CAL33(230911)

Witness Statement of Professor Christopher Ludlam to Schedule issued on

23 August 2011 related to topic C3A

'The use of blood product concentrates in Scotland in the period between the introduction of NHS heat treated products in 1984 and the supply of NHS products sufficiently treated to inactivate hepatitis C'

Preamble

**Consideration of therapeutic policy in the period 1984 – 1987 with respect to non-A non-B hepatitis cannot be considered in isolation from the risk of other viral infections, especially HIV.** This is especially so because in the mid 1980s HIV was seen as a more severe infection and therapeutic practice was principally guided by attempts to reduce the possibility of it being transmitted by blood products.

**Question One**

'Heat treated NHS Factor VIII (8Y), treated at 80 degrees for 72 hours, was introduced in England in September/October 1985 but it was not until May 1987 that NHS heat treated Factor VIII (Z8) treated with the same protocol became available for clinical use in Scotland. During this period, was there an awareness among treating haemophilia physicians that the Scottish NHS product was less effectively treated against non A non B hepatitis?'

1. **When NY 68 degree/2 hour was introduced in Scotland in December 1984 its safety with respect to HIV was uncertain but it was widely acknowledged that it was very likely to transmit non-A non-B hepatitis** (see accompanying summary – CAL32).

2. **During 1985 data, from the use of commercial products at other haemophilia centres outwith Scotland, started to accumulate to indicate that the 68 degree/2hour product might not be safe against HIV.** Hence in September 1985 it was withdrawn and replaced by the 68 degree/24 hour concentrate. There was no reason to believe that this product was non-infectious for non-A non-B hepatitis as users of commercial factor VIII dry heated concentrates had reported transmission of hepatitis by similarly (or more severely) treated concentrates.

3. **The viral safety, with respect to transmission of non-A non-B hepatitis, of the BPL product, treated at 80 degrees/72 hours, introduced in England in September 1985 was unknown at that time.** It was not until mid 1986 that evidence started to be reported to suggest that it might be a 'hepatitis reduced' concentrate. This concentrate was only available to meet approximately one third of the total use of factor VIII in England – the majority of patients were treated with commercial concentrates which were likely to transmit hepatitis.

4. **Thus during the period December 1984 and June 1986 there was no clotting factor concentrate available in Scotland (or anywhere else in the UK) which was reported and accepted to be 'hepatitis-safe'.** During this period it was necessary to assume that all concentrates could transmit the causative agent(s) for non-A non-B hepatitis. After June 1986 it was assumed that 8Y was less likely to transmit non-A non-B virus(es) than NY 68 degree/24 hour.

5. **Once Z8, heat treated at 80 degrees/72 hours, was in clinical use throughout Scotland from May 1987 onwards it was reasonable to assume that it was probably as virally safe as 8Y.** Thus after May 1987 all patients in Scotland were treated with a hepatitis safe concentrate, which contrasts with the situation which pertained in England. At this time Scotland may have become the first country in the world where all patients with haemophilia were treated with hepatitis safe concentrates.

6. **It is note-worthy that the majority of patients in England, during the period 1984-87 were treated with concentrates which transmitted hepatitis.** It was not until 1988/89 that commercial concentrates which did not transmit hepatitis became available (see UKHCDO Therapeutic Guidelines issued in 1988 and 1989). In England prior to October 1985, there was no concentrate in England which was hepatitis safe. After October 1985 only a minority of patients were treated with 8Y.

**Question Two**

'What was the treatment policy for patients with haemophilia in Scotland in the period between the introduction of NHS heat treated products in 1984 until the supply of "hepatitis-safe" NHS concentrates? More specifically, what steps were taken to reduce the risk of patients acquiring NANBH from their treatment?'

**Preamble**

7. **The vast majority of regularly treated patients with haemophilia A and B and vWD were already infected with non-A non-B virus(es) in 1984 and there was no evidence that repeated exposure to the responsible virus(es) was detrimental.** Therefore, in the majority of patients, the sole aim was to prevent HIV transmission and this was accomplished by using heat-treated concentrates, even although it was thought likely that they transmitted hepatitis viruses. The policy adopted in Scotland was as set out in the 14th December 1984 UKHCDO Circular by Professor Bloom.

8. **With respect to non-A non-B hepatitis safety there was no concentrate for treating haemophilia A available in the UK which was reported to be substantially 'hepatitis-reduced' until mid 1986.**

9. **Risks/benefits of cryoprecipitate.**

**Cryoprecipitate was a non-heated product, prepared from individual donors, which could transmit HIV and hepatitis viruses.** Once the lifetime patient exposure to cryoprecipitate reached approximately 100 donors (about 5 infusions in an adult) the risk of non-A non-B hepatitis approached 100%.

Until October 1985, donors were not tested for anti-HIV. After this date there was uncertainty about its efficacy to exclude all donations infectious for HIV. This was because there was uncertainty about the sensitivity of the anti-HIV test to detect all antibody positive donations. Furthermore there were potentially donors, recently infected with HIV, who were viraemic, but in whom the anti-HIV antibody had not yet arisen, and whose donation would therefore be infectious but would not be detected by the anti-HIV test. This is the so called 'window period' and can last up to about 6 months after primary infection with HIV. Later techniques were developed to detect HIV in the 'window period', in the absence of antibody, (NAT (nucleic acid testing) and these are now in current use for screening donations).

During the period 1984-1987, if only a single, or very occasional, treatment with a blood product was required, it could be argued that cryoprecipitate was safer, with respect to non-A non-B hepatitis, than heat-treated NHS concentrate. The disadvantage of cryoprecipitate, however, was that it was not heat-treated and therefore could transmit HIV.

10. **The number of patients not infected with non-A non-B hepatitis virus(es) and requiring treatment in the period December 1984 to May 1987 was very small** (in Scotland during this period it might be as few as 10 individuals or less). It comprised of new patients (mainly small children) with severe/moderate haemophilia A and an occasional adult with mild haemophilia or vWD.

11. **Therapeutic options, for the small group of patients with haemophilia A and vWD who were probably not infected by non-A non-B virus(es), to reduce the risk of non-A non-B hepatitis when patients presented with a bleed or required surgery were:**

a. **Children with severe/moderate haemophilia A were treated with cryoprecipitate or heat-treated factor VIII concentrate.** This group would require relatively frequent therapy. Concentrate had the advantage of being heat-treated and less likely to transmit HIV, whereas it was very likely to be infectious for hepatitis. Cryoprecipitate might expose the patient to a lower risk of hepatitis, depending upon the amount of donor exposure, in the short term, but there was the potential risk of HIV transmission (as it was an unheated product).

b. **For those with mild haemophilia and vWD the options were**

   i. **To manage without the use of a blood product**. If the bleed did not settle, however, much greater amounts of treatment were usually required later and the patient may well have sustained greater anatomical damage as a result of the delay. Prompt treatment with a single infusion of a factor VIII containing product for an early bleed usually stops haemorrhage.

   ii. **To use DDAVP where possible for the treatment of mild haemophilia A and vWD.** Not all patients, however, responded equally and predictably to DDAVP and it was therefore essential to demonstrate its efficacy in each individual patient by giving an elective test dose, prior to it being used therapeutically.

   DDAVP is usually reserved for treatment of a minor bleed requiring at most one or two doses. Repeated dosing is followed by a diminishing rise in factor VIII/vWF level, due to exhaustion of intracellular stores (tachyphylaxis). DDAVP has a prolonged action on the kidney, which lasts up to about 24 hours, inhibiting water excretion. With repeated doses water accumulates leading to electrolyte and osmotic imbalance in the blood which can have severe consequences.

It should be noted that DDAVP is contraindicated in small children (who are very liable to have fits in response to water retention leading to cerebral oedema), in individuals with symptomatic arterial disease, e.g. angina, and in older individuals who may have clinically silent arterial disease. In these latter two groups there is a risk of myocardial infarction, stroke or other serious arterial occlusion due to the rise in vWF level.

iii. **To use cryoprecipitate occasionally for treatment of haemophilia A when it was anticipated that only a single infusion (or very small number of infusions) would be necessary.** This might occur in patients with low levels of factor VIII in whom DDAVP would be ineffective or was contra-indicated.

iv. **To use heat-treated factor VIII concentrate**

1. Prior to August 1986, NY 68 degree/24 hour would have been used to treat a major bleed. This is likely to have transmitted non-A non-B hepatitis but not HIV.
2. After August 1986, 8Y 80 degree/72 hour was available for virally naive patients presenting with a major bleed. BPL generously responded to my request for a small supply for use in Scotland. When this initial stock was used up a further supply was obtained from Newcastle Haemophilia Centre.

12. **For those with haemophilia B the recommended therapeutic options were fresh frozen plasma or un-heat-treated NHS factor IX concentrate until October 1985 and 80 degree/72 hour concentrate thereafter.** The risk of HIV transmission by unheated NHS factor IX concentrate was much lower than for unheated factor VIII concentrate, but the risk of non-A non-B hepatitis transmission was probably equivalent to unheated factor VIII. During the period December 1984 to October 1985 (when SNBTS heat-treated factor IX concentrate became available) the therapeutic options which were used in Scotland were those set out in the UKHCDO circular of 14th December 1984.

These were to use fresh frozen plasma for 'virgin' patients and those with mild haemophilia B and to use NHS concentrate for those with moderate and severe haemophilia.

**Question Three**

'Were any of the "hepatitis-safe" Factor VIII products supplied to England made available to Scotland prior to May 1987?'

**13.** There was no concentrate of known proven hepatitis safety available prior to May 1987 in Scotland or elsewhere in the UK. There was emerging evidence that 8Y at 80 degrees/72 hours was possibly 'hepatitis reduced'. This potentially reduced hepatitis risk was conveyed in a paper to UKHCDO at its AGM by Dr Jim Smith in September 1986. At my request Scotland had acquired a small supply of 8Y in August 1986 from BPL. A further supply was subsequently obtained from the Newcastle Haemophilia Centre.

All patients with Haemophilia B in Scotland, after October 1985, were treated with the SNBTS factor IX concentrate heated at 80 degrees/72 hours. Subsequently this was demonstrated not to transmit non-A non-B hepatitis virus(es). I believe some of this product may have been made available by SNBTS to patients in England who were susceptible to hepatitis.

**Question Four**

'When the new products became available (Factor IX in October 1985 and Factor VIII in May 1987) what steps, if any, were taken to recall existing stocks?'

**14.** In October 1985 non-heated stocks of factor IX concentrate were recalled and withdrawn from stores and patients' homes and replaced with the 80 degree/72 hour concentrate.

My understanding is that in April 1987 the stock of 68 degree/24hour factor VIII concentrate became exhausted and was replaced with 75 degree/72 hour concentrate (of which only a small amount was manufactured) which was again replaced with the 80 degree/72 hour concentrate in May 1987.

.....CMR..... .....26/9/11.....

Signed Date