THE PENROSE INQUIRY

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SNBTS DOCUMENT REQUEST No:

2011/00105a

The Penrose Inquiry - Professor J D Cash, Drs B Cuthbertson and R V McIntosh - witness statement requests in relation to topic C3: Heat Treatment 1985-1987

As you will be aware, we are now seeking evidence in the above topic.

The Inquiry would be grateful if each of the above parties could provide a written statement of evidence to the Inquiry in respect of the matters set out in the schedule below.

As you will see, the schedule refers to certain supporting documents. These can be found in the compressed file attached. It will no doubt also assist your clients to have regard to chapter 11 of the Preliminary Report and to any supporting documents/documents referred to. We also enclose a draft Chronology for topic C3 for any assistance it may provide. We appreciate that your clients were not involved in every event detailed in the schedule. We are seeking evidence only on those events in which each individual was involved or those of which he was aware.

Witnesses should be advised that when compiling their witness statements, unnecessary duplication of material already provided to the Inquiry is to be avoided, with the result that it should be sufficient simply to refer to particular paragraphs or pages of existing material (e.g. the SNBTS Briefing Paper on the development of heat treatment of coagulation factors, prepared by Dr Foster in November 2010) if they consider that adequately answers the matter raised, rather than repeating existing material at length in their C3 statements. Dr Cash should, of course, feel free to defer to the PFC witnesses in respect of any technical issues he considers are more appropriately dealt with by them.

To enable the Inquiry to provide fair notice of the documents for this topic to all core participants in advance of the hearing, the statement is requested by Friday 12 August. Although we may have additional questions, please provide signed statements in first instance.

We hope that your clients' statements can be provided on a voluntary basis in the first instance. If there are any difficulties in obtaining a statement within the requested timeframe, however, then Lord Penrose will consider using his powers under the Inquiries Act 2005 and the Inquiries (Scotland) Rules 2007 to issue a formal notice requiring a statement to be provided by a particular date.

We are grateful to your clients for their assistance.

Please acknowledge receipt of this letter.

Yours sincerely

Angus Evans

SCHEDULE

Issue in respect of which a statement is sought

Topic C3
Hepatitis C - Viral Inactivation 1985-1987

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.

Factual Background

The factual background is more fully set out in chapter 11 of the Preliminary Report and in the enclosed draft C3 Chronology (A16854).

In short, in Scotland, in October 1985, PFC FIX concentrate which had been sufficiently dry heat treated (80°C for 72 hours) to inactivate NANBH/hepatitis C ("DEFIX") became available for clinical use. In May 1987 PFC FVIII concentrate which had been sufficiently dry heat treated to inactivate NANBH/hepatitis C (again, at 80°C for 72 hours) ("Z8") became available for clinical use.

In England and Wales, in October 1985, BPL FVIII and FIX concentrates which had been sufficiently dry heat treated (80°C for 72 hours) to inactivate NANBH/hepatitis C (respectively, "8Y" and "9A") became available for clinical use.

Matters to be included in the statement

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

Response: I defer to my PFC colleagues

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

Response: I defer to my PFC colleagues but recall it may have been in the late 1980s

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

   (a) Why was such heating of the existing intermediate NY FVIII product not introduced immediately? **Response: I recall there were a number of formidable technical challenges to be addressed before a satisfactory (reproducible) process was obtained. Most notable, I recall, was freeze drying. There was also time required for preliminary clinical studies, with regard to product tolerability and efficacy. In this regard, I recall that I found that operating outside the comfort of the Medicines Act (1968) gave rise to enhanced caution with regard to my involvement in developing new products and thus may have contributed in some measure to any delay.**

   (b) Why did it take until May 1987 before intermediate FVIII manufactured by PFC and dry heated at 80°C for 72 hours was available for clinical use? **Response: see 3a above**

   (c) What changes in the manufacturing processes were made, and when, to enable PFC to produce Z8 (dry heated at 80°C for 72 hours)? **Response: I defer to my PFC colleagues.**

   (d) What was the original timescale for the production and introduction of Z8? If that timetable was not met, when and why did it slip? **Response: I defer to my PFC colleagues**

4) Did PFC's work on the development of a high purity FVIII concentrate (NYU), in collaboration with Professor Johnson, result in any delay in the introduction of Z8? **Response: I defer to my PFC colleagues**

5) Did any difficulties in commencing clinical trials of Z8, because of concerns over compensation/indemnity, result in any delay in the introduction of Z8? **Response: I recall the issue of compensation/indemnity was first raised in the autumn of 1986 and not resolved until late February 1987. It follows that this may have been a material cause of delay, but I would judge by no more than 3 months.**

6) Did any wider management, organisational or other issues result in any delay in the introduction of Z8 e.g. by R&D staff not being sufficiently involved in the manufacture and production of products and processes that had been developed by them?[1] **Response: I defer to my PFC colleagues on the question of the interface between R&D and the Production Department.**

As regards the request for other potential issues, I would advise that consideration is given to the difficulties which arose in the development of *in vitro* virus inactivation validation studies at PFC and how these might have contributed to any delay. These developments were intended to provide preclinical data on efficacy of different heat treatment programmes. The delay in the introduction of this important development arose following an intervention by SHHD (1-12).

Finally, it is worth re-emphasising the complex problems PFC had with regard to its plasma supply during product development and implementing product change-over. As I recall, when the first heat treated VIII was issued, the unheated material was returned to PFC, heated and re-issued. It followed that the net demand on additional plasma sourcing of this transfer was marginal. However, in a situation where product cannot be recycled, and there is no permitted facility to boost a matching plasma intake, to cover the gap, then the logistics of introducing a new product (such as Z8 which was heated at 80 degrees centigrade for 72 hours) are much more challenging.

7) There was informal contact and exchange of information between PFC and BPL/PFL, in particular, between Dr Foster and Dr JK Smith. There appear to have been

[1] See, for example, Dr Perry's memo of 22.12.88 to Dr Foster and others (SNB.006.7120) and Dr Foster's letter of 21.11.90 to Dr Prowse (SNB.007.7576)

difficulties with more formal contact, in particular, at a senior, or managerial, level.[2] Did any difficulties at a more senior level inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y, including severe heating of the product? Did any such difficulties contribute to any delay in the development and introduction of Z8? **Response: It has always been my belief that had the two organisations (BPL and PFC) been able to pool their limited R&D resources, and perhaps some manufacturing resources, it may have made a significant difference, throughout the 1980s, to the availability of desirable plasma products in the UK. The most certain example of this was IVIG. It is my understanding that the availability of IVIG from BPL was some years after PFC had a licensed product. It follows that in this period IVIG was purchased at considerable cost to Regional Health Authority pharmacy budgets.**

8) The Central Blood Laboratories Authority (CBLA) Central Committee on Research and Development in Blood Transfusion first met on 21 June 1983.[3] It, presumably, provided a more formal forum for the exchange of information between the respective national blood transfusion services in respect of the research and development of coagulation concentrates. Dr Lane, the Director of BPL, was a member of the committee. While Dr Brian McClelland, Edinburgh BTS, was a member of the committee, there was no member from PFC.

   (a) Was the committee truly a UK committee or was its' role restricted to research and development in England and Wales?[4] **Response: Information received from SHHD and Dr Gunson led me to believe that this committee was never conceived as a UK committee (13). Certainly, there was no consultation by SHHD with the SNBTS prior to its establishment. Moreover, I was advised it was put together, at the behest of DHSS, in response to the demise of the MRC Blood Transfusion Research Committee. The explanation given by the MRC for the demise of this committee (SNB.002.5864) did not concur with the briefings I received, which included the Chairman of the committee.**

[2] see, for example, Dr Cash's letter of 17.12.82 to Dr Lane (SNB.004.3163) and Dr Cash's Background Notes dated 1.1.84 (SNB.011.1308)
[3] PEN.016.1156. The committee subsequently met on 7.11.83 (PEN.016.1130), 28.2.84 (PEN.016.1158), 9.11.84 (PEN.016.1148), 2.4.85 (PEN.016.1125), 9.7.85 (PEN.016.1142) and 19.12.85 (PEN.016.1152). The Inquiry does not have minutes for meetings of the committee in 1986 and 1987.
[4] See, in that regard the views of Mr Smart, Chairman of CBLA, as noted in SNB.006.5100 c.f. the views of Dr Cash, as expressed in SNB.011.1308

(b) Why was there no PFC representative on the committee? Ought there to have been such representation? If there had been such representation, is that likely to have led to the earlier and/or fuller exchange of information between BPL/PFL and PFC in respect of the development, manufacture and clinical use of 8Y, including severe heating of the product? If there had been PFC representation on the committee is that likely to have led to Z8 having been introduced earlier? **Response: I do not know why there was no place for PFC on this committee. I assume it was for the same reason that the SHHD Adviser in Blood Transfusion was also excluded. I never believed that this committee, in any of its forms, would bridge the wide gap between the SNBTS and BPL/NBTS because, at least in the 1980s, a desire to bridge this gap did not seem to enjoy the support of either DHSS or SHHD.**

(c) There appear to have been concerns in Scotland as to whether that committee was an appropriate forum for the exchange of information between BPL/PFL and PFC, based, at least partly, on the perceived "commercial brief" of the CBLA.[5] Did any such concerns about this committee inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y? Did any such concerns contribute to any delay in the development and introduction of Z8? **Response: Sadly, I would suggest that in the circumstances the best opportunity for exchange of information between BPL and PFC with regard to the development of 8Y and Z8 lay with the personal liaisons between Dr Foster's team and Dr Smith. Whilst uncomfortable with this position I was content for us to enjoy its rewards.**

9) Were more formal links between PFC and BPL/PFL desirable?[6] Were more formal links eventually established and, if so, when and how?

[5] see, for example, letter dated 11.12.86 from Dr Gunson to Dr Cash (SNB.002.4347); Dr Cash's reply of 9.4.87 (SNB.013.7021); minute dated 10.6.87 from Dr Smithies, DOH, (SGH.001.8487) with enclosure (SGH.001.8488); minute dated 26.8.88 from J Hamill, SHHD, (SGH.002.4677) and minute dated 30.8.88 from Dr Forrester, SHHD (SGH.002.4672)

[6] See, for example, the discussion at the meeting at the NIBSC on the virological aspects on the safety of blood products on 7.2.86 (SNB.005.1495)

Response: **In my view, formal links were desirable because I believed they were in the public interest. However, there was sufficient evidence that they did not enjoy the support of Ministers, despite the comments of Drs Moore and Smithies (14). To the best of my knowledge they were never established. I am not aware of records which demonstrate this committee ever sponsored or commissioned any research. The same applied to the ill fated NBTS Research Committee, promised in 1988 (15). Both these research committees were in existence at a time when the scientific challenges of the transmission of viruses by blood transfusion in the UK were formidable. As I recall they made no contributions to this or anything else. I suggest that Dr Brian McClelland would be a better judge of this.**

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

Response: **I defer to my PFC colleagues.**

Statement of Truth

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

J D Cash

Signed _____

Dated 8/9/11

References

1. Letter from Dr Perry to Professor Luc Montagnier dated February 1985 [SNB.007.4920]
2. Letter from JDC to Professor Weiss (Chester Beatty Institute) dated 25 November 1985 [SNB.007.5427]
3. Letter from Dr Haythornthwaite (MCA) to Dr Perry (PFC) dated 10 January 1986 [SNB.010.6247]
4. Letter from Mr Calder (SHHD) to Mr Hartley (DHHS) dated 6 February 1986 [SNB.010.6183]
5. Letter from JDC to Dr MacIntyre (SHHD) dated 18 January 1986 [SNB.005.8126]
6. Letter from Dr Perry (PFC) to Dr Forrester (SHHD) dated 5 February 1986 [SNB.013.3825]
7. Letter from Dr MacIntyre (SHHD) to JDC dated 6 February 1986 [SNB.005.8133]
8. Letter from JDC to Dr MacIntyre (SSHD) dated 7 February 1986 [SNB.005.8150]
9. Letter from Dr Perry (PFC) to JDC dated 20 October 1986 [SNB.014.0920]
10. Letter from JDC to Jim Donald (GM, CSA) dated 30 October 1987 [SGH.003.1540]
11. Letter from JDC to Duncan Macniven (SHHD) dated 11 November 1987 [SGH.003.1507]
12. Note of Meeting in SHHD dated 8 January 1988 [SNB.006.0859]
13. Letter from Dr Gunson (NBTS) to JDC dated 11 December 1986 [SNB.002.4347]
14. Note from Meeting on Advisory Committee on the National Blood Transfusion Service by Drs Moore and Smithies 10 June 1987 [SNB.006.0464]
15. Report by Dr Gunson to NBTS Directors on 14 October 1988 [SNB.011.5050]