Issue 2:

The production, supply and use of blood or blood products in Scotland during the period 1974 to 1991

Topics covered:

B2 – The use of blood product concentrates in Scotland, including any perceived disadvantages of such products, from their introduction in or around 1974; the continuation of the use of commercial concentrates in particular after:

- International realisation that these carried a risk of AIDS;
- The proposal by Dr Galbraith of the Public Health laboratory Service in May 1983 that use in the UK should be stopped;
- Significant progress towards self-sufficiency in the manufacture of blood products by the NHS in Scotland had been made.

B3 – The implementation of heat treatment against LAV/HTLV-III by the Protein Fractionation Centre in Scotland in December 1984, and the technological background to such implementation, including the history and exploration of methods of heat inactivation by the Scottish national Blood Transfusion Service.

C3 – The implementation of heat treatment sufficient to inactivate Hepatitis C in blood products by the Protein Fractionation Centre in Scotland in 1987, and the technological background to such implementation, including the achievement of this objective by the National Blood Transfusion Service in England and Wales in 1985.

Topic B2

PENROSE INQUIRY

TOPIC B2

Evidence was given on this topic by:-

(1) Dr Mark Winter (Days 15 and 16)
(2) Professor Charles Forbes (Day 17)
(3) Professor Christopher Ludlam (Days 18 and 19)
(4) Dr Anna Pettigrew (Day 20)
(5) Professor Ian Hann (Days 21 and 31)
(6) Dr Brian McClelland (Day 21)
(7) Dr Peter Foster (Days 22 and 23)
(8) Dr Frank Boulton (Day 24)
(9) Dr Robert Perry (Day 25)
(10) Professor John Cash (Day 25)
(11) Professor Andrew Lever (Days 26 and 27)
(12) Mr David Watters (Day 87)

The relevant statements on this topic are:-

(1) Dr Mark Winter PEN.015.0292 (including written submissions to the Archer Inquiry PEN.015.0283)
(2) Professor Charles Forbes PEN.015.0254
(3) Professor Christopher Ludlam PEN.015.0445, PEN.015.0468. PEN.015.0385 and PEN.015.0375
(4) Dr Anna Pettigrew PEN.015.0486
(5) Professor Ian Hann PEN.015.0370, PEN.015.0035, PEN.012.0270, PEN.012.0203 and PEN.012.0205
(6) Dr Brian McClelland PEN.012.0268 and PEN.015.0307
(7) Dr Peter Foster PEN.012.0148 and PEN.015.0101 plus attachments PEN.013.1208 - 1304
(8) Dr Frank Boulton PEN.015.0054 and PEN.015.0226
(9) Dr Robert Perry PEN.016.0460 and PEN.015.0062
(10) Professor John Cash PEN.015.0273 and PEN.015.0362
(11) Professor Andrew Lever PEN.015.0517

SNBTS briefing papers relevant to this topic are:-

(1) SNBTS paper – Events Concerning the Safety of Blood and Blood Products with Special Reference to the Treatment of Haemophilia PEN.013.0220
(2) SNBTS briefing paper on Self-sufficiency and the Supply of Blood Products in Scotland PEN.013.1125
(3) Addendum to SNBTS briefing paper on self-sufficiency PEN.018.0571
(4) SNBTS briefing paper on the Development of Heat Treated Coagulation Factors PEN.013.1309
(5) SNBTS briefing paper on Hepatitis Risk Warnings PEN.012.0286

TOPIC B2

The use of blood product concentrates in Scotland, including any perceived disadvantages of such products, from their introduction in or around 1974; the continuation of the use of commercial concentrates in particular after:

- **international realisation that these carried a risk of AIDS;**
- **the proposal by Dr Galbraith of the Public Health Laboratory Service in May 1983 that use in the UK should be stopped; and**
- **significant progress towards self-sufficiency in the manufacture of blood products by the NHS in Scotland had been made**

Inquiry Counsel Issues Nos 1-9:

1. **Following the first reports of AIDS in patients who had received treatment with blood or blood products, by what point should clinicians responsible for the care of haemophilia patients in Scotland have recognised a possible connection between AIDS and factor concentrates?**

2. **After the point identified in response to question 1 what, if any, steps should have been taken by haemophilia clinicians in Scotland to reduce or restrict the use of factor concentrates?**

3. **When should any such step or steps have been taken?**

4. **Would any such steps have prevented any person acquiring AIDS from treatment with blood products in Scotland?**

5. **Are the answers to questions 1 – 4 affected by focusing exclusively on concentrates produced by the NHS?**

6. **Why were more commercial concentrates used at Yorkhill in the early 1980s than at any other haemophilia centre in Scotland?**

7. **Should there have been an initiative to restrict the use of commercial concentrates in Scotland similar to the proposal of Dr Galbraith of the Public Health Laboratory Service and, if so, when and by whom should it have been taken?**

8. **If such an initiative could and should have been taken, would it have prevented any person acquiring AIDS from treatment with blood products in Scotland?**

9. **The quality of information and advice concerning the relationship between AIDS and blood products available to those with haemophilia and those responsible for their treatment in Scotland from**

    a) UKHCDO;

b) Government Ministers and officials and
c) The Haemophilia Society

in the period 1982 to 1985

As well as from the Scottish Haemophilia clinicians in practice at the material time, helpful reports were received from Dr Mark Winter PEN.015.0292 and Professor Andrew Lever PEN.015.0517. During the course of Dr Winter's evidence on the question of whether British blood was likely to be freer from viruses than American blood, the Chairman stated, "I would ask generally at this stage that we try very carefully to distinguish what would have been understood at the time from what can be seen in retrospect. This is an area in which it could be very very dangerous to allow hindsight to dictate the formation of views" (day 16, page 30). During the course of Professor Lever's evidence on the topic of contemporary evaluation of competing hypotheses as to the cause of immunodeficiency, the Chairman acknowledged the need to be extremely careful not to use hindsight to be critical of opinions expressed at the time (day 26, page 97) and, it is submitted, the same caution requires to be employed in any examination of questions such as "what steps should have been taken".

The chronology of the reports of AIDS in patients who had received treatment with blood or blood products need not be rehearsed here. For a summary see Professor Ludlam's paper "HIV Infection in Haemophiliacs" PEN.015.0385 and also "Historical Summary of AIDS in Haemophilia 1981 - 1985" PEN.015.0468. Whatever the pronouncements in Parliament, and notwithstanding the wording of the letter from the Haemophilia Society dated 4th May 1983 incorporating advice from Professor Bloom (DHF.001.4471), it appears that by about the Spring/Summer of 1983 the majority of Haemophilia clinicians were "signed up to the infectious theory" because of the report of the San Francisco infant (day 16, pages 34 and 35).

The report of the infant in San Francisco was described by Dr Winter as critical - see day 16, pages 7-8. At page 18 he described this report as doing much to move the aetiologies towards a transmissible agent.

Professor Lever in his evidence seemed more guarded, regarding the report of the San Francisco infant as "very compelling data for an infection" with a caveat that "… I think it's compelling but not absolutely conclusive … so there are alternative explanations for this. Again it's another piece, as you say, of the jigsaw, which is more and more suggestive of an infectious agent and a transmission by blood product" - see day 26, pages 49-50 and see also day 26, page 101.

Professor Ludlam described the report of the San Francisco child as "a significant event, not a clinching event" - day 18, page 117. See also Professor Forbes at day 17, pages 96-97.

Whatever competing theories persisted (and some from distinguished and powerful advocates), it appears that the majority of Haemophilia clinicians, whilst not 100% convinced, were of the view by mid 1983 that there was a strong possibility, perhaps a probability, that AIDS was transmissible by blood products. In addressing questions such as "at what point should clinicians responsible for the care of Haemophilia patients in Scotland have recognised a possible connection between AIDs and its factor concentrates" it is necessary to bear in mind Professor Lever's comment that "when one is faced with an inquiry like this which has diligently sought out every source of data that one can possibly get you are rather spoiled by having

access to many documents which wouldn't have been that easily available at the time" (day 26, page 128). In this regard, Professor Ludlam's comments about the notoriety of the MMWR reports is significant (day 18, page 95). This was of course in a pre-internet era. Perhaps the more pertinent question is, whatever the date at which the connection was or should have been made, what steps should or could have been taken to reduce or restrict the use of factor concentrates. It is of course necessary to appreciate the perception widely held at the time that NHS concentrates were likely to be "safer" than commercial (particularly American) concentrates.

Professor Lever suggested that "… it is no doubt impossible even yet to be prescriptive about what should have happened" (day 26 page 81) and perhaps most pertinently "I don't think there would have been an expert there who could justifiably have said "this is what's going to happen" as it turned out … far less have gone on to say "and this is what you must do"." (day 26, page 83-84). As Professor Forbes put it, "it was certainly not possible to stop the use of concentrate as bleeding would have resulted in death" (day 17, page 98).

There were recommendations from Professor Bloom in his circular letter of 24th June 1983 following upon a Reference Centre Directors Meeting on 13th May 1983 (SGH.002.2175). That letter addresses the risk -v- benefit conundrum, the conclusion being that the benefits of continuing treatment with concentrates outweighed the risks. That conclusion has to be understood in the context of contemporary knowledge of the disease.

Both GRI and ERI followed that advice. See Professor Forbes day 17, pages 108 and 111. At ERI Professor Ludlam had continued his predecessor Dr Davies' policy of not using commercial concentrates - day 18, page 59 but see page 70-71 also re. the restricted use of commercial concentrates in 1981 and 1982. Such limited use as was made of commercial concentrate at ERI was totally discontinued in May 1983 - day 18, page 41. See also document "Treatment Policy 1982-1984" PEN.015.0385.

The greater use of commercial concentrate at Yorkhill was explored with Professor Forbes on day 17, page 76 and Dr Anna Pettigrew day 20, pages 14, 16 and 18-21. Dr Willoughby's preference for commercial products was largely due to (i) his promotion of home treatment where cryoprecipitate was impracticable; (2) his innovative promotion of prophylaxis and because of the difficulty in obtaining sufficient supplies of NHS concentrate. When Professor Hann took over from Dr Willoughby in January 1983 he moved away from commercial concentrates because of the perceived risk of other viruses (not HIV but other viruses). See day 31, pages 69 and 78. Professor Hann's understanding of the reasons for Dr Willoughby's use of commercial concentrates was explored on day 31, page 79-80.

The suggestion of Dr Galbraith contained in his letter of 7th May 1985 (MIS.001.0005), i.e. to withdraw all blood products made from blood donated in the USA after 1978 until the risk had been clarified was, although understandable from a public health perspective, simply was not practicable. See Dr Winter, day 16 pages 53 and 65 and Professor Lever day 26, pages 87-88 and 92. In the absence of any viable alternative, it is difficult to see what option there was other than to continue with treatment. Certainly the Haemophilia Society, and individual patients it seems, were plainly resistant to the notion of a return to cryoprecipitate, which in any event, would not necessarily have prevented infection. The achievement, or near achievement, of self sufficiency, or at the very least, the far higher use of NHS product in Scotland resulted in one of the lowest HIV infection rates in the world.

- **The awareness by the SNBTS of the risk of transmission of viruses by blood products.**

The SNBTS was very aware of the risk of transmission of viruses by blood and blood products. The SNBTS was at the forefront of testing donations for hepatitis B infection[1] and provided written warnings of a risk of hepatitis with its coagulation factor concentrates[2]. The main objective of the SNBTS drive for self-sufficiency was to reduce the risk of transmission of viruses by reducing the need for the importation of blood products derived from paid donors, which were associated with a higher risk of disease transmission[3]. The SNBTS also carried out research into methods of removing viruses from coagulation factor concentrates[4] and into discovering the agent(s) responsible for non-A, non-B hepatitis[5].

1. PEN.130.220, page 33. Oral evidence of Dr Dow of 18 March 2011, pages 109-110.
2. PEN.102.0286.
3. PEN.013.1125, page 13.
4. PEN.013.1309, pages 32, 50-51.
5. PEN.012.0351, page 1; SNB.001.3932, page 2.

- **The awareness by the SNBTS of the risk of transmission of AIDS by blood products.**

The transmission of AIDS by Factor VIII concentrate in the USA was noted by SNBTS in August 1982[1] and was considered with haemophilia directors in September 1982[2] and in January 1983[3]. In addition, individual employees of the SNBTS were pro-active during 1983/84 in addressing concerns over the importation of commercial Factor VIII from the USA. Dr Boulton[4] communicated his concerns directly to the chair of UKHCDO, whilst Dr Foster[5] wrote to his trades union ASTMS to encourage the utilisation of the PFC for processing plasma from England and was invited to provide advice to The General Secretary of ASTMS, Mr Clive Jenkins, in his dialogue with the DHSS over the continued importation of commercial blood products. There is therefore good evidence to demonstrate that there was a high awareness within the SNBTS of the potential risk of AIDS.

However, the limited knowledge available in the period 1982-1984 meant that there was a broad spectrum of opinion. This can be illustrated by the position of the UK Haemophilia Society which, with access to information from leading medical and scientific experts, continually advised its members and the UK government that the risk of AIDS being transmitted by blood products was relatively small, stating for example in September 1983 "*Our message remains unchanged: THE ADVANTAGES OF TREATMENT FAR OUTWEIGH ANY POSSIBLE RISK. BALANCE THE RISKS for yourself, but we would state again that the risk of AIDS is tiny compared with the risks from untreated bleeding episodes"* [6]. Also in 1983, the UK Haemophilia Society urged the UK government not to restrict the importation of Factor VIII concentrate from the USA[7] and indicated a preference for commercial blood products in a report of January 1984, that was given to the UK government[8].

That AIDS was caused by a blood-borne virus that was transmissible by blood or blood products was not known internationally until April/May 1984[9]. That HIV had entered the blood supply in Scotland was not known until 26th October 1984[10].

Virtually all patients with bleeding disorders who were infected with HIV in Scotland were infected before it was known that AIDS was transmitted by a blood-borne virus, before it was known that the virus responsible could be inactivated by heat treatment and before a test for screening blood donations was available. However, the relatively high supply of local coagulation factor concentrates and the early introduction of heat treatment by the SNBTS meant that fewer patients with bleeding disorders in Scotland were infected with HIV than would be expected in comparison to the rest of the UK on a population basis[11].

1. PEN.015.0101, pages 6-7(witness statement of Dr Foster)
2. PR 8.16
3. PR 8.17
4. PEN.015.0226 (addendum to witness statement of Dr Boulton)
5. PEN.013.1280; PEN. 013.1283 and oral evidence of Dr Foster on day 23, pages 17-34
6. DHF.001.4767. Oral evidence of Mr Watters on day 87, pages 72-76
7. DHF.001.4413
8. DHF.001.5151 (note: a Department of Health annotation on the front page indicates that contrary to the evidence of Mr Watters (oral evidence, 19 January 2012, p.115, lines 14-16; p. 116, line20) this paper was submitted to DHSS.
9. PR 8.84
10. Oral evidence of Professor Ludlam on day 35, pages 96-97
11. PR 3.60, 3.61.

- **The awareness by the SNBTS of the evidence that HTLVIII may have entered the Scottish donor population evidence**

The first point at which there was evidence that HTLVIII may have entered the Scottish donor population was October 1984. The SNBTS had, in early 1983 acted on concerns that (a) AIDS might be caused by an infective agent, (b) there was some early evidence that AIDS could be a consequence of transfusion and (c) epidemiological information from the USA suggested that it might be possible to provide some protection by avoiding donation by groups of individuals defined by certain types of behaviour.

1. PEN.012.0268, PEN.015.0307
2. WIT.003.0036
3. Oral evidence of Dr B McLelland on day 12 Page 9

- **The performance of the SNBTS towards the production of sufficient blood products for the use by the NHS in Scotland**.

1) Planning undertaken by the SNBTS to meet the requirements for the treatment of people with Haemophilia.

As a result of long-term planning by the SNBTA and the SHHD, a new SNBTS plasma fractionation facility was established in 1975 with a capability for the manufacture of coagulation factor concentrates that was more than adequate to meet the expected needs of people with haemophilia in Scotland[1]. Subsequently, ongoing planning within the PFC led to the capacity for the manufacture of Factor VIII concentrate being increased (e.g. by purchase of additional freeze driers) in anticipation of a predicted increase in demand[1].

The SNBTS was first to recognise that the amount of Factor VIII concentrate needed to treat people with haemophilia A in the UK was much greater than had been estimated in the 1970's, by an Expert Group which had advised the UK government, and that the demand for Factor VIII concentrate would increase year-on-year[2].

1. PEN.013.1125, pages 37-38
2. PEN.013.1125, pages 22-23, 27-30; oral evidence of Dr Foster on day 22, pages 48-53.

2) The efforts made by the SNBTS to obtain the quantity of fresh plasma needed to produce the amount of Factor VIII concentrate that was required to treat patients in Scotland, according to UK clinical practice at the time.

SNBTS made very considerable efforts to obtain fresh plasma for the preparation of Factor VIII concentrate, primarily by promoting the practice of component therapy. As a consequence, much more fresh plasma for the preparation of Factor VIII concentrate, on a population basis, was supplied in Scotland than in the rest of the UK[1].

1. PEN.013.1125, pages 30-36, 67-72; oral evidence of Dr Foster on day 22, pages 62-75.

3) The research & development into the provision of Factor VIII concentrate undertaken by the SNBTS.

SNBTS researchers identified the main causes of yield factor VIII loss during the preparation of Factor VIII concentrate and devised suitable methods for minimising these losses and for improving production operations to enable throughput to be increased relatively easily and without a yield penalty[1].

1 1.PEN.013.1125, pages 50-54; oral evidence of Dr Foster on day 22, pages 117-119 and 6 Sep 2011, pages 30-49.

4) The amount of Factor VIII concentrate provided by the SNBTS to treat people with haemophilia A in Scotland according to UK clinical practice at the time.

The amount of Factor VIII concentrate supplied by the SNBTS was generally sufficient to treat people with haemophilia A in Scotland according to UK clinical practice at the time[1]. However, this may not always have been sufficient to meet all of the treatment needs of patients who began home therapy before the SNBTS was in a position to increase its output of Factor VIII concentrate to satisfy the resultant increase in demand[2].

The relatively high output of Factor VIII concentrate by the SNBTS resulted in fewer people with haemophilia in Scotland being infected with HIV than would have been expected in comparison to the rest of the UK on a population basis[3].

1. PEN.013.1125, pages 54-63
2. PEN.018.0571, pages 1-13
3. PR 3.60, 3.61, appendix 1

5) The quality of SNBTS Factor VIII concentrate used for the treatment of people with haemophilia A given the state of knowledge at the time.

   SNBTS Factor VIII concentrate always complied with the relevant quality specifications laid down by the British Pharmacopoeia[1]. SNBTS Factor VIII concentrate was approved by the Committee on Safety of Medicines (CSM) for a period of 5-years in 1978 and again in 1983[2] and was therefore of a quality that was judged to be satisfactory by CSM from 1978 to 1988. Both the solubility and the purity of the SNBTS Factor VIII concentrate were increased in 1979 as a result of SNBTS research, from which a new process for the preparation of cryoprecipitate was devised[3].

   1. PEN.013.1125, page 42; PEN.017.2723, page 6
   2. PEN.017.2723, pages 17-18, 35; PEN.013.0220, pages 38-39
   3. PEN.013.1125, pages 50-54; oral evidence of Dr Foster on 10 May 2011, pages 117-119 and 6 Sep 2011, pages 30-49

6) Was the use of SNBTS Factor VIII concentrate limited by serious adverse reactions to the product?

   In response to a suggestion to this effect, the SNBTS has produced a paper[1] which indicates that it has no evidence that there were serious adverse reactions which limited the use of the product. In addition, the use of commercial Factor VIII concentrates ceased in Scotland in the period 1984 to 1988[2]. This would not be consistent with use of SNBTS Factor VIII concentrate having been limited by serious adverse reactions.

   1. PEN.018.0571, pages 13-15
   2. PR 10.185; PEN.013.1125, page 61

Topic B3

PENROSE INQUIRY

TOPIC B3

Evidence was given on this topic by:-

(1) Dr Peter Foster (Days 41 and 42)
(2) Professor John Cash (Day 43)
(3) Professor Christopher Ludlam (Day 44)
(4) Dr Robert Perry (Day 45)
(5) Dr Bruce Cuthbertson (Day 46)
(6) Professor Willem van Aken (Day 47)
(7) Dr James Smith (Day 59)

The relevant statements on this topic are:-

(1)	Dr Peter Foster	PEN.012.1438 and PEN.012.1797
(2)	Professor John Cash	PEN.012.1912
(3)	Professor Christopher Ludlam	PEN.012.1688
(4)	Dr Robert Perry	PEN.012.1759
(5)	Dr Bruce Cuthbertson	PEN.013.0025
(6)	Professor Willem van Aken	PEN.012.1928
(7)	Dr James Smith	PEN.012.1551
(8)	Dr Brian McClelland	PEN.011.0062

SNBTS briefing paper relevant to this topic is:-

(1)	SNBTS briefing paper on the Development of Heat Treated Coagulation Factors	PEN.013.1309

TOPIC B3

The implementation of heat treatment against LAV/HTLV-III by the Protein Fractionation Centre in Scotland in December 1984, and the technological background to such implementation, including the history and exploration of methods of heat inactivation by the Scottish National Blood Transfusion Service.

Topic B3 Inquiry Counsel Issues Nos 1 – 6

1. **Was the approach taken to viral inactivation of clotting factor concentrates at PFC in the period 1980 to 1984 reasonable?**

2. **Was the degree of priority accorded to viral inactivation during this period reasonable?**

3. **When, and how far, was it appreciated that it was likely that there would be a need for the heat treatment programme to deal with the threat of AIDS?**

4. **Whether there could have been acceleration of the heat treatment programme around May 1983 in response to the AIDS problem. If so, should the programme have been accelerated?**

5. **Should there have been a change to dry heat treatment either in the summer of 1983 or at the beginning of 1984?**

6. **The nature and extent of liaison between the fractionation services in Scotland and England over the period 1980 to 1984 in relation to viral inactivation.**

- The SNBTS undertook suitable R&D into methods of heat inactivation of coagulation factor concentrates prior to the international realisation that these carried a risk of AIDS and gave this work an appropriate degree of priority.

  The SNBTS undertook R&D into methods for the removal of viruses from coagulation factor concentrates during the 1970s and began R&D into methods of heat treatment of coagulation factor concentrates in 1981, as soon as knowledge was available from Germany which suggested the possibility that this might be feasible[1]. The SNBTS studied the methods of both pasteurisation and dry-heat treatment[2] and was one of the first in the world to utilise marker viruses to determine the relative merits of these different procedures[3].

  R&D resources at this time were primarily concerned with three areas of activity; heat treatment; increasing yield and increasing purity. There was excellent communication and sharing of information with relevant R&D staff at BPL/PFL.

  The rapid introduction of HIV-safe Factor VIII by the SNBTS was actually dependent on two things:

(i) knowledge that HIV could be inactivated by dry heat treatment at 68°C (which was obtained by attending the Groningen Symposium, PR 11.191)
(ii) having a stock of manufactured Factor VIII available, for the immediate application of heat treatment, that was sufficient to supply all patients in Scotland[4].

Having a sufficient quantity of Factor VIII available for immediate heat treatment was a result of the increased yield that had been obtained from R&D into yield improvements. It was this that was critical to achieving a rapid introduction of HIV-safe Factor VIII, rather than R&D on heat treatment per se. Therefore, if R&D resources had been diverted to heat treatment at the expense of R&D into yield improvement, this would not have accelerated the introduction of heat treatment against HIV and may well have delayed it.

(Note: SNBTS R&D on yield and purification during this period formed the basis for the later development of both 8Y and Z8, the development of which may not have progressed if SNBTS R&D had been concentrated on heat treatment)[5].

References:

1. PEN.013.1309, page 55
2. PEN.013.1309, pages 34-35
3. Cuthbertson, oral evidence Day 46, pages 49-70
4. PEN.013.1309, pages 37-38
5. PEN.013.1309, pages 23-27

Also the oral evidence from:

- Dr Foster, Days 41 & 42
- Dr Cuthbertson, Day 46
- Professor Van Aken, Day 47
- Dr Smith, Day 59

- The SNBTS took suitable measures to review its strategy concerning the development of heat treatment of coagulation factor concentrates whenever there was an international realisation that these carried a possible risk of transmitting AIDS.

  The SNBTS strategy for the development of heat treatment was reconsidered in May 1983 when it was recognised that the potential risk from AIDS might require all Factor VIII to be heat treated, rather than the amount needed to treat those patients at risk of being infected with hepatitis, which had been the initial target[1]. A technical strategy for accelerating the development of pasteurised Factor VIII was outlined, but clinical evaluation of the product was not satisfactory and further R&D was undertaken in collaboration with researchers in the USA, to greatly increase the purification of Factor VIII to resolve technical difficulties and to aid clinical acceptability[1,2].

  As soon as it became known that HIV could be inactivated by dry heat treatment at 68°C, the strategy for the heat treatment of coagulation factor

concentrates was revised by the SNBTS, with the immediate emphasis being changed from pasteurisation to dry-heat treatment[3].

References:

1. SNB.007.3635
2. Oral evidence from Dr Foster on Day 41 (pages 151-160) & Day 42 (pages 1-16).
3. PEN.013.1309, pages 36-38, 51; PEN.012.1797, page 5.

Also oral evidence from:

- Professor Cash, Day 43
- Dr Perry, Day 45

- The early achievement by the SNBTS of the introduction of Factor VIII and Factor IX concentrates that were heat treated against HIV.

  Factor VIII

  The SNBTS immediately began to plan to dry-heat treat Factor VIII concentrate at 68˚C as soon as it was known that HIV could be destroyed by heating in this manner, as this was the quickest route to obtaining a product safe from HIV-transmission[1]. As a result, the SNBTS issued dry-heat treated Factor VIII concentrate routinely for all patients in Scotland within six weeks of obtaining this knowledge[1]. The SNBTS recalled its unheated Factor VIII concentrate as soon as the provision of its heat treated Factor VIII concentrate was secure[1,2].

  As a result of these actions, Scotland became the first country in the world to provide all patients with haemophilia A with a supply of Factor VIII concentrate that was safe from HIV transmission[3]. This could not have been achieved if Scotland had not possessed its own plasma fractionation capability.

References:

1. PEN.013.1309, pages 36-38, 58-59; oral evidence of Dr Foster, Day 42, pages 24, 57-67; Dr Perry, Day 45, pages 108-118.
2. PEN.013.1309, page 59; oral evidence of Dr Cuthbertson, Day 46, pages 84-86.
3. Oral evidence of Professor van Aken, Day 47, pages 38-39; Dr Smith, Day 59, page 136, Day 60, page 125.

  Factor IX

  The SNBTS immediately began to plan to dry-heat treat its Factor IX concentrate as soon as it obtained information that HIV could be destroyed by heating in this manner, as this was the quickest route to obtaining a product safe from HIV-transmission. The timescale for the routine introduction of SNBTS dry-heat treated Factor IX concentrate was determined by the need to ensure that the heat treated Factor IX concentrate was free from harmful thrombogenic adverse reactions. This required a specialised animal study of potential thrombogenicity to be undertaken. Results from early dry-heat treatment experiments by the

SNBTS increased concern that dry-heat treatment of Factor IX concentrate might cause thrombogenic adverse reactions and led the SNBTS to re-formulate its established SNBTS Factor IX concentrate to reduce this risk. The SNBTS had already begun a programme of work to establish the study of thrombogenicity in animals, in anticipation of heat treated products being developed. This programme of work was well advanced when knowledge of the sensitivity of HIV to dry-heat treatment became available. Therefore, both the reformulation of the product and the associated testing in animals were undertaken promptly[1]. Pending the introduction of its heat treated Factor IX concentrate, the SNBTS agreed with Haemophilia Directors to cease issue of unheated SNBTS Factor IX concentrate, as a heat treated commercial Factor IX concentrate, which was believed to be safe from HIV-transmission, had become available to Haemophilia Directors. Unheated Factor IX concentrate was recalled by the SNBTS as soon as supplies of heat treated Factor IX concentrate were secure[1,2].

References:

1. PEN. 013.1309, pages 50-52, 59-61; PEN.012.1797, pages 3-8; oral evidence of Dr Foster, Day 42, pages 82-87; oral evidence of Dr Smith, Day 60, page 125.
2. Oral evidence of Dr Perry, Day 45, pages 99-100,104.

- The potential for dry-heat treatment by the SNBTS of its coagulation factor concentrates before it was known that HIV could be destroyed by this procedure.

  Progress in science and in medicine is dependent on evidence, not on conjecture. Therefore, the SNBTS did not subject its supply of coagulation factor concentrates to dry-heat treatment before it had been discovered that such treatment could be effective against HIV (or the agents of NANBH), as this would not have been evidence based and would have provided no known benefit to patients to counterbalance potential risks, such as the formation of inhibitors to factor VIII or thrombogenic reactions to Factor IX concentrates.

References:

1. Oral evidence of Dr Foster, Day 42, pages 69-87
2. Oral evidence of Professor Ludlam, Day 44, pages 33-40
3. Oral evidence of Dr Perry, Day 45, pages 110-118
4. Oral evidence of Dr Cuthbertson, Day 46, pages 79-81
5. Oral evidence of Professor van Aken, Day 47, pages 45-52
6. Oral evidence of Dr Smith, Day 59, pages 136-140

Topic C3

PENROSE INQUIRY

TOPIC C3

Evidence was given on this topic by:-

(1) Dr Peter Foster (Day 56)
(2) Dr Bruce Cuthbertson (Day 57)
(3) Professor John Cash (Day 57)
(4) Dr Robert Perry (Day 58)
(5) Professor Christopher Ludlam (Day 58)
(6) Dr James Smith (Day 60)
(7) Dr Ronald McIntosh (Day 61)
(8) Mr Alexander Murray (Day 61)
(9) Mr Duncan Macniven (Day 61)
(10) Professor Willem van Aken (Day 62)

The relevant statements on this topic are:-

(1)	Dr Peter Foster	PEN.013.1381 and PEN.017.1556
(2)	Dr Bruce Cuthbertson	PEN.017.1200
(3)	Professor John Cash	PEN.017.0185
(4)	Dr Robert Perry	PEN.017.1219
(5)	Professor Christopher Ludlam	PEN.017.1620
(6)	Dr James Smith	PEN.017.1130
(7)	Dr Ronald McIntosh	PEN.017.1234
(8)	Mr Alexander Murray	PEN.017.1868
(9)	Mr Duncan Macniven	PEN.017.1604
(10)	Professor Willem van Aken	PEN.017.1597
(11)	Dr Brian Colvin	PEN.017.1672

SNBTS briefing paper relevant to this topic is:

(1)	SNBTS briefing paper on the Development of Heat Treated Coagulation Factors	PEN.013.1309

Topic C3

The implementation of heat treatment sufficient to inactivate Hepatitis C in blood products by the Protein Fractionation Centre in Scotland in 1987, and the technological background to such implementation, including the achievement of this objective by the National Blood Transfusion Service in England and Wales in 1985

Inquiry Counsel Issues Nos 1-4:

1. **Until the end of 1985, was it reasonable for PFC to continue with the NYU R&D project rather than to prioritise the development of an intermediate, albeit increased, purity FVIII concentrate that could be severely dry heated i.e. Z8?**

2. **Once a decision had been taken to prioritise the development of Z8, why did it take until April 1987 until Z8 was issued to patients?**

3. **To what extent, if at all, did concerns regarding the lack of compensation arrangements for the trial and use of Z8 cause or materially contribute to any delay in the issue of Z8 to patients?**

4. **Were any alternative options reasonably open to PFC during 1985 and 1986 that had a realistic prospect of resulting in the earlier availability of a FVIII concentrate that had been sufficiently treated to inactivate NANBH/hepatitis C, including seeking to severely dry heat the existing NY intermediate FVIII product or seeking to copy PFL/BPL's 8Y process?**

- The SNBTS undertook suitable R&D into methods of heat inactivation of coagulation factor concentrates making these products safe from the transmission of NANBH/HCV.

  The first application of heat treatment as a procedure in the routine production of SNBTS coagulation factor concentrates was in the manufacture of the SNBTS Factor VIII concentrate (product name NY) in 1984 to inactivate HIV. In this procedure, the freeze dried products, sealed in the final containers, were heated at 68°C for 2 hours and (in a later development) 68°C for 24 hours. These time/temperature conditions were the most severe to which the product could be exposed and still remain suitable and safe for clinical use. The application of "terminal dry heat treatment" in this way was implemented at the SNBTS as a rapid response to the world wide problem of the transmission of HIV by blood products(1)

  The terminal dry heat treatment at 68°C of the SNBTS Factor VIII concentrate NY was shown later to be effective in preventing the transmission of HIV but at the time of its implementation this could not have been known for certain. In addition, therefore, to the application of these particular heat inactivation conditions, research was also undertaken at PFC during 1985 to extend dry heat treatment beyond 68°C but this was not successful. Following these results, the previously established R&D programme at PFC on pasteurisation i.e. heat treatment in the liquid (wet) rather than the dry state continued to be progressed as

the preferred route to improving the safety of SNBTS coagulation factor concentrates[2].

The other principal centre in the UK for R&D on virus inactivation methodology in the manufacture of blood plasma products was the Plasma Fractionation Laboratory (PFL) at the Churchill Hospital in Oxford. The PFL was part of the same organisation (The Central Blood Laboratory Authority – CBLA) as the Blood Products Laboratory (BPL) which was the plasma products manufacturing facility in the Health Service in England and Wales. At PFL there was also an active interest in pasteurisation and the R&D teams (PFC and PFL) kept in close communication over this and other areas of their activities. A key feature of the work on pasteurisation at both PFC and PFL was the improved purification of Factor VIII to facilitate pasteurisation[3].

Out of this line of research, intended primarily for pasteurisation, came technological developments, first at PFL[4] then at PFC[5], which enabled the manufacture of new Factor VIII products (8Y and Z8 respectively) that could be subject to terminal dry heat treatment under more severe conditions than was hitherto thought possible.

The Factor IX concentrates produced at PFL/BPL and PFC had very similar methods of manufacture and required only a relatively straight forward (in processing terms) change to the product formulation to enable terminal dry heat treatment under the new more severe conditions that had been developed for Factor VIII concentrate[6].

The methods implemented, therefore, by the plasma product manufacturing facilities in the UK during the period 1985 – 1987 to improve the margin of safety of Factor VIII concentrates from the transmission of blood borne viruses and achieve a similar margin of safety for Factor IX concentrates, were in each case severe terminal dry heat treatment i.e. the heat treatment of the freeze dried product in the final sealed vials at 75°C or 80°C for 72 hours. Severe dry heat treatment was shown subsequently to prevent the transmission of NANBH and later to inactivate HCV following the discovery of HCV in 1989 and the development of the technology to detect the virus[7].

Severe terminal dry heat treatment of coagulation factor concentrates was applied successfully first at the PFL in late 1984 as part of the manufacturing process for a newly developed Factor VIII product (8Y) and the process was then transferred in 1985 to the PFL's parent organisation the BPL at Elstree, just outside London. The first severely dry heat treated Factor VIII product produced at the Protein Fractionation Centre (PFC) in Scotland was the Factor VIII concentrate code named Z8 and the initial clinical grade batches of this product were prepared during 1986. Factor IX concentrates which had been heated at 80°C began production at BPL and PFC during 1985[8].

The UK led the world in the development of severe terminal dry heat treatment as a method of virus inactivation; so much so that despite the UK market being open to commercial products from across Europe and the USA, 8Y was the first available NANBH/HCV safe coagulation factor concentrate in the UK (9). Also, through the development of severe dry heat treated Factor VIII and Factor IX concentrates, Scotland became the

first country in the world to have sufficient NANB/HCV safe coagulation factor concentrates available for the therapy of all haemophilia patients[10].

The achievement in Scotland of such a world leading position was as a result of a series of decisions made at the PFC which were based upon being well informed concerning the latest developments in the industry at that time; running successful and relevant programs of experimental work and maintaining the established close working relationship with PFL which included the exchange of information and results from each others R&D projects. In general, keeping up to date with the latest industry developments[11], running relevant experimental programmes[12] and maintaining contact with other related institutions[13] were all part of the work of R&D at the PFC.

The critical developments, information and decisions that determined the progress of the development of NANBH/HCV safe coagulation factor concentrates at the SNBTS were:

For Factor VIII

- The development in the 1970s and early 1980s of the SNBTS Factor VIII concentrate, NY, as a high yield, stable intermediate purity product. The NY process provided the manufacturing platform for self sufficiency in Factor VIII concentrate derived from volunteer unpaid donors which was considered a major safety feature for blood products before the development of virus inactivation/elimination technology and is still seen as important today[14]. The high yield and improved capacity of the NY process also meant that product stocks could be built up to facilitate the transfer to new products and allow the suspension of routine production to dedicate additional facilities and staff to development projects without interrupting the continuity of product supply[15].

- The demonstration in late 1983 that the then SNBTS intermediate purity Factor VIII product (NY) could not withstand terminal dry heat treatment at 70°C for 24 hours[16] together with the lack of success later in 1985 in attempting to extend the heat treatment of NY beyond 68°C[2]

- The position taken by SNBTS in early 1985 which was also the view held by many in the industry[17], that following the implementation of terminal dry heat treatment in the manufacture of coagulation factor concentrates as an initial measure intended to prevent the transmission of HIV, further improvement in the margin of safety of these products would be through pasteurisation i.e. heat treatment in the liquid (wet) rather than the dry state or by chemical treatment with solvent and detergent.

- The demonstration in a number of pilot scale production runs throughout 1983 and up to mid 1984 that although the pasteurisation of an improved purity version (ZHT) of the existing intermediate purity Factor VIII concentrate (NY) was technically possible it would be extremely difficult to transfer to

routine full scale production and would also result in a significant loss in yield[18].

- The decision to establish an R&D project at PFC in mid 1984 to develop a process for the production of a high yield, very high purity Factor VIII preparation (NYU) which would have been more suitable for pasteurisation[19].

- The information supplied by PFL in late 1984 as part of an on going exchange of data on heat treatment, that a newly developed Factor VIII concentrate (8Y) could be heated in the dried state at much higher temperatures than thought possible previously[20] and the view expressed by those at PFL that this property of the new concentrate was related to its purity in that the levels of heat labile proteins had been much reduced[21].

- A copy of the patent application for the 8Y process supplied by PFL in early 1985 which contained a description of the method of manufacture (excluding freeze drying) and the view taken by PFC that there were significant and difficult differences between the process technology and analytical techniques used in 8Y and those being used at PFC[22] in the Factor VIII products (NY HT 68/24; NYU) in production and development at that time.

- The demonstration later in 1985 that the very high purity Factor VIII preparation (NYU) being developed at PFC failed to freeze dry under the then routine production conditions(23) and when appropriate freeze drying parameters were used the freeze dried very high purity Factor VIII preparation could not withstand heat treatment at 80°C[24].

- The demonstration in the same series of experiments that small quantities of intermediate purity Factor VIII when freeze dried under the conditions developed for the freeze drying of the very high purity preparation, could withstand heating at 80°C[25].

- The information requested from PFL in November 1985 on the freeze drying cycle for 8Y[26] which showed that the principal features of product freeze drying temperature profile were similar to the cycle developed at that time at the PFC for the NYU product and under which conditions small samples of NYU material could be freeze dried so as to withstand severe dry heat treatment.

- The decision at the end of 1985 to develop an improved version (Z8) of the existing intermediate purity Factor VIII concentrate to provide a greater margin of safety against HIV such that clinical doses could be prepared in sufficiently small quantities to allow freeze drying in such a way as to make the product able to withstand severe dry heat treatment[25].

For Factor IX

- The recommendation by SNBTS in 1983 that the development of a heat treated Factor IX concentrate should include careful animal safety studies of the heat treated product prior to infusion into humans because of the thrombogenic potential of this type of product and the possible enhancement of thrombogenicity by any damage done during heat treatment[27].

- The demonstration in early 1985 that the existing Factor FIX concentrates produced at PFC and PFL, by practically identical processes, could physically withstand severe terminal dry heat treatment[28].

- The observation that following severe terminal dry heat treatment, the PFC and PFL Factor IX concentrates showed significant changes in the results of laboratory analyses for parameters that would normally indicate an increased potential for the product to induce thrombotic events[30].

- The demonstration that formulation of the Factor IX concentrates with an additional component (anti thrombin III) prior to freeze drying and severe terminal dry heat treatment prevented the changes in these laboratory measurements[31].

- The completion in mid 1985, of a joint R&D project with PFL/BPL, of animal studies which indicated that the severely dry heat treated Factor IX concentrates formulated with anti thrombin III were safe to begin infusions in humans[32].

Thus, the SNBTS did undertake suitable R&D into methods of heat treatment of coagulation factor concentrates to make these products safe from the transmission of NANB/HCV. This is evidenced by the clear continuity in the R&D work on heat treatment at the PFC and in the decisions that flowed from that work, resulting in the establishment of NANB/HCV safe products significantly in advance of similar developments internationally.

- The SNBTS undertook suitable measures to review its strategy concerning the development of NANB/HCV safe coagulation factor concentrates when it became known that these products could withstand severe dry heat treatment.

  When it became known to staff at the PFC (through contact with PFL) that it was possible to prepare a Factor VIII concentrate in a manner such that it could be subject to severe dry heat treatment, the PFC had by that time started an R&D project (the “NYU” project) on a process to produce a very high purity Factor VIII product[33] as part of the continuing work on pasteurisation[34].

  The view from the PFL was that the improved purity of their new product (8Y) was the critical feature in allowing it to withstand severe dry heat treatment[21] and when sufficient quantities of the NYU product had been

prepared, experiments on the formulation, freeze frying and severe heat treatment of the very high purity preparation were incorporated into this R&D project at the PFC[24].

Replicating the 8Y process at PFC was not immediately considered since the details of the 8Y process were not known initially to the PFC[35] due to the restrictions on disclosure of the process[36]. When, shortly afterwards more detailed information on the 8Y process became available, it was clear there were significant differences in the 8Y process from the practices at the PFC[37], not least in the measurement of Factor VIII activity[38], such that it would not have been feasible for the PFC to copy 8Y[39].

When as part of the R&D work on the freeze drying and dry heat treatment of the NYU product the observation was made that intermediate purity material could, with improved freeze drying, be subjected to severe heat treatment[40] this approach was also added to the R&D work on enhanced virus safety[41].

For a period, therefore, in the latter half of 1985, the R&D programme at PFC on improved virus safety of Factor VIII concentrates included continued work on making the NYU process suitable for production scale operation (as an adjunct to pasteurisation), terminal dry heat treatment of the NYU preparation and terminal dry heat treatment of an improved purity intermediate product[42].

Out of these options, the severe terminal dry heat treatment of an improved purity intermediate product (Z8) was selected as the candidate Factor VIII process that held out the prospect of successful transfer into production in the short term of a product with significantly improved safety from HIV transmission[43]. This recommendation was endorsed by the SNBTS Factor VIII Study Group and agreed with the Scottish Haemophilia Directors[44].

All of the required resources from R&D, Production, Quality Control and Engineering at the PFC were made available and were fully committed to this option[45].

In the case of Factor IX concentrate, at the outset of dry heat treatment the then existing product (with a minor modification later) was able to withstand severe dry heat treatment[29] and so no review of the manufacturing strategy was necessary and reverting to the previous work on pasteurisation[46] was not considered.

Therefore, the SNBTS did undertake suitable measures to review its strategy concerning the development of NANBH/HCV safe coagulation factor concentrates as evidenced by the amendment of its research programmes according to the latest available information and results and the selection of the preferred candidate process which did go on to deliver successfully the first NANBH/HCV safe products routinely available to the Health Service in Scotland, in advance of any of the commercial companies supplier the UK[47,56,57].

- The time taken by the SNBTS for the development, manufacture and introduction into clinical use of severe dry heat treated coagulation factor concentrates produced.

  The recommendation to transfer from R&D to Production a manufacturing method for the preparation of an improved purity intermediate purity Factor VIII concentrate that could withstand severe dry heat treatment was made on 23rd December 1985[48].

  The first batch of severe dry heat treated Factor VIII concentrate (Z8) that was available for clinical evaluation was placed at issue in early December 1986[49].

  Before going to issue, any batch of product for clinical use must complete and pass the necessary finished product Quality Control testing and release procedures which with complex pharmaceutical products such as those derived from human blood plasma can take up to two to three months or more to complete[50].

  The manufacture of the first batch of Z8 that went to issue for clinical evaluation began, therefore, in October 1986[51]. To transfer, successfully, a new process (albeit that part of the strategy for Z8 was to retain significant sections of the existing method of manufacture) from laboratory scale R&D to preparation at production scale of product suitable for infusion into patients in nine months was a remarkably quick development in particular for a pharmaceutical product of this type[52] which would normally be expected to take a number of years.

  Although Z8 was available for clinical evaluation in December 1986 the initial trial infusions were not carried out until early 1987 since arrangements for compensation of patients (should they suffer any significant adverse reaction) participating in clinical trials of SNBTS products were not in place by December 1986[53]. When these arrangements had been put in place, the first clinical trial infusions were carried out in March 1987[54].

  In the case of the development of a NANB/HCV safe Factor IX concentrate a single addition to the product formulation, which was relatively straight forward to introduce, was the only change to the method of manufacture that was needed to make the existing product suitable for severe dry heat treatment[40].

  The major part of the time taken, therefore, from availability of the technology to manufacture the new severely heat treated Factor IX concentrate until its clinical evaluation was occupied by detailed animal safety studies in a joint project with PFL/BPL and which all parties agreed were essential[55].

  Thus, the time taken to have available severe dry heat treated coagulation factor concentrates manufactured by the SNBTS was reasonable. This is evidenced, first, by the rapid development of the method of manufacture of a severe dry heat treated Factor VIII concentrate. Second, by establishing suitable arrangements for the compensation (should it have been needed) of patients who participated in clinical trials. Third, it was an essential precaution to undertake animal studies on the safety of heat

treated Factor IX concentrates, prior to their infusion in humans. Finally, SNBTS was a number of years ahead of all the major commercial companies in achieving the manufacture of coagulation factor concentrates that were safe from the transmission of Hepatitis C[56].

References

1. Penrose Inquiry Topic B3
2. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309) p39-40
3. JK Smith witness statement (PEN 017.1137) Supplementary note 6 section C second paragraph
4. PR Foster witness statement (PEN 013.1381) p2 paragraph (v)
5. RV McIntosh witness statement (PEN.017.1238) p5 response to question 4
6. B Cuthbertson witness statement (PEN.017.1200) p7 response to question 10
7. Bennet et al (1993) Transfusion Medicine, 3, 295-298
8. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309) p66
9. P R Foster witness statement (PEN.013.1381) pp29-32: Response to Question 11(iv)
10. Transcript of oral evidence from JK Smith, Day 60, p124 line 21 to p125 line 13
11. There are numerous examples throughout the evidence submitted to the Inquiry of SNBTS staff attending national and international meetings and conferences.
12. R V McIntosh witness statement (PEN 017.1238) p5: Response to question 4.
13. Transcript of oral evidence from P R Foster, Day 57, p6 lines 1 to 25
14. SNBTS Briefing Paper on the Regulation of the Manufacture of Medicinal Products Derived from Blood Plasma and the Preparation of Blood and Blood Components p7 paragraph 4.2.5
15. Transcript of oral evidence from R V McIntosh, Day 61, p6 lines 7 to 16
16. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309) p52
17. WG van Aken witness statement (PEN.017.1597) “International developments regarding inactivation of NANB hepatitis during 1985-1987”
18. Transcript of oral evidence from RV McIntosh, Day 61, p4 line 15 to p6 line 25
19. Transcript of oral evidence from RV McIntosh, Day 61, p7 line 9 to line 25 and p8 line 1 to line 18.
20. PR Foster witness statement (PEN.013.1381) p2 para. (iii)
21. JK Smith Witness statement (PEN.017.1132) response to question 1.
22. Transcript of oral evidence from RV McIntosh, Day 61, pp70 to77
23. Transcript of oral evidence from RV McIntosh, Day 61, p40 line 21 to p41 line 10.
24. Memo from PR Foster 22/OCT/1985 (PEN.171.376)
25. RV McIntosh witness statement (PEN.017.1236) p2 response to question 3(a)
26. Letter from JK Smith to PR Foster entry under 17th December 1985 on p61 of PEN.013.1309

27. Item 4 (f); Minutes of the meeting of the Directors of the SNBTS and Haemophilia Directors held in St Andrews House on Friday 21 January 1983 (SNB.001 5170)
28. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309) p52
29. Transcript of oral evidence from PR Foster, Day 57, p19line21 to line25.
30. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309)
31. PR Foster witness statement (PEN.013.1381) part (v) of response to question 10.
32. Littlewood et al (1987) Brit. J. Haematol. 65, p463-468
33. Transcript of oral evidence from RV McIntosh Day, 61, p14 line 22 to p15 line 8.
34. Transcript of oral evidence from RV McIntosh Day, 61, p4 line 15 to line 19
35. RV McIntosh witness statement (PEN.017.1236) p1 response to question 1.
36. JK Smith witness statement (PEN.017 1131) response to question3
37. Transcript of oral evidence from RV McIntosh Day, 61, p70 line 9 to p76 line 6.
38. PR Foster witness statement (PEN.013.1381) p23 to p25
39. JK Smith Witness statement (PEN.017.1132) Supplementary Note 6 para. F.
40. PR Foster witness statement (PEN.013.1381) response to question 3(a)
41. PR Foster witness statement (PEN.013.1381) response to question 3(b)
42. Transcript of oral evidence from RV McIntosh, Day 61, p35 line 4 to line 25; p36 line1 to line 23; p46 line 14 to line 25.
43. Transcript of oral evidence from RV McIntosh, Day 61, p48 line 22 to p49 line 15.
44. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309) p62
45. RV McIntosh witness statement (PEN.017.1236) response to question 3 (d)
46. MacLeod et al (1984) 18th ISBT Congress abstracts p34.
47. SNBTS Briefing Paper on the Development of Heat Treated Coagulation Factors (PEN 013.1309)
48. Transcript of oral evidence from PR Foster, Day 56, p112 line 25 to p115 line 6
49. Transcript of oral evidence from RV McIntosh, Day 61, p68 line23 to 25; p69 line 1 to 3.
50. Transcript of oral evidence from B Cuthbertson, Day 46, p38 line7 to p40 line 15
51. Transcript of oral evidence from RV McIntosh, Day 61, p69 line5 to line 12.
52. B Cuthbertson witness statement (PEN. 017.1200) response to question3 (b)
53. C Ludlam witness statement (PEN.017.1620) p3 para. 6
54. C Ludlam witness statement (PEN.017.1620) p3 para. 7
55. Transcript of oral evidence from JK Smith, Day 60, p76 line 8 to line 12
56. Transcript of oral evidence from PR Foster, Day 57, pp22-30
57. Personal Statement from Professor Ian Franklin to the Archer Inquiry appended to the witness statement from B Cuthbertson (PEN. 017.1208.)