WITNESS STATEMENT FROM DR R J PERRY

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.

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?***

I am unable to precisely identify the date on which the SNBTS/PFC first became aware of the BPL/PFL 8Y development. A detailed chronology of the PFC development and our knowledge of BPL/PFL activities is contained in the SNBTS briefing paper (November 2010) prepared by Dr Foster. This indicates that we were first briefed by Dr JK Smith from PFL on their 8Y developments in February 1985. It is quite possible that we had some knowledge of their activities prior to that from regular informal contact but I am aware of no documentary evidence to support this.

SNBTS and BPL FIX products were virtually identical and were both found to tolerate severe heating. This joint observation in early 1985 led to a collaborative programme between BPL and PFC to conduct safety evaluations of their respective products leading to their introduction in October 1985.

Further details are provided in the SNBTS briefing paper (November 2010)

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?***

The preliminary clinical trial of 8Y commenced around April 1985 in patients considered to be susceptible to hepatitis (NANB, HB) and HTLVIII.
In the absence of a specific test for NANBH such trials relied on rigorous, regular and frequent monitoring for abnormal liver function tests in suitable susceptible patients, including children. Such patients were rare and required a long period of surveillance to provide reliable and meaningful results. Also such patients would require to be exposed to multiple batches to ensure that the effect of heat treatment was consistent and reproducible between product batches – in terms of both freedom from transmission of NANBH and any other adverse reactions.
Therefore, although early results in a relatively small group of patients were reported by Dr Rizza (PEN.016.1152) as encouraging, it was not until the interim review point in this study (March 1986), reported in October 1986, to the UKHCDO, that the freedom of NANBH, HB or HTLVIII would have been described as likely. Even at this stage such a conclusion would have been regarded as cautionary and unconfirmed. The final report of this study was published in October 1988, confirming the absence of infection in the 32 patients studied.
Further studies complying with the internationally recognised guidelines (ICTH) were considered necessary and a new study was proposed in 1987. The results of this study were published in 1993.

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?

There are a number of reasons why this laboratory observation did not lead to the adoption of a strategy for the 'immediate' introduction of NY FVIII heated at 80°C.

SNBTS/PFC Strategy for FVIII Supply.

When it became known in 1984 that coagulation factor concentrates were implicated in transmission of HIV (HTLVIII as it was then called), the SNBTS and Haemophilia Centre Directors' strategy to protect patients from infection with HIV included the following key elements:-

1) Avoidance of the need to import commercial US products through its already established programme to achieve and maintain 'self sufficiency'.
2) The rapid and progressive development of manufacturing processes capable of inactivating HIV following the announcement that HIV could be inactivated by heat treatment. In the period from 1985 to 1987 the SNBTS developed and introduced three new products.
3) The development and implementation of a system of 'batch dedication' to reduce the exposure of patients to multiple batches of products. This system, introduced in early 1985, required the SNBTS to maintain high overall product stock levels to ensure that individual patients were treated with a single product batch for as long as possible. This had the important effect and goal of minimising the number of donors to whom patients would be exposed.

The key prerequisite to this strategy was the availability of high product and plasma stock levels (already achieved in 1984) and agreement that the successful development of new products would not necessarily require – in the absence of clearly apparent safety benefits of the new product - the immediate recall or exchange (and loss from the supply chain) of the superseded product. To do so would have prevented the SNBTS from maintaining the above strategy, resulting in a failure to meet the needs of all patients in Scotland, abandonment of batch dedication and the possible reliance on commercial products.

Technical Constraints

The discovery that the NYFVIII could withstand heating at 80°C was an observation arising from a laboratory experiment and provided no more than demonstration of principle that such an approach was feasible. It would not have been possible, without further substantial development, scale up and validation, to transfer this observation into routine practice.

Moreover the routine introduction of such a process, even if proven to be possible, would have required a substantial increase in the freeze drying cycle time, resulting in a commensurate reduction in freeze drying capacity and an unsustainable reduction in the capacity of the PFC to meet production and supply targets.

These factors, combined with a requirement to withdraw and discard of substantial stocks of the NYFVIII (68°/24hr) product (which had only been introduced into clinical use in September 1985), would have led to interruption/failure of product supply and exposure of patients to commercial product. In the absence of evidence that a severely heated product offered protection against NANBH, the PFC proposed an alternative development strategy which would continue to protect all patients from the HIV risks believed to be inherent in commercial products and deliver a product (Z8) comparable in its properties to 8Y. This strategy was discussed and agreed with the SNBTS and the Haemophilia Directors.

Details of the development of the SNBTS Z8 product and its introduction into clinical use are described in the SNBTS Briefing Paper (November 2010).

(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?

Details and chronology of the PFC Z8 development programme are described in the SNBTS briefing paper (November 2010).

The development of the Z8 product commenced at the beginning of 1986 as part of an agreed SNBTS plan to develop a reduced infectivity (NANBH) product available to all patients in Scotland as the third phase, following the

successful and early introduction of the two preceding heated NY products. Implicit in this plan was a requirement to provide a continuous and secure supply of product from local (Scottish) donors. In contrast to BPL, the SNBTS had adopted a phased development plan involving the progressive development and introduction of heated products, without interruption of supply. This plan was underpinned by an understanding and agreement that successive products would be introduced through the established batch dedication system when stocks of the previous product had been exhausted, and to ensure the availability at all times of adequate product stocks to meet planned demand. This strategy required that the PFC continue to routinely manufacture NYFVIII (68°C/24hr) until the Z8 product had been developed, validated at scale, transferred to routine production and safe working stocks established.

In July 1986 the routine manufacture of NYFVIII (68°C/24hr) was discontinued to allow the PFC to focus its development and manufacturing resources on the final development stages of Z8 and to subsequently build working stocks of Z8 for distribution through the batch dedication system. At this point it was estimated that sufficient stocks of NYFVIII were available to meet planned requirements until the Spring of 1987, which was therefore the estimated date for the transition from NYFVIII to Z8.

Z8 material for clinical evaluation was available in December 1986, approximately 2-3 months later than originally planned, as a result of unexpected problems arising during the early stages of large scale manufacture. The clinical evaluation of Z8 was not conducted until March/April 1987 until the SHHD reassurances concerning patient compensation had been received by the Haemophilia Directors.

This overall timescale from January 1986 to April 1987 for the design, development, scale up, transfer to routine production and clinical evaluation of a new and innovative FVIII product, whilst concurrently maintaining uninterrupted supply of NYFVIII and avoiding exposure of patients to imported FVIII products was, in my view, neither excessive nor unexpected.

(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)?

Full details of the Z8 development are described in the SNBTS briefing note (November 2010).

(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?

From the preliminary laboratory studies in early 1986 it was considered feasible that the new Z8 product could have been available for clinical evaluation in April and routine issue 3 months later. This assessment was presented to the meeting of the Haemophilia and SNBTS Directors in March 1986.

This was a preliminary (and clearly overoptimistic) estimate and was subsequently revised in the light of experience (by June 1986) to September 1986 for clinical evaluation and introduction into routine use in early 1987, following consumption of NYFVIII stocks as agreed with Haemophilia Directors.

Unforeseen freeze drying problems during scale-up and the additional work required to solve these (described in the SNBTS briefing paper, November 2010) delayed the availability of product for clinical evaluation until December 1986.

The planned clinical evaluation of Z8 in December 1986 was not carried out until March/April 1987, when the necessary assurances were received by the Haemophilia Directors concerning indemnification of patient volunteers.

However, given the accumulation of NYFVIII stocks by July 1986 (when it ceased to be manufactured) and the agreement to phase in the new Z8 product through the batch dedication system, the routine introduction of Z8 was determined primarily by residual NYFVIII stocks rather than the extended development and clinical evaluation timescales.

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?***

The development and implementation of Z8 took place over a period of about 12 months following the decision to pursue this technical option. This development programme was recognised as a critical development and was progressed as a top priority, largely though not completely to the exclusion of other lines of research, including the collaboration with Professor Johnson. I cannot recollect any occasions when this collaboration impeded work on Z8. Indeed my recollection is that Professor Johnson was fully briefed on our priorities, respected these and understood that our collaboration with him would effectively be on hold until completion of the Z8 development.

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?***

As discussed above, there were delays in subjecting Z8 to clinical evaluation arising from the compensation/indemnity issue, but for the reasons described above it is unlikely that this resulted in a delay in the phased introduction of the product for all patients in Scotland. Earlier completion of the clinical evaluation would have made the product available for specific patients identified by Haemophilia Directors eg those with little or no previous exposure to coagulation factor products.

However PFC had, at the request of Dr Ludlam, obtained small stocks of 8Y from BPL/PFL in 1986 which were made available for the treatment of patients (eg newly diagnosed, previously untreated or allergic reactions to existing product) for whom 8Y would be considered preferable until Z8 became routinely available.

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?***

Product development projects such as Z8 were typically led by a senior manager of the PFC Development Department. The management of the Z8 project involved a multidisciplinary project team with a membership drawn from Development, Production, Quality and Engineering departments. My recollection is that the Z8 project manager was closely involved in all stages of the development, including its transfer into routine production. There were undoubtedly frustrations, disagreements and necessary compromises when allocating resources (facilities and staff) between this project and competing requirements for other essential activities, but I cannot recall any occasion on which this led to significant delays.

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 difficulties with more formal contact, in particular, at a senior, or managerial, level. 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?***

I am not aware of any actions or inactions by senior managers in the SNBTS or the BPL which inhibited the free flow of technical information, meetings or mutual assistance in the development of both 8Y and Z8.

8) ***The Central Blood Laboratories Authority (CBLA) Central Committee on Research and Development in Blood Transfusion first met on 21 June 1983. 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?***

I had little, if any, personal involvement in this committee. The CBLA was the statutory body responsible for BPL and the International Blood Group Reference Laboratory. My understanding at the time (and now) was that the committee had no authority over the blood services in Scotland, Wales or Northern Ireland. My recollection is that it was never recognised as a UK committee and certainly never exercised any formal influence over the activities of the SNBTS – although the SNBTS took account of its actions and recommendations in its own planning processes.

I am unable to comment authoritatively on the value and importance of this committee from either a Scottish, English or UK perspective. However my impressions were that the committee exercised a primarily observational and reactive role in relation to policy, scientific or operational decisions taken elsewhere. For example, it would appear that the committee exercised little direction or supervision of BPL's development programme, but served as a forum in which BPL could inform interested parties of its development programmes managed and directed under the authority of the BPL Director – such as coagulation factor product development.

(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?***

I am unable to comment on why there was no PFC representative on this committee, other than to observe that, in the absence of any agreed UK role

for this committee, there would have been no expectation of any formal PFC involvement.

It is difficult to judge whether or not PFC representation on the committee would have enhanced the collaboration between PFC and BPL. There is little evidence from the notes of the meetings of any detailed scientific discussion on the 8Y development programme or specific policy guidance on the progress of such activities at BPL.

As indicated above, there was already a productive and unimpeded dialogue between BPL and PFC scientists during this period and, in the absence of a formal UK wide locus and authority for this committee, it seems unlikely that PFC involvement would have modified the outcome of the PFC or BPL development programmes - unless of course the committee had taken a closer and more direct role in the direction and management of product development programmes – which at that time it did not.

(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. 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?***

The concerns expressed by the SNBTS Directors in 1987 post-dated the development of both 8Y and Z8.

I cannot recollect any occasion during (or preceding) the development of 8Y or Z8 where the concerns expressed in 1987 led to either BPL/PFL or PFC withholding mutually useful information concerning the development of hepatitis/HIV safe plasma products.

From my perspective as PFC Director, the CBLA committee was not seen as an important or productive vehicle for scientific collaboration between PFC and BPL and, whilst I was enthusiastic to encourage collaboration, there was

little evidence from experience that the CBLA committee, or its suggested successor, would contribute to the achievement of that objective.

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

It is difficult to argue against a case for the closest possible cooperation between two UK NHS services engaged in identical and unique activities, albeit serving different parts of the UK population. The case for the closer professional, policy and scientific management of the Scottish and English Blood Services was repeatedly and consistently advocated by Professor Cash. However, there were a number of features of the respective services (both PFC and RTC's) which reflected significant differences in their size, political accountability, technologies, funding arrangements and management structures. My impression is that these differences widened throughout the 1980's, subsequently leading to quite distinct and separate policies and strategies. These included the introduction of cross charging for blood components and plasma products in England, a revised English 'definition' of self sufficiency, increased commercial activity, licensing of commercial plasma product manufacturing technology vs in-house development in PFC and significantly different qualitative and scale of fractionation technology. These divergent approaches tended to reduce rather than enhance opportunities for formal collaborative activity in the area of new product development.

Moreover, there was little evidence of or action from the SNBTS's statutory authority (CSA), SHHD or DHSS, to suggest an enthusiasm or determination for more formal links between the two services.

However, notwithstanding the absence of formal management structures, it is important to reiterate that there were many areas of highly productive collaboration and cooperation concerning reciprocal product supply, technology transfer, exchange of scientific information, capacity planning for UK plasma product demand and quality management issues.

Finally, whilst it is possible to conjecture with hindsight that more formal links could have delivered a different and by inference an improved outcome, it is equally possible that a more formal and centrally managed collaboration may have led to decisions to focus the work and resources of both teams on either pasteurisation or dry heat treatment but not both. In 1984/1985 the technically more complex pasteurisation process would probably have been the preferred scientific approach by both BPL and PFC to reduce or eliminate NANBH transmission by FVIII.

This narrowing of development activity may have precluded (or at best delayed) any parallel investigation by either BPL or PFC of the 'dry heat' treatment option and its subsequent successful development and rapid introduction into routine use.

I am not aware of any formal research links established subsequently (late 1980's onward) between BPL and PFC/SNBTS, other than occasional (ad hoc) meetings between the CSA and the CBLA to share information.

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?

The development and introduction of PFC's heat treated FIX product (HT DEFIX) is described in the SNBTS briefing paper, November 2010.

As described in this paper, and unlike FVIII, it was not necessary to establish a new manufacturing process to render the existing FIX product tolerant to heat treatment. It was only necessary to modify the product formulation and to conduct an animal safety study. These activities were carried out as a collaboration between PFC and BPL.

11) Additional questions for Dr Perry are as follows:

1) In his report dated 10 January 1986 for the meeting of the SNBTS and Haemophilia Centre Directors on 5 March 1986, Dr Perry referred to the high purity product being developed by PFC in collaboration with Professor Johnson

of New York University and stated that that product "may not require such vigorous heating conditions" as the BPL FVIII heat treated at 80°C for 72 hours. What was the basis for that statement? What were the "conditions" which "gave comparable levels of viral inactivation"?

I cannot be certain but I believe we had some preliminary evidence or observations at that time that the level of virus inactivation which could be achieved by heating was in part dependent on product specific activity (purity) and other parameters such as freeze drying.

The product being developed with Professor Johnson was designed to be a 'high purity' product with a possibility that comparable levels of virus inactivation might be achieved with reduced time and/or temperature. I do not recall the specific conditions I had in mind, and in any event this strategy was not adopted.

2) What type of FVIII product was batch 50700, referred to in Dr Boulton's letter of 22.8.86 to Dr Perry i.e. what was the name of the product (NY, ZHT or NYU?), what was the purity of the product and what viral inactivation procedures had it undergone?

Records indicate that the FVIII product was 'intermediate purity' NYFVIII (heated at 68°C/24hrs). The full batch number was 3412-50700 prepared in December 1985 and issued in its entirety to Edinburgh in July 1986.

3) What was the "eleventh hour problem with freeze-drying" encountered by PFC in producing Z8 referred to in Dr Perry's letter of 29.8.86 to Dr Boulton and how, when and by whom was it resolved?

The freeze drying problem concerned the control of one or more critical parameters during the freeze drying cycle (eg shelf temperature, vacuum, supercooling, etc) which resulted in reduced product solubility after heat treatment.

The problem was identified by Dr R McIntosh, the Z8 project manager. The nature of and solution to this problem is described in the SNBTS Briefing Paper, November 2010, pages 45-48. Z8 product for clinical evaluation subsequently became available in December 1986.

4) ***In his minute of 26.8.88 to the Chief Medical Officer, Mr J Hamill, SHHD, notes that from speaking with Dr Perry, Mr Hamill learned that collaboration between PFC and BPL/PFL "was not all that it might be". Was that the view of Dr Perry at the time? If so, what did Dr Perry mean by that? Did any difficulties in that regard inhibit in any way the exchange of information between BPL/PFL and PFC in respect of the development of 8Y? Did any such difficulties contribute to any delay in the development and introduction of Z8?***

I do not recall this informal discussion or its context, although I am in no doubt that it took place. Clearly the discussion post dated the routine introduction of both 8Y and Z8. The words used are apparently those of Mr Hamill to summarise my views.

I cannot recall the nature of the conversation or exactly what I was trying to convey to Mr Hamill. However it is possible that I was suggesting that there could be advantages to both PFC and BPL if the productive though informal arrangements were underpinned by a more formal process, particularly in relation to major new service developments (such as Intravenous Immunoglobulin (IVIG) which at that time was neither manufactured or supplied by BPL) and arrangements for 'cross border' product supply. At that time I believe my (informal) comments would have concerned wider issues of interest to both BPL and PFC (eg product licensing, emerging safety and quality regulations, product supply) rather than a specific reference to or advocacy for central management of product development programmes.

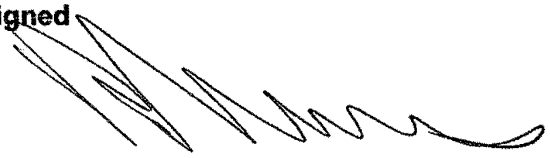
As stated above, the key scientific staff at PFC and BPL responsible for the development of Z8 and 8Y were, as far as I am aware, subject to no senior management influences which would inhibit their long standing professional

relationship, collaborative culture and regular free exchange of information. I can therefore confirm that, to the best of my knowledge, my comments would not have concerned our ability to collaborate freely and productively with senior scientific staff at BPL/PFL.

Statement of Truth

I believe the facts stated in this witness statement are true

Signed



Dated

2nd September 2011