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Witness Name: [Peter Reynolds Foster]
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THE PENROSE INQUIRY

Witness Statement of Peter Reynolds Foster in relation to topic C3: Heat Treatment 1985-1987

I, Peter Reynolds Foster say as follows:-

1) ***"When and how did the SNBTS/PFC first become aware of BPL/PFL's research and development work on 8Y, including severe heating of the product? When and how did the SNBTS/PFC first become aware that BPL/PFL were able to dry heat FVIII and IX concentrates at 80°C for 72 hours?"***

Response

i) In considering this question, I believe it is necessary to distinguish between PFL and BPL. Research on the development of coagulation factors was undertaken primarily at PFL, but large-volume production of Factor VIII was carried out at BPL. PFL was a unique, relatively small-volume, research/production facility which dealt only with coagulation factors and which was directed, managed and operated by research scientists. By contrast, BPL was a large-volume production operation in which research and production were the responsibility of separate departments and which encompassed manufacture of all of the major plasma products except for Factor IX concentrate which, to the best of my knowledge, was prepared only at PFL. Manufacture at PFC was much closer to that of BPL in its scale, breadth of operation and in its organisation.

ii) I cannot say for certain when I *"first became aware of BPL/PFL's research and development work on 8Y, including severe heating of the product".* Nevertheless, I will try to indicate what I knew, when I believe that I knew it and how.

iii) PFL: I first became aware in May 1984 that a discovery had been made at PFL which was to form the basis of the Factor VIII development that later became known as 8Y. This was described by Dr Smith in a letter to me that I received on 23rd May 1984 as *"we have stumbled (literally) on an intriguing alternative to zinc. I am trying to get a Crown record entered this week and will let you know immediately I have confirmation of this."* [SNB.007.4402]

iv) I believe that I learned more about this research over the subsequent months. For example, during discussions with Dr Smith and Mrs Winkleman, when they visited PFC on 24-26 June 1984 to observe the preparation of pasteurised Factor VIII (ZHT), but also via my colleague Dr Ronald McIntosh who was in regular contact with Mrs Winkelman, who had made the original discovery at PFL.

v) I was aware by late-November 1984 that the PFL were having some success in applying severe heat treatment to both Factor VIII (8Y) and Factor IX concentrates. In a letter that I received from Dr Smith on 5th December 1984[1], Dr Smith recorded the outcome of meetings that he had held with SNBTS staff, including myself, on 29th-30th November 1984 [PEN.012.1794].

He recorded that PFL were aiming to heat treat their Factor IX concentrate at 80°C for 72 hours and that I was intending to explore this with Factor IX (DEFIX) from the PFC (which I did). I remember that when I had this meeting with Dr Smith, he explained that he had chosen to heat PFL Factor IX at 80°C for 72 hours in order to be consistent with the heat treatment conditions that he believed 8Y might be able to withstand. I was also aware at this time that the ability of 8Y to withstand heating at 80°C for 72 hours was believed by Dr Smith and Mrs Winkleman to be due to the higher degree of purification of factor VIII that was obtained by the 8Y process.

vi) I believe that by late-November 1984 I was generally aware of the procedures used in the preparation of 8Y, most probably from informal discussions between Dr McIntosh and Mrs Winkleman, which Dr McIntosh had communicated to me. Details of the procedure were provided to me by Dr Smith on 16th April 1985 [SNB.007.5065] in the form of a patent application for 8Y, after the patent application had been filed.

vii) The patent application for 8Y [SNF.001.1091] had been filed on 5th March 1985. In this application, the resultant Factor VIII concentrate (8Y) was described as suitable for heat treatment either by pasteurisation at 60°C for 10 hours or dry heat treatment at 70°C for 24 hours. It is most probable that the suitability of 8Y to withstand dry heat treatment at 80°C for 72 hours was added 12 months later, as further information can be added to a patent application within the first 12 months of an application being filed, but is normally done at the 12 month point.

viii) Mrs Winkleman and colleagues from PFL/BPL visited PFC on 27th March 1985 to discuss the heat treatment of coagulation factor concentrates and I remember asking her about the strategy for the introduction of heat treated Factor VIII at BPL. She indicated to me that a final decision had yet to be taken between dry-heating the established BPL Factor VIII at 70°C for 24 hours or attempting to implement 8Y with dry-heating at 80°C for 72 hours. I was aware at this meeting that the 8Y process had been performed successfully at PFL, but regarded its satisfactory transfer to BPL and acceptable clinical performance of batches of 8Y prepared at BPL as being important milestones in determining the success of the project.

ix) BPL: I do not know precisely when I learned that PFL's 8Y process had transferred successfully to BPL. A meeting was held at PFC on 27th August 1985 which was chaired by Dr Cash and attended by Dr Smith (PFL) and Dr Snape (BPL; Head of Quality) to review heat treatment of Factor IX concentrates (the minute of this meeting was supplied with my response to further questions on my B3 witness statement that was provided to the Inquiry on 7th July 2011 [SNB.005.1203]). It is probable that we were also advised informally of progress with 8Y at BPL at this time. However, as the first batches of 8Y prepared at BPL were not issued until 19th September 1985, clinical experience of 8Y manufactured routinely at BPL would not have been available.

x) It was in late-October 1985 that Dr McIntosh first attempted to dry-heat treat high-purity FVIII from PFC's own development programme. I presume that his decision to attempt to dry-heat this material at 80°C was based on his knowledge that this had been achieved successfully with 8Y at BPL, a belief that high-purity factor VIII was more likely to withstand severe dry-heat treatment than established concentrates and

the fact that dry-heat treatment was the easiest of the potential virus inactivation options to examine (see also my response v to question 11i on page 18 below).

2) ***"When did it seem likely, from evidence of its clinical use, that the heating regime for 8Y (80°C for 72 hours) resulted in a product which did not transmit NANBH?"***

Response

i) At a presentation on 9th May 1986 in Australia, Dr Smith reported that "*It is too early to know whether NANBH transmission has been eliminated by severe dry heating*" (Smith et al. *Developments in Biological Standardization* 1987, **67**, 323-325)[2] [].

ii) On 9th October 1986, Dr Smith gave me a copy of his Interim Report on the BPL surveillance study [SNF.001.1123] that had been prepared for a meeting of the UK HCDO (PR 11.307) that was held in Edinburgh on the 10th October 1986. Data were provided on 10 recipients of 8Y and 6 recipients of 9A. If recipients of Factor IX are excluded, because the risk of NANBH transmission by unheated Factor IX might not have been the same as with unheated Factor VIII, then the calculated rate of NANBH infection for 8Y was from 0-30%. I am not sure if this estimated rate of infection meets the definition of "*likely*" to be free from transmission of NANBH or not.

iii) When the final report of the study was published in the Lancet on 8th October 1988 [LIT.001.0330] (PR 11.308), it seemed to me that this was the first time that I considered it "*likely*" that "*the heating regime for 8Y (80°C for 72 hours) resulted in a product which did not transmit NANBH*" as, to the best of my knowledge, this was the first publication of these data that had been peer-reviewed.

iv) Although this final report claimed that the risk of NANBH transmission was 0-9%, there were a number of reservations about the study.

- Firstly, it was acknowledged that the study did not comply fully with the protocol that had been established for this purpose by the International Committee on Thrombosis and Haemostasis (ICTH).
- Secondly, it was noted that one potential case of NANBH transmission was excluded from the analysis.

•Thirdly the analysis combined recipients of Factor IX (9A) with recipients of Factor VIII (8Y). Although both products were heat treated at 80°C for 72 hours, I am not sure that it is valid to combine patient data from two different products in which the baseline (unheated) risk of NANBH transmission may not have been the same. If the recipients of Factor IX are excluded, then the measured risk of NANBH transmission for 8Y from this report was 0-14% compared with an estimated risk of 90% from unheated large-pool Factor VIII concentrates.

v) As a result of incomplete compliance with the ISTH protocol a second, more rigorous surveillance study of 8Y (PR 11.365) was proposed to HCDO on 25th September 1987 (PR.11.367). The results of this second study were published in 1993 (Rizza et al. *British Journal of Haematology* 1993, **84**, 269-272)[3] [LIT.001.0864] and confirmed the absence of transmission of both NANBH and hepatitis C in 27 recipients of 8Y.

3) ***"In October 1985 PFC discovered that their existing intermediate NY FVIII product withstood heating at 80°C:***

(a) Why was such heating of the existing intermediate NY FVIII product not introduced immediately?

Response

i) This discovery resulted from an experiment which was performed by Dr McIntosh in the R&D department at PFC on 21st October 1985. The purpose of the experiment was to investigate the freeze drying and dry heat treatment of a sample of high-purity factor VIII that had been prepared in the research laboratory. This was the first time that the research into the development of a high-purity Factor VIII concentrate had advanced to a point where there was sufficient product available in the research laboratory to investigate freeze drying of the product. As there was only a small quantity of high-purity factor VIII available, the volume of the samples that were freeze dried was only a few ml per vial.

ii) Dr McIntosh chose to include the existing PFC Factor VIII (NY) as a 'control' and, in doing so, he freeze dried this in the same small volume of a

few ml per vial. By contrast, the standard NY product was prepared at a volume of 40ml or 50 ml per vial.

iii) This experiment had been performed using a newly designed freeze drying procedure and it was not practicable to freeze dry 40ml or 50 ml per vial using the new freeze drying procedure, because this would have taken much longer than normal and would have greatly exceeded the available freeze drying capacity at PFC.

iv) It was estimated that this new freeze drying procedure could be accommodated in production if the volume of factor VIII solution per vial could be reduced to 15ml. The Z8 process was designed to achieve this, whilst retaining the same dose size of about 200 IU FVIII per vial.

(b) ***Why did it take until May 1987 before intermediate FVIII manufactured by PFC and dry heated at 80°C for 72 hours was available for clinical use?***

Response

i) The development of a protein pharmaceutical from the research laboratory to clinical use normally goes through a number of typical phases, completion of which usually takes a number of years. For Z8, these typical phases were as follows:

- Design of the process method and determination of optimal parameters at each process step in the research laboratory. This phase of work was begun by Dr McIntosh on 21st November 1985,
- Scale-up of the whole process to pilot scale operation, including the specification and purchase of equipment, solving of any problems that emerged. This phase of work was begun on 23rd June 1986,
- Scale-up of the whole process to full-scale operation, including production trials to resolve any problems that emerge and to re-optimise process parameters. This phase of work was begun on 4th August 1986,
- Production of material for clinical evaluation (bearing in mind that it would normally take some 2-3 months to manufacture a batch of Factor VIII

concentrate). Z8 for clinical evaluation was available for issue on 2nd December 1986.

• Completion of clinical trials to establish that the efficacy and tolerability of the product are satisfactory. This phase was completed on 10th April 1987.

• Routine production and building of stocks to ensure that the supply of product to patients will be secure.

ii) A number of unexpected problems emerged during the development of Z8.

• In the procedure used for the concentration and formulation of the product (known as ultra-filtration), it was discovered that although the equipment had performed well at small-scale, it was unsatisfactory on scale-up as the standard pumps available for processing at this larger scale either damaged factor VIII or were unable to provide the fluid velocity needed to prevent blockage at the membrane. An investigation was undertaken by Dr McIntosh to locate companies who might be able to supply a suitable pump and alternative pumps had to be evaluated thoroughly in trials with appropriate solutions of factor VIII (Z8) before a suitable pump was found.

• It was estimated, from trials at pilot-scale, that the length of time needed to carry out the process at full-scale would exceed the availability of staff under the existing PFC staffing arrangements. As establishing new terms and conditions of employment in the NHS was not straightforward, it was decided instead to modify the process to ensure that it could be performed without a need to alter terms and conditions of employment. Some revision and re-optimised of the process was required as a consequence.

• Once sufficient material from production was available to fill the largest production-scale freeze driers it was found that a proportion of vials would not withstand heating at 80°C. This unexpected behaviour was discovered to be related to variations in the crystalline structure that was formed during freezing of the product at the beginning of the freeze drying process. A new freezing procedure was devised in September 1986 to overcome this problem.

iii) These matters are described in greater detail in my SNBTS Briefing Paper on the Development of Heat treatment of Coagulation Factors that was submitted to the Inquiry with my B3 witness statement on 16th December 2010; see pages 43 – 48.

(c) What changes in the manufacturing processes were made, and when, to enable PFC to produce Z8 (dry heated at 80°C for 72 hours)?

Response

Production of Z8 required a new manufacturing process to be established, from the recovery of cryoprecipitate paste onwards. These changes have been described by me in an earlier witness statement concerning the methods of preparation of Factor VIII and Factor IX concentrates at the PFC that was submitted to the Inquiry on 11th July 2011.

(d) What was the original timescale for the production and introduction of Z8? If that timetable was not met, when and why did it slip?"

Response

I had originally advised Dr Perry that material might be available for clinical evaluation in April 1986. This estimate was included in a briefing note for Haemophilia Directors that was written by Dr Perry in February 1986 [SNB.001.5484] (PR 11.269; 11.270; 11.272). My estimate was wrong for a number of reasons:

- I had assumed that material prepared at pilot-scale would be used for the clinical determination of efficacy and tolerability, as this had been the approach taken previously with pasteurised Factor VIII (ZHT). This approach was not followed with Z8 and material was not released for clinical evaluation until after full-scale production had been established. I was not involved in this decision as this was the responsibility of the PFC Quality Manager.

- A number of unexpected problems emerged, all of which took time to solve (see response 3b ii) above).

4) ***"Did PFC's work on the development of a high purity FVIII concentrate (NYU), in collaboration with Professor Johnson, result in any delay in the introduction of Z8?"***

Response

i) I do not believe that PFC's work on the development of a high purity FVIII concentrate (NYU) in collaboration with Professor Johnson resulted in any delay in the introduction of Z8. Once a decision had been taken to develop Z8, this project was given the highest priority and research on the development of a high-purity Factor VIII concentrate was effectively shelved.

ii) I believe, on the contrary, that the development of Z8 would not have succeeded without the knowledge gained from working with Professor Johnson, in particular the discovery in late-1985 that freeze drying was the critical step in achieving heating at 80°C rather than the degree of purity of Factor VIII. The importance of the freeze drying method had not been appreciated at PFL/BPL. See also my response to question 3 a.

iii) In the absence of this knowledge, I am not aware of any organisation that succeeded in achieving 80°C dry-heat treatment of Factor VIII based on the findings of BPL. I am aware of two organisations that attempted to do this and failed; Cutter Biological in the USA and CSL Australia. The experience of these two organisations suggests that if PFC had attempted to develop 80°C dry-heat treatment of Factor VIII any earlier, we would most probably have failed because we would not have appreciated the importance of freeze drying. CSL Australia did introduce a product comparable to 8Y in 1990, following advice from PFC on freezing and freeze drying.

5) ***"Did any difficulties in commencing clinical trials of Z8, because of concerns over compensation/indemnity, result in any delay in the introduction of Z8?"***

Response

i) I was not involved in the planning of clinical trials of Z8, nor was I involved in discussing or progressing the topic of compensation/indemnity, except that I was present at a meeting between SNBTS Directors, Haemophilia Directors and SHHD Officials on 14th November 1983 [SNB.001.5188] when this subject was raised by Dr

Ludlam. I was also present at subsequent meetings on 2nd February 1984 [SNB.001.5252], 7th March 1985 [SNF.001.0241] and 9th February 1987 [SGF.001.2261] at which this matter was discussed. I can no longer recall any of these discussions, except that the matter appeared to me to have been resolved at the meeting of 9th February 1987 [SGF.001.2261].

ii) When Factor VIII that had been heat treated at 68°C for 2 hours was introduced by the SNBTS, material was supplied for clinical evaluation on 3rd December 1984 and authorisation was obtained for the product to be routinely distributed by 10th December 1984, i.e. a timescale of 7 days.

iii) By contrast, Z8 that had been placed at issue on 2nd December 1986 was issued to Edinburgh BTS for clinical evaluation on 22nd December 1986. The first results from the clinical evaluation were provided to the PFC on 31st March 1987 [SNB.006.5609] and authorisation to the PFC from Dr Cash to issue Z8 for routine clinical use was received at the PFC on 14th April 1987(Cash JD. Letter to Dr RJ Perry, 10th April 1987)[4]

Routine distribution of Z8 was begun on 15th April 1987 ie. a timescale of 4.5 months.

iv) Although I was not involved in planning or progressing clinical trials, I was generally aware that the residual stock of PFC's established Factor VIII (NY), heated at 68°C for 24 hours, was running low as production had been halted in July 1986 (see 6 iii below), putting pressure on the need to expedite the clinical evaluation of Z8. For example, on 14th November 1986, the Production Manager at PFC advised that there was only about 2 months supply of NY at the Edinburgh Regional Transfusion Centre (Grant W. Factor VIII – Z8 Preparation, PFC note dated 14th November 1986)[5].

v) At the meeting of 9th February 1987 between SNBTS Directors, Haemophilia Directors and SHHD, it became clear to me that clinical evaluation of Z8 had not been progressed because of the issue of compensation/indemnity. At the time, I had expected the clinical evaluation to be completed as quickly as possible. However, on reflection, I can appreciate the concern of Dr Ludlam that suitable arrangements for compensation should be in place, particularly as Z8 was being subjected to a degree of

heat treatment which was "*viewed with some astonishment by other fractionators at the time*" (Report of the Lindsay Tribunal of Inquiry, p93).

6) ***"Did any wider management, organisational or other issues result in any delay in the introduction of Z8 e.g. by R&D staff not being sufficiently involved in the manufacture and production of products and processes that had been developed by them?"***

Response

i) I do not believe that any wider management, organisational or other issues resulted in any delay in the introduction of Z8 (other than those described in section 3b ii).

ii) In order to comply with Good Pharmaceutical Manufacturing Practice (GMP), R&D and Production activities must be kept separate. Therefore, when a new product is being established in Production, formal responsibility necessarily lies with the Production Manager and with the Quality Manager. The role of R&D in these circumstances is to work closely with colleagues in Production and Quality Departments to ensure that new technology is introduced effectively and efficiently.

iii) To establish the Z8 process as rapidly as possible, production of the established Factor VIII concentrate (NY) was halted in July 1986. This decision enabled Production facilities to be available to progress the project and Production staff to be available to participate fully. The project was led by Dr Ronald McIntosh of R&D and fully involved all relevant staff from the R&D, Production and Quality departments, with progress being reviewed by the project team and technical decisions being taken collectively. Dr McIntosh continued to lead the project in this manner until routine production was established.

iv) In the development of biopharmaceutical products, it is normal for incremental improvements and fine-tuning of production operations to continue to be made long

after a process has been established in Production, sometimes for many years. At PFC these changes (known as 'Process Modifications') were managed formally by the Quality Manager and the Production Manager according to GMP guidelines, with input from R&D as required.

v) It was the degree of involvement of R&D in these later activities, after the production of Z8 had been established, that was the subject of comments in the documents of December 1988 [SNB.006.7120] and November 1990 [SNB.007.7576] which are cited by the Inquiry.

7) ***"There was informal contact and exchange of information between PFC and BPL/PFL, in particular, between Dr Foster and Dr JK Smith. There appear to have been difficulties with more formal contact, in particular, at a senior, or managerial, level. Did any difficulties at a more senior level inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y, including severe heating of the product? Did any such difficulties contribute to any delay in the development and introduction of Z8?"***

Response

i) I always found senior staff from BPL/PFL to be friendly and helpful and cannot remember even a single episode when this was not the case throughout my employment with the SNBTS. Nor do I remember being aware of "*difficulties with more formal contact, in particular, at a senior, or managerial level*".

ii) I do not believe that exchange of information between BPL/PFL and PFC was inhibited by "*any difficulties at a more senior level*", nor do I believe that such difficulties contributed to "*any delay in the development and introduction of Z8*".

iii) From my perspective, communications between SNBTS and BPL/PFL were excellent and involved not only myself with Dr Smith, but included:

- Dr Pepper (SNBTS Headquarters Laboratory) with Dr Smith,
- Dr McIntosh (PFC R&D) with Mrs Winkelman and Mr Evans (PFL R&D scientists),

- Dr Cuthbertson (PFC Head of Quality) with Dr Snape (BPL Head of Quality)
- Dr Perry (PFC Director) with Dr Smith and Dr Snape.

8) ***"The Central Blood Laboratories Authority (CBLA) Central Committee on Research and Development in Blood Transfusion first met on 21 June 1983. It, presumably, provided a more formal forum for the exchange of information between the respective national blood transfusion services in respect of the research and development of coagulation concentrates. Dr Lane, the Director of BPL, was a member of the committee. While Dr Brian McClelland, Edinburgh BTS, was a member of the committee, there was no member from PFC.***

(a) ***Was the committee truly a UK committee or was its' role restricted to research and development in England and Wales?"***

(b) ***"Why was there no PFC representative on the committee? Ought there to have been such representation? If there had been such representation, is that likely to have led to the earlier and/or fuller exchange of information between BPL/PFL and PFC in respect of the development, manufacture and clinical use of 8Y, including severe heating of the product? If there had been PFC representation on the committee is that likely to have led to Z8 having been introduced earlier?"***

(c) ***"There appear to have been concerns in Scotland as to whether that committee was an appropriate forum for the exchange of information between BPL/PFL and PFC, based, at least partly, on the perceived "commercial brief" of the CBLA. Did any such concerns about this committee inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y? Did any such concerns contribute to any delay in the development and introduction of Z8?"***

Response

i) I was not aware of this Committee and I am unable to comment on its role or its composition.

ii) I do not believe that PFC representation on this committee would have enabled Z8 to have been introduced earlier.

iii) I can only think of two occasions when exchange of information on 8Y may have been influenced by the "*commercial brief*" of CBLA; firstly, when Dr Smith wrote to me on 22nd May 1984 "*I am trying to get a Crown Record entered this week and will let you know immediately I have confirmation of this*" [SNB.007.4402] and secondly, when details of the method of preparation of 8Y were provided to me only after a patent application had been filed. As a wider release of these details could have undermined the validity of the patent application I believe that it was understandable that I was not given details of the 8Y process earlier. I do not know the period of time between the method for the preparation of 8Y being determined at PFL and the date on which the patent was filed.

iv) I do not believe that either of these occasions contributed to any delay in the development or introduction of Z8, as the critical importance of the method of freezing drying had not been recognised at BPL or at PFC and details of the freeze drying method were not included in the patent application for 8Y.

9) ***"Were more formal links between PFC and BPL/PFL desirable. Were more formal links eventually established and, if so, when and how?"***

Response

i) From my perspective, scientific communications between PFC and BPL/PFL were excellent. I believe that scientific communications would not have been improved by a more formal arrangement and that a more formal arrangement could have resulted in less effective communication, due to scientific staff perhaps being more circumspect or reserved because of the higher degree of formality involved. A greater degree of administration would also have been required, which would have been more time-consuming and may also have delayed communications.

ii) I am not sure that "*more formal links between PFC and BPL/PFL*" were ever "*established*". Some joint studies were carried out in which respective products from each organisation were subjected to a specific evaluation. These studies concerned the evaluation of Factor IX concentrates, in a study proposed by Dr Cash which Dr Smith agreed to join in January 1984, and a virus inactivation study of BPL products, using marker viruses, that was undertaken by the PFC at the request of Dr Lane (BPL Director) in March 1986.

iii) I was involved in both of these studies and believe that communications between SNBTS/PFC and BPL/PFL were generally similar to those that took place with 8Y.

iv) In the mid-1990s, PFC and BPL also engaged in the development of a proposal concerning the validation of dry heat treatment processes and presented this position jointly at a formal meeting with the Medicines Control Agency. Despite the formality of this situation, communications between PFC and BPL were similar to those experienced during the development of 8Y and Z8.

10) ***"Why was PFC able to make available for clinical use FIX concentrate that had been dry heat treated at 80°C for 72 hours in October 1985 but FVIII concentrate that had been subjected to a similar heat treatment regime (i.e. dry heated at 80°C for 72 hours) was not available for clinical use until May 1987?"***

Response

i) The reason for this difference in timing was primarily due to two factors; firstly, differences in the ability of established Factor VIII and Factor IX concentrates to withstand severe dry heat treatment and secondly, to changes in the strategy of the SNBTS in response to new information relating to the inactivation of HIV by dry heat

treatment. The contribution made by each of these factors can be illustrated by considering the key events chronologically.

ii) In the early 1980s, PFC pursued the application of pasteurisation to Factor VIII and Factor IX concentrates [SNB.007.4480] as this was the only procedure for which there was clinical evidence that it might be effective in eliminating transmission of NANBH. See PR 11.74 and my SNBTS Briefing Paper on the Development of Heat treatment of Coagulation Factors that was submitted to the Inquiry with my B3 witness statement on 16th December 2010; see page 39, para 2.

iii) To assist the introduction of pasteurisation of factor VIII, PFC began work in August 1984 on the development of a much more highly purified Factor VIII concentrate, which was also aimed at addressing the concern of clinicians that impurities present in lower purity Factor VIII concentrates were the cause of immune disturbance in patients.

iv) I learned on 2nd November 1984 at a symposium in Groningen that HIV could be destroyed either by pasteurisation or by dry-heat treatment (PR, 11.91). SNBTS decided to apply dry heat treatment to its Factor VIII and Factor IX concentrates, as this procedure was much easier to apply than pasteurisation and could therefore be introduced more quickly.

v) The PFC Factor VIII concentrate was unable to withstand dry heat treatment at temperatures higher than 68°C. By contrast it was found that the PFC Factor IX concentrate could withstand dry heating at 80°C for 72 hours if a small change was made to the composition of the product (the addition of the protein anti-thrombin III).

vi) As this change to the composition of Factor IX concentrate was relatively

straightforward, the timescale for the introduction of severe dry heat treated Factor IX concentrate was primarily determined by the time taken to carry out a safety study concerning the risk of thrombotic reactions. Further information on this has been provided in my response to questions from the Inquiry concerning my witness statement on topic B3 that was submitted to the Inquiry on 7th July 2011.

vii) Dry-heat treatment of Factor VIII at 68°C was introduced rapidly to prevent HIV transmission and was a temporary arrangement pending the development of a product capable of preventing the transmission of NANBH.

viii) During 1985, R&D at PFC focussed primarily on the development of a high-purity Factor VIII concentrate to assist the introduction of pasteurisation, as this was the only virus inactivation procedure for which there was clinical evidence that NANBH transmission might well be eliminated.

ix) I was aware by late-1984 of two other techniques that were under development that might be capable of eliminating the transmission of NANBH. These were the solvent/detergent (s/d) technique under development at the New York Blood Center and severe dry heating at PFL.

x) Whether or not either of these techniques would eliminate transmission of NANBH was not known in 1985. However, during 1985, I believed that PFC's research on the further purification of factor VIII was compatible with both of these alternative techniques, should either prove to be superior to pasteurisation, as further purification was required to remove the chemicals used in the s/d technique and the achievement of severe dry heating of Factor VIII at PFL was believed to be due to the increased purity of factor VIII.

xi) In November 1985, PFC received a manuscript that had been submitted to the Lancet by Dr Prince of the New York Blood Center, in which Dr Prince cast doubts on the effectiveness of dry heat treatment against HIV (PR, 11.256;11.259) [SNB.007.5358][SNB.007.5360].

xii) Haemophilia Directors were also aware, in January 1986, of probable transmissions of HIV via commercial heat treated Factor VIII (Minutes of the Eighth Meeting of the AIDS Group of Haemophilia Centre Directors, Department of Health, Freedom of Information on Blood Products, File 22/1, volume 61, document no. 4606)[6] [DHF.002.0675]; knowledge that was made public at a Conference on AIDS on 11th-12th February 1986 (PR,11.265). It is conceivable that I was aware of this information in late-1985, but I cannot be certain of this.

xiii) On the 17th December 1985, I received details of the freeze drying procedure used in the preparation of 8Y [SNB.007.5458] which I had requested from Dr Smith on 13th November 1985 [SNB.007.5355]. This information was consistent with the probability that the ability of 8Y to withstand severe dry heat treatment was related to the method of freeze drying, rather than to its purity per se; a possibility suggested by the results of an experiment performed by Dr McIntosh (PFC R&D) on 21st October 1985. (See paragraphs 1x and 3a above)

xiii) The situation was reviewed at an ad-hoc meeting of senior PFC staff on 23rd December 1985, at which concern over the effectiveness of dry heat treatment against HIV led to us to agree that a greater degree of heat treatment of PFC Factor VIII should be implemented as quickly as possible.

xiv) Our discovery, in late-1985, of the importance of the method of freeze drying, led us to judge that increased heat treatment could be achieved most quickly by developing

a new Factor VIII concentrate, using procedures that would, as far as possible, be compatible with PFC's existing operation. This was essentially option 2.2 from my memorandum to Dr Perry of 18th December [SNB.013.6680] which I had written to assist our review of 23rd December 1985.

xv) In order to apply severe dry heat treatment to Factor VIII it was necessary to:

- reduce the volume of solution per vial from 40 or 50 ml to 15 ml,
- to change the chemical composition (formulation) of the solution to increase the stability of factor VIII, using techniques that had been discovered by myself and Dr McIntosh,
- to alter the method of freeze drying of the product.

A new manufacturing process was devised to achieve this. This process is described in my witness statement concerning process used at PFC that was submitted to the Inquiry on 11th July 2011. It took the PFC about 12 months to develop and implement this new process (the Z8 process), with material being available for clinical trial at the beginning of December 1986; thereafter the determination of clinical efficacy and tolerability of Z8 took some 4.5 months to complete.

11i) ***"Is the account of heat treatment by Dr RV MacIntosh on 9 May 1985 at the meeting of the SNBTS Coagulation Factor (Neoantigen study group meeting) correct? Did the reference to dry heating being "preferred" to wet heat apply to both the intermediate FVIII product and the high purity product under development?"***

Response

i) The meeting of the 9th May 1985 was arranged by Professor Cash to consider with Dr Bird (a Clinical Immunologist from Newcastle General Hospital) the view that he and his colleagues had published in the Lancet of 19th January 1985 (Bird AG, Codd AA &

Collins A. Haemophilia and AIDS. *Lancet* 1985, **1**, 162-163)[7][SNB.008.5887] in which they "*did not agree with the advice to switch completely to heat treated Factor VIII*" that had been given in a Lancet editorial of 22nd December 1985. It was the opinion of Dr Bird and his colleagues that there was "*a considerable danger that the unproven benefits of heat treatment will be offset by potential risks – one of which, antibody (inhibitor) formation, would be irreversible*" and that "*the increased protein load and aggregate content may hasten clinical expression of the retrovirus through immune stimulation.*"

ii) I was unable to attend this meeting and Dr McIntosh attended in my place. As I was not present at the meeting, I do not know if the minute is a correct record of the comment made by Dr McIntosh.

iii) Assuming that the minute is correct in this respect and given the purpose of the meeting, I would understand that Dr McIntosh was explaining that when we learned on 2nd November 1984, that HIV could be inactivated by either pasteurisation or by dry-heat treatment, we had chosen to introduce dry-heat treatment rather than pasteurisation, as this could be done more quickly. Therefore, I believe the reference at this time only concerned the intermediate-purity product.

iv) I am sure that in May 1985 Dr McIntosh would have appreciated that dry-heat treatment would have also been easier to apply to high-purity Factor VIII than pasteurisation. However, the issue at this time was not how easy a technique would be, but which virus inactivation technique, if any, would be effective in preventing transmission of NANBH.

v) Of the potential virus inactivation techniques available for the treatment of high-purity factor VIII, Dr McIntosh did, in October 1985, examine dry-heating first because this was the easiest of the potential techniques to investigate.

11ii) ***"In his letter to Dr JK Smith dated 13.11.85, what did Dr Foster mean when he stated that the preliminary data which suggested that drying conditions may be particularly critical for the subsequent sensitivity of both protein and virus components to heating was "not unexpected"?"***

Response

i) My comment followed the discovery by Dr McIntosh that, on using a new freeze drying cycle, a sample of intermediate-purity Factor VIII tolerated dry heat treatment at 80°C for 72 hours, whilst a sample of high-purity Factor VIII did not.

ii) Although this discovery was at first surprising, I considered, on reflection, that the notion that the freeze drying cycle might influence the ability of a freeze dried biological substances to withstand dry-heat treatment was not unexpected.

iii) In the preparation of a plasma product, plasma is processed via a number of sequential steps. It was not unusual for the outcome at a step to be influenced by the outcome from the preceding step. It was my awareness of this possibility that led me to consider that the outcome of a dry-heat treatment step might be influenced by the the preceding freeze drying step.

iv) It was this thought process that caused me to wonder if the procedure used to freeze dry 8Y might, in some way, be responsible for its ability to tolerate dry- heat treatment at 80°C for 72 hours, even though no details of the freeze drying procedure had been included in the 8Y patent application, indicating that PFL/BPL could not themselves have considered the freeze drying procedure to be particularly relevant.

v) The importance of the freeze drying process was subsequently accepted by PFL/BPL and a freeze drying project was launched at PFL/BPL in April 1986 in order to resolve serious problems that had emerged in the manufacture of 8Y (Winkleman L &

Evans DE (1987). Freeze drying 8Y: progress report April 1986-March 1987. *BPL R&D reports.* Oxford, Plasma Fractionation laboratory)[8].

vi) It is conceivable that the manufacture of 8Y at BPL would have been much less successful, or have failed altogether, without this recognition of the important role played by the freeze drying process.

vii) Further information on the importance of the freeze drying process and, in particular, the importance of the structure of the crystals formed during freezing prior to drying, is given in my SNBTS Briefing Paper on the Development of Heat treatment of Coagulation Factors that was submitted to the Inquiry with my B3 witness statement on 16th December 2010; see pages 45-47.

11iii) ***"In the following passages of Dr Foster's memo of 18.12.85 to Dr Perry:***

a) What is meant by "the high ionic strength" of the NYU product and why did that cause problems with heating (paragraph 1 of the memo)?"

Response

i) The ionic strength of a solution is a measure of the concentration of substances present that carry an electric charge; for example, salts such as sodium chloride.

ii) The high-purity factor VIII solution was formulated using a number of chemicals of this type, as we had discovered that a "high ionic strength" was needed to stabilise the factor VIII and to prevent it from being lost by sticking to the surface of the glass vial. This was much less of a problem with intermediate-purity Factor VIII as the factor VIII here represented only a very small proportion of the protein present and therefore only a very small proportion of the protein that was lost by sticking to the surface of the glass vial.

iii) The presence of charged chemicals, such as sodium chloride, can depress (lower) the freezing-point of a solution. For example, it is well known that the freezing-point of sea-water is depressed because of the salt present.

iv) Similarly, the freezing point of protein solutions can be depressed by the presence of charged chemicals such as salts.

v) When a protein is freeze dried it is important the solution is first frozen to a point where all material at the molecular level is solid (i.e. not mobile). With proteins, this point is known as the temperature of incipient melting, whereas for a salt solution it is known as the eutectic temperature.

vi) In considering why high-purity Factor VIII had failed to withstand dry heat treatment at 80°C, I was speculating that the high ionic strength might have depressed the point of incipient melting to a temperature below the temperature being used to freeze the high-purity factor VIII solution prior to freeze drying, thereby making the dried product more vulnerable to dry-heat treatment.

b) ***"What were the difficulties in adopting/adapting the BPL methods (paragraph 2.3). Why did PFC not decide to adopt/adapt the BPL method at that time?"***

Response

i) I believed that there were a number of difficulties associated with the method used at BPL to prepare 8Y. These are described, in a section headed 1986, on pages 43-44 of my SNBTS Briefing Paper on the Development of Heat treatment of Coagulation Factors that was submitted to the Inquiry with my B3 witness statement on 16th December 2010.

ii) One aspect that was of particular concern to me was the use of a high concentration of heparin as precipitant at the key purification step in the 8Y process.

iii) A high concentration of heparin had been used previously by Canadian researchers (Dr Gail Rock and her colleagues) in a method that they had devised for the preparation of Factor VIII concentrate , which had received considerable attention in a number of countries (PR, 11.52).

iv) Unfortunately, the promise held out by this method was not substantiated. This was mainly because heparin interfered in the assay that had been used to measure factor VIII activity and difficulty in preventing this interference had produced misleading results.

v) The Canadian and other researches had used a standard assay to measure factor VIII activity, known as the one-stage assay. However, the results from the one- stage assay were found to be wrong when samples were tested using an alternative assay, known as the two-stage method, in which interference from heparin was less pronounced.

vi) This discrepancy between the one-stage and two-stage assays in the results of the Canadian method had been found by Dr Smith at PFL, as PFL was one of few Centres in the world to routinely use the two-stage assay, which had been originally devised in Oxford.

vii) The 8Y process was based on results from the two-stage assay and the two-stage assay method was specified in the patent application for 8Y. However, at the PFC, the much more common one-stage assay was the standard method used to measure factor VIII activity.

viii) Therefore, if PFC had adopted the 8Y process it would have been necessary to change the standard PFC method of factor VIII assay from the one-stage to the two-stage method, especially given the misleading results from the Canadian process using the one-stage assay.

ix) The assay of factor VIII activity is highly specialised and the two-stage method is generally regarded as more difficult and more laborious than the one-stage method.

x) Given the difficulties associated with the assay of factor VIII activity, I regarded a move from the one-stage to the two-stage assay as representing a risk, as the time required to make the change would have caused an inevitable and unpredictable delay. Even if the two-stage assay could have been introduced successfully, the fact that it was more laborious to perform would have reduced the number of assays that could be carried out and slowed down our work as a consequence.

xi) I was also concerned that residual heparin in the final product could be masking an instability of factor VIII in 8Y which had yet to be discovered. A similar a concern over the presence of heparin in Factor VIII concentrates was held by Professor van Aken (Director of the Central Laboratories of The Netherland Red Cross) with regard to the use of heparin in the Canadian method for the preparation of Factor VIII (Report of the Lindsay Tribunal of Inquiry, page 54.)

xii) The method for the preparation of 8Y had been adapted from the method devised at the PFC for the pasteurisation of factor VIII (i.e. the ZHT process). The Z8 process was also adapted from the ZHT process and can therefore be regarded as an indirect adaptation of the 8Y process, using zinc precipitation rather than heparin precipitation for the reasons given above.

xiii) This inter-relationship between the 8Y and Z8 processes illustrates how fractionators could learn from each other, but utilise the knowledge gained in a manner that was compatible with their own manufacturing operation.

xiv) That PFC should decide to a devise process that was more compatible with its own existing operation was normal practice in the plasma fractionation industry. For example, in a review of Factor VIII production the authors noted:
"*Fractionation exploits a unique and limited resource to provide many proteins with a wide and fluctuating range of market values. It is, therefore, hardly surprising that no two companies use the same fractionation scheme. Each must be flexible enough to respond to its particular market and possible changes on the horizon. In particular, national fractionators with a virtual monopoly of the plasma supply of a country must be ready to interpolate new processes, perhaps initially for only a few users, without disturbing the efficient recovery of established proteins.*" (page 291 of Smith JK, Snape TJ & Lane RS. Advances in plasma fractionation and in the production of Factor VIII concentrates. In: *Factor VIII-vWF*, volume 1.(eds. Seghatchian MT & Savidge GF). CRC Press, 1989, pp289-300)[9].

c) *"What work, by whom and when had previously been undertaken at PFC into investigating/adopting/adapting the BPL process?"*

Response

i) The 8Y process was to a large extent adapted from the ZHT process for the preparation of pasteurised Factor VIII that was under development at the PFC during the period 1982-1984. The ZHT process was devised largely by myself and was itself based on a process for the preparation of pasteurised Factor VIII that had been devised at Behringwerke in Germany (PR 11.44; 11.45).

ii) The principal changes made at PFL/BPL were to use heparin as a protein precipitant, rather than zinc, in the key purification step and to replace pasteurisation with dry-heat treatment.

iii) As the use of heparin at the concentration employed in the 8Y process was not compatible with the standard assay used at PFC to measure Factor VIII activity, then no work was done at the PFC on this step. We chose instead to retain the procedure of zinc precipitation, which was compatible with the one-stage assay and with which we were already familiar. In the event, zinc precipitation was introduced successfully in 1986 in the preparation of Z8; it was also used successfully in the preparation of high-purity factor VIII and continued to be used at the PFC until the centre closed.

d) ***"What was meant by the statement that FVIII assays were "still the rate limiting factor" (page 2, second last paragraph)?"***

Response

i) All investigations concerning the preparation of Factor VIII concentrate require the biological activity of factor VIII to be measured.

ii) The measurement of factor VIII activity uses assay procedures which attempt to simulate blood clotting. Given the complexity of the blood clotting process, factor VIII assays are highly specialised procedures which are difficult to perform.

iii) Given the nature of the factor VIII assay, these were performed in a specialised laboratory at the PFC which had been specifically established for this purpose and which was dedicated to performing coagulation factor assays. This practice also ensured that R&D samples were tested by established assays that had been properly validated and approved. However, because of the specialised nature of these assays, the coagulation laboratory at the PFC carried out assays for manufacturing as well as

for R&D.

iv) Although this laboratory worked flat out, it was always easier to devise and to undertake experiments than it was to assay the resultant samples. Therefore it was inevitably the case that the availability of factor VIII assays was generally the rate limiting factor in factor VIII R&D, especially as priority was normally given to assays for manufacturing (PR 10.45)

v) The throughput of the coagulation assay laboratory was enhanced continually by increasing staffing and by using automated equipment. However, the purchase of automated equipment was subject to NHS financial procedures whereby bids for capital items were submitted for approval on an annual basis. Therefore, it remained the case that the time taken to perform assays was usually the rate limiting factor in research into the preparation of coagulation factor concentrates.

e) ***"What was meant by "if pressure on heat inactivation demands it" (page 2, last paragraph)?"***

Response

My comment concerned the evidence that was emerging that HIV might be more resistant to dry-heat treatment than the original experiments in the USA had indicated (see my responses 10x and 10xi above) and that dry-heat at 68°C might not be fully effective against HIV.

11iv) ***"When were commercial manufacturers able to produce and supply factor VIII and IX concentrates that were sufficiently treated to inactivate NANBH/hepatitis C and by what methods of viral inactivation? Further to that, it may be sufficient for Dr Foster to refer to tables 1 to 5 in Kasper et al, "Recent evolution of clotting factor concentrates for hemophilia A and B",***

Transfusion, 1993;33:422-434 (SGH.002.1947) and to identify those products which did not transmit NANBH/hepatitis C."

Response

i) In my opinion a number of commercial coagulation factor concentrates were sufficiently treated to inactivate NANBH/hepatitis C. I will list these according to Tables 1 to 5 in Kasper et al [SGH.002.1947].

ii) I do not know precisely when manufacturers were able to produce and to supply these products but I believe that these dates would closely equate with (a) the date that either a USA FDA licence or a UK licence was granted, whichever was the earlier (produce) and (b) the date that a UK licence was granted (for supply in UK), although any supply in the UK for clinical trials and for named-patient use would have been earlier. I have given the dates for the granting of a UK licence to the best of my knowledge based on information from the UK Medicines and Healthcare products Regulatory Agency (MHRA).

iii) Products From Table 1 (Kasper et al.), Armour Pharmaceutical Company

FACTOR VIII:

Humate-P, treated by pasteurisation at 60°C for 10 hours; FDA licence May 1986, manufactured in Germany by Beringwerke; UK licence in March 1984, but not generally available in the UK due to very low level of exports from Germany.

Monoclate-P, treated by pasteurisation at 60°C for 10 hours; FDA licence 1990; UK licence December 1999.

FACTOR IX:

Mononine, treated with sodium thiocyanate; FDA licence August 1992; UK licence February 1993.

iv) Products From Table 2 (Kasper et al), Alpha Therapeutic Corporation

FACTOR VIII:

Profilate SD, treated with solvent/detergent; FDA licence July 1989; I do not know if this product was available in the UK.

Profilate OSD, treated with solvent/detergent; FDA licence May 1990; I do not know if this product was available in the UK.

Alpha-8, treated with solvent /detergent; FDA licence pending November 1992; I do not know the date that a UK licence was granted, but I do have a UK patient information leaflet dated December 1992 which is probably the date from which this product was supplied in the UK.

FACTOR IX:

AlphaNine SD, treated with solvent/detergent; FDA licence August 1992; UK licence October 1993.

v) Products From Table 3 (Kasper et al), Hyland Division, Baxter.

FACTOR VIII:

Hemofil M, treated with solvent/detergent; FDA licence February 1988; UK licence June 1994.

vi) Products From Table 4 (Kasper et al), Cutter Biologicals, Miles, Inc.

FACTOR VIII:

Koate HS, pasteurised at 60°C for 10 hours; FDA licence April 1986; not available in the UK to the best of my knowledge.

Koate HP, treated with solvent/detergent; FDA licence March 1989; UK licence June 1994.

FACTOR IX:

Konyne 80, treated with dry heat at 80°C for 72 hours; FDA licence April 1991; I do not know if this product was available in the UK.

vii) I believe that three methods of virus inactivation provided treatment of coagulation factor concentrates that was sufficient to inactivate NANBH/hepatitis C:

- pasteurisation at 60°C for 10 hours,
- solvent/detergent treatment,
- dry-heat treatment at 80°C for 72 hours.

viii) Despite the general safety from transmission of NANBH/hepatitis C, coagulation factor concentrates prepared either by pasteurisation or by solvent/detergent treatment have been associated with occasional transmission of viruses.

ix) Pasteurised coagulation factor concentrates have been associated with the transmission of:

- hepatitis C (Gerritzen A, et al. Acute hepatitis C in haemophiliacs due to 'virus inactivated' clotting factor concentrates. *Thrombosis Haemostasis* 1992, **68**, 781[10]; Schulman S, et al. Transmission of hepatitis C with pasteurised factor VIII. *Lancet* 1992, **340**, 305-306[11]).
- hepatitis B (Brackmann HH & Egli H. Acute hepatitis B infection after treatment with heat inactivated factor VIII concentrate. *Lancet* 1988, **2**, 967[12]; Jantsch-Plunger V, et al. PCR detection of a low viral load in a prothrombin complex concentrate that transmitted hepatitis B virus. *Vox Sanguinis* 1995, **69**, 352-354[13]).

x) Solvent/detergent-treated coagulation factor concentrates have been associated with the transmission of:

- hepatitis C (Evensen SA, et al. Hepatitis C virus seroconversion in a haemophiliac treated exclusively with solvent/detergent-treated clotting factor concentrate. *European Journal of Clinical Microbiology& Infectious Diseases* 1995, **14**, 631-632[14]).
- HIV (Cho YK, et al. Molecular epidemiologic study of human immunodeficiency virus 1

outbreak in haemophiliacs B infected through clotting factor 9 after 1990. *Vox Sanguinis* 2007, **92**, 113-120[15]).

- hepatitis A (PR, 11.434, 11.435) in:
  - Belgium (Peerlinck K & Vermylen J. Acute hepatitis A in patients with haemophilia. *Lancet* 1993, **341**, 179[16]),
  - Germany (Gerritzen A, et al. Acute hepatitis A in haemophiliacs. *Lancet* 1992, **340**, 1231-1232[17]; Chudy M, et al. A new cluster of hepatitis A infection in haemophiliacs traced to a contaminated plasma pool. *Journal of Medical Virology* 1999, **57**, 91-99[18]),
  - Italy (Mannucci PM. Outbreak of hepatitis A among Italian patients with haemophilia. *Lancet* 1992, **339**, 819[19] [SNB.013.9202]; Mannucci PM, et al. Transmission of hepatitis A to patients with haemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. *Annals of Internal Medicine* 1994, **120**, 1-7.[20]),
  - Republic of Ireland (Temperley IJ, et al. Clotting factors and hepatitis A. *Lancet* 1992, **340**, 1466[21]; Johnson Z, et al. An outbreak of hepatitis A among Irish haemophiliacs. *International Journal of Epidemiology* 1995, **24**, 821-828.[22]),
  - Republic of South Africa (Cohn RJ, et al. Acute hepatitis A in haemophiliacs. *Thrombosis & Haemostasis* 1994, **75**, 785-786.[23]),
  - United States of America (Centers for Disease Control. Hepatitis A among persons with hemophilia who received clotting factor concentrates – United States, September –December 1995. *Morbidity & Mortality Weekly Reports* 1996, **55**, 841-844.[24]).

11v) ***"As it turned out, (dry) heat treatment at 80°C for 72 hours was required to inactivate NANBH/hepatitis C in factor VIII and IX concentrates. Why was severe (dry) heat treatment required for these blood products when, in respect***

of albumin, a lesser heating regime i.e. (wet) heating at 60°C for 10 hours, inactivated NANBH/hepatitis C?"

Response

i) Heat is a form of energy which can damage biological substances primarily by increasing molecular motion or vibration within macromolecular entities, such as proteins and viruses.

ii) Blood-borne viruses exist naturally in an aqueous (i.e water) environment in which the virus can be said to be fully hydrated.

iii) The flexibility of macromolecular entities can be reduced by removal of water molecules. Therefore, various processes of water removal (i.e.dehydration) can be used to preserve biological substances against heat-induced damage, in order to increase the shelf-life of a product.

iv) Freeze drying is a method used to remove water (i.e to dehydrate) from biological substances in order to preserve them.

v) Human Albumin is an aqueous solution of protein in a liquid state in which the biological substances present are fully hydrated. By contrast, freeze dried coagulation factors in a dried-state are dehydrated products which contain less that 2% residual water.

vi) The hepatitis C virus in Human Albumin can be considered to be fully hydrated and therefore more susceptible to heat induced damage than when in a dehydrated state, such is in freeze dried preparations of coagulation factors.

vii) Therefore, it would be expected that more heat would be needed to destroy the

hepatitis C virus present in freeze dried coagulation factor concentrates than in an aqueous solution of Human Albumin, where the viral particles can be considered to be fully hydrated and therefore more susceptible to heat induced damage.

12. A list is appended of the new documents that I have cited.

Statement of Truth

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

Signed .....

Dated ..... 7 September 2011 .....