation.
- Fractionators resisted almost viscerally a conjunction of Factor VIII and high temperature. (The two independent discoveries that heating might be feasible were made serendipitously by relatively inexperienced workers in pursuit of other aims entirely).
- It was thought that any abuse of Factor VIII by heat, even if its activity survived, would be likely to alter its structure so that it became antigenic, provoking dreaded inhibitory antibodies in patients. There were no convincing *in vitro* tests for such subtle alterations of molecular structure.
- It was obvious that effective pasteurisation would be at the cost of Factor VIII yield. This cannot be easily accepted by a national Service struggling to reach or maintain self-sufficiency.

- Heating in the dry state might be less stressful to Factor VIII, but more difficult to apply homogeneously, and certainly less effective against viruses than heating in solution at the same temperature for the same time.

JKS Note 2. Pasteurisation of albumin is not directly transferable to Factor VIII.

Albumin is a relatively small protein of simple secondary and tertiary structure (folding and interplay of primary chains). Its physiological function is primarily osmotic, i.e., it retains and to some extent regulates water in the vascular system. It has no enzymic activity, although it does have specific sites for binding of lipids. Even this simple protein will rapidly become irreversibly insoluble (denatured) if heated in solution – just like a boiled egg. However, if its lipid-binding sites are occupied by certain fatty acids, e.g. caprylate or tryptophanate, the cross-linking which leads to denaturation is prevented and the albumin will not denature even after 10 hours at 60°C; this treatment is severe enough to kill all bacteria and viruses [I simplify]. The unique feature of albumin is that this protection from heat denaturation is achieved using a very low concentration of a substance naturally present in plasma, and which is readily tolerated except in rare cases of allergy. This means that large volumes of pasteurised albumin can be given safely to boost plasma volume in patients who have lost a lot of blood. Moreover, since the protectants are harmless and do not have to be removed, heating can be done in the final container.

Contrast albumin with coagulation factors, particularly Factor VIII as possibly the worst case. Factor VIII is a much larger molecule. Although there is a region of the molecule which can be identified with its specific function in the coagulation cascade, the expression of this activity requires that the entire molecule retain its intact structure, dependent on the integrity of many weak intra- and inter-chain bonds. These are easily broken by insults like heating. Activity is easily destroyed by proteolytic enzymes which abound in plasma after even minimal activation of the coagulation cascade. The integrity of the molecule is also dependent on retention of a metal ion, calcium, which is readily removed by some of the aqueous solutions commonly used in plasma processing. All these features of Factor VIII make it necessary to work as fast and as cold as possible throughout its processing – typically in the 1980s one would seek to go from frozen plasma to vials of sterile, frozen concentrate within 8 hours, exposing solutions at room temperature for the shortest possible time.
It therefore does not come naturally to a fractionator, used to handling Factor VIII with kid gloves, to place a dry preparation into an oven at 80°C or to place a solution in a water-bath at 60°C. (Water from a domestic hot tap is usually less than 50°C and you would not want to take a bath in it).

Unlike albumin, there is no fortunate short-cut to protecting Factor VIII (and most other plasma proteins) against heat. They need to be protected by high concentrations of salts, amino acids or sugars, at far higher than physiologically-tolerable concentrations. These protectants then have to be removed in later stages which can be quite demanding and likely to lose yield. It transpires that for Factor VIII, the preferred protectants are sugars and glycine, which at the high concentrations used make a sticky solution, difficult to work with at large scale. Even after pasteurisation, the common methods for recovering a small amount of protein from a large volume of viscous liquid were challenged to the limit in the early 1980s. In addition, these post-heating manipulations must be done in an expensive, controlled environment to avoid recontamination; there is no question of pasteurising in the final

container. (One incentive for PFC to purify and concentrate Factor VIII before pasteurisation was that all downstream processing would be greatly simplified by volume reduction.)

JKS Note 3. The clinical trial of PFC's first pasteurised Factor VIII (late 1983) and its impact on the pasteurisation programme.

The purpose of this note is to offer an independent interpretation of PFC's pasteurisation programme, from its 1983 clinical trial up to its undated demise.

Q.24 and PR Ch. 11 [11.143 and 11.158] juxtapose two accounts of the adverse reaction in Dr.Ludlam's patient. I am not qualified to conclude whether these two assessments are compatible. It is not clear that either Dr. Forbes or Dr. Ludlam actually declined to continue with the trial. In one reading [11.163 and 11.164], Dr.Ludlam was understandably reluctant only to put the same patient to further risk of distress. He may have considered that this was the only patient in his care who was suitable for such trials.

Let me try to summarise, from one fractionator's narrow viewpoint, the situation in late 1983. PFC had developed a pasteurisation process, sufficiently innovative to avoid other companies' patents, which gave an acceptable yield of Factor VIII, in a convenient, soluble form, showing (with the best tools available at the time) no significant damage to the proteins. The process was well enough characterised to support scale-up for widespread use, without exorbitant expenditure. It was anticipated that improvements in process efficiency (and conceivably safety), by incorporating a chromatographic stage, would follow with little delay. Preliminary evidence from Behringwerke's pioneering work suggested a reasonable probability that the product would not transmit NANBH. Although yield was lower than with the existing concentrate, there would be enough, even initially, to treat those patients still at risk of contracting NANBH. It is almost certain that those patients would have been protected also from the AIDS "epidemic" which was about to break.

PFC seems to have taken the setback stoically, and set to vigorously in pursuit of significant improvements; development of a chromatographic purification to replace or supplement zinc/heparin precipitation; and more severe heat treatment to compensate for the protective effect of the protein stabilisers on viruses [11.185, and see JKS Note 1]. It appears that SNBTS was taking the design of a second trial of heat-treated product into its own hands and that Dr.Perry at PFC was the prime mover [11.174 - 11.178, SNB.007.4407]. Contrary to the inference in [11.187], Dr.Cash's memo did not discuss adverse events in the preliminary study. Although there are indications [SNB.007.4447] that such a trial was planned to begin in September 1984, the PR presents no evidence that it ever took place. Dr.Foster was sufficiently confident of the success of PFC's pasteurised product that the process was offered to NYBC and to Pasteur Institute for evaluation of virus inactivation over the improved pasteurisation step. All this is indicative of careful planning for an orderly trial and introduction of an improved, pasteurised Factor VIII.

At the end of November 1983 [11.208], Dr.Perry acknowledged that, in the wake of CDC's advance results reported at Groningen, dry-heating was being proposed "as a short-term measure" to deal with HIV, but it is clear that an improved pasteurised Factor VIII, only "some months" away, was still intended to be PFC's sole Factor VIII concentrate thereafter. Since no-one at the meeting disagreed, one may conclude that this was still firm SNBTS policy (nor did the clinicians present demur).

However, there is very little on PFC's pasteurisation of Factor VIII in later documents in the PR [11.214 onwards], except to express PFC's continuing, rational view that it represented the best chance of inactivating NANBH [11.226-11.227]. Momentum towards a likely heat treatment against NANBH was lost because of the increasing priority accorded to AIDS. That appeared to be a simple task for dry-heating, but the quest for ever-greater margins of security of HIV inactivation led to adoption of dry-heating severe enough to have an impact on NANBH as well [11.238 onwards].

JKS Note 4. Why did fractionators in Scotland and England take different decisions on heat treatment of Factor VIII?

JKS Note 1 summarises why, up to 1981, any suggestion of heating Factor VIII would have been considered outrageous by an experienced fractionator. News of Behringwerke's promising results changed that perception (effectively in 1981-82). Since at that time I was in immediate charge of coagulation factor development and manufacture at both PFL, Oxford and BPL, Elstree (I will sometimes use "BPL" as shorthand), my interpretation of activities and decisions in the early 1980s may be of interest to the Inquiry. I must stress that, in communications between BPL (usually myself) and PFC (usually Dr.Foster), we did not seek to know the forward plans of the other Service, ask for advice on policy, or attempt to influence the other's decisions. [The first time a common policy was discussed and carried through was in the context of dry-heated Factor IX – a special case where both Services were dependent on a single scarce resource, the dog DIC model developed in Scotland.]
This Note will also show how much BPL's severely-constrained attempts at virus inactivation owed to generous assistance from PFC. Out of admiration for my own diligent and resourceful colleagues at PFL and BPL, I always contest claims that we were just "lucky"- that's not how it works. However I do have to admit that we had a smoother ride than usual to 8Y, while PFC kept having the success they deserved dashed from their grasp by external events beyond their control [JKS Note 3].

4.1 Why did PFC start to take an active interest in pasteurising Factor VIII (1981-83)?
Initial interest was quickly channeled as only one of several plausible options before the Factor VIII Safety Action Group [11.57, 11.62]. *[I will not pursue here why the other options ultimately fell by the wayside or were overtaken]* While PFC had the obvious team to lead this part of the work, they would gladly acknowledge well-focused assistance from other SNBTS laboratories, particularly later in testing and characterisation. Behringwerke was a well-respected company. If they said a process was feasible it was worth pursuing, even if one remained sceptical about yield (undisclosed at that time) and about proof that viruses were efficiently inactivated. It was unlikely that Behringwerke would be in a position to offer licences for some time, and royalties might be prohibitive. Having been shown that something might work in principle, fractionators usually believe that they can improve on the original and possibly avoid patent problems. Over quite a short time, PFC did just that. PFC's confidence in following their own ideas was not a case of "Not Invented Here" – the issues were far too important for vanity.

4.2 Why did BPL appear not take such an active interest in pasteurising Factor VIII (1981-83)?
BPL knew of Behringwerke's claims from our own reading and from Dr.Foster's notes of meetings we could not attend. We may initially have been more sceptical than PFC about the

chances of inactivating NANBH (see JKS Note 1), but promising noises did start to emerge from Germany and formal trials were being set up. Although NBTS was at last engaged in a determined programme to increase the plasma supply to BPL, the gap between reality and the ideal of self-sufficiency was very much wider than in Scotland; a Factor VIII product with reduced yield certainly could not be envisaged except for selected patients – a difficult notion to sell to RTDs and HCDs. Above all, BPL was in the throes of a stop-gap building improvement programme while a modern plant was being designed, authorised and constructed. There were neither suitable premises nor staff resources to undertake a difficult long haul, developing a high-risk product, especially one which demanded complex aseptic processing after the virus-inactivation stage. PFC had the resources, suffered fewer or less severe drawbacks than BPL in this period, and were above all willing to keep BPL informed of their much more rapid progress. BPL was grateful for PFC's vigorous leadership, and content to do what we could to keep contact with their programme, e.g., by confirming that their candidate processes worked in conjunction with our fractionation scheme. BPL tacitly undertook to share with PFC anything promising which might come out of our broadly-based programme on "front-end" processes, in attempts to increase the purity of Factor VIII going into virus inactivation.

4.3 Why did BPL appear to take more interest in dry-heating than did PFC (1983-84)?
PFC was alerted to the feasibility of dry-heating of Factor VIII by the curious "Rubinstein abstract" at a conference in Budapest in 1982. BPL had not attended, but Dr.Foster kindly shared with me what little he had gleaned from the meeting [SNB.010.4452]. (Most people interpreted the undisclosed "heating" of Hyland product at that meeting as pasteurisation of some kind.) It must be emphasised that there was no indication whatever that this dry-heating had inactivated any virus, simply that Factor VIII recovery from several widely-available concentrates had been much higher than early failures in several laboratories would have led one to expect. PFC may quickly have tried heating their current NY concentrate, but if they were impressed by the yield I do not recall any excitement. There was no rational justification for diverting resources away from a pasteurisation programme which was fulfilling or exceeding early expectations.

On the other hand, dry-heating was "something we could do" in England. PFL undertook a survey of existing batches of product manufactured at both labs, with promising results, most batches surviving heating at 60°C for 24-72 hours with a loss of only 10-20% Factor VIII activity [See JKS Note 5 on clinical trials]. We still had no prospect of measuring ourselves the inactivation of NANBH or surrogate viruses, but if one or other lab elsewhere came up with such proof, it would be possible to borrow their magic (fractionators are shameless plagiarists) – even if we had to swallow hard and pay royalties. One of the happy accidents of this period was the particular conditions of routine freeze-drying both at PFL and BPL. PFL had a single, elderly and rather idiosyncratic Usifroid freeze-dryer. Vials of Factor VIII had to be frozen externally and loaded into the dryer, which then went through a long, conservative cycle yielding a very dry product, which happened to favour heating.

Dry-heating also became one of the virus-inactivation options which PFL would add on to promising candidate "front-end" processes. One of the processes we were investigating, on a very small scale, was PFC's zinc/heparin precipitation [11.83]. In the course of a routine survey of variables, the technician made a large error in calculating the weight of heparin to be used, and encountered an unusually heavy precipitate of fibrinogen. Rapidly acknowledging his error, he and the principal investigator nevertheless went ahead with the planned assay of the Factor VIII remaining in solution, and were astonished to find a very

high recovery. When this "partitioning" of Factor VIII from fibrinogen was optimised it was found that best results were obtained using heparin alone, at much higher concentration than used in PFC's original zinc/heparin process. This step proved to eliminate a fiddly adsorption step in our current scheme and, after adding another precipitation method conveniently emerging from our front-end work at the time, a ten-fold purification over the current product was achieved. It often takes a long time to develop formulation and drying of a new concentrate, but we were fortunate to find a simple formulation which freeze-dried using the cycle applied to the current product. This very dry concentrate could then be heated at quite high temperatures without loss of solubility and with an acceptable loss of Factor VIII. This dry-heated concentrate was coded 8Y in the R&D lab, and the name stuck. 8Y is still (2010) in production at BPL, although not for the UK.

It cannot be too strongly emphasised that, satisfying as this successful development might be, there was no Eureka moment. I was still firmly convinced that dry-heating would be much less effective than pasteurisation against tough viruses like NANBH. PFL persisted with catch-up on pasteurisation of both Factor VIII and Factor IX, well into 1984, on the basis of PFC's updates on their progress.

4.4 Why did BPL decide to run with dry-heating in late 1984?

Briefly, as a stop-gap measure in the hope of making Factor VIII safe from transmitting AIDS; in this, the only difference between PFC and BPL was that we had the option of higher temperatures which might offer a wider margin of safety. By the time of Gallo's ?April 1984 publication, there was little resistance to the conclusion that AIDS was caused by a blood-borne virus (then called HTLV III, later HIV). Already US fractionators, disappointed with failure of dry-heating at 60°C to inactivate NANBH, were holding out the probability that AIDS virus was being inactivated. Many UK HCDs were clamouring for these products, usually at the cost of having to enter their few previously-untreated patients into clinical trials. BPL continued to be unconvinced that inactivation was sufficiently proven to justify heating of the national product. Sufficient proof was forthcoming at the Groningen meeting in early November, which I had managed to attend. On my return a small informal group reviewed the status of our and PFC's pasteurisation work; the trade-off between severity of heating applied to 8Y and the associated loss of Factor VIII; and the progress of the new manufacturing plant at Elstree. It was decided:

- The small, high-precision oven at PFL would be used to heat retrospectively all batches of the current Factor VIII held in stock at PFL and BPL, at 70°C for 24h (or, if that proved unsatisfactory, 60°C for 72h).

- PFL would complete the scale-up of 8Y to 300 kg (plasma weight) and prepare batches heated at 80°C for 72h for clinical trial. BPL would continue to produce the current concentrate, with the prospect of moderate dry-heating, switching to 8Y, with hands-on assistance from PFL staff, when the requisite equipment had been specified and delivered.

Perhaps this summary will be sufficient for the Inquiry. I have limited ability to document actions in England, but if necessary can point to some material in the public domain which is compatible with this account drawn from memory. The sequence of events leading to dry-heating of Factor IX at the same temperature will be evident from the account in the PR, and I have nothing important to add or subtract.

4.5 Why did PFC not take short cuts to a hepatitis-safe Factor VIII by buying-in "successful" processes?

Until 1983 Behringwerke had the only published heating process with any clinical evidence of having inactivated NANBH. By that time, PFC had advanced to the point of pilot batches and clinical trial for immediate safety and efficacy and were lining up HCDs for trials of NANBH transmission. PFC had reason to believe that their yields of Factor VIII were better than those claimed for Behringwerke's original patented process; that further improvements were achievable; and that their product could withstand extra heating, validated by the best available methods to inactivate high titres of hardy viruses. The method was probably safe from patent infringement – I am not aware that Behringwerke ever tried to contest this – and therefore no royalties would need to be paid. PFC had no motive to buy in Behringwerke's process even when the first trial ended in setback [JKS Note 3], since they were confident that purification methods already in the pipeline would reduce the risk of idiosyncratic or true allergic reactions. Buying-in ("technology transfer") sounds easy but invariably takes much longer than predicted by those who are selling it.

[At some point, the US fractionator Cutter (Bayer), then in at least a loose partnership with Behringwerke, adopted the latter's improved process, possibly after failure to bring their own pasteurised candidate to market. The pasteurised product was sold as Hemate P or Humate P. Possibly because of low yield and high price, it never enjoyed a mass market for haemophilia A, but later found a niche in treatment of von Willebrand's disease (VWD).]

Turning now to the "successful" 8Y, again it is hard to find a point in our development when it would have been rational for PFC to change horses. Certainly throughout 1985, before a certain number of documented non-transmissions had accumulated, I continued to believe that dry-heating would not be completely effective against NANBH. Sooner or later we would hit a plasma pool with a donation of very high concentration of the virus, and even 8Y's 80°C roasting would fail to kill it all. If BPL had been in a position to adopt a good pasteurisation process, I would have pressed for it, at least as an option in 1985. However, commissioning of the new plant stretched out to 1987 and the opportunity did not arise. It was mid-1986 before I felt 8Y had done enough to go public with "promising" results. By that time, PFC had caught up on the dry-heating front – primarily to provide a greater margin of HIV inactivation - adapting the zinc/heparin process and rigorously optimising freezing and drying. The resulting product, Z8, had very similar properties to 8Y and could be heated similarly. By the end of 1986 this product awaited only clinical trial, delayed yet again, apparently by HCDs' reservations which I am not qualified to assess. At no point in the second part of 1986 would it have been sensible to switch to 8Y, with an inevitable learning-curve and delays in procurement, qualification and training.

JKS Note 5. Clinical trials of 8Y

During 1983, and probably prompted by the news that NHS Factor VIII was eliciting NANBH almost as frequently as US concentrate, PFL revived an old idea to try and protect patients not yet infected. In the 1970s, BPL had produced a very small volume of Fibrinogen for Isotopic Labelling, used to detect occult clots in thrombotic patients. Plasma for FIL was collected from a very select group of donors whose blood had never appeared to cause hepatitis in recipients, and the plasma was quarantined for at least 6 months (in case of late evidence of infection) before aseptic fractionation. The 1983 development built on the plasmapheresis of a panel of donors in Leeds RTC, under the enthusiastic leadership of

Dr.Angela Robinson. Again, this panel consisted of donors who were documented as having given four units of whole blood without apparent transmission of hepatitis, the new twist being that plasma could be drawn every few weeks and accumulated in quarantine. PFL then made batches of Factor VIII from 100 kg pools of this "accredited" or "Green 4" plasma – i.e., at the lowest feasible scale. The "Northern Centres Trial" was set up in late 1983 to conduct clinical assessment of NANBH transmission, using a well-tried protocol.

By early 1984, PFL had investigated dry-heating of several batches of our current product. In March 1984, PFL issued dry-heated F.VIII concentrate to three clinicians in England, under the named-patient system. These batches were derived from the small pools of Leeds accredited plasma, as "the best we could do". We explicitly held out no expectation that the heating had inactivated any blood-borne virus, but the clinicians undertook regular lab testing which might reveal transmission of either AIDS or NANBH. We learned by the end of 1984 (published only much later [Colvin et al. Clin Lab Haematol1986; 8:85-92]) that neither virus had been transmitted to any of these three patients, but I certainly took little comfort from this apparent, anecdotal success; in fact, I do not believe today that the 60°C/72h applied to those batches necessarily inactivated NANBH. It is at least as likely that there was no infective donation in the starting pool of plasma. [The Northern Centres Trial, of unheated Factor VIII from accredited donors, did start but fell victim to the call for dry-heating to defeat AIDS. There was an anecdotal report of at least one transmission of NANBH by these unheated batches, but I cannot document that.]

In the wake of the decisions summarised in JKS Note 4.4, PFL started a crash programme to "retro-heat" all PFL and BPL stocks of Factor VIII. By mid-December's HCD's meeting which (more or less) "recommended" that heated products should be used henceforth in UK, we had sufficient stock to protect all patients thought to be still free of HIV. Although NBTS decided against that policy as discriminatory, by the start of 1985 all HCDs in England&Wales "were aware" that heated product could be made available to treat any named patient, with the tacit provision that he was followed up conscientiously for transmission of HIV or NANBH. Formal national roll-out to all HCDs requesting heated product started in February 1985, with no obligation of follow-up, and no unheated product was issued by BPL after 2 May 1985. I believe there were a very few NANBH transmissions by this retro-heated Factor VIII. Clinicians were free to use unheated product and some certainly exercised this choice, presumably drawing on stocks issued before May. Unheated stock was not positively withdrawn from RTCs or HCs, with the consent of the UK Medicines Regulatory Authority.

Since December 1984, PFL had scaled up 8Y for clinical trial of safety and efficacy, which I believe was conducted satisfactorily in February 1985. 8Y had become the sole Factor VIII manufactured at PFL, with BPL following through in ?May 1985 after procurement of equipment, technology transfer and training. In March, HCDs were informed that 8Y was available for clinical trial, in patients who met the trial criteria of "previously untreated or minimally treated" and provided that the HC would undertake the very onerous schedule of blood sampling and testing. The criteria for patient selection and interpretation of any lacunae in testing were not as rigorous as those promulgated in 1986 by ICTH. [This is perhaps not the place for my views on the merits of these protocols]. For various reasons beyond the scope of these Notes, take-up of 8Y for trial was slow, but the handful of brave HCDs who agreed to offer suitable patients were very enthusiastic. Uptake started to snowball as one commercial concentrate after another was reported to have transmitted NANBH (or even HIV). I collected our handful of data for oral presentation in Melbourne and London in 1986,

where the trial design was heavily criticised. On first publication in January 1986 [Colvin et al Lancet 1988: 814-816] 32 patients had been studied without satisfying these criticisms, which were answered effectively only in 1990 when the same and later patients were tested for anti-HCV with no evidence of transmission.

To link up with JKS Note 4.5 and my remit to testify on developments up to the end of 1985, I must repeat that there was at that point only the slightest encouragement (6 patients, not all fully compliant with protocol) who had completed their follow-up. There was no justification for BPL to jump up and down and proselytise for 8Y. With a dozen or so good sequences under our belt by mid-1986, I would have been more bullish. I cannot recall SNBTS asking for frequent updates on the trial, but I would have had no reason to withhold information or interpretation when requested.

BPL's calvary was not in bringing 8Y to fruition, but in proving that NANBH was not being transmitted. Fortunately, by September 1985 8Y was standard issue for England&Wales and a gratifying number of HCs adopted it in preference to commercial concentrates. The safeguarding of our haemophilia population was not unduly delayed. This would not have happened without the generous trust and sterling efforts of our HCDs.

Some remarks on specific sections of the Preliminary Report.

1.55 This is mistaken. PFL and PFC worked well together, not least in parallel development of innovative Factor IX concentrates in the early 1970s. Lively cooperation continued throughout the period I have been asked to review.

3.38 In my recollection, this did not become an issue in the period you ask me to consider (to 1985), except when some HCDs were permitted to buy expensive US Factor VIII for prophylaxis, not just treatment of bleeds. Their justification was that boys with haemophilia deserved to pursue every sporting activity enjoyed by those with normal coagulation.

4.35, 4.37 It is understandable that patients should have forgotten such details. Until mid-1970s most doses would have been made up by a doctor or nurse, who would have been supplied with an information leaflet, including hepatitis warnings, in every box. However, from that time most patients would have been on self-therapy and every vial label carried such warnings, as a condition of Product Licences issued in 1976. It is hard to believe that, at this time, any patient would have declined treatment, even after the most pessimistic recital of the known hepatitis risks from his doctor.

5.109-5.110 The use of all concentrates amounts to fewer than 100 vials of 250 IU, a flea-bite against the colossal amounts of cryo.

5.121 Failure of planning cannot be held against Scotland. Execution of sound plans took longer than we wanted, because of the unusual challenge of building a pharmaceutical plant within the investment and procurement patterns adopted by the SHHD at that time.

5.126 The summary is incisive but fair. However, did these tensions between demand, funding and planning not exist in many other specialities? In retrospect, haemophilia treatment and fractionation were not starved as much as some other services, although administrative delays were frustrating and did sometimes affect our responsiveness.

8.13 It is probably fair to say that until about this point UK clinicians were crossing their fingers, hoping AIDS would transpire to be miraculously confined to US. [This was in fact my own initial reaction to US newspaper reports during 1981]. In the light of this, the UK response noted in 8.16 *et seq* is reasonably prompt.

10.2 It should be appreciated that 500,000 IU is only 2000 vials of 250 IU, not an enormous amount. Interest might profitably focus on why HCDs were making these purchases, against essentially free PFC products. The period 1981-83 is of course rather odd because of AIDS and the heat treatment saga.

10.3 This is perceptive. E&W only ever achieved self-sufficiency in provision of F.VIII to "all patients whose HCDs prescribed it". However, that was always a smaller proportion of total use than it was in Scotland, whose claim is more nearly accurate.

10.5 This surge in demand represented a huge improvement in the lives of haemophilia patients. We should be rejoicing rather than seeing only a failure in planning and provision.

10.8-10.9 Table 1 interpretation is confused. Presumably SNBTS will correct it.

10.17-10-31 The issue of cryo v. concentrate was quite complicated. If invited, I could try to explain the various threads in this old story and the impact of cryo on the supply of modern concentrates.

10.272 The "purity issue" here must be distinguished from the wish in the early 1980s to improve the purity of Factor VIII in order to facilitate heating.

11.7 Here and elsewhere in the PR there may be some confusion between "monoclonally purified" F.VIII and "synthetic" or "recombinant" F.VIII manufactured by genetic engineering. At about this time, several companies were claiming (on the slenderest of evidence, soon discredited) that intermediate-purity F.VIII, such as 8Y, contributed to degradation of immunity in AIDS. [I should apologise for using a colourful short-cut, which might seem derogatory today, to denote patients of long standing who had almost certainly been exposed to the hepatitis viruses. My covering notes were for very narrow circulation, as will be apparent from the preponderance of jargon.]

11.13-11.14 Fairly crude F.VIII concentrates had been available in both Scotland and E&W since at least the mid-60s.

11.14 I cannot recall any particular incident (I had left PFC by this date), but moderate adverse reactions to all F.VIII concentrates were common, at least through the 1970s.

11.16 By this time at PFL, I was not aware of this work. "Purification" in this context denotes "removal of <u>some</u> of the confounding proteins", notably fibrinogen. I doubt that "isolation" was a serious aim.

11.25 Nevertheless, the twin MRC trials did have a major impact on our perceptions of NANBH. One patient died of fulminant NANBH. This was published – see 11.36. The hepatitis problem was a major drawback to using PCCs for, e.g., warfarin reversal and cover for liver biopsy, where the risk-benefit ratio was high. Not so in severe haemophilia B.

11.44 The first "publication" in 1980 was in the company's house-journal [See Snapshots Q.4]. Detection and immediate translation of the 1981 paper indicates how conscientiously Dr.Foster kept up with current literature. The wording "would have" risks implying that PFC did not keep abreast of every source of information. That is patently untrue.

11.49-11.51 The incredulity expressed by the well-informed Dr.Cash is very telling. That response, or worse, would have been typical of any scientist in the field to a suggestion that he should heat F.VIII to 60°C. In the absence of yield and other crucial information from Behringwerke, there was no reason to see pasteurisation as an immediate prospect for a national product. [See JKS Notes 1, 4.1 and 4.5]. The PR comes close to implying negligence, insularity or lack of perspicacity. I see no justification for that.

11.57 This was worth quoting at length, if only to show that Scotland was taking the problem very seriously, was putting its best minds to work, was utilising the most recent scientific and medical literature, and was leaving no promising stone unturned.

11.58 I can see no evidence for the implication here that at least some of this group was dead weight. Or for the corollary; that a fresh mind is unlikely to bring anything worthwhile to collegiate discussions? This sounds to me like a well-organised, well-informed Group, able

to prioritise projects jointly and rationally – not an over-populated committee, each participant with his own agenda (see 11.81). I can testify that BPL received assistance from other members of the Group, not only PFC participants.

11.62-11.63 This section confirms that Scotland had its priorities right at the time, was backing its selected horses very sensibly, and was energetically tackling obstacles to success. The most intractable problem was the issue of proving non-infectivity of treated concentrates. I confirm that chimps were not realistically available, and that infectivity in other animal hosts was very contentious; that is the only area in which anyone could perceive a heavy dependence on active collaboration with friendly labs in other lands.

11.67 This meeting was not about virus inactivation. PFL had nothing to offer Scotland in the way of advice about virus reduction, except possibly my customary surly scepticism.

11.72-11.73 This account would tell me that PFC scientists were alert to all ideas, went out of their way to get crucial details, and assessed them with critical insight – always in the context of supplying a national requirement.

11.79 Why should they? They were not specially equipped to provide any answers, and had delegated several well-qualified SNBTS groups to do so.

11.90-11.93 The policy decided held up pretty well, but was not followed to the letter. The prior commitment of rare, untreated patients to trials of commercial products was certainly an obstacle to clinical demonstration of the safety of 8Y and 9A, and probably even more so in Scotland. The PR's comment in 11.92 appears to be critical. It should be noted that Regulators in UK and US did not permit claims like "hepatitis-safe" to be used without chimp studies or other convincing clinical evidence.

11.95 The summary (first and third bullets) states the position of the authority figures in UK hepatology, but several Cassandras were already in the ring (Preston, Mannucci...).

11.118-11.120 The question of neo-antigens continued to bedevil all proposals for virus inactivation, and remained in some Regulatory minds for a surprisingly long time, given the lack of relevant clinical evidence. I suspect that it was sometimes used to delay choices between several evils, when theories were in more plentiful supply than evidence. Cf. the view that AIDS was caused (later, "exacerbated") by "junk protein" in the NHS' primitive concentrates.

11.122 No shame attaches to a quality failure in the first scaled-up batches of any product, since a new process is always rather improvised.

11.130-11.135 This Report is very thoughtful, indicating alertness to valuable work being done elsewhere, even prior to publication, and a prudent assessment that pasteurisation might not be sufficient – hence SNBTS should keep working on auxiliary and alternative measures.

11.150 Dr.Rizza and I, whose offices were only about 20m apart, frequently discussed our urgent common interest in AIDS, hepatitis and NANBH. Dr.Rizza effectively led our clinical trials while I did some of the leg-work. We would not have disclosed to the other any details learned in confidence. During the period in question, I was *de facto* in charge of England's efforts to investigate processes for inactivation of viruses in plasma protein concentrates,

essentially at PFL, Oxford. For that and historical reasons I was the natural target for correspondence with PFC on these topics.

11.151 While these results looked promising, it must be remembered that 1983 had been marked by disappointing clinical results from dry-heating. Furthermore, there were clear indications of batch variation, by then attributed to lack of control over moisture content. Implementation was triggered only by the information given at Groningen in November. It is possible that the unnamed author had access to PFL's earliest dry-heating results, apparently also assembled in July 1983, and extrapolated them along an optimistic trajectory.

11.156 This refers to my note to Dr.Foster on 5 January 1984 [SNB.007.4052], attaching a redacted version of a PFL internal memo. Dr.Foster and I were decidedly not on circulation lists for each other's raw internal memos. The redaction obscures the fact that this is a report from Lowell Winkelman to me as her line manager and probably others in the interested BPL/PFL group. In para 4.2 she refers to "my memo of July 1983", i.e., LW's internal memo to me and others. The PR seems to have misinterpreted this as my (JKS) having copied preliminary dry-heating results to Dr.Foster in July 1983. This is not the case. LW's memo is clear that the July results, while not unpromising, left many questions unanswered; the memo I largely shared with Dr.Foster in January 1984 presents work in progress to answer some of those questions. A delay of 6 months may seem sinister today, but it reflects our different levels of interest in dry heat and pasteurisation in that period (see JKS Notes 4), and also that we did not burden each other with unconfirmed, anecdotal results – we would wait until a consistent pattern emerged. We may have had the odd telephone conversation in the interval, or even met during the conference season. It would scarcely be surprising if the information supplied in January 1984 were more advanced than the admittedly over-enthusiastic memo of July 1983. It must be recalled that PFC had little reason to take an interest in dry heating in 1983 and much of 1984.

Note that para 2 of the report demonstrates that the target was NANBH but that we had little hope at the time of being able to link these heating conditions to any impact on viruses.

11.157 I did not attend the CBLA meeting of 14th October 1983 [DHF.002.4834], or any other session of that committee, nor do I recollect ever being asked to prepare a report specifically for it. I am at a loss to square this minute with the unrealistically optimistic "CBLA document" of 26 July 1983, and mystified by the first sentence of 3.2.1, which implies that we had results on infectivity of small pools; these were simply calculations of risk based on "incidence of transaminitis" in recipients of blood components. Had I been asked in early October 1983 to provide a brief position statement, it would have resembled 3.2.2(a). Although we had at least one dry-heating experiment under our belt, dating from July 1983, I doubt that anything done in the interval to October would have led us to suspect that we were about to achieve any reduction of NANBH. It would be January 1984 before we had obtained a minimum of solid information to report, to either PFC or CBLA.

11.173 I was employed solely at PFL, Oxford, 1975-79. From 1979-82 I was active daily on both PFL and BPL sites, in different roles. I moved permanently back to PFL, with a new remit, in January 1983 and was based there until the lab was closed in 1992. One of these letters (see also Ref. 249) clearly shows Oxford's keen, continuing interest in PFC's pasteurisation, as late as May 1984, probably with a view to some modest scale-up. There is no evidence here of a fixed "policy" of dry heating at PFL.

11.179 This illustrates the Haemophilia Society's relative lack of concern about NANBH, even at this late date.

11.190 The presentation by Dr.Mannucci suggests that PFC was as far ahead as anyone else, and provided no incentive to take their eye off pasteurisation.

11.191-11.193 This is the turning-point in priorities (for both PFC and PFL), from "a cautiously implemented programme to kill NANBH" to "something quick against AIDS". No-one was happy about it, but failure to react to the news from CDC could have been considered negligent (in my view, then and now).

1.194-11.202 The nominal aim of all these claims is to deal with hepatitis. Really it was about dealing with AIDS, but lab and clinical evidence was still too slender (and fallible) for FDA to let the companies claim this openly. At no time during this flurry of publication was there any encouragement to believe that dry heating would tackle NANBH – with hindsight, probably because temperatures were not high enough, or surrogate virus work had not been sufficiently ambitious.

11.204-11.205 In other words, PFC put dry-heated VIII in clinical hands within less than 3 weeks of the CDC news, and sufficient preliminary results to move to general issue within one or two more weeks!

11.228 That position was not too different from mine – I thought we were fixing AIDS but would most probably have to return to pasteurisation to defeat NANBH.

11.254-11.255 The issues of freeze-drying and of plasma conditioning are not really linked.

11.256-11.257 Prince's paper would certainly have been an incentive to provide a larger margin of safety (although I don't think 68°C F.VIII ever transmitted HIV). It would be natural then to review whether BPL's 80°C technology had anything to offer in pushing NY to higher temperatures; and also to hedge by continuing to pursue higher purification, should that prove to be the limiting factor.

11.261 Prof. Bloom's results have nothing to do with virus safety.

11.262 It is probable that the pessimists (e.g. Prince and Minor) were correct, and that dry-heating at 68°C has a limited capacity to inactivate HIV. However, donor screening and donation testing would by now have reduced the maximum probable burden of HIV in a plasma pool. It was never claimed that virus inactivation could replace other safeguards; many stages in the plasma cycle contribute to safety of the product.

11.263 To be more frank, the chimp model was now <u>discredited</u> for NANBH.

11.267 Dr.Perry's overview in Ref. 365 confirms a point in my correspondence with Dr.Pepper (Ref. 362), that even modest manipulations of formulation and FD cycles could lead to <u>both</u> improvement in FVIII yield and enhanced resistance of viruses to heat treatment.

1.272 The author conflates paras 1 and 2. I believe Dr.Perry is quoting a general view, not mine. The specific activity of 8Y usually fell in the range 3-5 iu/mg, depending on the quality

of plasma. More to the point, the lower limit specified was 2 iu/mg; that must have been validated, i.e., product with that Sp. Act. had been heated successfully.

11.274 In line 3, the author possibly means "resistant" rather than "sensitive".

11.279 PFC's generous cooperation in carrying out the first validations of virus inactivation under 8Y and 9A conditions was quite invaluable at a time when BPL, in the throes of a huge building programme, did not yet have its own suitable facilities. (See also 11.285). It encouraged hope that severe heat treatment might really be effective against NANBH, although there was still uncertainty whether the chosen surrogate viruses were appropriate. The exchange of material probably also prompted, or accelerated, PFC's thorough investigation of the freezing/drying variables which might be responsible for 8Y's satisfactory performance (see also 11.287).

1.290-11.291 It may not be obvious to all readers that 80°C is not "33% higher than 60°C". In the context of protein denaturation and inactivation of viruses, its effects are at least 100 times greater. This new information from Prince would therefore not be a disincentive to PFC in continuing to strive for 80°C dry heating, and it caused no panic in England.

11.299 I would have passed on this information had I known of it. In any case, the news would not have surprised me, and it had no implication for our 80°C products.

11.310 This work was about the softening phase preceding the thawing of plasma to obtain cryoprecipitate.

11.312, 11.310-11.320 This was all part of a joint programme on collection of plasma by different means, in different anticoagulants, etc. There is virtually no connection between this and virus inactivation, save in demonstrating that we were used to co-operating with each other.

11.313 This is fair, but the document – which I can't recall ever seeing before – was written in 1991. We were by no means as confident about "effectiveness" in 1985, if by that the author means freedom from NANBH transmission.

11.322-11.328 The scale-up period for Z8 must have been frustrating, but such problems are normal in the industry. I interpret Dr.Dawes' examination of 8Y etc. as showing that, in contrast to these samples of Z8, 8Y and the existing NY suffered surprisingly <u>little</u> change over severe heating. The low fibronectin concentration was part of 8Y's design, and an upper limit was imposed in the batch-release specification.

11.339 I don't understand what Prof. Bloom meant by "in the air". As chairman of HCDs, he should have known that there had been no seroconversions to HIV and no case of NANBH from the use of 8Y and 9A, now over about 18 months of full-scale issue from BPL.

The text of the PR now goes beyond the period I have been asked to consider

Name JANET K. SMITH
Signature
Date 22 June 2011