SNBTS
DOCUMENTATION
REQUEST
2011/00121

WITNESS STATEMENT FROM DR R J PERRY

PENROSE INQUIRY - DR ROBERT PERRY
EVIDENCE ABOUT PACKAGE INSERTS USED WITH PFC CONCENTRATES AND THE RISK OF HIV TRANSMISSION

Topic B5

Issue in respect of which a statement is sought

1. Thompsons have applied to the Inquiry to have certain supplementary questions put to Dr Perry in written form as set out below.

2. By way of background you will remember that this issue was raised during the course of Dr Perry's evidence in connection with the B5 topic on 24 June 2011 (transcript from page 95). It is submitted that the absence of any warning of the risk of HIV in the package inserts which accompanied PFC products in the early to mid 1980s is a matter of relevance to the Inquiry's consideration of the B5 topic. The evidence which Dr Perry was able to give on this issue to the effect that the package inserts were designed, in part at least, for the information of patients and that this matter was not spoken to by any other witness. It is submitted that (a) that Dr Perry is the witness best placed to answer questions on this issue (as is shown by the fact that he was able to address the issue in a letter to Dr Cash dated 14 March 1988 at SNB.001.0445 at 0448) and (b) that there are certain aspects of this matter which ought to be followed up with him.

3. Lord Penrose has approved the request and I am asked to forward the undernoted questions to you and to ask for Dr Perry's written responses to them as soon as practicable.

Questions

(1) In SNB.001.0445 at 0448 in paragraph 5(vii) you mention "package inserts (or other formal product documentation)". What do you mean by "other formal product documentation"? What was the purpose of that other documentation?

Response:

'Other formal product documentation' meant printed information on product vial labels and packaging containers in which the product was supplied. This information would include product name and description, vial content (expressed in International Units) and excipients (inactive constituents), storage conditions, reconstitution instructions, drug status (i.e. POM – prescription only medicine), batch number, expiry date and any warnings, such as hepatitis risk. The information to be provided was prescribed by regulatory standards and pharmacopoeia monographs in force at the time.

In common with other medicines the information was intended to identify the product and describe to users its correct use and storage.

Although the products were supplied to some patients for self administration on home therapy programmes, as prescription only injectable products (POM), the information provided in product leaflets, labels and packaging was primarily designed and intended for prescribing doctors. This is evident from the detailed technical, medical and pharmaceutical information provided and the specialist language used in product insert leaflets at that time. Patients who self administered their treatment would have had sight of such leaflets but they were not the primary audience for whom the information was intended. Discussion with patients of treatment options and associated risks was and still is exclusively the responsibility of treating doctors. Manufacturers are not permitted or expected to engage in direct contact with patients. However, it was later concluded that patients should get specific information. From 1994, Patient Information Leaflets became a legal requirement and these were issued with PFC products along with the Technical Information Leaflets intended for health care professionals.

(2) What discussions were there amongst the staff of the PFC of the possibility of including reference to the risk of HIV transmission on package inserts included with their factor concentrates between 1982 and 1985? Who was involved in these discussions? When did these take place?

Response:

I cannot recall whether or not, in 1982 and 1983, I had any discussions with the PFC Director (Mr Watt) concerning the inclusion of AIDS warnings in PFC product insert leaflets. I do not know if Mr Watt discussed the possibility of including AIDS warnings in PFC leaflets with others, including Dr Cash as National Medical Director.

However I did lead a review of the packaging systems for PFC FVIII and FIX products during this period which resulted in the introduction of new multi-vial packaging. Product warnings on both product packaging and leaflets remained unchanged and continued to refer only to a hepatitis risk.
As a member of the Committee on Safety of Medicines Sub-Committee on Biological Products at that time, Mr Watt would have been one of the first to appreciate if such warnings were required or advisable and I am sure that he would have advised me accordingly if this had been the case.
I cannot recall whether or not in 1984 (following my appointment as Director) I discussed with others in PFC or elsewhere the possibility or desirability of modifying our 'warnings' to include AIDS. I think it is possible that such discussions took place with eg Dr Cash, Dr Boulton and the Haemophilia Directors. For example Dr Foster has advised me that he recalls that in late 1983 the SNBTS (Professor Cash) suggested, at a meeting between SNBTS and Haemophilia Directors, the inclusion of an AIDS warning but that this suggestion was rejected by those present in the belief that such action might cause patients unnecessary anxiety. However the SNBTS has been unable to find any record of this.
In any event no action was taken to include any specific reference to AIDS or HIV until HT DEFIX was issued in September 1985.

(3) Why and by whom was it decided that there should be no reference to the risk of HIV transmission in PFC factor concentrate package inserts over that period?
Response:
The PFC did revise its product leaflets in April 1985 with the introduction of FVIII NY (68°/24hrs). The revised leaflet and product label stated that 'The freeze dried product has been heat treated but cannot be assumed to be non infective'. The term 'non-infective' being intended to encompass all potential blood-borne infections, including HIV/AIDS.
In Addition, when the new heat treated DEFIX product was issued to all centres in October 1985, it did include mention of HIV, as follows: " In addition, product, plasma pools and individual donations are tested for the presence of antibody to HTLVIII. The product has been heat treated at 80° C for 72 hours in the freeze dried state. This treatment is expected to inactivate viruses associated with the Acquired Immune Deficiency Syndrome.."

However I am unable to find any reference to or evidence of a process which led any individual(s) to recommend in favour of or against the introduction of AIDS warnings for FVIII products.

Prior to 1985, product information supplied by the PFC/SNBTS reflected the background of knowledge and guidance available between 1982 and 1984 i.e.

- *There was no requirement or advice from the UK licensing authority to include such warnings for products used in the UK.*
- *In contrast to products imported from the USA, and prior to October 1984, there was no evidence that products manufactured from UK plasma had transmitted HTLVIII.*
- *Prior to 1984 there was no consensus on the causal relationship between AIDS and treatment with coagulation factor products.*
- *To the best of my knowledge the PFC/SNBTS received no requests or advice from the Haemophilia Directors to include such warnings. It is highly unlikely that the PFC/SNBTS would have included AIDS warnings without their express agreement and support.*
- *The inclusion of such warnings in product literature required some measure of evidence that a genuine risk existed. In the absence of such evidence it would be inappropriate for a manufacturer to provide warnings which could cause anxiety and alarm to patients and which might cause patients to reject life-saving treatment.*
- *Knowledge that haemophilia doctors would not require or benefit from cautionary statements in product literature in assessing and communicating risks and treatment options to patients.*

PFC products for the treatment of haemophilia were manufactured and supplied for use to a small group of haemophilia doctors in Scotland. These doctors were well known to the SNBTS medical and scientific staff. Haemophilia doctors were well informed of the situation concerning AIDS and the implications for patient care, from discussions with the SNBTS (and vice versa) and their knowledge of wider UK and international opinion. The amendment by the SNBTS of its product leaflet to include a specific and unquantifiable risk warning would have done little, if anything, to enhance their knowledge or their communications and discussions with patients; especially as the topic of AIDS was being widely discussed and considered by haemophilia doctors at the time, as evidenced by the formation of an AIDS working party by HCDO in the early 1980s.

(4) Why was it considered appropriate to include a reference to the risk of hepatitis transmission in the PFC factor concentrate inserts over that period?

Response:

Prior to and during the period 1982-85, hepatitis transmission by coagulation factor concentrates was widely recognised and documented. Accordingly all manufacturers were required (by regulatory authorities) to include hepatitis warning statements with their product packaging and information leaflets. For example, the British Pharmacopoeia monograph on "Dried Factor VIII Fraction", published in 1986, included the requirement in the labelling section that there was a statement "that the preparation cannot be assumed to be free of hepatitis virus". Similar wording was included in previous editions of the BP.

(5) From whom did the PFC staff take advice about the risks of transmission of HIV via PFC concentrates between 1982 and 1985?

Response:

Various discussions and meetings involving the SNBTS with government Health Departments (SHHD, DOH) and regulatory bodies (eg NIBSC, DHSS Medicines Division) took place during this period, but I do not recall that this produced any guidance or advice concerning the risk of HIV transmission by products prepared in the UK from voluntary donors.

There was no evidence that HTLVIII had entered the UK blood supply prior to late-1984 and any estimates of risk associated with UK products were speculative.

The PFC maintained an awareness of international developments through its network of professional and scientific contacts and by monitoring of the scientific literature. This body of knowledge was supplemented by frequent and regular discussions with Haemophilia Directors, SNBTS medical experts (eg Dr Boulton) and the SNBTS National Medical Director (Dr Cash) – both of whom acted as medical advisors to PFC.

In 1983 PFC submitted its FVIII licence (NY) for renewal by the Committee on Safety of Medicines. This submission included the product insert leaflet which made no mention of HTLVIII or AIDS. This application was approved without alteration, indicating that the Committee on Safety of Medicines did not, at that time, expect plasma products derived from UK donors to carry warnings

concerning AIDS. The PFC received no subsequent request or advice from the Licensing Authority or the Medicines Inspectorate to include AIDS warnings.

(6) What advice was given to the PFC over that time period about the risk of HIV transmission from PFC factor concentrates?

Response:

I do not recall the PFC receiving any specific advice or guidance concerning the risk of transmission of HIV/AIDS by its products. This does not imply an absence of discussion and speculation within the SNBTS which increasingly dominated this period. However in the absence of any reports or data suggesting that HIV had entered the Scottish blood supply it is difficult, even with the benefit of hindsight, to identify what advice could have been given to the PFC, which could subsequently have been translated into warning statements and used by Haemophilia doctors in their discussions with patients.

(7). Was there an awareness of within the PFC of the fact that American products had such warnings on their inserts from around October 1983? In relation to this question Dr Perry's attention is drawn to the following passage from the report of the Commission of Inquiry on the Blood System in Canada (the Krever report) which, in Thompsons' view, provides interesting material as to the international standards referred to by Dr Perry in his letter of 14 March 1988:

> ***"When fractionators prepared their vials of factor concentrate in packages for shipping, they included printed information about the concentrates, their proper use and possible risks in using them. In the autumn of 1983 and in early 1984, US fractionators added warnings about the risk of AIDS to the information in the product inserts - Armour, for its factor VIII concentrate, in October 1983; Cutter for its commercial factor VIII concentrate, in January 1984; and Hyland for its factor VIII concentrate, in March 1984"* (Krever report, page 399)**

Response:

It is important to appreciate that the section quoted above from the Report of Justice Krever concerns concentrates prepared from plasma collected in the USA. Although Cutter Laboratories did include warnings with its products prepared from USA plasma from January 1984 (as described in Krever, p399) it did not provide such warnings in 1984-1985 with products derived from plasma

collected in Canada and processed under contract for distribution in Canada (Krever, page 400). That the same company adopted different positions in relation to the origin of the plasma used, suggests that the risk of AIDS was still considered to be primarily associated at that time with plasma collected in the USA from paid donors.

Product literature from commercial companies was periodically received at the PFC and/or gathered at international conferences attended by PFC staff. I am unable to recollect the extent to which these documents would have been examined at the time by myself or by senior PFC colleagues. I would have been aware at the time that, in common with all plasma products from the USA, these products carried warnings of product infectivity but I cannot recall if I was aware of specific AIDS or HTLVIII warnings.

It remains unclear when warnings on HIV/AIDS were universally included by commercial manufacturers or indeed when product containing these AIDS warnings emerged through the supply chain for use in the UK.

For example in the leaflet dated February 1985 for the Cutter heat treated product Koate –HT there is in the 'warnings' section a typical hepatitis statement but no specific mention of AIDS or HTLV. This leaflet in its 'Further Information' section only mentions that

> *'Studies have demonstrated that the heat treatment process used in the production of Koate-HT inactivates potential infectious viruses, including a retrovirus, but it has not yet been established that the agents of any major transmissible disease would be inactivated'.*

This information is clearly intended for health care professionals rather than an attempt to provide information to patients.

I am unable to recall or find evidence for the precise time when 'mandatory' AIDS/HTLVIII/HIV warnings were universally required and adopted, but my understanding is that such warnings were adopted by different manufacturers at different times in the light of emerging evidence of the causal relationship between AIDS and treatment with coagulation factor products and a desire to provide some measure of defence against future litigation.

It is noteworthy that by 1984 there was emerging data to support this causal relationship for products derived from USA paid donors but at that time there was no such evidence for products prepared from European volunteer/unpaid donors.

When it became clear, in October 1984, that there was a risk from SNBTS products, we quickly issued heated NY product (68°/2hr) and subsequently

modified the leaflet for inclusion with the later FVIII product (NY 68°/24hr) to include the term 'non-infective' which was intended to cover all risks from blood borne infectious diseases. However, it was not until we issued advance heat treated (80°/72hr) products (HT DEFIX and Z8), that we specifically referred in the product leaflets to AIDS in the (correct) belief that these products no longer carried the risk of HIV transmission.

(8) To what extent did such awareness impact upon the attitudes of the PFC staff to including such a warning on their factor concentrate inserts?
Response:
I cannot recall any discussions amongst PFC staff, Professor Cash or Dr Boulton concerning the introduction of AIDS warnings in PFC product inserts. I believe the general view held by the PFC, the SNBTS and Haemophilia Directors was that the epidemiology of AIDS in the US, and particularly amongst US paid donors, was quite different from that in the UK. This view prevailed both before and after the introduction of warnings with product inserts from the USA. Moreover there was a preference, expressed by both the clinicians and patients, for UK NHS products which were considered to provide a substantially greater margin of safety with respect to AIDS. The inclusion of an AIDS warning on PFC products, similar to that on USA products, would have removed or diminished this important distinction and may have resulted in a greater use of commercial products in Scotland, with a higher incidence of HIV infection in Scottish patients as a consequence.
However, I appreciate that this opinion is based on hindsight and I cannot recall if this was the rationale at the time.

4. As a separate matter it has been suggested that the Inquiry might wish to consider some further investigation relating to the issue of package inserts and the opportunity for information to be conveyed to Scottish patients specifically about the risk of HIV transmission associated with factor concentrates. In that connection it has been suggested that the Inquiry might seek copies of inserts used in commercial products in the early 1980s. It will be remembered that, in June 2010, you provided us with a document "Hepatitis Risk Warnings" which is in Courtbook as PEN.102.0286. That document, which was obviously in response to a question specifically about

hepatitis, incorporated material produced to the Archer Inquiry including various SNBTS and commercial leaflets.
Having looked again at this document and the commercial leaflets provided with it can we assume that these are the only commercial leaflets from the period in question which are in the possession of your clients?

Response:
Neither I nor other SNBTS staff have been able to locate any further commercial leaflets from the period in question beyond those already supplied to the Inquiry.

Statement of Truth

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

Signed: .....

Dated: 5/11/2011.....