WITNESS STATEMENT FROM DR R J PERRY

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.

INTRODUCTORY COMMENTS

Prior to my appointment within SNBTS I was employed as Chief Analyst in the Regional Sterile Supply Unit of the West Midlands Regional Health Authority. This new NHS unit was established for the large scale pharmaceutical manufacture of sterile injectable preparations for the region and my role included the development and management of Quality Control systems and procedures necessary for the commissioning and operation of the unit within standards of Good Pharmaceutical Manufacturing Practice applicable to the industry in general.

In March 1981 I was appointed in SNBTS as Quality Control Inspector in the Protein Fractionation Centre (PFC). This was a new post. Its role, inter alia, was to develop and implement Quality Assurance systems and controls as part of a programme to bring the Centre into compliance with modern standards of Good Pharmaceutical Manufacturing Practice. I reported to the PFC Director (Mr J G Watt).

In January 1984 I was appointed Acting Director of PFC following the departure of Mr Watt. This appointment was made substantive in 1985 reporting formally to the Committee of Management of the CSA and responsible for all activities of the Centre – subject to the responsibilities and duties of the SNBTS National Medical Director.

Clearly I had no involvement in or knowledge of discussions, actions or decisions on the above or other issues prior to March 1981.

STATEMENT IN RESPONSE TO SPECIFIC QUESTIONS

Paragraphs 1 and 2 – initial SNBTS research on removal of viruses from coagulation factor products – early 1970's

My knowledge from this period comes from a general historical understanding of industry developments and discussions with colleagues after joining SNBTS in 1981.

It is correct, as stated, that SNBTS was involved in research and development aimed at the removal of viruses from coagulation factor products. It is also correctly observed that this early work concerned removal rather than inactivation of viruses. The first screening test for a potential blood borne virus (hepatitis B) was introduced around 1970. The test was relatively insensitive compared to today's standards and products such as coagulation factors prepared from large plasma pools continued to carry a risk of Hepatitis B transmission. This work sought to reduce, but not eliminate the known residual risk following the observation that separation techniques could potentially partition viruses into waste fractions and thereby reduce the risk of hepatitis B infectivity of these early coagulation factor products. At this time there were no techniques known to the industry (e.g. heat) which were capable of inactivating viruses without damaging or destroying the product. Indeed at this early stage in the international development of such products the prospect of discovering such techniques was considered remote.

Paragraph 3 – SNBTS participation in MRC Working Party on Post transfusion Hepatitis.

This predated my employment in SNBTS and I have no knowledge of who attended this meeting from Edinburgh and SE Scotland BTS. However it seems likely that this would have been Dr McClelland.

Paragraph 4 – Awareness in PFC of development of an apparently Hepatitis Safe Factor VIII by Behring.

This predated my employment in SNBTS and I cannot be sure if Mr Watt or other staff in PFC knew of this development before Dr Cash's note to Mr Watt.

I am not aware of any publications predating this and typically commercial companies would not disclose such information prior to completion of studies to justify their safety claims and completion of patent protection to protect their intellectual property. Thus I believe it unlikely that PFC staff were aware of this development prior to its disclosure at the Bonn meeting referred to by Dr Cash.

I became aware of this development and its significance soon after joining SNBTS in March 1981 including the widely held view that the very low yield of the process (~8%) made it unsuitable for widespread use. Indeed the method was not routinely adopted at scale by Behring until 1985 following process modifications to improve both its yield and economic viability.

Paragraph 5 – SNBTS research on pasteurisation in response to development in Europe.

It is correct that research on pasteurisation of coagulation factor products began in Scotland in 1981. This was in response to the knowledge that a manufacturer (Behring) had demonstrated, at least in principle, that Factor VIII could be subjected to pasteurisation at 60° for 10hrs in the presence of stabilisers, albeit at a very low yield. Initially the work at PFC was focussed on identifying stabilisers and conditions which might allow it to develop a pasteurisation process without breaching Behring's patented process.

I am not aware of any other developments in or news from 'the rest of Europe' which may have influenced this decision. The question posed by the Penrose team (and the narrative in the Preliminary Report e.g. paragraph 11.50) also appears to suggest that there was widespread activity throughout Europe on this topic. There was not to the best of my knowledge any such activity in any

of the European fractionation centres – at least none which was in the public domain – except of course that reported by Behring in 1980.

Also, at this time, Dr Cash was increasingly expressing his view during informal discussions and conversations that manufacturers (including PFC) should begin to address the challenge of producing non-infective (with respect to hepatitis) products and that the prevailing view that risks of infectivity were greatly outweighed by the benefits of increased treatment would not be sustainable in the longer term.

Paragraph 6 – Priority of research into Viral Inactivation of FVIII in 1982

The Factor VIII study group was an important development in SNBTS and was established to coordinate all available resources in SNBTS to meet the challenges of self-sufficiency and to establish this as a national priority. I attended this meeting together with Dr Foster and Mr Watt from PFC. At this time the PFC work on virus inactivation was only at a preliminary stage without any clear reportable outcomes. My recollection from the meeting is that safety issues were discussed in general leading to agreement to establish a safety sub group. Whilst this is not recorded in the report of the meeting this would not necessarily be unusual for such internal reports. The importance of product safety was certainly recognised in these discussions but so was the recognition that any method likely to improve safety would reduce product yield. Thus consideration of FVIII processing yield and FVIII content of plasma were considered essential prerequisites to progress on product safety if the goal of self sufficiency was to be achieved and maintained.

Paragraph 7 – Investigation of Behring pasteurisation method.

The report of this sub group meeting in March 1982 recommended further exploration of three options:-

1. Use of gamma irradiation to be pursued by SNBTS HQ laboratory.

2. Pasteurisation using methods similar to that of Behring – to include work on the requirement for higher purity FVIII capable of withstanding the pasteurisation process. This option would be pursued by PFC.

3. Methods capable of physically removing virus from FVIII.

My recollection is that the first two options were the favoured candidates.

Paragraph 9 – Selection of heat treatment (pasteurisation) as preferred option.

By October 1982 SNBTS had eliminated irradiation and virus removal as options for increasing FVIII safety. Irradiation in particular led to complete destruction of the product at doses necessary to achieve a sufficient degree of virus inactivation.

Therefore heat (pasteurisation) was selected as the preferred option not only because of the reported success of Behring but also because other lines of SNBTS research had proven unsuccessful.

It is not correct to assume that the choice of pasteurisation by either Behring or SNBTS was based simply on prior experience with equipment and facilities for albumin production.

Pasteurisation has, since the 1940's, been routinely applied to albumin manufacture throughout the industry following a very early observation that albumin was a relatively stable protein in the liquid state and which, following the addition of non toxic stabilisers such as sodium caprylate, could withstand heating at 60 degrees. Importantly these stabilisers do not require to be removed following pasteurisation of the product in its final container. Following the observation that these conditions resulted in a product free from the risk of virus transmission, the practice of albumin pasteurisation, in the presence of stabilisers, at 60 degrees for 10 hours became the industry and pharmacopoeial standard for albumin products. Pasteurisation processes

were also widely practised in the wider pharmaceutical and food industries where it was necessary to reduce or remove microbiological contaminants.

In contrast coagulation factor proteins were known to be unstable proteins in the liquid state and were rapidly destroyed at elevated temperatures. Despite knowledge and experience of pasteurisation process technology there were no known stabilisers which could prevent destruction of coagulation factors and other proteins present in coagulation factor products exposed to elevated temperatures. Therefore the major challenge in developing virus safe coagulation factor products was the identification of pharmaceutically suitable additives (stabilisers) capable of protecting unstable coagulation factor proteins from the effect of heat, reducing the concentration of other heat labile proteins in the product and developing processing methods (including the potentially necessary requirement to remove stabilisers after pasteurisation) which would result in a product with acceptable yield. These were complex scientific problems which required to be understood and resolved before the relatively simple technical process of heating could be applied. In comparison to these scientific challenges the pasteurisation step itself was seen as relatively straightforward using pre-existing equipment.

Following the discovery by Behring of suitable stabilisers, SNBTS embarked on a programme to develop a similar process which was capable of delivering an acceptable product yield and which did not infringe the Behring patents.

SNBTS (and probably Behring also) selected pasteurisation at 60 degrees for 10 hours because such established processes were already known to produce safe albumin products and it was thought likely that such processes would similarly deliver safe coagulation factors.

The availability or otherwise of equipment to carry out the specific pasteurisation step in the overall process was a relatively minor consideration.

Paragraph 10 – Cooperation between BPL/PFC and priority of virus inactivation in England circa 1982

Although I was not directly involved in discussions between PFC and BPL at this time my recollection is that there were regular and frequent exchanges of scientific and technical information between the two organisations – primarily between Drs Foster and Smith who had previously worked closely together as colleagues at PFC. Although there was no formal agreement between the two organisations underpinning their cooperation I am equally not aware that there were any constraints placed on them.

I am unable to comment with any authority on whether or not virus inactivation was a priority in England at that time. I am (and was at the time) not aware of any substantive programmes of work at BPL concerning virus inactivation and this appears to be confirmed by the cited correspondence from Dr Smith. Clearly BPL would have been aware of industry developments and, like PFC, would have had major programmes aimed at increasing product yield and plasma quality in the pursuit of increasing NHS product supply.

Paragraph 11 – Freeze Drying at PFC

Factor VIII and FIX concentrates prepared by PFC and all other manufacturers at that time (and indeed to date) had to be freeze dried to provide pharmaceutical product stability and an acceptable shelf life (~2 years). FVIII and FIX are labile products which when stored in solution rapidly deteriorate over a few days.

Therefore all FVIII and FIX products prepared at that time by PFC were freeze dried preparations. PFC had two production scale freeze driers used primarily for FVIII and FIX.

Paragraph 12 – Correspondence between Dr Cash and Dr Lane concerning UK FVIII developments and clinical trials.

The correspondence cited concerns over the emergence of commercial so called 'hepatitis reduced' FVIII products in the UK and the professional view

that any claims concerning reduction of hepatitis risk or routine use of such products should be underpinned by clinical trials. My understanding is that Dr Cash had revised his original advocacy for such trials in favour of a strategy which would provide more time for similar NHS developments (i.e. development and execution of clinical trials) – as described in the text of paragraph 12.

The letter also illustrates Dr Cash's consistent desire and advocacy for a closer and more formal cooperative relationship between the UK blood services concerning the development of safer NHS products. My interpretation of his reference to the 'furtive' contact between Drs Foster and Smith is simply an expression of his concern that the informal and productive cooperation between England and Scotland required to be strengthened by more formal collaborative arrangements and closer governance by senior managers of the respective services. Dr Cash, typically, expressed this view using arguably provocative language to emphasise his point. His letter would have been interpreted by recipients as meaning that the prevailing arrangements were, in his view, inadequate to meet the emerging challenges facing UK NHS manufacturers rather than an implication that current contacts were somehow inappropriate. The letter was copied to SHHD but I have no knowledge or recollection of whether its content became known to Mr Watt or other PFC staff. In any event I do not recall its content having any impact on the local PFC development programme which continued to focus on the development and preparation of a pasteurised product for initial clinical trial.

My interpretation of Dr Cash's letter is that the letter is correct as written (i.e. there is not an omission of 'not' in the fourth last line on page 1). My interpretation is that Dr Cash felt that our longer term NHS interests would be best served by <u>not</u> placing pressure on commercial organisations to conduct formal clinical trials of their so called 'hepatitis reduced' products using scarcely available UK patients so that NHS manufacturers would be able to access these patients for clinical trials of NHS products when available.

I am not aware of how or whether this specific difference of opinion was resolved although thereafter SNBTS had turned its attention to organising clinical trials of its pasteurised FVIII product. Subsequently the emerging threat of AIDS became increasingly evident and the desire to demonstrate the reduction in hepatitis risk from treated products was overtaken by the more urgent requirement to address the AIDS risk.

Paragraph 14 - Dominant themes in Early 1983.

The Preliminary Report correctly identifies the dominant themes in early 1983. However it is also important to recognise that the pursuit and maintenance of self-sufficiency and product yield was a high priority for SNBTS particularly in light of the knowledge that the eventual introduction of NHS heat treated products would, as a result of yield penalties, potentially reduce the overall amount of FVIII available to patients. Actions to mitigate this possible effect required a continued emphasis on programmes to improve product yield.

Paragraph 15 – Reciprocal reporting between England and Scotland.

Although there continued to be no formal collaboration or reporting between Scotland and England the established cooperation continued particularly between senior operational managers at PFC (myself and Dr Foster) and their counterparts at BPL (Drs Smith and Snape).

Paragraph 16 – Cross reference between heat treatment and AIDS March 1983.

I did not attend this meeting. However it seems likely that the mention that 'AIDS might appear in the UK' would have come from Dr Ludlam.

It is not surprising or significant that heat treatment and AIDS were not cross referenced in the minute. The reference to heat treatment was a report from Mr Watt concerning progress with the PFC heat treated product and the reference to AIDS was an update report from Dr Ludlam. The absence of any

cross reference in the minute does not necessarily imply that there was no discussion of the two potentially related topics at the meeting – it seems more likely that any such discussion was inconclusive and therefore not recorded. Also at that time it was far from established or accepted that AIDS had a virus aetiology.

Paragraph 17 – Proposals for acceleration of the heat treatment Programme.

My interpretation of Dr Foster's memorandum to Mr Watt is that he was offering an option of utilising existing equipment to carry out the pasteurisation step of the new FVIII process in light of the possible need for introduction of heat treated product for all patients to protect against the emerging problem of AIDS compared with previous estimates of the need to initially supply only 30% of product as heated material. Dr Foster offered interim arrangement using existing equipment (in particular albumin pasteurisation cabinets) pending a 'fully engineered' solution and associated funding. It is correct that this relatively simple expedient would have allowed PFC to both accelerate and expand its capacity for the production of heat treated FVIII – subject of course to all other stages of the development programme being satisfactorily completed.

It is also correct that the above pre-existing pasteurisation cabinets were able to be used for the initial dry heat treatment process introduced at the end of 1984 prior to the procurement and commissioning of the purpose built heating cabinets originally designed and specified by BPL. These cabinets, although routinely used for albumin pasteurisation at 60 degrees, were capable of operation at 68 degrees. This was a significant factor in PFC's ability to rapidly introduce its first heat treated FVIII product in late 1984 for all patients in Scotland.

Paragraph 18 – Timescales for introduction of heat treated FVIII.

I have no first hand knowledge of the correspondence referred to in paragraph 18. My interpretation of Dr Cash's comments concerning funding of an accelerated heat treatment programme is that the Deputy Chief Medical Officer (SHHD) had taken the view that the development of a heat treatment programme for FVIII was at least in part a response to views expressed by the UK Medicines Inspectors and that such views did not provide the necessary authority for healthcare developments in Scotland. I have no knowledge of the 'instructions' issued by SHHD to CSA around this time.

However Dr Cash, in his letter to Mr Watt, appears to have been signalling the need for an alternative strategy, including a presentational restructuring of the wider PFC development programme in order to circumvent any CSA/SHHD constraints and secure the necessary funding for the accelerated programme proposed by Dr Foster and Mr Watt. Such an approach would not have been unprecedented. My recollection is that notwithstanding the above funding issues concerning scale up of production and its routine introduction the development programme continued to progress at pilot scale within existing resources.

In any event, during the period in question (2nd half of 1983) the rate determining factor in moving the programme forward was the organisation and conduct of suitable initial clinical trials. Following reports of an unacceptable reaction in one trial patient, it was necessary for PFC to revise the manufacturing process in anticipation of further clinical trials in 1984. By this time it became clear that full implementation of the pasteurised product was unlikely to be completed in 1984.

Paragraph 19 – Details of Professor Johnson's FVIII method – 'particularly efficacious steps'

I cannot recollect what the 'particularly efficacious steps' in this process were but am confident that Dr Foster will be able to provide details.

Paragraph 21 – Effect of Mr Watt's resignation on the virus inactivation programme.

Mr Watt resigned in July 1983 and following his earlier than planned departure in December 1983 I was appointed as acting Director of PFC.

It is not possible to meaningfully judge the general impact of his departure but by this time the PFC programme on heat treatment was well advanced and there are no specific instances of delays or failures of the development programme attributable to his departure.

Paragraph 22 – Relationship between Dr Cash and Mr Watt.

Both Mr Watt and Dr Cash were energetic and influential individuals both within and outwith SNBTS and were both committed to promoting SNBTS as a pre-eminent organisation in the field of transfusion and plasma fractionation.

When working together they were capable of robust disagreement but also powerful cooperation. They also exhibited a mutual respect for each other.

However most importantly during my three years as a senior manager working with and for Mr Watt I cannot recall an occasion in which the idiosyncrasies of their personal and professional relationship became an obstacle to progress in either PFC or the wider SNBTS.

I believe it would be an over simplification therefore to suggest that their relationship was not in good repair, particularly if this assessment is based solely on a letter from Dr Cash who, as mentioned previously, was capable of exaggeration for the purpose of emphasis.

Paragraph 25 – BPL disclosure to PFC January 1984.

The disclosure of information from Dr Smith to Dr Foster in January 1984 was not unusual either in content or detail and was typical of the practical

cooperation which existed at this operational level. Both were recognised experts in the field and this degree of disclosure was nether surprising or remarkable. Dr Smith had previously visited PFC in September and November 1983 to discuss coagulation factors and virus inactivation and my recollection is that PFC was aware of the BPL work as a result of these visits and discussions. The disclosure in January provided further detail.

At this time PFC continued to be committed to pasteurisation as its preferred method, believing it to be pharmaceutically preferable and capable of greater virus inactivation compared with dry heat treatment. The latter was confirmed by earlier studies at PFC in November 1983 when heating of freeze dried PFC product either destroyed the product (70 degrees) or provided only modest levels of virus inactivation (60 degrees). Despite knowledge of an adverse reaction in one of the initial clinical trial recipients, PFC remained confident of a successful outcome. Plans for process modifications to address the likely causes and further clinical trials had already been established and PFC continued to plan on the basis of a phased introduction of heated product throughout 1984 and into 1985.

A further rationale for this approach was that in the event that the PFC process was unsuccessful it could revert to the BPL dry heat method – and vice versa.

Paragraph 26 – Dr Ludlams report of adverse reaction to heat treated product.

I am not aware of the circumstances of these apparently differing descriptions and reports of this patient adverse reaction. It may be that Dr Ludlam had by January 1984 further information and data concerning the reaction or indeed that his initial report was understated in the minute of the meeting. It should also be noted that in the report enclosed with Dr Ludlam's letter a subsequent infusion of <u>unheated</u> material was carried out on the same patient on 7th December 1983 (as a placebo control) to confirm that the adverse reaction described on 14th November was caused by the heat treatment of the product

rather than it being a random or idiosynchratic patient reaction. This infusion did not produce a similar adverse reaction. This additional information clearly was not available when Dr Ludlam initially reported on the 14th November 1983.

I do not recall whether or not I was surprised when I learnt of the content of Dr Ludlam's 11 January 1984 letter.

It is also not necessarily the case that the two reports are inconsistent. The original description of the specific reactions as minor would not preclude them being significant and unacceptable, notwithstanding that similar reactions were not observed in other patients. They were consistent and repeatable reactions in Dr Ludlam's patient and in the light of this there was a consensus on the need to revise the manufacturing process and/or product formulation prior to any further studies. It is entirely appropriate that Dr Cash, as the senior medical expert in SNBTS, would have expressed his view concerning the significance of these reactions.

It is also likely that SNBTS (PFC or Dr Cash) would have required a formal letter from Dr Ludlam concerning his experience with the clinical trial product which he may have requested from Dr Ludlam but it is equally likely that Dr Ludlam wrote his letter after he had fully evaluated the trial results.

Dr Cash and/or Dr Ludlam may be able to provide more detailed information.

Paragraph 27 – Significance of English reports on dry heat treatment – possibility of PFC changing tack.

By January 1986 PFC was aware of the information regarding the Hyland product and this together with PFC in house studies of virus inactivation in freeze dried product reinforced the view that only pasteurisation would offer the prospect of a hepatitis safe product. Also there was no information available worldwide to suggest that heat treatment of freeze dried product at

e.g. 60 degrees would be capable of inactivating an AIDS virus – if indeed this was subsequently found to be the cause of AIDS.

These data and information therefore provided no compelling justification to 'change tack' to the BPL approach although, as noted in the minute of the FVIII Study Group, SNBTS agreed to continue to study heating of freeze dried product in its HQ laboratory whilst continuing to progress the preferred pasteurisation option within PFC.

Paragraph 28 – Costings and Timescales for SNBTS introduction of heat treated FVIII.

Following my appointment as acting Director of PFC in January 1984 a key priority was to progress plans for the development, clinical trial and routine introduction of heat treated FVIII. My proposals and cost estimates were intended to provide a realistic and achievable programme from an operational viewpoint including the essential requirements for process engineering, optimisation process, validation, training and clinical trials. The programme was intended to provide material for clinical studies during 1984 followed by full routine implementation in 1985.

At that time there was probably a recognition that the PFC pasteurisation option was technically more challenging, and therefore likely to take longer than the relatively straightforward process of heating a freeze dried product.

By early 1984 there was no information available suggesting that AIDS had entered the Scottish blood supply and the causative agent of AIDS remained unidentified.

Accordingly this remained the preferred option of SNBTS, Haemophilia Directors and SHHD to address the problem of hepatitis transmission and AIDS, if subsequently found to be caused by a heat resistant blood borne virus.

Even with hindsight, and certainly by today's standards, it is difficult to envisage how the proposed timescale could have been shortened.

Paragraph 29 – Availability of 'hepatitis reduced FVIII concentrates reported by Dr Craske.

In his report Dr Craske described the current and imminent availability of hepatitis reduced FVIII products. Importantly those products identified by Dr Craske were 'in preparation or available for clinical trial' – not for routine use.

At this time the initial PFC pasteurised product had already been trialled by Drs Ludlam and Forbes and a revised preparation was expected to be available for further trial in April 1984. Dr Ludlam would have been aware of these plans and around the end of March 1984 Dr Cash was also in contact with Dr Rizza in England concerning possible collaboration in trials of the PFC product.

It is most likely therefore that Dr Craske would, quite appropriately, have been made aware of these developments in Scotland through either Dr Ludlam or Dr Rizza who were both involved in discussions by UKHCDO and its working parties. Confirmation of this may be available from Dr Ludlam.

Equally it is possible that this information was provided directly by SNBTS but I have no recollection of this.

At this time (March 1984) the availability of the revised PFC product for clinical trial being available shortly was not an over-optimistic estimate based on the plans and information available from SNBTS.

Paragraph 30 – Did issues of funding delay research.

As indicated in paragraph 30, funding for the PFC heat treatment project was approved by the BTS Sub Committee in February 1984.

Despite the delays in making available the necessary funds noted in the Preliminary Report, I do not recall these having a material impact on the overall progress of the project. The funds were primarily required to scale up from pilot scale to full scale routine implementation, which would most likely have involved expenditure towards the end of this period 1984/85. My letter to CSA also indicated that a proportion of the funds would require to be spent beyond 1984/85, further suggesting that administrative delays in funding were not, at that stage, critical to success.

As noted, PFC received a speedy response to its urgent request for access to these funds.

Paragraph 31 – Developments in virus inactivation (HTLVIII) end of 1984.

This was a critical period in our understanding of AIDS. Firstly, we had just learnt from Dr Ludlam that a batch of FVIII prepared by PFC from Scottish blood donations had been implicated in the transmission of HTLVIII to a number of patients in Edinburgh. This provided clear evidence that AIDS/HTLVIII had entered the Scottish blood supply.

Secondly, information presented by scientists from the Communicable Disease, Centre in the US at the meeting in Groningen, Netherlands on November 1st 1984 demonstrated, for the first time, that the now accepted causative agent of AIDS (HTLVIII) was heat sensitive and could be substantially inactivated at relatively low temperatures (68 degrees) in freeze dried FVIII products.

Thirdly, evidence became available from the Cardiff meeting and the Groningen meetings indicating no apparent HTLVIII infection in susceptible individuals treated for ~12 months with Hyland FVIII heated at 60 degrees. This was the first clinical evidence available to demonstrate the efficacy (against HTLVIII) of heat treatment of freeze dried concentrates.

The above information, available for the first time, immediately and quite dramatically changed perceptions of risks and benefits associated with dry heat treatment – not only by SNBTS but also internationally. Therefore, with the knowledge that NHS products had transmitted HTLVIII, that HTLV was heat labile, and that relatively modest heat treatment of freeze dried product could deliver effective levels of virus inactivation the immediate priority shifted from hepatitis safety to HTLVIII safety. Moreover, residual concern regarding generation of inhibitors through the use of heated products was now perceived as an acceptable risk compared with the benefits of reducing or eliminating the risk of HTLVIII transmission.

In the light of the above new information PFC immediately evaluated the extent to which the current PFC product could be heated at 68 degrees – with a view to making a heated product immediately available for all patients in Scotland and Northern Ireland. Proposals to achieve this were presented to Dr Cash who supported this course of action. The existing PFC product was found to tolerate heating at 68 degrees for a maximum of two hours. Following clinical evaluation product heated in this way was subsequently distributed throughout Scotland and Northern Ireland and unheated material recalled. SNBTS is aware of no reports of HTLVIII/HIV transmission by its FVIII products following this course of action.

Although intended initially as an interim process to protect against HIV/HTLVIII pending the development of the PFC pasteurised product, the imperative to increase the margin of safety of FVIII products with respect to HIV/HTLVIII led to further refinements of this process and ultimately discontinuation of the pasteurisation project in favour of terminal heat treatment of freeze dried product.

Paragraph 32 – Infection of Edinburgh patients with AIDS virus.

Details known to SNBTS and myself of the events surrounding this discovery, its notification and follow up actions have already been provided to the Inquiry

Team in the form of a paper entitled "Actions surrounding FVIII batch 023110090 (NY 3-009)".

My understanding from the records available is that the initial information concerning this group of patients was first known to SNBTS on the evening of the 26th October 1984 when Dr Ludlam contacted Dr McClelland of Edinburgh and SEBTS.

The information provided to Dr McClelland by Dr Ludlam originated from studies of patient samples in a research assay for HTLVIII, developed and carried out by Dr Richard Tedder.

Paragraph 34 – Dr Perry's knowledge of infection by PFC product.

The interpretation of the PFC Heads of Department minute of 26th October 1984 implying that I had prior (confidential) knowledge of the HTLVIII transmissions in Edinburgh is not unreasonable.

However the documents available from this period indicate quite clearly that the initial notification to SNBTS was from Dr Ludlam to Dr McClelland on the evening of the 26th October 1984. I have no recollection of any notification from Dr Ludlam or any other colleague prior to this date or reason to suppose I would have had such prior knowledge.

A literal interpretation of the minute is an equally likely proposition.

There is no doubt that I was aware of the HTLVIII transmissions at the meeting of 13 November 1984.

Paragraph 35 – Equipment for initial dry heat treatment process.

The rapid introduction of dry heat treatment of FVIII in November 1984 was possible because all the necessary equipment was in place. In particular the pasteurisation baths used for albumin manufacture (at 60 degrees) could be

readily adapted and validated for the heating of FVIII (at 68 degrees) with satisfactory temperature control. These were used on an interim basis pending the procurement (in 1985) of specialist pharmaceutical ovens capable of operating to the required tolerances. Manufacturing scale freeze driers were already in routine use for the manufacture of existing unheated coagulation factor products. Thus all the necessary equipment was available to support this fast track development.

Paragraph 36 – Why did SNBTS/PFC not introduce dry heating earlier at the beginning of 1984?

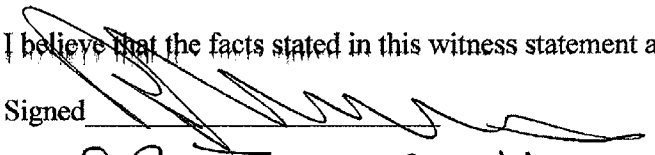
It is correct to state that the necessary equipment and technology was available at PFC (and probably throughout the industry) to carry out dry heat treatment on the products available at the beginning of 1984, and we now know that the actions taken at the end of 1984 prevented further HTLVIII transmissions from SNBTS products. While it is possible to suggest with hindsight that dry heat technology could and should have been implemented earlier, it is difficult to reconstruct the complex and often confused body of scientific, medical and regulatory opinion which prevailed 12 months prior to the actions taken by SNBTS in November 1984. It is necessary to identify the wider considerations, beyond those purely of equipment availability, which informed SNBTS decisions at that time. These included that:-

1. the cause of AIDS had yet to be established and agreed by the medical and scientific commu nity.
2. the cause of AIDS was a new virus was a distinct possibility. However there was no information or evidence that dry heat treatment would be effective. Indeed the evidence available based on knowledge of Non A, Non B and hepatitis B transmissions was that such treatment was unlikely to be effective.
3. PFC studies carried out in late 1983 indicated that heat treatment of PFC's existing product, at temperatures and for time periods then considered likely to be effective against Non A, Non B hepatitis (e.g. 68 degrees, 24 hrs), rendered the product insoluble.

4. the medical and scientific community continued to express concerns that the heat treatment of FVIII concentrates might increase the incidence of inhibitor development in patients, and that without any evidence that such treatment could inactivate the AIDS virus, such risks were considered to outweigh the benefits (if any).
5. the formal regulatory position in the UK and elsewhere was that there was inadequate evidence of any benefit (in terms of virus safety) from dry heat treatment (for either AIDS or Hepatitis) to justify the licensing of commercial dry heat treated products. Indeed applications for licences by commercial manufacturers were refused by the UK licensing authority until around February 1985.
6. at that time the modern 'precautionary principle' was a less developed approach to blood safety compared with today and interventions on blood or plasma product safety required a greater body of scientific evidence to justify their implementation – particularly if such interventions themselves carried unquantifiable risks. At the beginning of 1984 this body of evidence was not considered by the medical and scientific community to be available.
7. this cautious approach was also adopted by most manufacturers of coagulation factor products and heated products were not introduced into routine use until 1985. Importantly, in many cases and unlike Scotland, their introduction was not accompanied by a recall of unheated products.

Statement of Truth

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

Signed 

Dated 23 June 2011