The Penrose Inquiry

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The Penrose Inquiry – Heat Treatment from 1985 – 1987 (i.e. with a focus on Non-A/Non-B Hepatitis (NANB)).

Question:
Could/should SNBTS-PFC have introduced factor VIII-concentrate, which was sufficiently treated to inactivate NANB, prior to May 1987 in particular against the background that BPL was able to make such a concentrate available from October 1985?

For this witness statement I have used the following documents:

- Preliminary Report of the Penrose Inquiry (2010);
- SNBTS Briefing Paper on the Development of Heat Treatment of Coagulation Factors by Dr Peter Foster (November 2010); [PEN.013.1309]
- Events concerning the Safety of Blood Products with Special Reference to the Treatment of Haemophilia, SNBTS (October 2009); [PEN.013.0220]
- C 3 Viral Inactivation Chronology (Draft 10-6-11);
- Written Statements by
  Dr. J.K.Smith in relation to topic C 3 in the Penrose Inquiry;
  Dr Peter Foster in relation to topic C 3;
  Dr Robert Perry in relation to topic C 3 (draft);
  Dr R.McIntosh in relation to topic C3.

The BPL Factor VIII concentrate

The development of the factor VIII concentrate referred in the above question started in around May 1984 at PFL (Plasma Fractionation Laboratory; a specialized facility at Oxford) when it was observed that heparin could be used to produce a high purity factor VIII. Later in 1984 it was observed that the product could withstand severe dry heating. At that time this effect was thought to be related to the high purity of the product but later other factors such as the conditions of freeze-drying were considered to have been at work (witness statement of Dr Smith). After PFL had prepared such dry-heated factor VIII successfully at pilot scale, BPL took it over and started the manufacturing at large scale and later provided batches for clinical testing. The eventual product, 8Y, was dry heated at 80°C for 72 hours.

BPL and SNBTS/PFC discussions and joint activities

The developments related to the new BPL product (8Y) which were part of discussions and joint activities of BPL (and PFL) and SNBTS/PFC and may be used to answer the question of the Penrose Inquiry, can be summarised as follows (Note: when referring to the Preliminary Report, I have used parts of the same text of the Preliminary Report):

The Preliminary Report of the Penrose Inquiry (Chapter 11, page 478, item 11.190), describes that during a meeting in Cardiff in November 1984 Dr. Lane (BPL) spoke about methods of heat inactivation that might be tried. He intimated that BPL had a dry product available for trial. Most likely "dry product" refers to a dry heated Factor VIII concentrate that was originally developed at the PFL in Oxford.
He also told the audience that the purity of product influenced the effect of heat treatment: he said "Factor VIII may need to be much purer before it can be safely heat-treated." Although this is an interesting suggestion it is not clear which purity was required, which degree of virus inactivation was achieved and if the yield of factor VIII and its solubility were influenced by the heating conditions. It is possible that due to the preliminary status of the findings at PFL Oxford such information was not yet available.

The next relevant development described in the Preliminary Report is a meeting with BPL which was attended by Dr Cash who reported in January 1985 (items 11.215-11.217) that BPL "had planned to use 70°C (dry) for 1 day". Dr Cash wrote that BPL appeared to be well advanced on the production of a very high purity product. Furthermore it appeared that the PFL/BPL method would be patented in due course and SNBTS would have free (Crown) access at that time. Dr Perry confirmed that BPL had a preference for heating at 68-70°C for 24 hours and mentioned that there were difficulties related to the solubility of the product. He also knew that the high-purity BLP product was an extension of the zinc process.

In January 1985 general knowledge about BPL's research and development work appears to have circulated within SNBTS but is not clear how detailed that knowledge was (item 11.217). However, factors such as the use of high concentrations of heparin and size exclusion chromatography (for solvent exchange) were known (Statement of Dr. McIntosh). Since the PFL/BPL method would be patented in due time (see above) it is unlikely that further details would have been made available as long as the patent was not yet submitted.
Patent application was filed ("in record time") on 5 March 1985 and a copy of the patent specification was sent by Dr Smith to Dr Foster on 11 April of that same year (witness statement of Dr Smith).

At about the same time PFC considered applying heating of 68°C for 2 hours in the dry state which with the existing product would not compromise its solubility and based on an external study might cause 4 to 5 log inactivation of HTLVIII virus (item 11.218).

In early 1985 (no specific date), following the observation that Factor IX products of SNBTS/PFC and BPL were both found to tolerate severe heating, a collaborative program was initiated to conduct safety evaluations of both Factor IX products (Statement of Dr. Perry).

According to the SNBTS briefing paper prepared by Dr P.Foster, in February 1985 PFC was briefed by Dr Smith from PFL about the development of 8Y. Dr Smith visited PFC to discuss heat treatment of coagulation factors. In the same month PFL had prepared a trial batch of the new factor VIII concentrate called 8Y, which was dry-heated at 80°C for 72 hours for clinical evaluation (Statement Dr Smith).

In April 1985 PFC (Dr Foster) received a copy (from Dr Smith, BPL) of the patent specification for the 8Y product of BPL (item 11.245). Soon thereafter representatives of PFC visited BPL and were offered full details of the production method of 8Y. In the Preliminary

Report it is not mentioned how the PFC people interpreted the feasibility, safety and recovery of the BPL-method.
SNBTS was approaching completion of work on the purification of factor VIII but it is not clear if this was considered to be useful for the BPL method of Factor VIII production. From the statement of Dr Smith it can be deduced that he was not positive about this.

In July 1985 it was reported in the CBLA's central committee that clinical trials of BPL's 8Y (dry heated at 80°C for 72 hours) were being conducted. At about the same time positive results were obtained from a clinical trial of PFC's Factor VIII concentrate dry-heated at 60°C for 24 hours.
On 15 July 1985 Dr Perry wrote to Dr Lane (BPL) proposing to exchange trial protocols with the aim to achieve commonality.

In September 1985 BPL started the general issue of higher purity factor VIII concentrate (8Y).

In November 1985 PFC (Dr Foster) wrote to BPL (Dr Smith) asking about the freezing conditions for the new Factor VIII concentrate, which might be particularly critical for the effect of the heating (item 11.254).

Later, in December 1985, it was decided by SNBTS/PFC that an intermediate purity Factor VIII concentrate that could be heated at 80°C should be developed (Statement Dr Perry).

At a meeting in February 1986 at the National Institute for Biological Standards and Control (NIBSC) (Potters Bar) on the virological aspects of the safety of blood products there was general agreement that closer scientific liaison between BPL and PFC should be established to exchange technical and scientific information regarding the safety of blood and blood products (item 11.303).

Item 11.272 (page 497) of the Preliminary Report refers to a document (SNB.001.5484) which reflects a change of scientific opinion (of PFC and BPL) regarding the degree of purity of Factor VIII which is needed to allow severe (80°C for 72 hours) heat treatment. Although no specific date is given in the Preliminary Report it is likely that this change occurred in February or March 1986. The outcome of research performed at PFC demonstrated that severe heating can be tolerated even at low purity provided that a number of key process steps (in particular the conditioning of plasma) are carefully controlled before the start of heat treatment. It should be emphasized that up till that time the high purity of the factor VIII concentrate was claimed to be crucial for the efficacy of the BPL method. This new information had significant advantages for PFC which manufactured an intermediate purity Factor VIII: it allowed non-infective intermediate purity products to become available more quickly and at higher yield. It was expected that such a dry heated product would be available for evaluation in April 1986 (items 11.272 and 11.274).

Scientists from BPL and SNBTS exchanged experiences about plasmapheresis and virus inactivation studies in March 1986 and thereafter (item 11.279). From these discussions it emerged that the efficacy of virucidal processes like heating is influenced by product freezing and freeze drying. It was decided that a protocol would be developed by both parties which simulated the routine BPL formulation of Factor VIII concentrate and treatment conditions. As BPL was involved in chimpanzee studies concerning validation of virus inactivation, PFC hoped to use these results for its own validation of virus inactivation.

At a meeting with the haemophilia directors in March 1986 Dr Cash informed about the limitations of certain types of dry heating (item 11.274). At the same meeting Dr.Perry reported that PFC had decided to introduce an intermediate product which is 2 to 3 times more pure than the existing Factor VIII concentrate but can be dry heated at 80°C for 72 hours and hopefully would be available for clinical use within 3 months (item 11.274).

An interim review of the clinical trial with 8Y, in March 1986, showed that it was likely that the product was free of NANBH, Hepatitis B and HTLV III. The final report of this trial became available in October 1988 (Statement Dr Smith).

In May 1986 an outline of the experiments was exchanged between BPL and PFC (see item 11.287) to evaluate virus inactivation in the production of 8Y, the systems and equipment, as well as the model viruses used for these experiments.

At the Congress of the ISBT and the ISH in Sydney (May 1986) SNBTS/PFC reported that it was the nature of the freeze drying process rather than the purity of the product which was critical to allow heat treatment of Factor VIII (and Factor IX) at more severe conditions (such as 80°C for 72 hours) (item 11.289).

In September 1986 Dr Smith (BPL) prepared an interim report on the study of previously untreated patients who had received heat treated (80°C for 72 hours) and had been followed up for at least 16 weeks. No clinical or laboratory events attributable to HIV, NANB and Hepatitis B were found. It was concluded - *inter alia*- that although none of the patients had developed adverse signs, the results were not totally conclusive and a prospective clinical trial was to follow (item 11.307).

The product description of 8Y produced by BPL together with the clinical trial protocol were sent to PFC in August 1986 when Scotland agreed to participate in the clinical study (11.309). (Note: The clinical trial was completed in 1988 but needed to be repeated as international guidelines for such studies were not met (Report Dr P.Foster). The study was repeated and once completed showed the safety of 8Y with respect to Hepatitis C) (item 11.307).

PFC designed a process for dry heated Factor VIII concentrate similar to that of BPL. After pilot-scale experiments were completed in mid-1986, full-scale manufacture of the product (called Z8) started in August 1986. The first batches for clinical testing were released in December 1986 (Report of Dr. Foster).

According to the report of Dr P.Foster ("Events concerning the safety of blood and blood products with special reference to the treatment of haemophilia", October 2009, page 24), BPL issued 8Y routinely from September 1985 but output was insufficient to cover the need. Patients in England remained largely dependent on imported FactorVIII concentrates heated at 60 - 68°C.

In the meantime PFC informed BPL that it planned to manufacture and test a Factor VIII product heated at 80°C for 72 hours (comparable to 8Y) which would be used for phase II and III clinical studies in 1986 and 1987.
In addition it was suggested by Dr Perry that for the period of July to September 1986 PFC could probably get supplies of 8Y from BPL for special cases (item 11.316). BPL replied that some 8Y had been set aside for Scottish use (item 11.318).

In December 1986 there was an exchange of information concerning the effects of plasma conditioning on subsequent cryoprecipitation and cryoextraction which reflected new know how not sewn up by the patent and providing analytical support and theoretical under-pinning (item 11.311).

Once clinical trials regarding the efficacy and tolerability of Z8 were completed in April 1987, the product became issued routinely. Clinical evidence confirming that Z8 was safe with respect to transmission of HCV became available in 1993 (Report Dr.P.Foster, page 25).

In England 8Y was issued from 18th September 1985. However, until 1989 output of BPL was only able to meet about 30% of the factor VIII concentrate needed. The remainder of the need in England and Wales was provided by commercial imported products (heated at 60 - 68˚C) that were not necessarily safe from hepatitis (Report Dr.P.Foster, page 21).

International developments regarding inactivation of NANB hepatitis during 1985 – 1987

The evidence that HIV is inactivated by dry-heating at 60 - 68˚C led many manufacturers of plasma products to introduce dry-heating. However, it appeared that these heating conditions are not sufficient to inactivate NANB hepatitis. Hepatitis viruses resist heat inactivation better than HIV does.
In 1985 – 1987 several dry or wet-heated products, heated at 60 to 68 ˚C for 10 to 72 hours, were licensed by the Food and Drug Administration (FDA) in the USA (item 7.42). However, when the positive results of animal testing were not confirmed when higher infectious doses were used and when a number of clinical studies in various countries did not substantiate the initial positive animal results, the confidence in this method for the inactivation of NANB hepatitis dropped. To give an example; the study by Colombo et al ("Transmission of Non-A/non-B hepatitis by heat-treated factor VIII concentrate", the Lancet, page 1-3, July 6,1985) of 13 haemophilia patients given Hemofil T, in 84% NANB hepatitis developed during the next 12 months. Other dry-heated Factor VIII concentrates were introduced with heating conditions varying from 60 to 68˚C for 24 to 72 hours. Furthermore heating in moist conditions was introduced in the United States but in formal trials of such products the rate of hepatitis transmission, although being reduced, was not obliterated.
A different inactivation method using a combination of solvent-detergent that preserved the clotting activity was reported in 1984 and in the following years became used by various manufacturers of plasma products. Combinations of the solvent tri (n-butyl) phosphate and non-ionic detergents such as polysorbate 80 and Triton X-100 at 24 ˚C for a minimum of 4 to 6 hours were shown to inactivate hepatitis viruses. Such mixtures disrupt the lipid membrane of enveloped (hepatitis) viruses which are then unable to bind and infect cells. No transmission of hepatitis virus (or of HIV) has been observed in any of the clinical trials reported published in 1988 and 1992.

Could/should SNBTS have introduced Factor VIII concentrate which was sufficiently treated to inactivate NANB hepatitis prior to May 1987?

In December 1985 SNBTS/PFC decided that an intermediate purity Factor VIII concentrate that could be treated at 80˚C should be developed. Before that moment, in fact starting in 1981, SNBTS investigated pasteurisation of Factor VIII concentrate with the objective to inactivate the agent(s) responsible for the transmission of NANBH. The initial pasteurisation project, the Zinc Heat Treatment process, was stopped at the end of 1984, at which point

priority was given to the high purity pasteurisation project with Professor Johnson of New York University (the NYU process). In addition, at the end of 1984 dry heat treatment (initially 2 hours at 68°C later 24 hours at 68°C in the presence of sucrose) of Factor VIII was developed with the aim to inactivate HIV. During the period of October 1984 to January 1985 the preparation of Factor VIII concentrate at PFC was largely suspended to introduce changes in the production facilities which were required by the Medicines Inspectorate. Meanwhile there was evidence from the literature that dry heating at 68°C was insufficient to prevent transmission of NANBH. There were also concerns about the degree of dry heating required to inactivate HIV. In early 1986 SNBTS started research to increase the degree of dry heating using factor VIII concentrate of a higher purity than its existing FVIII product, but less pure than 8Y, and discussed with PFL heat treatment at 80°C for 72 hours. PFC's severe dry heated product, Z8, was available for clinical trials in December 1986 and was introduced into clinical use from April/May 1987.

In retrospect it may be asked if PFC should have changed its policy at an earlier stage, i.e. before December 1985. In my opinion, which is shared by Dr Smith, PFC had good arguments to pursue the wet heating of factor VIII concentrate as it was doing. Before December 1985 it was uncertain if the BPL product would be safer than the SNBTS/PFC product.

The next question is if the communication between BPL/PFL and PFC was sufficient to allow PFC to keep track of the development of 8Y. First of all it should be emphasized that close professional and scientific collaboration between BPL and SNBTS was repeatedly and strongly advocated by Dr Cash. From the various witness statements it is obvious that between 1983 and 1986 several exchange visits took place from PFC and PFL. Dr Perry and Dr Foster regularly discussed and exchanged information with Dr Smith (PFL). The patent application of 8Y was sent to PFC (Dr Foster) very shortly after it was submitted by PFL. In conclusion, in my opinion, there does not appear to have been a lack of shared information which might have impeded the progress of developing heat treated Factor VIII by PFC.

Once SNBTS/PFC had decided to start the development of an intermediate purity Factor VIII concentrate that could be treated at 80°C it took till August 1986 before the first production-scale trial batch of Z8 begun, till the end of December 1986 when Z8 became available for clinical evaluation and till April/May 1987 to start routine use of Z8. During this period the project had to be taken from the laboratory scale to pilot scale and subsequently to large production scale. This involved the development of new purification of Factor VIII and its concentration, the formulation of the product, the heat treatment and the proper freeze drying conditions. Although several of these methods were well known at PFC, it is time-consuming to determine the proper conditions for each of them to create optimal Factor VIII yield and solubility of the product. In addition standard operating procedures (SOP's) for quality control and product release need to be developed.
In my opinion it is quite an achievement to successfully complete all this within one year (in fact between June and December 1986).
The experience of BPL shows that it may take considerable time (almost 4 years) before there is sufficient stock of 8Y to meet the demand of all patients.

To conclude: In my opinion it is very unlikely that SNBTS/PFC could have introduced Factor VIII concentrate that was sufficiently treated to inactivate NANB hepatitis before 1987.

W.G. van Aken, 7 september 2011