WITNESS STATEMENT FROM DR R J PERRY (DRAFT)

Issue in respect of which a statement is sought

AIDS/HIV

The use of commercial products in Scotland, including the continuation of such use after:

(a) international realisation that these carried a risk of AIDS;

(b) the proposal by Dr Galbraith of the Public Health Laboratory Service in May 1983 that use in the UK should be stopped; and

(c) significant progress towards self-sufficiency in the manufacture of blood products by the NHS in Scotland had been made.

INTRODUCTORY COMMENTS

Prior to my appointment within SNBTS I was employed as Chief Analyst in the Regional Sterile Supply Unit of the West Midlands Regional Health Authority. This new NHS unit was established for the large scale pharmaceutical manufacture of sterile injectable preparations for the region and my role included the development and management of Quality Control systems and procedures necessary for the commissioning and operation of the unit within standards of Good Pharmaceutical Manufacturing Practice applicable to the industry in general.

In March 1981 I was appointed in SNBTS as Quality Control Inspector in the Protein Fractionation Centre (PFC). This was a new post. Its role, inter alia, was to develop and implement Quality Assurance systems and controls as part of a programme to bring the Centre into compliance with modern standards of Good Pharmaceutical Manufacturing Practice. I reported to the PFC Director (Mr J G Watt).

In January 1984 I was appointed Acting Director of PFC following the departure of Mr Watt. This appointment was made substantive in 1985 reporting formally to the Committee of Management of the CSA and responsible for all activities of the Centre – subject to the responsibilities and duties of the SNBTS National Medical Director.

Clearly I had no involvement in or knowledge of discussions, actions or decisions on the above or other issues prior to March 1981.

The following statement and recollections are made from the perspective of a senior manager in PFC aware of the general emerging international discussions concerning AIDS but not involved in considerations of the risks and benefits of different options for patient treatment. Indeed the SNBTS was not directly involved in the care of haemophilia patients which was clearly understood and accepted by both SNBTS and SHHD to be the sole responsibility of Haemophilia Directors. At this time self-sufficiency was an accepted goal for Scotland which dominated its planning throughout the

1980's. It was also accepted that prescribing doctors were free to exercise their own judgement in the choice of either SNBTS or commercial products preserving the important principle of clinical freedom. Therefore whilst SNBTS and Haemophilia Directors collectively embraced the goal of self sufficiency the use of NHS products was not and could not be enforced by SNBTS. For its part SNBTS focussed its activities on the collection of plasma and delivery of a range of products of sufficient quantity and quality to meet the best estimates of future demand agreed between SNBTS, Haemophilia Directors and SHHD.

STATEMENT IN RESPONSE TO SPECIFIC QUESTIONS

Section 1. By the beginning of 1983, was there any recognition that the arrival of AIDS, and its possible connection with (US) commercial blood products, required a re-assessment of the risks/benefits associated with the use of commercial rather than NHS product? Why was there no discussion about the possible connection between AIDS and commercial blood products?

My recollection is that there was in SNBTS awareness and informal discussion of AIDS and its suggested possible connection with the use of blood products. This awareness was derived from attendance at international meetings, monitoring of the scientific literature and regular professional contact with other organisations. Information gathered in this way would have been circulated within SNBTS and where appropriate to Haemophilia Director colleagues.

However, by the beginning of 1983 the international scientific and medical understanding of AIDS and its consequences remained confused, rapidly changing and poorly understood with a range of explanations and theories emerging to explain this new disease.

AIDS appeared to be largely confined to the US and its causal relationship to haemophilia through treatment with FVIII concentrates was tentative and by no means proven. In the minutes of meeting of UK Haemophilia Directors in September 1982 (which I attended) it was recorded as a 'remote possibility' that commercial blood products were involved in the development of AIDS in 3 US patients. This was probably typical of the prevailing UK view at the time and that there was certainly no evidence to justify a departure from the haemophilia treatment regimes which were being developed – and importantly which were highly dependent on the use of imported US commercial products in England and Wales and to a lesser extent in Scotland. It is important to emphasise and understand the dramatic improvement in haemophilia care which had become available from the use of coagulation factor concentrates and my impressions from that time were that these very substantial benefits were considered to greatly outweigh any theoretical and unproven risk from AIDS. Also there was a prevalent view (or at least a hope) that AIDS was a phenomenon likely to be largely confined to the US. The so called precautionary principle which today underpins blood and plasma product safety interventions was far less evident at that time and interventions related

to product and patient safety would have required a much greater body of scientific evidence than was available then to justify their application – particularly if these would have diminished the availability of products for patient treatment. Finally, and notwithstanding emerging international scientific discussion on the possible link between AIDS and FVIII concentrate products, imported commercial products were subject to formal regulation under the Medicines Act (1968) and through the UK Licensing Authority (Committee on Safety of Medicines, CSM). Up to and beyond the beginning of 1983 the regulatory status of these products remained unchanged and by implication could continue to be prescribed for patients. It is likely and appropriate that this formal position would have informed the policies and decisions of treating doctors.
The role of PFC/SNBTS was primarily one of manufacturer and supplier of treatment products and accordingly could not have been involved in any formal assessment of the risks and benefits associated with the use of alternative (and competitor) commercial products – reflecting the separation of responsibilities between manufacturer/supplier and treating doctors.

In any event, and from the perspective of PFC/SNBTS, Scotland had embraced the importance of and benefits of self-sufficiency, was making rapid progress toward that goal including the development of a 'hepatitis reduced' heat treated product and was focussing its efforts on a programme to eliminate the requirement for commercial products.
As indicated above SNBTS had no direct role in the treatment of haemophilia or the prescribing of products and therefore played no part in any formal consideration of risks and benefits associated with the use of commercial product (either generally or in relation to specific patients) other than through regular professional contact and information exchange. I cannot recall from memory or establish from records the extent to which SNBTS considered these issues formally other than the clear recollection of its consistent and sustained advocacy (primarily through its National Medical Director) for the use of NHS products wherever possible and in line with the stated SHHD policy for self sufficiency. The clear separation of responsibilities between SNBTS as manufacturer and supplier of products and Haemophilia directors as prescribing doctors was carefully respected and maintained.
However SNBTS medical and scientific staff would have held personal and speculative views on AIDS and there was periodic informal discussion on the topic but in the absence of both a formal requirement or responsibility for it to intervene or advise on the use of licensed commercial products and the paucity of scientific information available it did not, to the best of my knowledge, express a formal view or make any specific recommendations.

Section 2(iv) Was there in fact a reluctance to involve them (see comments in letter dated 8 August 1985 referred to in paragraph 8.36, footnote 55 regarding their status)?

My impression at that time was that Scottish Haemophilia Centre Directors were closely involved in and participated in the work of this UK group. SNBTS and other UK Blood Services were not members but were periodically invited

to meetings to discuss issues of common interest – such as NHS plasma collection, product supply and NHS product developments.
I have no knowledge of the formal position of Scottish Haemophilia Directors in this group or the reasons for their apparent absence from this meeting.

Section 2(vi)Dr Galbraith's recommendation to cease importation of US commercial products.

Was there ever any thinking along these lines in Scotland?

Prior to the publication of the Preliminary Report I had no knowledge or recollection of this event. I have subsequently been unable to find any evidence that SNBTS Directors may have been aware of this recommendation or its rejection by DHSS – apart from the reference to it in the briefing note of the English Directors meeting prepared by Dr Mitchell (which only seems to mention a DHSS response to media reports) and in the reply from Professor Bloom to Dr Boulton (paragraph 8.29). In any event I am not aware of any discussion taking place in SNBTS or SHHD in response to this information. This is not wholly surprising since SNBTS had no involvement in or responsibility for importation or use of commercial products and it is highly unlikely that SHHD would have taken a contrary view to DHSS. Moreover at this time the scientific case for a causal relationship between FVIII products and AIDS had still to be accepted with sufficient confidence to justify such action. This was the prevalent view (from my perspective) in SNBTS at that time and, from the information available, certainly the formal view of UK Haemophilia Directors, the UK Haemophilia Patient Organisation and most importantly the UK medicines licensing authority which had taken no action to suspend or revoke UK licences for US products. My impression was also that this position was consistent with that of other countries.
By mid 1983 there may have been an increasing recognition of a possible causal relationship between AIDS and US commercial blood products and there was an increasing interest in the topic generally amongst SNBTS staff and within SNBTS committees. Whether or not the emerging information and evidence was sufficient to justify a ban on the importation or use of commercial product may have been the subject of informal and frequent discussion within SNBTS but its efforts remained focussed on the supply and safety of its own products – although of interest to SNBTS the safety, licensing, importation and use of commercial products were subjects outside the scope of its activities or responsibilities – these were matters for DHSS Licensing authority, Health Boards and Haemophilia Directors. It is possible that SNBTS Directors held a view, that this may have been conveyed informally to professional colleagues in SHHD and Haemophilia Directors but I was not aware of any formal SNBTS position except for its consistent advocacy for the use of NHS products and its determination to make these available in sufficient quantity to meet the needs of patients in Scotland.
Finally I am not aware of any requests to SNBTS at that time to consider and plan for a ban on imported products – although by mid 1983 it was already generally felt that the majority of Scottish needs were being met with NHS/PFC products.

Section 2 (vii) Prioritising Product Use.

The PFC had no involvement in the treatment of patients or recommendations for the treatment of specific patient groups (eg children, mildly affected patients, use of DDAVP etc). Accordingly I am unable to provide any information or recollection concerning the questions posed which are matters for Haemophilia Directors.

Section 2(viii) Attendance at WFH and ISTH meetings, Karolinska Institute 1983.

I have no information concerning attendance at this meeting from Scotland. It is likely that this regular and important annual meeting would have been well attended by Scottish professionals but this is a speculative comment.
It is possible that Dr Foster's reports from the meeting would have been circulated within PFC and SNBTS as part of the prevailing practice of information gathering and exchange but I am unable to confirm that this occurred on this occasion.
The content of Dr Foster's report illustrates the continuing uncertainty and absence of any international consensus on how best to manage the emerging AIDS problem without endangering treatment regimes for patients.

Section 2(ix) Dr Galbraith's submission to the Biological Sub Committee of the Committee on Safety of Medicines.

The above committee was comprised of scientific and medical 'experts' supported by a secretariat comprised of expert assessors. The function of the committee was primarily to assess applications from manufacturers for marketing authorisations (licences) to supply products for the treatment of UK patients within the terms of the Medicines Act, 1968. It also had UK wide responsibility for the review of medicines already in use. It is reasonable to assume that its secretariat and expert members would have been aware of evolving international scientific opinions.
At this time the expert membership included the Directors of both BPL (Dr R Lane) and PFC (Mr J Watt) although importantly their membership was in a personal expert capacity rather than in a representative role of their respective organisations or countries. Moreover, the proceedings of the committee were conducted under strict confidentiality (to protect the commercial interests of applicant manufacturers) and accordingly would not have been available for discussion within SNBTS. Mr Watt served on this committee until 1986 (including a 2-3 year period following his resignation from SNBTS) and thereafter I was appointed to the committee (1986) until 1990 when, following the removal of Crown Immunity the continuing involvement of NHS product manufacturers in the work of the committee was seen as a conflict of interest.
Mr J Watt was a serving member of the committee in July 1983 at the time of Dr Galbraith's submission but I have no knowledge of whether or not he attended the specific meeting on 13 July.
In any event he was not present as a representative of Scotland or SNBTS and through the rigorous and formal enforcement of confidentiality would have

been unable to report the outcome from this meeting to SNBTS or other colleagues.
I have no knowledge or recollection of whether Dr Galbraith's recommendation and the decision to reject it were communicated to eg SHHD (or SNBTS) in any other way. It is possible that this occurred since the UK Licensing Authority officially comprised all UK Health Ministers. However since the decision was to maintain the 'status quo' it is equally possible that wider communication of the recommendation and its rejection would have been considered unnecessary.

Section 3(i) Attendance at Aarhus conference

I am unable to provide any additional information concerning attendance at this conference. SNBTS or Haemophilia directors may be able to provide information concerning attendees, if any, from Scotland.

Section 3(ii) Geneva Conference

I am unable to provide any further clarification concerning distribution of information and SNBTS reports (Mr Watt, Dr McClelland) arising from the Geneva Conference in 1983.
The WHO final report would have been widely available to interested parties.

Section 3(iii) maintaining the use of commercial concentrates

Yes, this is an accurate impression.
The impression gained from the perspective of the Scottish NHS manufacturer (PFC) was that, despite the uncertainty and often conflicting scientific opinion there was a strong desire to maintain the level and quality of treatment offered by concentrate products. In Scotland, by this time (end 1983), this objective did not require a choice between commercial or NHS concentrates. I recall (though can find no evidence or place this accurately in time) a brief period in which planning for reverting to the use of cryoprecipitate was discussed as a possible outcome of the emerging AIDS problem. In any event this was not progressed as a serious option given the, by now, minimal requirements for commercial FVIII and perhaps the belief (subsequently found to be incorrect) that, thus far, there was no evidence that AIDS had entered the Scottish blood supply.

Section 3(iv) Avoidance of non essential use of blood or blood products

I am unable to comment on this question which concerns the clinical practice of doctors involved in the direct care of haemophilia patients.

Section 3(v) Awareness of AIDS in Scotland

My impression was that AIDS was still not prevalent in Scotland around the end of 1983, that no haemophilia patients had been identified with symptoms

of AIDS and that AIDS had not entered the Scottish blood supply. Indeed, indirect corroborative evidence for this view was that, following the realisation that Scotland had a significant surplus of FVIII, this was subsequently supplied to England in the belief that its use would reduce the requirement there for imported (and less safe) material.

Section 4 Continued use of small amounts of commercial products and availability of heat treated commercial concentrate

By the beginning of 1984 SNBTS had achieved and exceeded its goal of self sufficiency although we were aware that there remained a small residual requirement for commercial product for particular clinical circumstances or individual patients. These requirements were considered and accepted as appropriate matters for haemophilia directors and in any event the quantities of product involved by this time were very small.

Section 4 Use of Heat Treated Concentrates in Scotland - When were physicians able to begin using heat treated commercial concentrate?

Availability of Commercial Concentrates

My understanding of the availability and use of commercial heat treated products in the UK is as follows:-

US regulations in the early 1980's concerning the export of pharmaceuticals required (prior to the US Drug Export Amendment Act, 1986) that products were licensed by the US FDA as a precondition for export. At this time heat treatment was aimed at reducing the hepatitis risk from coagulation factor concentrates.

The first of the heat treated commercial FVIII concentrates (HemofilT,60 degrees/72hrs, Baxter) was licensed by the FDA in March 1983.

This product was available in the UK (under the provisions of the UK licensing Authority Clinical Trial Exemption Scheme) around July 1983 for clinical evaluation in a trial designed by Haemophilia Reference Centre Directors to determine the extent to which it reduced the risk of hepatitis in patients with little or no previous exposure to FVIII concentrates. The ethical dilemma facing haemophilia doctors was described in the report of 11th July to Haemophilia Centre Directors.(paragraph 8.40)

A UK licence application submitted by the company in September 1983 for this product was rejected by the UK Licensing Authority and the company were criticised for making unjustified claims concerning reduced AIDS risk.

In January and February 1984 the US FDA licensed heated products from Armour Pharmaceutical Company and Alpha therapeutic Corporation respectively.

A subsequent UK Licence application from Armour was rejected by the UK Licensing Authority in July 1984.

Meantime a very cautionary approach to the use of these heat treated products had been adopted in the US arising from their continued ability to transmit hepatitis, the unknown effectiveness of heat treatment in reducing the risk of AIDS and concerns that heat treatment may increase the risk of adverse event and inhibitor formation in recipients. This, I recall, was also a major concern in the UK. particularly in the absence of information

demonstrating reduced hepatitis risk. Unheated products continued to be licensed and prescribed.
Following the key discovery that AIDS was caused by a virus which could be readily inactivated by heat treatment the UK Licensing Authority took steps to encourage manufacturers to submit licence applications for heat treated products and licences were granted for Profilate, Factorate HT, HemofilT, Koate HT and Kryobulin TIM in February 1985.
Therefore between mid 1983 and February 1985 heat treated commercial concentrates were available in the UK. They were not licensed for routine use but could be used in approved clinical trials or on a named patient basis according to the judgement of treating doctors.
I am not aware of the extent to which Haemophilia Directors in Scotland participated in studies of so called hepatitis reduced commercial products during this period although there is evidence of their preference to support the clinical evaluation of the initial SNBTS heat treated product during 1984.

Availability of SNBTS Heated Products
The first SNBTS heat treated FVIII product (pasteurised, 60°C, 10 hrs) was made available for initial clinical evaluation in September 1983.
SNBTS heat treated FVIII concentrate (68°C, 2hrs, freeze dried) was available for initial evaluation in November 1984 and distributed for the use of all Scottish haemophilia A patients in December 1984.

In late 1984 following the discovery that SNBTS FVIII products had been potentially implicated in the transmission of HTLVIII to a number of Edinburgh haemophilia patients and the subsequent scientific announcement that HTLVIII could be readily inactivated by heat (68 degrees), SNBTS immediately acted to heat treat all existing stocks of FVIII concentrates, conduct a rapid clinical evaluation of the heat treated product and recall all stocks of unheated product from throughout Scotland. This exercise was conducted in December 1984/January 1985 successfully meeting the objective of ensuring that all haemophilia A patients in Scotland (prescribed SNBTS product) were able to be treated with heated NHS material from January 1985. There were no known further transmissions of HTLVIII/HIV by SNBTS coagulation factor concentrates following these actions.
These events are described in detail within the Preliminary Report.

R J Perry
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