STATEMENT BY PROFESSOR G F SAVIDGE FOR THE INDEPENDENT PUBLIC INQUIRY INTO CONTAMINATED BLOOD AND BLOOD PRODUCTS

My full name is Geoffrey Francis Savidge, and I was until my retirement in September 2006 Haemophilia Reference Centre Director and Professor of Coagulation Medicine (King's College, London) at St Thomas' Hospital, from 18th September 1979. By training I am a physician and medical scientist rather than a conventional haematologist. I am a graduate of the University of Cambridge, have specialist accreditation in medicine and clinical chemistry, and have been awarded higher research degrees through thesis and dissertation at the internationally renowned Institute of Coagulation Research within the Faculty of Biochemistry at the Karolinska Institute in Stockholm, Sweden.

In the preparation of this statement I have used the following sources of information:-

1. available medical and scientific literature between 1979 and 1986 on haemophilia, AIDS and nonA-nonB hepatitis (Hepatitis C) that any competent haematologist should have been familiar with or have been referred to on expert recommendation. Some literature on nonA-nonB hepatitis prior to 1979 and after 1986 has been assessed, but documents and views on these subjects after 1986 have been excluded to eliminate bias associated with wisdom after the event.
2. proceedings/minutes of medical, scientific and strategic advisory groups that were relevant during the appropriate period, and recommended, but not necessarily documented, clinical practice protocols used to manage patients at that time.
3. documents prepared as part of the Defence in the Haemophilia Class Action, and expert witness documents prepared for the Court on behalf of the Claimants for the HIV and Hepatitis C medical negligence cases in the High Court.
4. as a UK trial coordinator/senior UK member from 1981 until 1985 in 2 international clinical trial groups assessing the safety and efficacy of US heat treated factor VIII concentrates, information was obtained from trial documents and discussions subject to the trial sponsors approval.

For the sake of brevity and clarity, I would like to address the situation relating to diverse aspects of haemophilia management in relation to contaminated products prior to 1979 and subsequently between 1979 and 1986.

1. Following the World Health assembly 1975 regarding the acquisition of individual European State self sufficiency of blood and blood products from non-remunerated voluntary donors and its intended implementation in the UK, any level of implementation or even planning seems to have been unequivocally delayed, possibly in part due to anticipated difficulties in restructuring and increasing funding of the Blood Transfusion Service. Additionally in 1979 and 1981, even on inspection, BPL was considered to be antiquated, exhibited poor manufacturing practices leading to excessive product recalls and QA failures, yet remarkably retaining through notionally cost neutral concepts (pro rata return of fractionated Factor VIII, IX and albumin to the BTS for its plasma and cryoprecipitate) some 50-60% of the coagulation factor market in the UK with a product known to be 100% contaminated with non-A non-B hepatitis (HCV).

2. In conjunction with all these changes, there was a concerted effort from leading haemophilia physicians and from the Haemophilia Society to increase the individual patient consumption of factor VIII, in particular to initiate self infusion home treatment policies and prophylactic treatment regimens particularly in children. These changes were considered to be of priority as the UK had been known for many years of all the developed countries in EU and in the US to offer remarkably low levels of factor replacement for the general management of patients. Such 'false economy' resulted in extensive long terms problems, with associated joint and muscle disease that was considered to be an excellent example of poor cost benefit. The funding of such projected increased expenditure on product would require central support, that was only forthcoming through the RHAs funding for the allocation to all DGHs to disperse to each and every discipline to fund ongoing service and proposed development. Consequently little money if any reached hospitals treating haemophilia patients with the proposed requirement for

additional replacement therapy, and further reliance of any increased product supply was demanded of an inert Blood Transfusion Service and a terminally failing BPL fractionation facility. Thus extra money when found was spent on the purchase of commercial imported factor VIII concentrate, usually from the US, in preference to the safer cryoprecipitate that was the recommend treatment of children and mild haemophilia patients (assuming failure with DDAVP) generally available (in some regions in excess). The US commercial concentrate was considered to be more user friendly, it could be stored at room temperature and was eminently more suitable for patients on home care programmes.

3. National organisation of haemophilia care through the UKHCDO (United Kingdom Haemophilia Directors Organisation) was started in the late 60s in order to collect data nationally on haemophilia patients including demography and blood product treatment. The functions of the national organisation were documented in HC (76)4 as a 3 tier structure. The UKHCDO was essentially an unincorporated association of interested haemophilia physicians from the largest and most influential centres in the UK making up the executive committee that functioned as an *ad hoc* advisory group. The group was small and made up of centre directors from London (Royal Free and St Thomas'), Scotland (Edinburgh and Glasgow), Belfast, Cardiff, Manchester, Newcastle, Sheffield and Oxford. The general body of the UKHCDO was made up of about 100 smaller centres, usually run as part of general haematology departments. During the early 1990s, the UKHCDO was 'regionalised' following the publication of HSG (93)30 and incorporated a large number of smaller centres into the executive committee. The UKHCDO had no formal affiliation with the NHS through the DOH, any Royal College or learned society (eg: BSH) and functioned as an isolated and autonomous advisory body with its own self appointed working parties, essentially to its own members. On a few occasions the DOH required some national haemophilia statistics or treatment projections. Views and opinions involving observations of important health issues in haemophilia patients from members of the executive committee were relayed by informal

delegation through the Chairman (or occasionally vice-chairman) usually to those committees (eg DOH, CSM, CBLA, National Blood Transfusion Organisations, etc) where actual decisions on haemophilia management, blood product production and funding etc would be taken and implemented. Little if any information was reported back on what the chairman actually discussed at these numerous committees although in several matters eg: blood product projected usage, no heed was taken of the UKHCDO data, and deliberations of these committees involving information from the UKHCDO and their decisions were not fed back in a cogent form either to the executive or to the full body of members of the UKHCDO.

4. It was very clear from research undertaken in the UK and elsewhere on adults and children with haemophilia that large donor pool factor VIII concentrate made from domestic UK plasma was similarly infected with that agent causing nonA-nonB hepatitis as all other large donor pool factor VIII concentrates from other plasma sources. Single treatment exposure to such materials in many cases led to the development of chronic liver disease that in several individuals would have a fatal outcome. International recommendations were made recommending cleaner factor VIII concentrates, the use of the recently licensed vasopressin analogue DDAVP in certain cases of haemophilia to prevent hepatitis transmission, and more widespread use of single donor cryoprecipitate for the management of children and mildly affected patients with haemophilia. This information was ignored or not considered to be of sufficient priority in the decision to continue to permit BPL, with its 50-60% market share, to manufacture large donor pool factor VIII concentrate with substantially poor manufacturing practices (see inspection reports) and without formal licences (Crown Immunity exempting BPL from the stringent safety requirements of the Medicines Act 1968). Additionally, although ample supplies of cryoprecipitate were available (UKHCDO minutes p10 17.10.83, and deliberations of the Working party on the treatment of haemophiliacs by the W Midland RHA during 1981-1982) these were not used since a reduced return on BPL product was expected due to alterations at BPL in May 1982. Addiitionally, the regional treating doctors in the W Midlands advocated US commercial Factor VIII in preference to cryoprecipitate,

although some slight compromise was reached (06,12,82) Imported commercial factor VIII concentrates were considered to be less safe than the BPL product solely on the grounds of perceived and unproven lower infectivity (slightly fewer donors samples in the final pools for fractionation), and this must have been common knowledge to all treaters of haemophilia patients at that time. Unlike BPL, the majority of commercial blood product manufacturers and even some fractionation facilities in France (CRTS as a state facility) for some years had been developing factor VIII concentrates treated with pasteurisation, dry heat, organic solvents etc to render them free from potentially infective agents (eg viruses) responsible for known disorders transmissible by blood products (at that time HBV, HAV, CMV and non-A non-B hepatitis HCV), and that these newer products would, on the balance of probability reduce the morbidity and mortality among haemophilia patients worldwide. It is unclear as to why no efforts were made to advise BPL on the urgency and the necessity to produce safer products, but from my recollections of the discussions at the UKHCDO there seemed to be little positive interest to propose altering the status quo of BPL or even the Blood Transfusion Service to consider more extensive screening of donors, contemplating improved fractionation practices, or R & D liaison with other manufacturers even for contract fractionation purposes if the products proved to be safe and efficacious. The overwhelming body of world medical, scientific and patient opinion at this time was to introduce steps to tighten donor selection of plasma and to produce inactivated and safer factor VIII and IX concentrates. It was on this basis that I chose to discuss with my patients the possible advantages of clinical trials of heat inactivated products available at the time following reports from Behring's trial in Europe in 32-34 patients treated for 2 years with pasteurised Factor VIII concentrates without biochemical evidence of non-A non_B hepatitis (first heat treated full product licensed in UK min August1984 probably after submission in early 1983 and data published in Lancet 1986). Heat treated trials started at St Thomas' Hospital with Hemofil T produced by Baxter in 1982 and with Alphanate HT (heptane treated) in 1983/1984. The enrolment of patients into these hepatitis trials was not considered to be consistent with UKHDCO policy and members were warned against adopting a similar unilateral approach to these

issues. This was hardly remarkable since several of the senior members or the UKHCO (and certainly the Chairman) had been involved in discussions with Behring as early as 1981 when data from their trial had been revealed formally, possibly with the object of securing clinical trial subjects or even for contract fractionation arrangements with BPL. The outcome of these meetings was not reported to the UKHCDO but clearly Behring was not invited back!

5. Under the leadership of Dr Craske who was in charge initially of the Hepatitis Working Party and subsequently the AIDS Working Party, initially a waiting brief was introduced and throughout 1981 through to July 1982 AIDS related disorders were reported exclusively among homosexual men in the US. However in July 1982 (MMWR 31; (27) 365, 3 haemophilia patients were reported to have similar immune dysfunctions as in homosexuals with Pneumocystis implying the possible agent for AIDS could be transmitted by blood products. During the latter part of 1982 much attention was paid to intra venous drug abusers who had contracted AIDS and in November 1982 (03,10,82) the Medical and Scientific Council (MASAC) of the US Haemophilia Foundation deliberated in written form the proposal to exclude high risk donors from blood donation. This recommendation was followed in the press (LA Times v section 1 p3 18.01.83, a haemophilia unit was cautioned NY Times v 132 p10 19.01.83 and further MASAC recommendations including cryoprecipitate in all children under 4 years of age and in newly identified previously untreated patients and in clinically mild and infrequently treated patients. The expanded use of DDAVP (American Medical News 04.02.83) was also recommended and that all surgical procedures in haemophilia patients should be reassessed with respect to risks of infection from concentrates and whether such surgery could be delayed. No such recommendations were made by the UKHCDO until June 1983, although cryprecipitate had been in surplus for some years and BPL was showing its usual predictably low output of concentrate. US Health Officials recommended the introduction of surrogate testing in blood donors and exclusion of high risk groups (February 1983). It was quite clear by late 1982 that there was concern that high risk donors were infecting the large plasma pools used to fractionate concentrates and

voluntary exclusion of donors was recommended. Additionally commercial companies were introducing surrogate tests to exclude contamination from further donor groups, and were expediting their production of heat treated products, although originally intended for hepatitis, were considered to be a possible approach to eliminating a possible viral infectious cause of AIDS. These developments led to Inter agency recommendations for blood collection agencies published to prevent AIDS (HHS news 04.03.83 and FDA 24.03.83). During 1983 there was a plethora of reports in the literature on Haemophilia and various aspects of AIDS and immune suppression. The Lancet confusing the issue considerably, clearly to the benefit of the reactive UK haemophilia treaters, by comparing the apparent favourable AIDS incidence in patients receiving products made from either domestic plasma or from US imported products made from plasma collected in 1981, with the incidence when product made in 1983 was reportedly given. The authors of these articles and editorial in the Lancet were believers in the perceived lower infectivity of the BLP product and represented the UKHCDO on a number of influential committees. In May 1983, however key reports appeared. The Lancet, i, 956 reported an infant with Rhesus disease developed an AIDS related opportunistic infection after receiving blood from a donor who died of AIDS 17 months after donation. This illustrates that AIDS is a transmissible agent in the transfused blood that was not another identifiable virus. Barre-Sinoussi reported in Science, 220, 868 that retrovirus cultured from patients with pre AIDS PGL grew in CD4 cells for 7 days producing a cytopathic effect on healthy lymphocytes, and the presence of reverse transcriptase would indicate a heat sensitive retrovirus (HTLV III, LAV and finally HIV 1) was responsible for AIDS. These sources of information were available a considerable time prior to publication that led in February in the US to conclude that heat treated factor VIII from homosexual excluded donors would be available first in March/April 1983. In fact the FDA issued full licenses to these heat treated products in late 1983/early 1984 on the basis of the previous years epidemiological results and scientific data probably dating back to 1982. At this time and with increasing reports of AIDS antibody negativity associated with heat treated product therapy, one can question why such extensive delays

were incurring in the UK to license these products and recommend abandonment of untreated sources of factor VIII concentrates that continued to use inadequately screened donor plasma fractionated by a facility known to be of poor quality and productivity yet continued to enjoy with its contaminated untreated product some 60 % of the UK market.

6. During the years 1983 to 1985, the UKHCDO received little if any information concerning haemophilia treatment from the representative Professor Bloom regarding information from other more influential committees, but recommended in December 1984, some 14 months after the US recommendations on cryoprecipitate and 3 months after MASAC declared the overall use of heat treated products for haemophilia, that heat treated factor VIII concentrate should be used, with the caveat that NHS untreated product would be the second choice if treated products were unavailable. This could be hardly termed expedient and to some extent preserved the political and financial future of BPL. This recommendation had in all likelihood been cleared through all the committees before announcement, probably to ensure that the caveat was included. The fact that the DOH had granted full licenses to heat inactivated products as early as August 1984 may have influenced the decision, although BPL continued to produce untreated products under Crown Immunity. It was not until June 1985 that Professor Bloom on behalf of the UKHCDO (BMJ, 290, 1985) recommended the use of heat treated factor VIII concentrated instead of BPL factor VIII and cryoprecipitate. This decision was probably taken with the knowledge that BPL had an interim heat treated product for use under Crown Immunity and also were researching into a definitive heat treated Factor VIII concentrate with the help of the SNBTS that had itself produced a heat treated factor VIII far earlier.

SUMMARY

From the events prior to 1979 and between the years 1979 – 1986, decisions regarding blood products for the management of haemophilia were in my view prioritised by the financial and political considerations of the Blood Transfusion Services and by the BPL plasma fractionation facility. In terms of factors of relevance to the failure of the Blood Transfusion Services and BPL in effecting self sufficiency and eliminating plasma product contamination, one must attribute the failures to poor leadership relying on the assumed safety of BPLs products and reluctance to endorse intensive research into treat inactivated products, and inferior reactive management to restructure the Blood Transfusion Service to introduce greater safety aspects with donor selection and improved productivity and efficiency to achieve self sufficiency. Central financial considerations determined by general health care political motives, in my view, led to the eventual lack of political will to spearhead these essential changes that were quite evident by 1978 for hepatitis and 1982 for HIV which for the experts in the field felt assured that a potential public health catastrophe was beginning to unfold.

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