Witness Name: Dr Peter Foster
Statement No.: WITN6914071
Exhibits: WITN6914072 - WITN6914115
Dated: 31st October 2022

INFECTED BLOOD INQUIRY

SECOND WRITTEN STATEMENT OF PETER R FOSTER

I am providing a Second Written Statement to the Infected Blood Inquiry following my oral testimony at Aldwych House, London, on 24th and 25th March 2022.

The purpose of my statement is:

A. To provide information on questions put to me at the oral hearing, to which a follow-on response was requested:

B. To assist the inquiry by clarifying and explaining some of my answers at the oral hearing:

A. To provide information on questions put to me at the oral hearing, to which a follow-on response was requested:

1. Pool Sizes at the PFC (24th March 2022, transcript pages 81-82).

1.1 I was asked by Counsel to the Inquiry to comment on the accuracy of the Inquiry presentation of 23rd March 2022 concerning the size of plasma pools at PFC (24 March 2022, transcript pages 81-82).

1.2 I replied that the volume of 114 litres for 1978/79 given in the table on page 9 of presentation INQY0000346 was *"far too small"* (transcript page 81, lines 24-25) but that the increase in pool sizes shown in the figure on page 11 of INQY0000346 was "*correct"* (transcript page 82, line 23).

1.3 When I gave my answer that "*114 is far too small ",* I had failed to appreciate that the figure of 114 litres given on page 9 of INQY0000346 was meant to represent the smallest volume of plasma pool that had been processed in 1978/79, as this information was in a footnote (footnote 24) on the page that I was shown.

1.4 That 114 litres was the smallest pool volume in 1978/79 is correct. From my experience, I believe that this relatively small pool size of 114 litres was determined by the availability of fresh frozen plasma at that point in time, rather than any other consideration.

1.5 Having reviewed the raw data on which the Inquiry based its figures for PFC pool size, I agree that the figures presented by the Inquiry on 23rd March 2022 were generally correct.

1.6 During my oral testimony I also explained the impact of GMP constraints of aseptic dispensing and freeze drying on pool size (transcript 25th March pages 150-152) [WITN6914001_0134].

1.7 In my first witness statement I described how sampling requirements also impacted on products from very small pools (e.g. 12-32 donations), with all vials of factor VIII

being required for sterility and Quality Control testing, according to GMP requirements, leaving nothing for the treatment of patients [WITN6914001_0135].

1.8 Similar considerations applied to larger volume pools, as a batch of less than 100 containers (vials) required 10% or 4 containers, whichever was the greatest, to be used for sterility testing.

1.9 For example, a plasma pool of 10 litres (40-50 donations) would have resulted in the production of about 10 vials of FVIII of which 4 (40%) would be taken for sterility testing with at least another 4 vials for other QC purposes, leaving only 2 vials (20%) for the treatment of patients.

1.10 For a batch of 100 containers (vials) or more, the number required for sterility testing was 20 containers or 2% whichever was the greatest. For example, a plasma pool of 100 litres (400 – 500 donations) would have produced about 100 vials of FVIII, from which 20 (ie. 20%) would be used for sterility testing and another 4 vials for additional QC purposes, leaving 76 vials (76%) available for the treatment of patients.

1.11 Regulatory requirements also specified a minimum of 1000 donations for the manufacture of normal immunoglobulin, to ensure the presence of a full spectrum of antibodies [NHBT0000236_13].

1.12 The Plasma Fractionation Laboratory (PFL) in Oxford did not manufacture immunoglobulin, so this requirement did not apply to production at PFL.

1.13 Immunoglobulins were manufactured at BPL and at PFC. Therefore, both were required to use a minimum of 1000 donations (ie. equivalent to 200 – 250 litres plasma) for the preparation of normal immunoglobulin.

2. UK HCDO Document re. Dry Heat Treatment (24th March 2022, transcript pages 90-91,155-156 and 25th March 2022, pages 7-8).

2.1 In noting that I had not had access to minutes of meetings of HCDO, I pointed out that I was now aware that these minutes contained useful information concerning the

technique used by Baxter to enable their Factor VIII concentrate, Hemofil, to be dry heat treated for 72hours at 60ºC.

2.2 I was asked to provide the Inquiry with the document in question and now do so.

2.3 The document that I referred to was the 1982-1983 report of Dr Craske for the UK Haemophilia Centre Directors Hepatitis Working Party – Appendix C (i) [WITN6914072], especially the following section:

These products seem to be of 3 types:-

The freeze dried product is heated in the presence of compounds (e.g., sucrose) which stabilise the factor VIII activity, but reduce the quantity of infective virus in the product by pasteurisation. Heat inactivation is applied to the point where there is no sifnificant loss of factor VIII coagulent activity. The temperature is usually 60°C , the exact conditions are a commercial secret, but the heat is known to be applied after the freeze drying process.

Two such products are:-

(i) Hemofil T (Exception from Clinical Trial Certificate obtained) - trial now underway

(ii) Factorate HT - available in 3 months

2.4 Of particular interest was the addition of sucrose to freeze dried Factor VIII concentrate, which enabled Hemofil T to withstand dry heat treatment at 60ºC.

2.5 Although this report of Dr Craske is dated 11/7/83, it appears to have been included in a set of HCDO papers [WITN6914072], one of which was dated 4/10/83, by which time it was known that Hemofil T had continued to transmit non-A, non-B hepatitis [PRSE0002333].

2.6 I do not believe that my access to this information when it was issued would have caused SNBTS to change its R&D strategy for virus inactivation from pasteurisation to dry heat treatment.

2.7 The SNBTS choice of pasteurisation was based on published clinical evidence concerning the absence of non-A, non-B hepatitis infection in patients treated with pasteurised FVIII [PRSE0002249].

2.8 In contrast to pasteurisation, there was no evidence from studies in patients, either at the date of this HCDO report, or subsequently, that dry heat treatment at 60ºC for 72 hours inactivated the infectious agent responsible for non-A, non-B hepatitis [WITN6914001_0073], which was the original aim of heat treatment.

2.9 According to Mannucci "*…the study carried out by Colombo et al…..to avoid transmission of hepatitis had led to unsatisfactory results with regard to dry heating…..it was evident from the follow-up of the first few patients enrolled in our study that a large number of them had developed hepatitis . Such information was verbally communicated by me to a large number of haemophilia treaters who met in Barcelona on the occasion of the Congress of the European Society of Haematology in September 1983* [PRSE0002333].

2.10 The option of dry heat treatment at this time was therefore speculative, with arguably insufficient evidence to ethically justify experimenting on patients.

2.11 That the dry heat treatment method applied by Baxter, and similar methods, would inactivate the infectious agent responsible for AIDS was not discovered until late-1984 [WITN6914001_0074].

2.12 PFC introduced dry heat treatment of its Factor VIII concentrate as quickly as possible after learning on 2nd November 1984 that HIV could be inactivated by a dry heat treatment similar to that used by Baxter with Hemofil T [PRSE0002291_058].

2.13 PFC began to routinely dry heat treat its Factor VIII at 68ºC for 2 hours on 18th November 1984, with heat treated Factor VIII being available for clinical evaluation from 3rd December 1984 and issued for general use on 10th December 1984 [PRSE0002291_059].

2.14 PFC chose heating conditions that also enabled its 12-month supply of Factor VIII in stock to be dry heat treated. This enabled:

- the supply chain to be filled immediately,
- all unheated Factor VIII to be recalled,
- heat treatment to be applied to all batches of Factor VIII prepared from mid-October 1983.

2.15 Consequently, heat treatment that was effective against HIV was applied to all batches of FVIII concentrate prepared between October 1983 and October 1984, a period when the incidence of HIV infection in Scotland was rising sharply [WITN6914073] [WITN6914074]

2.16 Similarly, all unheated Factor VIII that had been issued for use had been derived from plasma collected before October 1983, when the risk of HIV infection was lower.

3. My March 1983 Presentation at the Edinburgh Haemophilia Centre

(25th March 2022, transcript pages 78-79)

3.1 I was asked by Counsel to the Inquiry to explain my references to "*heat*" in my presentation that were cited as "*Abbott, 1977"* and *"ARC, 1981*" (transcript page 78, lines 23-25) which suggested that plasma proteins other than albumin were being heat treated.

3.2 I said that I thought these references concerned a protein known as Antithrombin III, but that I would have to check them to find out (transcript page 79, lines 6-9).

3.3 I can confirm that both of these references to "*heat*" [PRSE0001201_0006] concerned antithrombin III which, in both cases, was stabilised by sodium citrate to enable it to withstand pasteurisation at 60ºC for 10 hours.

3.4 The first reference [WITN6914075] was a short abstract from the 1977 Congress of the International Society of Thrombosis and Haemostasis in Philadelphia, USA. I did not attend this conference, and do not know when I first read the abstract.

3.5 The second reference was a paper published in the Journal of Biological Chemistry in December 1981 [WITN6914076] in which sodium citrate was also used to stabilise antithrombin III. As PFC did not subscribe to this journal, I would probably have obtained a copy via a literature search during 1982, by which time R&D aimed at pasteurising FVIII had already begun at PFC.

3.6 Although sodium citrate was able to stabilise antithrombin III, I was aware by December 1980 that it did not stabilise factor VIII activity and actually caused factor VIII to become unstable [WITN6914077].

3.7 These findings did not suggest that heat treatment of antithrombin III was applicable to Factor VIII. However, I believe that by the time I had obtained this information, Behringwerke had reported the pasteurisation of Factor VIII and research on this had begun at PFC.

B. To assist the inquiry by clarifying and explaining some of my answers at the oral hearing:

4. Product Warnings (25th March 2022, transcript pages 19-32)

4.1 The document with examples of product warning on which I was questioned during the oral proceedings was a poor copy which was not legible in places. I informed the Inquiry that a better copy was available (25th March, transcript page 30, lines 15-19).

4.2 I did provide a good quality, colour copy of this document with my draft rule 9 response [WITN6914078] but, without my realisation, the Inquiry replaced this with an inferior version [PRSE0002726] for my finalised statement to be signed.

4.3 The inferior version [PRSE0002726] was used by the Infected Blood Inquiry in my oral hearing on 25th March 2022 and that of Dr Perry on 1st April 2022.

4.4 Unfortunately the quality of the copy used in these oral proceedings was so poor that important details, such as the warnings printed on the vial label were not legible.

4.5 Although the product information leaflets were written for health professionals, all patients on home therapy would have had access to the warnings on the vial label as they were attached to each vial of concentrate.

4.6 I believe it would assist the Inquiry, its core participants and the infected and affected if document PRSE0002726 could be replaced by the higher quality version that I provided originally [WITN6914078].

5. Freeze Dried Cryoprecipitate (25th March, transcript pages 37-44)

5.1 I was asked by Counsel to the Inquiry if concern over meeting GMP requirements was related to "*the particular facilities at Law Hospital*" (25th March, transcript page 40, lines 12-14).

5.2 I replied that "*it did include that but it went way beyond that….the way the process was carried out did not comply with GMP regulations set out by the Department of Health.*" (25th March, transcript page 40, lines 15-18).

5.3 I would like to clarify the factual basis for my response, as Freeze Dried Cryoprecipitate (FDC) could not be manufactured to UK GMP standards for a number of technical reasons, even within a new facility.

5.4 According to DHSS guidance on GMP:

"*Solutions and liquids can be sterilised by filtration through a sterile filter of nominal pore size of 0.22 microns (or less)*" SBTS0000423_004, at page 62, para 9.81).

5.5 Because of its composition, the cryoprecipitate to be freeze dried could not be filtered through a sterile filter of nominal pore size of 0.22 microns or less and could not therefore comply with this requirement of GMP.

5.6 The GMP guidance also stipulated that:

"*Equipment should be designed and installed so that it may be easily cleaned, disinfected or sterilised as required*" *[*SBTS0000423_004], at page 57, para 9.44).

5.7 In addition to the premises of Law Hospital being completely unsuitable for the manufacture of pharmaceuticals, the equipment used for the preparation of FDC was not easily cleaned, nor was it sterilisable. Even with new equipment in a new facility, because of the type of freeze drier required, it would not have been possible to seal the bottles within the freeze drier to ensure product sterility.

5.8 For the purposes of Quality Control (QC), the UK GMP regulations define a 'Batch' as:

"*A defined quantity of material, or bulk, intermediate or finished product that is intended*

or purported to be uniform in character and quality, and which has been produced during a defined cycle of manufacture…" [SBTS0000423_004], at page 97).

5.9 In preparing FDC by the process developed at Law Hospital, 5 individual donations of cryoprecipitate were pooled into each bottle and a number of bottles then freeze dried together [RLIT0001695]. Therefore, (according to para 5.8) each bottle of FDC represented a batch, making testing for Quality Control and sterility according to GMP guidance impossible, as testing of multiple bottles that were representative of the batch was required (see para 1.7-1.10).

5.10 This inability to comply with GMP meant that FDC production could not be sited within an existing GMP facility (such as PFC or BPL) without destroying the GMP status of that facility.

5.11 My opinion that FDC could not be produced in compliance with GMP was shared by the then PFC Director Mr Watt, who wrote to Dr Cash on 2nd December 1981: *"Such a product is not possible within GMP guidelines but can be produced. Such production would have to be carried out on the basis of named patient dispensing, outside the control of the medicines inspectorate but subject to legislation such as the Pharmacies Act. It would be possible for the PFC to support such an endeavour by lending such laboratory and general services facility as may be necessary but separate premises (which could be attached to the existing buildings) with separate equipment would be required." [*WITN6914001_0131].

5.12 In my opinion, the only way forward for the preparation of FDC by SNBTS would have been construction of a new, stand-alone facility, with special authorisation from the Medicines Inspectorate for non-GMP manufacture.

5.13 The report of the Medicines Inspectorate which finally condemned the FDC facility at Law Hospital was dated 10th March 1982 [SBTS0000407_006]. I estimate that a new FDC facility would have taken some 2-3 years to construct and commission.

5.14 FDC was not suitable for heat treatment. As heat treated PFC Factor VIII concentrate was available from 10th December 1984, unheated FDC would have soon become redundant because of the greater risk of HIV infection, even if SNBTS had

proceeded to plan a new FDC facility immediately following the March 1982 report of the Medicines Inspectors.

6. <u>Dry Heat Treatment of FVIII, 1983/84</u> <u>(25th March 2022, transcript pages 85-86)</u>

6.1 I was asked by Sir Brian Langstaff if I had known that the FDA had licensed Hyland's heat treated Factor VIII concentrate (Hemofil T) in March 1983 (transcript page 85, lines 11-13).

6.2 I answered that I was not sure, but such licensing would have been based on chimpanzee data (transcript page 85, lines 14-17). On reflection, I would like to offer some additional information.

6.3 In my presentation to the staff of the Edinburgh Haemophilia Centre of 8th March 1983, I noted that according to a study in chimpanzees, not all of the hepatitis B infectivity had been inactivated by the heat treatment of Hemofil T [PRSE000120_0019]. This suggested that the degree of heat treatment applied might not be effective in preventing transmission of hepatitis B to patients.

6.4 Subsequently, the dry heat treatment of Hemofil T failed to prevent transmission of non-A, non-B hepatitis in clinical trials, a finding reported by Mannucci in September 1983 [PRSE0002333] [HSOC0001563], and noted by SNBTS in January 1984 [PRSE0000428].

6.5 I first learned that Hemofil T had been licensed by the FDA in March 1983 from a paper by Kasper et al [WITN6914079] when it was published in 1993. It is my understanding that the FDA licence for the unheated version, Hemofil, was retained by Baxter and that this continued to be their main product. According to Kasper et al. "*Given the failure to inactivate hepatitis virus, and the fear that FVIII, a strong antigen, might provoke more frequent inhibitor formation if altered at all by heating, the advent of heated concentrate was initially greeted with caution by the Medical and Scientific Advisory Council of the National Hemophilia Foundation.*"

6.6 An application for a UK Product License for the dry heat treated Factor VIII, Hemofil T, was rejected by the UK Committee on Safety of Medicines on 14th September 1983, [PRSE0001214] viz:

> On the evidence before them the Sub-Committee on grounds of safety, quality and efficacy was unable to recommend that the Product Licence should be varied as indicated.
>
> The Sub-Committee considered that
>
> 1. justification should be provided for the inclusion and choice of the heat treatment step.
>
> 2. the heat-treated product was inadequately characterised.
>
> 3. inadequate evidence of safety and efficacy was provided.

6.7 The CSM sub-committee also noted:

> 1. Promotional letters making unjustified claims on improved safety margins in respect of infection and AIDS were seen by the Sub-Committee and strongly deprecated.

6.8 On 7th March 1984, The Committee on Safety of Medicines did grant a UK product licence to the pasteurised Factor VIII concentrate of Berhringwerke (under the parent company Hoechst Lt) [WITN6914080], although the product was never marketed in the UK, most probably because the very low yield of factor VIII meant that the company had insufficient for distribution out-with Germany.

6.9 Although Hemofil T had been approved for clinical trial in the UK in 1983 [WITN6914074], it was not approved for general use in the UK until February 1985 [PRSE0001083_046], after evidence had become available that HIV could be inactivated.

6.10 The transmission of NANBH to patients by Hemofil T led Baxter to propose in 1987 that an infective agent responsible for NANBH might be resistant to heat inactivation and could be a prion [WITN6914081]. This suggests that the company did not believe that a commercially viable Factor VIII concentrate, that was safe from NANBH infection, could be obtained by heat treatment.

6.11 SNBTS changed its immediate strategy from pasteurisation (to inactivate NANBH) to dry heat treatment (to inactivate HIV) in November 1984, as soon as there was preliminary evidence that HIV could be inactivated by this procedure, not only heating newly prepared batches of FVIII concentrate but also heating a 12-month supply in stock (see para 2.14-2.15).

6.12 In her oral testimony Ms Douglas said that in early 1983 the Swiss Red Cross "*were doing all they could with heat treatment and filtering to remove the risk of AIDS transmission"* (transcript 15th September, page 18, lines 12-13).

6.13 For clarification, at this time the Swiss Red Cross was producing Freeze Dried Cryoprecipitate which could not be filtered to remove bacteria, or be heat treated. Subsequently, the Director of the Swiss Red Cross was found guilty of negligence for not providing heat treated FVIII in 1985-1986, by which time it was known that HIV could be inactivated by heat treatment [WITN6914082].

6.14 The development of filtration technology suitable for the removal of HIV from coagulation factor concentrates was first reported in 1989 [WITN6914083]

6.15 In summary:

- The degree of heat treatment used with Hemofil T (ie. dry heat for 72 hours at 60ºC) failed to destroy the infectious agent(s) responsible for NANBH,
- The general introduction of dry heat treatment before November 1984 would not have been evidence based and would have meant treating patients according to speculation, something that the Committee on Safety of Medicines rejected,
- The SNBTS strategy of focussing on the development of pasteurisation, rather than dry heat treatment, was based on the absence of hepatitis infection in clinical studies concerning pasteurised factor VIII and was consistent with decisions taken by the Committee on Safety of Medicines,
- SNBTS changed its immediate strategy from pasteurisation to dry heat treatment in November 1984, as soon there was preliminary evidence that HIV could be inactivated by this procedure.

7. **Achieving Viral Safety** (25th March 2022, transcript page 99)

7.1 In considering the dates when viruses of concern were discovered and the dates when effective virus inactivation technologies were developed, Counsel to the Inquiry pointed out that progress had been made in virus inactivation technology before the hepatitis C virus was discovered (transcript page 99, lines 15-17).

7.2 I agreed, but stated that this involved "*extremely difficult studies in patients which we didn't carry out in Scotland*" (transcript page 99, lines 18-20). I would like to clarify my answer.

7.3 I posed the question "*how do you remove something that hasn't been discovered?"* (transcript page 99, lines 7-8).

7.4 I said that because in science and in engineering, substances (such as viruses and proteins) are separated from one another by design by exploiting differences in their known properties. For example, the discovery of the AIDS virus enabled samples of the virus to be grown in the laboratory and research undertaken to discover how the virus could be eliminated from coagulation factor concentrates.

7.5 If a substance has not been discovered any relevant properties are not known and therefore cannot be exploited to achieve a separation. In these circumstances the only option is trial and error by experimentation, assuming that some measurement of failure or success is available, such as infection or non-infection of patients, something so extreme it could only be used as a last resort.

7.6 For the elimination of the agent responsible for non-A, non-B hepatitis from coagulation factor concentrates, the results of experiments in chimpanzees [WITN6914084] had not been reproduced in patients [PRSE0002333] [HSOC0001563]. This outcome left further research dependent on the measurement of the presence or absence of infection in patients as the only option available for determining if a product in development was safe from NANBH or not, prior to the virus responsible (hepatitis C) being discovered.

7.7 The patients in question were those who were not already infected with NANBH, whose medical condition required them to be treated with concentrates and who would almost certainly have been infected with NANBH if given an established concentrate.

7.8 That is what I meant by "*extremely difficult studies in patients*" which became known as studies in 'Previously Untreated Patients', often shortened to 'PUPs'.

7.9 I described PUP studies as "*extremely difficult*":

- because there were few patients who were suitable,
- untreated patients are usually newly diagnosed and haemophilia is usually diagnosed in early childhood. Therefore, many of these patients would have been children, with informed consent being required from parents or guardians,
- undertaking safety studies in children, involving treatment with concentrates, raised ethical questions, especially as medical advice in the early 1980s was that children and patients who required little treatment should, if clinically appropriate, be treated with cryoprecipitate to minimise risks of infection,
- blood samples from patients were subjected to surrogate tests for non-A, non-B hepatitis, with the recommendation by the International Society of Thrombosis and Haemostasis being that negative results should be obtained from 20 recipients, treated with at least 10 batches of the concentrate under investigation, before the product could considered to be free from NANBH transmission [WITN6914085]
- sampling was relatively onerous for the patients involved, with blood samples to be taken before treatment and then every two weeks after treatment for four months, followed by monthly samples for a further two months.

7.10 When I said "*which we didn't carry out in Scotland*", I meant that clinical research of this type was not undertaken with PFC products until there was good evidence that relevant products would not transmit HIV or NANBH (Hepatitis C).

7.11 A PUP study was subsequently carried out with PFC products that had been subjected to severe dry heat treatment [WITN6914086]. This study was begun in 1988, only after BPL's findings on its equivalent products had been published [WITN6914062] and there was therefore a high degree of confidence that non-A, non-B hepatitis would not be transmitted by the equivalent PFC concentrates.

7.12 The PUP study with PFC products was necessary to obtain evidence on freedom from transmission of non-A, non-B hepatitis/hepatitis C that was required by the CSM for product licensing.

7.13 As Counsel for the Inquiry pointed out, both BPL and PFC were able to provide Factor VIII and Factor IX concentrates that were safe with respect to non-A, non-B hepatitis some years before the hepatitis C virus was discovered.

8. Pasteurisation of FVIII (25th March 2022, transcript page 122-124)

8.1 I was asked by Counsel to the Inquiry if appropriate stabilisers could have been discovered earlier if greater priority had been given to research on heat treatment "*given that we know there were indeed such methods that did later prove to be successful"* (transcript page 123, lines 18-19)

8.2 I answered that it was the universal view that factor VIII was so sensitive that heat treatment would not be possible (transcript page 122, lines 15-17) and that removal of the stabilisers from the product would be difficult *"as processes for purifying Factor VIII hadn't been devised."* (transcript page 123, lines 10-11). I would like to add some additional information for clarification.

8.3 The original method of pasteurising factor VIII was not viable, as the 8 % yield reported by Behringwerke in 1981 [PRSE0003591], was too low for the process to be applied beyond the production of small quantities.

8.4 According to Kasper et al. "*Heating in solution was also associated with a very low yield. In early years, these concentrates could be made only in small quantities for limited numbers of patients."* [WITN6914079].

8.5 This very low yield was due to insufficient stabilisation of factor VIII activity during pasteurisation and to a high loss of factor VIII over the precipitation procedure used to remove the stabilisers from the final product, something that was not required with albumin.

8.6 Therefore, most of Behringwerke's FVIII, derived largely from US paid donor plasma, continued to be supplied unheated.

8.7 The general application of pasteurisation to factor VIII by Behringwerke required further developments to the process that utilised both an additional stabiliser, reported by myself in 1983, and new technology for purifying FVIII, that I had helped to identify, and which was only available from mid-1984.

8.8 It was these, and other aspects, on which PFC's R&D had focussed with the aim of achieving pasteurisation of factor VIII with a much higher yield.

8.9 As I stated in my oral evidence:

"It required further research to understand why Factor VIII was so unstable. And then to address that point as well" (transcript page 124, lines 15-17)

8.10 Behringwerke went on to modify their process to achieve an acceptable yield, with a new patent filed on 31st August 1984 [WITN6914087]. That a patent was granted, signifies that the patent agencies considered that the claims made by Behringwerke were inventive (ie. original).

8.11 Although Behringwerke filed their new patent application on 31 August 1984, the worked example in the patent application was carried out with 250g cryoprecipitate, which equates to about 25 litres of plasma. I estimate that about a further two years would have been required to scale-up the new process and achieve successful routine manufacture. This is consistent with the preliminary results of their phase 1 clinical trial, which would normally precede routine manufacture, being reported in June 1986 [WITN6914088] and results from a new PUP study being published in 1990 [WITN6914060].

8.12 According to their new patent, the modifications made by Behringwerke included the addition of calcium to increase the stabilisation of factor VIII (see patent claims 1,2,5,14,15 and example 3) and the use of ion exchange chromatography to remove the carbohydrate and amino acid stabilisers from the final product.

8.13 That factor VIII activity could be stabilised by adding calcium had been discovered by myself and published in preliminary reports in 1983 [WITN6914077] [WITN6914089] [PRSE0004094].

8.14 My discovery that factor VIII could be stabilised during processing by adding calcium was based on:

- my observation of December 1980 that factor VIII became unstable after the addition of sodium citrate, which was known to function as an anticoagulant by removing calcium from the blood coagulation system,
- information in a study published in 1982 which found, using newly developed monoclonal antibodies, that the different sub-units of the factor VIII molecule were held together by calcium [WITN6914090].
- it was as a result of this discovery that I explored adding calcium to the factor VIII process to increase the stability of factor VIII activity such that further processing could be tolerated without an unacceptable loss of factor VIII activity.

8.15 From my experience, I believe that the only ion exchange resin that was suitable for large-scale production of factor VIII, at this time, was a gel known as QAE-Sepharose, which was first developed by the company Pharmacia in mid-1984. QAE-Sepharose was identified as suitable for the large-scale processing of factor VIII by Dr Johnson and myself at a meeting with Pharmacia on 24th July 1984 [PRSE0002291_057].

8.16 I believe that it was only following these process modifications, and their scale-up, that Behringwerke achieved a yield of factor VIII that was high enough for pasteurisation to be applied to all of their Factor VIII production.

8.17 In 1992, Behringwerke's pasteurised Factor VIII concentrate was reported to have transmitted hepatitis C in routine use [WITN6914091] [WITN6914092].

8.18 In 1994, Behringwerke's pasteurised Factor IX concentrate transmitted hepatitis B to over 30 non-haemophilic patients [WITN6914093].

8.19 Following these virus transmissions, Behringwerkes' pasteurisation process was reviewed by the German Regulatory Authority which concluded *"the effectiveness of the inactivation is subject to fluctuations and is influenced by the stabilisers which have been added to maintain biological activity" and* advised that a second virus inactivation procedure was required to complement the pasteurisation process [WITN6914094].

8.20 In addition, pasteurised Factor VIII concentrates from two different manufacturers were discontinued in 1993 and 1997 following the formation of factor VIII inhibitors in people with haemophilia A [WITN6914065] [DHSC0020815_09] [WITN6914063] [PRSE0003191] [EXPG0000044_0070].

8.21 In summary:

- The original method for pasteurising factor VIII, that was discovered adventitiously, could only be applied to a limited extent because of the very low yield of factor VIII.
- Subsequently Behringwerke developed a modified process, based on new knowledge, some of which was derived from PFC's research, which did provide a satisfactory yield.
- To the best of my knowledge, this modified method for the preparation of pasteurised factor VIII depended on knowledge of the factor VIII molecule that was published in 1982, combined with a new ion exchange reagent for chromatographic purification that first became available in mid-1984.
- Beringwerke's pasteurised Factor IX concentrate transmitted hepatitis B, causing the German Regulatory to conclude that the effectiveness of pasteurisation of coagulation factor concentrates was variable.
- Some pasteurised factor VIII concentrates were discontinued following the development of inhibitors in patients.

9. <u>Research on Heat Treatment of FVIII</u> <u>(25th March 2022, transcript page 95, 100)</u>

9.1 On being questioned why research on the heat treatment of factor VIII had not begun earlier, I answered:

• "*It was so inconceivable that it literally wasn't something that I would have imagined could have been possible."* (transcript, page 95, lines 10-12), and

- "… *I think that if you look at the history, there had been attempts to heat materials, including plasma and a whole host of different methods, using UV radiation and chemicals, through the 1950s and 1960s, and they all resulted in failure"* (transcript, page 100, lines 19-24).

I believe that it could be helpful to the Inquiry if I explain why I gave these answers.

9.2 My position that heat treatment of factor VIII was inconceivable was based on my knowledge and experience of the temperature related instability of factor VIII activity, both in plasma and during the manufacture of concentrates.

9.3 I believe that this position was shared by all of those with whom I worked during the 1970s; including Dr Smith, Mrs Middleton and Mr Watt at PFC; Dr Prowse, Dr Pepper, Dr Boulton and Dr Cash of Edinburgh BTS and Dr Johnson of New York University Medical Center, who was advising PFC on research aimed at the physical removal of hepatitis viruses from factor concentrates.

9.4 As I noted, considerable research on removing the risk of hepatitis transmission by blood and blood products had been carried out before 1970, but had been unsuccessful. These researchers had examined a variety of different methods, including heat treatment, chemical treatments in which 550 chemicals were examined and irradiation with UV-light, cathode rays and gamma rays [PRSE0002291_013].

9.5 As researchers tend not to publish negative results, it is probable that additional research was undertaken but not reported. For example, Dr Edwin Cohn, who led the development of pasteurised albumin, had "*initiated a search for a stabilizing agent that would enable a heat treatment for gamma globulin analogous to that being used for serum albumin. However, efforts in that direction were not successful and had been abandoned* [WITN6914055].

9.6 Dr Cohn's failure to extend pasteurisation beyond albumin was explained in 1984 by Dr JT Edsall, a colleague of his who had contributed to the discovery of a stabiliser for albumin, who explained why this was unique to albumin. [PRSE0000345]. This demonstrated that even in 1984, Dr Edsall could not conceive that proteins other than albumin could be heat treated.

9.7 After failing to extend pasteurisation beyond albumin "*Dr Cohn's suggestion was to concentrate the virus in one fraction and remove it this way.*" [WITN6914095]. This comment demonstrates that Dr Cohn must have believed that heat treatment of plasma proteins, other than albumin, was impossible and had turned instead to research on physical methods of virus removal, which is what PFC was engaged in when I joined in 1973.

9.8 In 1978, Dr Rosemary Biggs wrote "*There are two urgent problems which need solution, one concerns the production of virus free fractions, and it is to be hoped that progress will be made in testing plasma submitted to fractionation procedures to eliminate virus.*" [WITN6914096].

9.9 This comment suggests that Dr Biggs, the leading UK expert in haemophilia and its treatment, envisaged that freedom from hepatitis transmission could only be achieved by donor screening, not by heat treatment.

9.10 In December 1983, Professor J Garrott Allen wrote to PFC to comment on our letter to the Lancet which mentioned the pasteurisation of factor VIII [WITN6914069]. He wrote: "*The method I developed which eradicated the activity of the hepatitis viruses B and non-B in plasma, but also inactivated the labile clotting factors, especially Factor VIII, was to incubate it at 32C for 6 months. My question is, how can factors II, V and VIII be sufficiently preserved at 60C to be clinically useful, and yet be free of the hepatitis viruses B and non-B?*" [WITN6914097].

9.11 The research that Professor Garrott Allen cited was published in 1954. It therefore appears that he had rejected the idea that factor VIII might be heat treated in 1954 and continued to believe this in 1983.

9.12 I was subsequently told by Dr Alan Johnson of New York University Medical Center, one of the world's leading researchers on FVIII concentrates, that he had attempted to apply both dry heat treatment and pasteurisation to FVIII concentrates but had failed with both [WITN6914001_0050].

9.13 These comments from distinguished researchers, illustrate the universal belief that the ability of albumin to withstand pasteurisation was unique and that the idea that equivalent chemicals might be found to stabilise factor VIII had been long rejected.

9.14 It was not until Behringwerke announced the pasteurisation of Factor VIII in October 1980 and then, in 1981, published the chemicals that they had used to stabilise factor VIII, that the possibility of heat treating factor VIII became conceivable to a new generation of researchers, despite the very low yield.

9.15 In contrast to these earlier researchers, PFC did succeed in heat treating labile coagulation factors to inactivate infective agents responsible for hepatitis and AIDS, including:

- Factor VIII Concentrate,
- Factor IX Concentrate,
- Fibrinogen,
- Thrombin,
- Prothrombin Complex Concentrate

10 R&D on Heat Treatment at PFC (25th March 2022, transcript page 100)

10.1 I would like to comment further in response to the question from Counsel to the Inquiry in which she asked me "*Would it be fair to characterise the failure to attempt to heat treat concentrates earlier … as a failure of imagination rather than a lack of technology"* (transcript page 100, lines 12-18).

10.2 Contrary to being a "*failure of imagination"*, PFCs R&D contributed to:

- the achievement of Scottish self-sufficiency,
- the development of coagulation factor concentrates from PFC that were safe from transmission of HIV,
- the development of coagulation factor concentrates from PFC that were safe from transmission of hepatitis C,
- the development of 8Y by BPL,
- the successful pasteurisation of factor VIII by Behringwerke.

10.3 The challenge facing PFC scientists when I joined in 1973 was to increase factor VIII yield to minimise the need to use imported Factor VIII concentrates and, at the same time, to determine how to eliminate agents associated with hepatitis infection.

10.4 Prior to beginning R&D on heat treatment in 1981, research had been undertaken at PFC during the 1970s on physical methods of removing the risk of hepatitis infection from factor concentrates, as heat treatment was literally inconceivable (see section 9).

10.5 From 1976, PFCs R&D had focussed on broader questions concerning the low yield of factor VIII, including why factor VIII activity was so unstable.

10.6 This broader research employed a new method for detecting the factor VIII molecule that had been developed by Dr Ian Peak in Cardiff in 1979 [WITN6914098].

10.7 Factor VIII was typically measured in terms of its biological activity ie. its ability to clot blood. However, when this activity was lost or reduced it was not known if this was due to the factor molecule being physically removed during processing or because the factor VIII molecule was damaged in some way.

10.8 For the first time, the new assay of Dr Peak enabled loss of factor VIII activity by physical removal to be identified independently from loss by inactivation of the factor VIII molecule [WITN6914099] [WITN6914019].

10.9 This systematic research into the behaviour of factor VIII led me to discover, in December 1980, that the addition of the anticoagulant sodium citrate was largely responsible for factor VIII being unstable both in plasma and during the manufacture of concentrates.

10.10 After it had been reported by Fass et al. in 1982 that the sub-units of the factor VIII molecule were held together by calcium [WITN6914090], I determined that the citrate-induced loss of factor VIII activity that I had observed could be prevented by adding calcium to the factor VIII solution [WITN6914077] [WITN6914100] [WITN6914050].

10.11 This addition of calcium was used in:

- the development of severe dry heat treatment by BPL (8Y) [WITN6914101],
- the development of severe dry heat treatment by PFC (Z8) [WITN6914024],
- the development of a higher yielding method of pasteurisation by Behringwerke [WITN6914087] as explained in section 8 and,
- the successful use of solvent-detergent treatment and chromatographic purification of factor VIII at PFC [WITN6914102].

10.12 I chose not to apply for a patent for the addition of calcium to factor VIII, as I believed that the discovery was so important it should be made freely available to all manufacturers of FVIII as soon as possible, which I did by early presentation and publication of the results.

10.13 The more broadly based R&D strategy of PFC also resulted in:

- the development of a method for thawing plasma continuously for the preparation of cryoprecipitate (patent application filed 2nd April 1981) which increased Factor VIII yield by about 50%. This not only allowed Scotland to reach self-sufficiency in the supply of Factor VIII concentrate, but also to establish a 12-month stock of Factor VIII. It was this stock of Factor VIII that enabled PFC to distribute sufficient dry heat treated Factor VIII concentrate for all patients in Scotland and Northern Ireland from 10th December 1984 (see para 2.14-2.15).
- the discovery of a method for reducing the fibrinogen content of Factor VIII concentrates without loss of factor VIII, which involved precipitation with zinc + heparin (patent application filed 14th January 1983). This discovery was shared with Dr Smith at PFL and led indirectly to the development of 8Y [WITN6914103].

10.14 Inventive contributions by PFC included methods for:

- Continuous-flow plasma fractionation, (patent application filed 28th March 1969) [WITN6914104],
- Large-scale preparation of cryoprecipitate with a high factor VIII yield, (patent application filed 2nd April 1981) [WITN6914105],
- Reducing the fibrinogen content of factor VIII solutions, (patent application filed 14th January 1983) [WITN6914106],

- Preparation of fibrinogen, dry heat treated for 72 hrs at 80ºC, (patent application filed 8th December 1994) [WITN6914107],
- Preparation of thrombin, dry heat treated for 72 hours at 80ºC, (patent application filed 24th February 1995) [WITN6814108],
- Preparation of a Liquid Intravenous Immunoglobulin, (patent application filed 20th March 1997) [WITN6914109],
- Inactivation of viruses in protein solutions using ultraviolet irradiation, (patent application filed 2nd Oct 1998) [WITN6914110]
- Removal of infective prion proteins (e.g. vCJD) from Immunoglobulin and Albumin, (patent application filed 19th January 1999) [WITN6914111],
- Removal of prion infectivity (e.g. vCJD) from chromatography resins and equipment, (patent application filed 18th June 2002) [WITN6914112],
- Preparation of immunoglobulin products in high yield, (patent application filed 5th December 2006) [WITN6914113].

11 Different R&D Strategies of PFC and PFL/BPL (26th July, transcript page 11)

11.1 During the oral testimony of Professor Aileen Keel, Counsel to the inquiry asked her *"Was it your understanding, therefore, that the different heat treatment strategies adopted by BPL and PFC were in some way coordinated so as to be complementary?"* (26th July transcript, page 11, lines 4-7).

11.2 Professor Keel answered "……*there definitely was a degree of complementarity, whether that was deliberate or serendipitous evades me at this time."* (26th July transcript, page 11, lines 9-11).

11.3 As Professor Keel was unable to fully answer the question, I would like to assist the Inquiry by explaining why PFC and BPL adopted different R&D strategies.

11.4 PFCs R&D strategy was always evidence based and was receptive to change according to new evidence if and when it emerged. For example:

- practical research on the pasteurisation of factor VIII was begun on 2nd September 1981 after information on the technique used by Behringwerke had been obtained and translated,

- research aimed at pasteurising factor VIII and factor IX concentrates continued after clinical data were obtained from Behringwerke in August 1982 that demonstrated an absence of hepatitis infection in recipients,
- PFC R&D continued to focus on pasteurisation during 1983 and 1984, as no other virus inactivation procedure had been shown to prevent NANBH infection in patients,
- In January 1984, a note of an SNBTS meeting recorded "*Work conducted by Dr Smith BPL suggests there is no yield penalty for dried FVIII if it is heated to 60ºC for 3 days. This would be investigated, but it was noted that the current Hyland product made by this method is still infective"* [PRSE0000428].
- In 1984, PFC began research into greatly increasing the purity of factor VIII aimed, in part, at simplifying the pasteurisation process,
- On 26th October 1984, preliminary research on dry heat treatment was begun at PFC as evidence had emerged that an animal virus, similar in type to HIV, might be inactivated by dry heat treatment at 68ºC (CBLA0001898),
- On 2nd November 1984 evidence of a high degree of inactivation of HIV by dry heat treatment at 68º for 1 hour was presented at a symposium in Groningen,
- on 18th November 1984 PFC began dry heat treatment of its FVIII concentrate at 68ºC for 2 hours November and distributed heat treated factor VIII to all transfusion centres in Scotland and Northern Ireland on 10th December with unheated factor VIII being recalled,
- as a result of further PFC research, production of dry heat treated factor VIII at 68ºC for 24 hours was begun on 20th January 1985,
- PFCs research to develop a highly purified factor VIII concentrate continued throughout 1985, with this technology (ion exchange chromatography) being considered compatible with pasteurisation, advanced dry heat treatment or solvent detergent treatment, whichever, if any, was found to be effective against NANBH.
- On 23rd December 1985, senior PFC staff agreed to recommend that PFC develop a factor VIII concentrate equivalent to 8Y of BPL to increase the margin of safety against HIV. This followed receipt of a pre-publication copy of a letter to the Lancet [PRSE0002534], by Dr Prince of the New

York Blood Center, which reported that dry heat treatment at 60ºC resulted in less inactivation of HIV than expected and a discovery at PFC that the ability of 8Y to withstand dry heat treatment at 80ºC was due the method of freeze drying instead of the higher purity that BPL had believed to be responsible [WITN6914001_0089-0090].

- Full scale production batches of the resultant product (Z8) were available from 2nd December 1986, some two months after Dr Smith had presented data to UK HCDO on an absence of NANBH in 10 recipients of 11 batches of 8Y [CBLA0002348].

11.5 It is my understanding, based on conversations with Dr Smith, that the decision to focus on research on dry heat treatment at PFL/BPL was pragmatic, as a pasteurisation process could not be accommodated in the existing BPL facility.

11.6 Dr Smith confirmed this in his witness statement [WITN3433001];

- "*I always considered that dry-heating was unlikely to succeed against NANBH, and that we should be ready to exploit pasteurisation whenever BPL's premises might permit it."* [WITN3433001_0027],
- *"…the physical obstacles to developing pasteurisation in the existing BPL plant, deferred pasteurisation indefinitely." [*WITN3433001_0028],
- "*I would like to have had the kind of physical facilities necessary to exploit pasteurisation, and it is conceivable that had PFL been able to combine efforts with PFC we might both have arrived at a common goal sooner, but even in retrospect that seems unlikely." [*WITN3433001_0034],
- "*..production of pasteurised F.VIII and F.IX would have had to await commissioning of the new facility at BPL.."* [WITN3433001_0037].

11.7 The outcome of these different strategies is summarised in a brief chronology of the introduction of NHS heat treated Factor VIII concentrates taken from [PRSE0002291] and [PRSE0003122].

Table 1. Chronology of the Introduction of Heat Treated FVIII Concentrates by PFC and BPL/PFL

Date	PFC	BPL/PFL

14th Jan 1983	patent filed for purification of FVIII by precipitation of fibrinogen with zinc + heparin. Formed the basis of pasteurised FVIII (ZHT) and dry heat FVIII (Z8). [WITN6914106]	
8th Feb 1983	production of 1st pilot batch of pasteurised FVIII (ZHT) for clinical evaluation	
7th Nov 1983		production of pilot batch of 60ºC/72 hr dry heat treated FVIII (designated HT1) for clinical evaluation
May 1984		issue of pilot production batch of 60ºC/72hr dry heat treated FVIII (HT1) for clinical evaluation
25th Sep 1984	production of 11th pilot batch of pasteurised FVIII (ZHT) for clinical evaluation	
18th Nov 1984	production begins of 12-month stock of FVIII (NY) dry heat treated at 68ºC/2hr,	
10th Dec 1984	68ºC/2hr dry heat treated FVIII issued to all Centres.	
10th Dec 1984	unheated FVIII recalled	
20th Jan 1985	production begins of FVIII (NY) re-formulated to tolerate dry heating at 68ºC/24hr.	
Feb 1985	batch dedication system implemented.	first issue of 70ºC/24 hr dry heated FVIII (designated HT2).

		trial issue of 80ºC/72hr dry HT FVIII (8Y)(designated HT3). issue of unheated FVIII continues.
5th March 1985		patent filed for FVIII purification by precipitation of fibrinogen by heparin. suitable for pasteurisation or dry heat at 70ºC for 24 hours (HT2). formed the basis for dry heat FVIII (8Y) (HT3). [PRSE0000770]
14th March 1985	issue of 68ºC/24hr dry heated FVIII for clinical evaluation. issue of 68ºC/2hr dry heated FVIII continues to enable batch dedication to be maintained, in agreement with HCDs.	
28th March 1985		last issue of unheated FVIII from PFL
2nd May 1985		last issue of unheated FVIII from BPL
May - Sep		limited availability of 70ºC/24hr dry heat treated FVIII (HT2) and 8Y (HT3)
4th Sep 1985	routine issue of 68ºC/24hr dry heat treated FVIII with batch dedication. no further issue of 68ºC/2hr dry heated FVIII.	
18th Sep 1985		8Y issued routinely by BPL
23rd June 1986	first pilot production batch of 80ºC/72hr dry heat treated FVIII (Z8)	

2nd Dec 1986	production scale 80ºC/72 hr dry heat treated FVIII (Z8) available for clinical evaluation	
22nd May 1987	routine issue of Z8 with batch dedication	

11.8 The supply of NHS FVIII concentrates during the transition to heat treated FVIII. Taken from [PRSE0001083_0055] [PRSE0003122].

Table 2. Supply of NHS Factor VIII Concentrates from 1983/84 to 1987/88.

Year	FVIII (iu/pop) from PFC to NHS Scotland	FVIII (iu/pop) from BPL/PFL to NHS E&W
1983/84	1.45 (unheated)	0.49 (unheated)
1984/85	1.37 (all heated from 10th Dec '84)	0.51 (some heated)
1985/86	1.11 (heated)	0.46 (0.32 heated, 0.14 unheated)
1986/87	1.49 (heated)	0.51 (heated)
1987/88	1.67 (heated)	0.44 (heated)

Based on 1985 population of 5 million for Scotland and 55 million for England & Wales.

See Table 1 for the different heat treatment methods and their dates of introduction.

11.9 In summary, I believe that:

- PFC was first in the world to manufacture all of its FVIII concentrate safe from infection with HIV,
- PFC was first in the world to supply all of its patient population with FVIII concentrate safe from infection with HIV,
- BPL was first in the world to manufacture all of its FVIII concentrate safe from infection with hepatitis C,
- PFC was first in the world to supply all of its patient population with FVIII concentrate safe from infection with hepatitis C.

12. Discovery of the Cause of AIDS (25th March 2022, transcript pages 139-140)

12.1 I was asked by Counsel to the Inquiry if "*any efforts were made to access LAV from the Montagnier group in 1983 or '84"* (transcript page 139, lines 5-6).

12.2 In my response I commented that when this work was first published it "*went under the radar."* (transcript page 139, lines 18-19 & 124). I would like to explain why I used the expression "*went under the radar".*

12.3 My comment concerned a paper from Barré-Sinussi et al. that was published in Science on 20th May 1983, which described the isolation of a retrovirus from an AIDS patient and proposed that this virus (named LAV) could be the cause of AIDS [PRSE0004469].

12.4 My comment that this paper "*went under the radar*" is based on the absence of any reference to this paper in contemporaneous UK documents, including:

- a meeting of the MRC working party on AIDS on 10th October 1983 [CBLA0001749].
- briefing papers on AIDS that were provided by DHSS and HSE to the UK Advisory Committee on Dangerous Pathogens for their meeting of December 1983 [WITN6914017_16-49].
- a plenary lecture to the British Blood Transfusion Society (which I attended) on transfusion transmitted infections by the leading UK transfusion virologist, Dr R Tedder, on 17th December 1983 [WITN6914120].
- a meeting of the SNBTS Factor VIII Study Group held on 12th January 1984 [PRSE000428].

12.5 The failure to appreciate the findings of Barré-Sinussi at the time of publication has been ascribed to the paper's summary having been written by Dr Robert Gallo, to make it appear that the French findings confirmed those of his own paper in the same issue of Science, rather than representing a new finding.

12.6 "*Montagnier explained that he felt 'I had no other choice for having our manuscript accepted for publication than to accept the modifications introduced by Dr Gallo, who was the referee of this work'.*" [WITN6914121].

12.7 According to John Crewdson, author of a textbook on Robert Gallo, the leading UK AIDS expert Dr Robin Weiss, was misled by this "*Based on the Pasteur's Science paper, Weiss had serious doubts that the French really had found a new human virus*" [WITN6914121].

Statement of Truth

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

Signed GRO-C

Dated 31 October 2022

Table of Exhibits:

Date	Notes/Description	Exhibit Number
28 September 1983	Craske J. *UK Haemophilia Hepatitis Working Party. Annual Report for the Year 1982-3.* HCDO	WITN6914072
2005	Health Protection Scotland. *HIV in Scotland Review, 2004.* HPS Weekly Report 2005, 39 (3), 18-20.	WITN6914073
1986	Robertson JR, et al. *Epidemic of AIDS related virus (HTLV-III/LAV) infection among intravenous drug abusers.* Br Med J (Clin Res Ed) 1986, 292, 527-529.	WITN6914074

June 1977	Holleman WH, et al. *Isolation of human antithrombin-III by affinity chromatography on heparin Agarose (abstract).* Thromb Haemostasis 1977, 38, 201	WITN6914075
10 December 1981	Busby TF, et al. *Thermal Denaturation of Antithrombin III: Stabilization by Heparin and Lyotropic Anions.* J Biol Chem 1981, 256, 12140-7.	WITN6914076
1983	Foster PR, et al. *Stability of factor VIII during the preparation of an intermediate-purity factor VIII concentrate.* Br J Haematol 1983, 53, 343.	WITN6914077
September 2007	Foster PR. *Response to the Archer Inquiry. Examples of Warnings Issued with Coagulation factor Concentrates.* SNBTS	WITN6914078
1993	Kasper CK, et al *Recent evolution of clotting factor concentrates for Hemophilia A and B.* Transfusion 1993, 33, 422-434.	WITN6914079
7th March 1984	Committee on Safety of Medicines. *Minutes of the Sub-Committee on Biological Products held on 7th March 1984 (Appendix B).*	WITN6914080
1987	Kingdon HS et al. *"Agents Causing Non-A, Non-B Hepatitis: Could One Be a*	WITN6914081

	Prion?" Medical Hypotheses, 1987, 22, 329-333.	
1998	McGregor A. *Former head of Swiss Red Cross blood service guilty of endangering life.* Br Med J 1998,352,1916.	WITN6914082
1989	Hamamoto Y, et al. *A novel method for removal of human immunodeficiency virus: filtration with porous polymeric membranes.* Vox Sang 1989, 56, 230-236.	WITN6914083
August 1984	Hollinger BL, et al. *Reduction in Risk of Hepatitis Transmission by Heat-Treatment of a Human Factor VIII Concentrate.* J Inf Dis 1984, 150, 250-262.	WITN6914084
1989	Mannucci PM & Colombo M. *Revision of the Protocol Recommended for Studies of Safety from Hepatitis of Clotting Factor Concentrates.* Thromb Haemostasis 1989, 61, 532-4.	WITN6914085
1993	Bennett B, et al. *Study of Viral Safety of Scottish National Blood Transfusion Service Factor VIII/IX Concentrate.* Transf Med 1993, 3, 295-8.	WITN6914086
27 August 1991	Heimburger N et al. *Pasteurized, Isoagglutinin-Free Factor VIII Preparation and a Process for its Production.* United States Patent No. 5,043,428	WITN6914087

13th June 1986	Schimpf K, et al. *Comparison of recovery and half-life of a new factor VIII high purity concentrate (FVIII C HS) with a factor VIII HS (Haemate P) [Abstract]* Proc WFH Congress1986, p.231.	WITN6914088
4 July 1983	Foster PR, et al. *Factor VIII Stability During the Manufacture of a Clinical Concentrate.* Thromb Haemostasis 1983, 50 (1), 117	WITN6914089
March 1982	Fass DN et al. *Monoclonal Antibodies to Porcine Factor VIII Coagulant and Their Use in the Isolation of Active Coagulant Protein.* Blood 1982, 59, 594-600.	WITN6914090
1 August 1992	Schulman S, et al. *Transmission of hepatitis C with pasteurised factor VIII.* Lancet 1992, 340, ii, 305-6.	WITN6914091
1992	Gerritzen A, et al. *Acute Hepatitis C in Haemophiliacs Due to 'Virus Inactivated' Clotting Factor Concentrates.* Thromb Haemostasis 1992, 68, 781.	WITN6914092
1995	Jantsch-Plunger V, et al. *PCR Detection of a Low Viral Load in a Prothrombin Complex Concentrate that Transmitted Hepatitis B Virus.* Vox Sang 1995, 69, 352-4.	WITN6914093

11 August 1994	Löwer J. *Reducing the Risk of Transmission of Haematologenous Viruses with Medicinal Products made by Fractionation from Plasma of Human Origin.* Bundesanzeiger 1994, 161, 9243-4 (English translation)	WITN6914094
1971	Diamond KL. *Edwin Cohn Memorial Lecture. The Fulfilment of his Prophecy.* Proc. XXIVth Scientific Meeting of the Blood Research Institute, page 438.	WITN6914095
1978	Biggs R. *The Treatment of Haemophilia A and B and von Willebrand's Disease.* Blackwell Scientific Publications, page 187.	WITN6914096
21 December 1983	Garrott Allen J. *Letter to Dr AG Welch SNBTS PFC.* Stanford University Medical Center, California, USA.	WITN6914097
1979	Peake IR et al. *An Immunoradiometric assay for procoagulant factor VIII antigen: results in haemophilia, von Willibrand's disease and fetal plasma and serum.* Br J Haematol 1979, 42, 269-281.	WITN6914098
1980	Foster PR et al. *Intermediate Purity Factor VIII Concentrate: Changes in Antigen and Coagulant Activity during*	WITN6914099

	Production. Br H Haematol 1980, 46, 334.	
1988	Foster PR, et al. *Studies on the Stability of VIII:C during the manufacture of a Factor VIII Concentrate for Clinical Use.* Vox Sang 1988, 55, 81-89.	WITN6914100
26 February 1986	Smith JK. *Freeze-drying. Letter to Dr DS Pepper SNBTS Headquarters Unit Laboratory.* Plasma Fractionation Laboratory 26th February 1986.	WITN6914101
2000	Foster PR et al. *Studies on the Removal of Abnormal Prion Protein by Processes Used in the Manufacture of Human Plasma Products.* Vox Sang 2000, 78, 86-95.	WITN6914102
22nd May 1984	Smith JK. *Letter to Dr P Foster, Protein Fractionation Centre.* Plasma Fractionation Laboratory	WITN6914103
10th January 1978	Watt JG. *Blood Plasma Fractionation.* US patent 4,067,863	WITN6914104
20th January 1987	Foster PR. *Method of Extracting Cryoprecipitate from Frozen Blood Plasma.* US Patent 4,638,048	WITN6914105
14th January 1983	Bier M & Foster PR. *Purification of Antihemophilia Factor VIII by Precipitation with Zinc Ions.* US Patent 4,406,886	WITN6914106

3rd November 1998	McIntosh RV & Hardy JC. *Heat Treated Blood Plasma Protein.* US Patent 5,831,027	WITN6914107
25th May 1999	MacGregor IR, et al. *Thrombin Preparation.* US Patent 5,907,032	WITN6914108
26th November 2002	McIntosh RV & Welch AG. *Composition Comprising Immunoglobulin.* US Patent 6,485,932	WITN6914109
1st July 2003	Gunn A, et al. *Device for Treatment of Biological Fluids.* US Patent 6,586,172	WITN6914110
24th July 2012	Welch AG & Foster PR. *Treating Protein Containing Liquids.* US Patent 8,226,776	WITN6914111
7th August 2007	Foster PR, et al. *Removal of Prion infectivity.* US Patent 7,752,720	WITN6914112
12th June 2008	Eaglesfield P, et al. *Protein Purification.* International Patent Application WO 2008/068455.	WITN6914113
17 December 1983	Tedder R. *A Virologists View of Transfusion.* Proceedings of the Inaugural Meeting of the British Blood Transfusion Society. BBTS 1983	WITN6914114
2002	Crewdson J. *Science Fictions.* Little, Brown and Co. pages 82 and 548.	WITN6914115