Revised Response of Dr P R Foster to a Request of 28th April 2011 from Mr A Evans of the Penrose Inquiry Concerning Topic B3.

Since my response to the questions posed by Mr Evans was submitted to the Inquiry on 8th June 2011, I have obtained further information from additional documents that I managed to find and from contacting relevant former colleagues concerning the points raised in section 6 of the letter from Mr Evans (copied below). As I now have further information, I would like to submit a revised response, in which my answer to the questions raised in section 6 of the request from Mr Evans has been extended.

Dr Peter R Foster
2nd July 2011.

The Penrose Inquiry – Heat Treatment to 1985 – Dr Foster's witness statement and SNBTS Briefing Paper on the Development of Heat Treatment of Coagulation Factors (SNBTS Briefing Paper)

Witness statement

The Inquiry has reviewed Dr Foster's draft witness statement on the above topic. We have made some tracked amendments to the original statement (primarily minor typos, spelling and formatting errors – see separate word document attached), and also have the following additional questions.

1. **Page 8 – paragraph 1**

Dr Foster explains that his suggestion that the University of Bristol Medical School undertake research into eliminating the risk of hepatitis in Factor VIII was met with disbelief. Can Dr Foster briefly explain why?

Response

I am not sure why my suggestion was met with disbelief. There are a number of possibilities that I can think of:
(i) that they believed that the task was impossible,
(ii) that it was beyond the capability of their department,
(iii) that the topic was not compatible with their research programme,
(iv) that the topic was inappropriate because it concerned 'applied' research rather than 'pure' research, which was often regarded in academic circles as being intellectually superior.
My belief at the time was that their reaction was related to (iv) and that my suggestion that they should undertake 'applied' research was taken as an insult to the intellectual standing of their department.

2. **Page 14 – paragraph 3**

In paragraph 3 mention is made of Behring and Travenol presenting at a symposium in Cambridge in 1981 on "Advances in Blood Transfusion." Would it be correct to say that Behring and Travenol were competing directly in research into viral inactivation at this time?

Response

i) Neither Behring nor Travenol were "*presenting*" at this symposium. The symposium was sponsored by Travenol, but the company did not make any presentation at the symposium. A trade exhibition was held in conjunction with the symposium at which I believe Behring had a commercial stand along with numerous other companies. This commercial exhibition was held in the same hotel, but in a separate area to the symposium, and comprised trade-stands, with company literature, supported by sales representatives.

ii). I now know that both Behring and Cutter (Bayer) were undertaking research into heat treatment at this time, although this was not disclosed by Cutter (Bayer) at the time. I do not know when Baxter/Travenol began its research into heat treatment.

iii). The symposium was intended for the Directors of the UK blood transfusion services and attendance was by invitation only; however, I did notice that some commercial representatives did attend the presentations. None of the presentations concerned heat treatment.

3. **Page 17 – paragraph 2**

In paragraph 2 Dr Foster indicates that he first learned of the concept of applying heat treatment to coagulation factors concentrates in the freeze dried state at the 1982 ISBT Congress. Was this the report by Rubenstein referred to at page 3 of the conference report (SNB.010.4452)?

Response

This is correct, I was referring to the work of Rubenstein which was published in the book of abstracts that was issued to delegates at the 1982 ISBT Congress.

4. **Page 25 – paragraphs 2 and 4**

In this paragraph Dr Foster indicates that his memo (SNB.007.3635) followed the announcement of 23 April 1984 that the virus responsible for AIDS had been discovered. We would assume that this cannot be correct as Dr Foster's memo is dated 1983 and was, therefore, written before the virus responsible for AIDS was discovered. Can Dr Foster confirm that this is correct? In view of this, does Dr Foster wish to answer the question again?

Response

This is correct. I have revised my witness statement accordingly.

In paragraph 4, mention is made of "pilot-scale". Can Dr Foster elaborate on what this means in this context.

Response

In this context, the term "pilot-scale" means the preparation of small batches of pasteurised Factor VIII at a volume of production that would be representative of full-scale manufacture without requiring or consuming large volumes of plasma.

5. **Page 35 – paragraph 4**

Dr Foster indicates that he first heard of the HIV infections on the morning of Friday 26 November 1984. Should this actually be 26 October 1984 given that the PFC Heads of Department meeting (SNB.010.3479), was on 26 October 1984 (see also page 36, para 6 of Dr Foster's statement)?

Response

October is correct but, on reflection, and in the absence of documentary evidence I cannot be absolutely certain of the exact date other than it was shortly before Wednesday 31st October when I travelled to Groningen. I have revised my witness statement accordingly.

6. ***SNBTS Briefing Paper – Factor IX***

At pages 50-52 of the SNBTS Briefing Paper provided with his witness statement, Dr Foster explains the background to the development of heat treated Factor IX concluding at page 52 that *"heat treated Factor IX concentrate was issue routinely*

from the beginning of October 1985". Can Dr Foster give us an explanation for the interval between the introduction of heat treated Factor VIII (December 1984) and heat treated Factor IX (October 1985). Can Dr Foster also explain what is meant by the statement that *"the animal model was difficult and costly to establish"*? What were the specific costs and difficulties confronted in setting up the animal model?

Response

Overview

i). The interval between the introduction of heat treated Factor VIII (December 1984) and heat treated Factor IX (October 1985) was due to additional time being required to complete a specialist animal safety study, which addressed a specific safety issue which concerned Factor IX concentrates and which did not apply to Factor VIII concentrates. In addition to establishing the animal model, the study resulted in a requirement for the method of preparation of the Factor IX concentrate (DEFIX) to be revised and additional time was required to manufacture batches of the product using the revised procedure.

ii) The animal safety study concerned the degree to which heat treated Factor IX might cause a thrombogenic reaction (i.e thrombosis) in recipients. The possibility of such reactions in people with haemophilia B was already known to be a serious, sometimes fatal complication of treatment with unheated Factor IX concentrates. It was therefore conceivable that heat treatment might enhance this risk and even make the product lethal. Abnormal results from an *in vitro* (laboratory) test of heat treated Factor IX, increased this concern and led to a revised form of Factor IX concentrate being devised. It was this revised form of heat treated Factor IX concentrate that was eventually provided.

iii). The animal safety study was carried out at the Department of Clinical Veterinary Medicine at Cambridge University and was commissioned for the SNBTS by Dr JD Cash with support from Dr CV Prowse (SNBTS) and Dr J Dawes (Medical Research Council). The study was carried out jointly with PFL (Oxford)/BPL (Elstree) for whom Dr JK Smith was the lead investigator.

Key Dates are as Follows

iv). The possibility of heat treating both Factor VIII and Factor IX concentrates was discussed at the joint meeting between Haemophilia Directors (Scotland), SNBTS Directors and Officials of SHHD on **21 January 1983**. In his notes for the meeting Dr Cash proposed that heat treated Factor IX concentrate should be subjected to an animal safety study on thrombogenicity [SNB.001.5170]. It was emphasised that the time required to complete this study would mean that the development of a heat treated Factor IX concentrate would be expected take longer than the development of a heat treated Factor VIII concentrate. The minute of the meeting records that progress with factor IX would be "*slower than with factor VIII because of the necessity to submit the heated IX concentrate to intensive animal studies in order to*

confirm that the heat treatment had not resulted in a thrombogenic product." [SNB.001.5160].

iv). The type of animal study required was considered by Dr Cash and colleagues at a meeting at the SNBTS Headquarters on **7 February 1983**. [SNF.001.3459] It was agreed that "*The model of choice is the normal anaesthetised dog, due to consideration of blood volume and venous access, as described by Cash et al (Thromb Diath Haemorrh, 1975, 33, 632-639)*[1] [LIT.001.0959] *but to include some newer assays".* Nine assays were specified for testing blood samples obtained from the animals and various difficulties were noted (CV Prowse, Proposal for Factor IX Concentrate: Thrombogenicity Testing in Animals. Note of Meeting Held at SNBTS Headquarters Unit, 7 February 1983).[2] [SNF.001.3459]. The new assays were to be developed by Dr Joan Dawes, who was employed by the Medical Research Council.

v). At a review meeting held by Dr Cash on **19 January 1984** [SNB.008.6698], it was noted that all of the assays were now available and the rate limiting factors were:
- Provision of adequate volumes of PFC heat treated Factor IX concentrate,
- Provision of a suitable animal test facility.

Further details of the study protocol were drawn up, including:
- The need to administer negative and positive controls,
- The administration of heated and unheated Factor IX concentrates at a dose of 100 IU/Kg body weight,
- The administration of heat treated Factor IX at doses of 200, 400, and 600 IU/Kg body weight, and studies of batch-to-batch variation.

It was also noted that Dr Smith had confirmed that PFL (Oxford) were willing to participate in the study and to share the costs. (AJ Macleod, Note of Headquarters Discussion Meeting held on 19 January 1984).[3] [SNF.001.3429].

vi). The Department of Clinical Veterinary Medicine at the University of Cambridge was selected for the animal study, under the direction of Dr JD Littlewood. According to SNBTS laboratory notebooks, preliminary testing of blood samples taken from the animals was begun by the SNBTS in **July 1984**.

vii). At this time, the method of heat treatment of Factor IX that was being developed by the SNBTS concerned pasteurisation, similar to the approach being taken with Factor VIII. However, when it was learned on **Friday 2 November 1984**, at the meeting in Groningen, that HIV could be inactivated by dry heat treatment [SNB.008.6528] it was decided to consider the application of dry heat treatment to Factor IX concentrate, as this could be introduced more quickly than pasteurisation.

viii). Dr Prowse was present at the meeting in Groningen and, at my request, he reviewed the schedule of animal infusions immediately on his return to Edinburgh , to indicate the amounts of heat treated Factor IX concentrate that would be required for the thrombogenicity safety study. (Prowse C, Requirements for Dogs (IX studies '84/'85), Note, **Monday 5 November 1984**).[4] [PEN.012.1793].

ix). Meetings were held subsequently with Dr Smith on **29-30 November 1984** to establish the joint programme of work between SNBTS and PFL/BPL. The outcome of these meetings is described in a letter from Dr Smith, containing an outline schedule of animal infusions (Smith JK, Dog infusions of factor IX concentrate, Letter to Dr P Foster, Dr C Prowse & Dr J Dawes, **4 December 1984**).[5] [PEN.012.1794].

x). A further meeting was held on **28 January 1985** at which a detailed programme of animal infusions was drawn up. This was followed by a memo from myself, suggesting a revised schedule to shorten the timescale to the provision of heat treated Factor IX (Foster P. Dog IX Study, Memorandum to R Perry, J Cash, C Prowse & J Dawes, **20 February 1985**).[6] [SNF.001.3363].

xi). The amounts of Factor IX concentrate that would have to be supplied by the PFC and the expected timescales for administration to animals were also defined (Foster P, Dog IX Study, Memorandum to R Perry, Heads of Department, Section Managers & A MacLeod, **20 February 1985**).[7] [SNF.001.3369].

xii). The infusion of negative (albumin) and positive (thrombin) control solutions to the animals was begun on **8 March 1985**.

xiii). SNBTS heat treated Factor IX concentrate (DEFIX, dry heated for 72 hours at 80°C) was supplied for animal infusions on **15 March 1985**.

xiv). It was discovered that DEFIX heated in this manner failed to comply with one of the in vitro laboratory tests (the thrombin-fibrinogen time, designated T/∅) used as a measure of potential thrombogenicity. The same observation was made at PFL (Oxford). In addition to raising concern over the safety of heat treated Factor IX concentrate with respect to thrombogenic reactions in patients, compliance with this test was necessary to meet both the product release specification of the PFC and the specification of the European Pharmacopoeia. Therefore, research was undertaken to try to discover a means of preventing this behaviour. It was found that this could be achieved by the addition of the protein anti-thrombin III (Foster P & McQuillan T, Heated FIX, Memorandum to R Perry, J Cash, J Dawes & C Prowse, **1 April 1985**).[8] [SNF.001.3399].

xv). It was proposed[8] on **1 April 1985** that PFC prepare an amount of dry heated (80°C/72h) Factor IX concentrate, with added anti-thrombin III, for testing in the animal safety study. The preparation of this material was begun on **3 April 1985** using a human anti-thrombin III supplied by PFL (Oxford).

xvi). After results from the animal study concerning the revised Factor IX concentrate had been reviewed, a decision was taken to manufacture a batch of heat treated DEFIX, with the new formulation, for clinical evaluation (B Cuthbertson, Notes of Meeting on **20th May 1985** to Discuss Heat Treatment of FIX, 21st May 1985).[9] [SNF.001.3335]. Manufacture of this batch was begun on **29 May 1985**

xvii). Heat treated (80°C/72 h) DEFIX, containing anti-thrombin III, was released for clinical trial by the PFC on **15 July 1985.** The product was administered to different

patients with haemophilia B on **17 July, 3 August** and **6 August 1985.** The resultant data were reviewed by Dr Cash on **9 August 1985** and approval was given by him to release the product routinely.

xviii). The remaining vials of the batch that had been manufactured for clinical trial were supplied to Edinburgh BTS for general issue from **12 August 1985**.

xix). A joint meeting was held with the SNBTS & PFL/BPL to review progress (Anon. Notes of a Meeting to Discuss Cambridge/FIX/Dog Studies, **27 August 1985**)[10]. [SNB.005.1203]

xx). To provide sufficient Factor IX concentrate for the treatment of all patients with haemophilia B in Scotland, it was necessary to manufacture further batches of Factor IX concentrate with anti-thrombin III added. This material became available from **1 October 1985.** Unheated DEFIX was recalled by PFC on **28 October 1985.**

xxi). Details of the animal study were published (Littlewood JD, Dawes J, Smith JK, Feldman PA, Haddon ME, McQuillan T, Foster PR, Ferguson J & Prowse CV. British Journal of Haematology 1987, **65**, 463-468).[11] [LIT.001.0837].

Costs

xxii). During initial discussions of the project, it was thought that the study might be expensive. The PFL (Oxford) was therefore invited to participate in the study to share the expected cost. No information on the costs of the study has been found. Professor Cash has no recollection of the costs. Neither Professor Prowse nor Dr Dawes believe that the project was delayed by financial considerations. Dr Dawes was awarded an MRC grant of £230 000 from October 1983 for a period of 5 years which encompassed her work on this project (Pepper DS & Dawes J. *SNBTS Bloodletter,* November 1983)[12] [PEN.012.1796]. I do not believe that progress at the Protein fractionation Centre was affected by financial considerations.

List of New Documents Cited.

1. Cash JD, Dalton RG, Middleton S & Smith JK. Studies on the thrombogenicity of Scottish factor IX concentrates in dogs. *Thrombosis et Diathesis Haemorrhagica* 1975, **33**, 632-639.

2. Prowse CV. Proposal for Factor IX Concentrate: Thrombogenicity Testing in Animals. *Note of Meeting held on 7 February at SNBTS Headquarters Unit,* 8 February 1983.

3. Macleod AJ. Headquarters Discussion Meeting, *Note of Meeting Held on 19 January 1984*, January 1984

4. Prowse C, Requirements for Dogs (IX Studies '84/'85), *Note*, 5 November 1984.

5. Smith JK, Dog infusions of factor IX concentrate, *Letter to Dr P Foster, Dr C Prowse & Dr J Dawes*, 4 December 1984.

6. Foster P. Dog IX Study, *Memorandum to R Perry, J Cash, C Prowse & J Dawes*, 20 February 1985.

7. Foster P, Dog IX Study, *Memorandum to R Perry, Heads of Department, Section Managers & A MacLeod*, 20 February 1985).

8. Foster P & McQuillan T, Heated FIX, *Memorandum to R Perry, J Cash, J Dawes & C Prowse*, 1 April 1985.

9. B Cuthbertson, Notes of Meeting to Discuss Heat Treatment of FIX, 20th May 1985, 21 May 1985.

10. Anon. *Notes of a Meeting to Discuss Cambridge/Fix/ Dog Studies, 27 August 1985.*

11. Littlewood JD, Dawes J, Smith JK, Feldman PA, Haddon ME, McQuillan T, Foster PR, Ferguson J & Prowse CV. Studies on the effect of heat treatment on the thrombogenicity of factor IX concentrates in dogs. *British Journal of Haematology* 1987, **65**, 463-468).

12. Pepper DS & Dawes J. Recent Research Grant Awards: MRC/SNBTS Blood Components Assay Group. *SNBTS Bloodletter, No.11,* November 1983.