TRIBUNAL OF INQUIRY INTO INFECTION WITH HIV AND HEPATITIS C OF PERSONS WITH HAEMOPHILIA AND RELATED MATTERS

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STATEMENT OF DR TERENCE SNAPE

I, Terence Joseph Snape of GRO-C Herts, GRO-C England will say as follows:

Qualifications and Experience

1. My curriculum vitae is contained in appendix 1 to this statement. I hold a degree in Chemistry from the University of Oxford (1970) and a PhD in Non-Clinical Medicine from the University of London (1982). My PhD thesis was entitled "The Development of a System for the Control of Coagulation Factor Concentrates for Clinical Use". I have worked since 1970 in the development, manufacture and quality control of human plasma products. I am currently employed as Technical Director of Bio Products Laboratory ("BPL"), with responsibility for quality assurance and regulatory affairs.

2. I am currently a member of the British Pharmacopoeia Committee H (Biologicals). I am also the UK expert representative on the European Pharmacopoeia Group 6B (Blood Products). I have served on a range of standing advisory committees to the UK Health Departments, including a period as a member of the Biologicals Sub-Committee of the UK Committee on Safety of Medicines. I am currently appointed to the UK Health Departments' advisory committee on Microbiological Safety of Blood & Tissues ("MSBT"). In recent years my professional interests have focused on the scientific, technical and regulatory interactions necessary for the manufacture of virus safe blood derivatives and the establishment and maintenance of a blood plasma supply infrastructure to support such manufacture.

My work at Plasma Fractionation Laboratory ("PFL") and at BPL

3. In August 1970 I commenced work as scientist in charge of production at PFL in Oxford. I worked at PFL until January 1982, when I transferred to BPL at Elstree.

4. PFL was situated within the Oxford Haemophilia Centre, in the Churchill Hospital at Oxford, affording a close working relationship with what was then the doyen UK haemophilia centre. PFL was the pilot plant for BPL, undertaking processing on reduced scale (perhaps one tenth of full scale) as an aid to process development. PFL fractionated plasma for BPL from 1968 to its closure in 1992. It was administratively part of BPL.

5. BPL was originally known as "Blood Products Laboratory" but changed its name to its present title in April 1990. BPL was set up in 1954 as part of the Lister Institute of Preventive Medicine, to manufacture blood products for the National Health Service ("NHS") in England and Wales. It is now administered by the National Blood Authority ("NBA"), as an operational unit of the National Blood Service ("NBS") in England, which is part of the NHS.

6. In 1975 I became the scientist responsible for quality control at PFL and from September 1981 to January 1982 was acting head of PFL in a temporary capacity, responsible to the then Director of BPL (Dr Richard Lane) for all operations at PFL. In January 1982 I moved to BPL, where my responsibilities included quality assurance and control on both the Elstree and Oxford sites. PFL closed in March 1992, with all of its functions, and most of its staff, transferring to BPL.

Production of Coagulation Factor Concentrates in England and Wales

7. BPL and PFL produced Factor VIII concentrate from about 1968. Initially, the process used was a method developed in Sweden by Blombäck (1958). We worked with plasma batch sizes of up to 70 litres, recovering albumin and immunoglobulins as well as Factor VIII. PFL also manufactured Factor IX concentrates, from its own plasma, and from an intermediate fraction transported to Oxford from Elstree. No Factor IX was produced on site at Elstree until 1976, when the process was transferred from Oxford. The Factor VIII produced using the Blombäck technology was not very pure – most of the protein in the final product was fibrinogen, which made it difficult to dissolve. Because of this, and because the volume to be injected for a therapeutic dose was quite large (greater than 100ml), the product was unsuitable for home therapy and was always administered in the haemophilia centre.

8. By 1974 BPL and PFL had switched from the "Blombäck" process for factor VIII manufacture to a process developed in New York by Johnson (Newman et al 1971). For ten years after that, Factor VIII was produced at both laboratories using the "Johnson"

method of production. The key to the success of the Johnson method was separation of cryoprecipitate from the plasma (leaving much of the fibrinogen still in the plasma). The cryoprecipitate, which contained up to 80% of the factor VIII in the original plasma, was then treated to recover the factor VIII in a freeze-dried concentrate. The resulting factor VIII concentrate was much easier to dissolve and contained more units of factor VIII per ml ("potency"), making home therapy possible. This improved solubility, together with increased potency and higher "yield" of factor VIII, were the main benefits of the Johnson process over the original Blombäck process (which made use of ethanol precipitation, rather than cryoprecipitation, to recover the factor VIII from plasma). The "yield" for such a process (usually expressed in units/kg) is a measure of how many units of the coagulation factor can be made available to the patient from a given weight of plasma.

9. By 1975 the plasma pool sizes at BPL had increased to 160 litres (less than 1000 donations) - which was still extremely small by commercial standards, where pools of 1,000 litres would have been the norm. The batch size (number of vials of concentrate per batch) was correspondingly small and, because of the unavoidable requirement to take significant numbers of vials from each batch for testing, yield was lower than if larger batches were processed. This focus on batch size (more importantly, on the number of individual plasma donations contributing to the start pool) was not unreasonable at a time when virus inactivation techniques were not applied (they were not available) and the inclusion of an infected donation in a pool meant potential product infectivity. By the early 1980s, batch sizes had increased, but plasma was still pooled from donations from fewer than 5000 donors for the manufacture of BPL Factor VIII (or Factor IX). Indeed, donor pool size would have been smaller, except that most plasma fractionated by BPL was recovered plasma (recovered plasma donations are smaller than donations obtained by plasmapheresis, <250ml compared with ~800ml, and donors are bled less frequently so that most fractionation pools would only ever contain one donation from a given donor). In the 1990s, when the effectiveness of in process virus inactivation had been demonstrated, pool sizes used by main-stream fractionators increased, almost without limit. The implications of donor pool size for product safety are considered again under the heading **"Virus Safety considerations in the manufacture of Fractionated Plasma Products"** below.

10. Prior to 1998 (and the concern for the theoretical risk of variant Creutfeldt-Jakob disease – "vCJD"), BPL used only plasma from volunteer, unpaid, donors for the production of

plasma fractions. This plasma was supplied from collection centres of the NBS in England and Wales. BPL was not directly involved in donor recruitment and plasma collection – though, as part of the NBS in England, we were able to influence the quality systems employed and contribute to improving the quality of donor plasma. From May 1998, the Secretary of State for Health authorised the purchase of non-UK plasma by UK fractionators and, since September 1998, clotting factors manufactured by BPL have been manufactured exclusively from US paid-donor plasma (collected by plasmapheresis).

11. During 1985, with development focus on elimination of virus risk, BPL introduced a new factor VIII concentrate (type 8Y) and a new factor IX concentrate (type 9A) These products were heat treated in the freeze-dried state (at 80°C for 72 hours) to inactivate hepatitis and AIDS viruses – the method remains to this day the single most effective established dry heat process for virus inactivation. The development programme is described in greater detail below, under the heading "**Viral Inactivation of Coagulation Factor Concentrates – Heat Treatment"**. Table 1 lists the factor VIII and factor IX products manufactured by BPL (and PFL) to date.

Virus Safety considerations in the manufacture of Fractionated Plasma Products

12. Plasma fractionators have always been aware of the potential for transmission of blood-borne virus infectious agents by products manufactured from human blood plasma, and have sought to implement strategies which would mitigate this risk. It is possible (with benefit of hindsight) to make some general comments in this regard:

    a. The most effective strategies have always proven to be those based on several combined elements (donor selection, donation testing, appropriate processing including virus inactivation); in comparison, strategies based on a single contributing effect proved very vulnerable.

    b. The strategy elements available to the fractionator in this year 2000 include:

        i. Donor selection to exclude donors in identified risk groups

        ii. Testing for virus markers and genomic material of known viruses

        iii. Plasma inventory hold based on knowledge of "window period" (the period of time which may elapse between a donor being infected and that infection being recognisable by available tests)

iv. Look-back, tracing and donation exclusion, on the basis of post-donation information

v. Virus inactivation targeting known blood-borne viruses

vi. Process segregation down-stream of virus inactivation (to avoid re-infecting the product)

(Only the first of these – knowledge of donor risk factors and the ability to exclude donors accordingly – was available in the 1980s.)

c. In the 1980s, the relative risk associated with plasma products differed with product type – the risk associated with clotting factor concentrates (which typically could not be subjected to any effective virus inactivation) was greater than that associated with immunoglobulin preparations (for reasons that could not be fully explained at the time) and for albumin preparations (reflecting deliberate inclusion of a virus inactivation step – pasteurisation)

d. There is no single "magic bullet" – no virus inactivation mechanism universally applicable to all plasma products and effective against all viruses. A virus inactivation procedure developed and applied to one product by a given manufacture will not necessarily translate to another product/manufacturer.

e. The most powerful combined strategy can be defeated if good manufacturing practice ("GMP") is not observed (for example if product already subjected to virus inactivation is re-infected in later processing, or if the virus inactivation process itself is performed incorrectly – perhaps by inadequate control of temperature or time).

13. It was widely recognised by fractionators in the 1970s that Factor VIII and Factor IX concentrates were capable of transmitting, and did indeed transmit, infection. In England and Wales, the requirement to bleed only volunteer, unpaid, donors has always limited the number of "risk" donors entering the system. Implementation of donor testing for hepatitis B, from the early 1970s, specifically reduced the risks of transmission of this infection. Even with these measures in place, it was known from the middle of that decade that treatment with coagulation factor concentrates was associated with a significant risk of infection with non A non B hepatitis ("NANBH"), and a small residual risk of transmitting hepatitis B ("HBV"). The risk of NANBH infection was high because

the background incidence of the infective agent in the donor population was sufficient to guarantee that, even with the relatively small pools used in the UK in the 1970s, most pools would include one or more NANBH infected donations. There was of course no means of testing for NANBH until the late 1980s – indeed no single virus had been identified as the cause of the infection.

14. I recall that, by 1982, Craske had shown the incidence of overt NANBH after treatment with coagulation factors, to be 4-20 times greater with US commercial concentrates than with NHS (BPL/PFL and PFC) concentrates. At the time, this was attributed to reduced virus burden in the NHS product. A study in 1984 by Kernoff showed that almost 100% of haemophiliacs treated only with NHS concentrates showed evidence of NANBH.

15. I also recall that, by 1982, donor screening appeared to have eliminated any difference between NHS and US commercial concentrates in respect of hepatitis B transmission. The Merck, Sharp & Dohme (MSD) hepatitis B vaccine was licensed in the UK in May 1982 and became available in the autumn of that year. These factors combined to make hepatitis B transmission by coagulation factor concentrates quite unusual after 1982, though it still occurred.

16. Since the 1970s it has been argued (and largely accepted) that increased pool size and the use of paid donations carry greater risk of infection than the use of small pools from voluntary unpaid donations. The protection afforded by the use of unpaid donations is directly translated to recipients of single donor products (unless the recipient is unfortunate enough to be treated with the one, unrecognised, infective donation) but greatly diminished when donations from many donors, even voluntary unpaid donors, are mixed and used in one pool to produce coagulation factors. In the absence of reliable screening tests (and there were none for NANBH in the early/mid 1980s) the larger the donor pool size, the greater the risk of unwittingly including an infective donation. Since pools had to be above a certain size for cost-effective production of the amounts of concentrate demanded for treatment of affected individuals, the risk of NANBH infection was significant. Any risks associated with increased donor pool size, or donor selection issues implicit in the use of paid donor plasma, were most significant for coagulation factor concentrates, which enjoyed neither the protection afforded by presence of neutralising antibodies (immunoglobulins), nor the benefit of in-process virus inactivation, either deliberate (albumin) or serendipitous (immunoglobulins).

17. Prior to the advent of effective virus inactivation methods, there was therefore a significant risk of infectivity from all coagulation factor concentrates made from pooled plasma (including those products made by BPL). The incidence of infection would have been determined by the amount of virus in the product being administered. There was a consensus view (in the UK at least) that coagulation factor concentrates made from unpaid (UK) donors carried a lower virus burden than those made from donations from paid (US) donors. Certainly, US fractionation pools were much larger (up to 20,000 donations used in a plasma pool), but more important was the failure, at the time, of the paid donor system to exclude donors with a life-style risk. In January 1982 BPL increased maximum donor pool size to 7500 donations.

Viral Inactivation of Coagulation Factor Concentrates – Heat Treatment

18. There are basically two approaches to heat treatment:

    a. Heating in aqueous solution ("pasteurisation"), typically to 60°C, for up to 10 hours, in the presence of appropriate stabilisers to avoid denaturing protein;

    b. Heating a freeze-dried product (dry heat treatment) – most successfully at 80°C, for up to 72 hours, with control of product moisture content to guarantee effectiveness.

19. It is also important to distinguish between:

    a. Application of heat to the finished product, in its final container (in which case the virally inactivated product is "secure");

    b. Application of heat to a bulk intermediate (in which case down-stream processing must be secure from any other activity that might reinfect the product).

20. A heat treatment process (pasteurisation – heating of the solution at 60°C) was developed and applied to albumin products in the USA in the 1950s, and has been used for albumin products by all fractionators since that time. In this regard, albumin was considered by fractionators to be special, added stabilisers allowing it to withstand heating to a significant degree. (For quite different reasons, immunoglobulin preparations also appeared to enjoy substantial freedom from virus risk – explicable in large part on the basis of their content of protective antibody and by some aspects of the methods used to produce them).

21. Prior to the 1980s, coagulation factor concentrates enjoyed no such freedom from risk and transmission of virus infection is well recorded. Factor VIII activity was known to be highly sensitive to heat and the concept of heating to inactivate hepatitis virus(es) only developed in the late 1970s. It was assumed that heat-treatment of coagulation factor concentrates would denature the active principle (factor VIII or factor IX), rendering the products ineffective – or at least so affecting yield as to make the process untenable. Important considerations were the potential for heating to promote the generation of unwanted antigenic material (which might elicit allergic or inhibitory responses in the patient) or to generate activated clotting factors capable of inducing fatal thromboembolism.

22. Under these circumstances, consideration was given to stabilisers which, when added to the production process, would protect the active protein(s), preventing denaturation whilst at the same time not affecting the hoped for viral inactivation effect of the heat. In 1980 Behringwerke, a German manufacturer, developed a Factor VIII product which was wet heated in a solution of stabilisers at 60°C for 10 hours. Behringwerke secured a US patent for the process (1981). It was acknowledged that the yield for the process was extremely low as a direct consequence of inclusion of the wet heat treatment step, even in the presence of stabilisers.

23. The amounts of coagulation factor concentrates required for use in the UK increased year on year. In this context, the supply of plasma from unpaid British donors, and the facilities at BPL, were potentially limiting (redressed by 1988, with commissioning of the new manufacturing unit at BPL). It was therefore always important to strike a balance between process yield (to meet the demand for concentrates) and expectations of reduced risk of virus transmission. Since there was no reliable, available, method of determining the extent of reduction in NANBH infectivity conferred by any development, judgements involved a measure of pragmatism. I recall that, at the time, the Behringwerke development was not regarded by us as a practicable option.

24. In August 1982 we became aware of a report presented to the Budapest meeting of the International Society of Blood Transfusion ("ISBT") by a US worker (Rubinstein), in which it was claimed that up to 50% of the factor VIII in a freeze dried concentrate survived heating at 80°C for 10 hours. Unfortunately, after heating, the product was insufficiently soluble to allow clinical use! Dry heating at a lower temperature (60°C) did give clinically acceptable product. I recall that no data was provided on effectiveness

of virus inactivation. The work was the subject of an influential patent application in 1983.

25. As a consequence of these two independent observations, the early 1980s saw most fractionators investigating the virus inactivation potential of different heat treatment regimens on their processes for manufacturing factor VIII and (as second priority) factor IX concentrates. Prior to the first report of AIDS in a haemophiliac in July 1982, the objective was to inactivate hepatitis viruses – in particular the then unidentified agent responsible for NANBH. Differences between manufacturers' products meant that tolerance of heat varied and different manufacturers arrived at different regimens (60°C/24 hours, 68°C/72 hours).

26. In the absence of accessible and reliable methods for measuring the impact of new processes on infectivity, such studies typically involved exploration of the acceptable limits of " heat abuse" for a given factor VIII formulation. Some manufacturers (a few, from USA) had access to chimpanzee infectivity studies, providing indicative evidence of the effectiveness of virus inactivation. These products continued to be associated with transmission of NANBH, indicating that none were virus-safe and casting doubt on the value of the chimpanzee studies for this purpose at least. Most manufacturers were restricted to establishing the most extreme conditions consistent with retaining acceptable product characteristics (potency/yield, solubility, appearance, freedom from measurable degradation of protein and, in the case of prothrombin complex concentrates, freedom from thrombogenic potential). Assessment of effectiveness of the virus inactivation step would come as much from clinical follow-up as from prospective study. To this end, in 1984, a protocol was drawn up under the auspices of the International Committee on Haemostasis and Thrombosis ("ICTH") for such clinical follow-up studies. This protocol defined the number of batches (10), the number of patients (20) and a test regimen over a 6 month follow-up period.

27. In this period, and up to mid-1984, we investigated both wet heat (pasteurisation – studies coded 8H) and dry heat (studies coded 8Y). We worked in collaboration with the Protein Fractionation Centre ("PFC") of the Blood Transfusion Service in Edinburgh, Scotland. We also followed the work of other fractionators, and discussed these developments with haemophilia treaters in England.

28. In July 1982 the first report of AIDS related symptoms associated with a haemophiliac was published and of course fractionators, like haemophilia treaters, were very concerned about whether the causative agent of AIDS could be transmitted through factor concentrates. Of course, until the causative agent had been identified and characterised, it was not possible to conclude that heat treatment of concentrates would help to prevent transmission of AIDS to haemophiliacs.

29. I recall the announcements by Hyland/Travenol and other manufacturers from mid 1983 onwards of methods of dry heat treatment of Factor VIII which it was claimed could reduce the levels of infectious agents in factor concentrates, including NANBH and also possibly the causative agent for AIDS. It was also claimed that these products had minimal side effects and the technologies produced yields that were viable.

30. At this time we, and haemophilia treaters, were closely following the debate about the causative agent of AIDS. There was especially heated debate about the respective safety of heat treated US concentrates (manufactured from US paid-donor plasma) and unheated products (concentrates and cryoprecipitate, manufactured from UK unpaid-donor plasma) which made up two thirds of the product then being used in the UK. Thus, in 1983, BPL supplied 42% of the 70 Million iu factor VIII used in the UK and 100% of the factor IX concentrate. The remaining supply was made up of 37% commercial concentrate and 21% cryoprecipitate.

31. I recall that there was concern that the number of clinical trials would escalate before there was any reasonable expectation that an appropriate heat-treatment regimen had been established. This was also associated with a concern to avoid generation of factor VIII inhibitors as a result of denaturation by heating.

32. In October 1984 we were informed that a donor to a batch of NHS Factor VIII in England had developed AIDS. This batch, manufactured by BPL, had been supplied to a number of haemophilia and transfusion centres and a recall was instituted.

33. We also became aware in late 1984 that a number of patients in Scotland, treated exclusively with Factor VIII from a batch produced by PFC in Edinburgh, using plasma from unpaid donors to the SNBTS, had developed HIV antibodies. The batch had not been heat treated and this incident underlined the importance of moving to a virus inactivated product as soon as possible.

34. By mid 1984, consensus emerged internationally that HTLV III (later described HIV) was the causative agent for AIDS. In October 1984 there was verbal communication (from the US Center for Disease Control, "CDC") that this virus was susceptible to inactivation by heat treatment. These facts led to an intensification of BPL's efforts to establish heat treatment regimens for our factor VIII and factor IX concentrates. This took the form both of progressing already established programmes for development of a new product, "tailored for heat treatment", and of evaluating the impact of heat on our existing products (8CRV, made at Oxford, and HL, made at Elstree).

35. By October 1984 the pilot plant at Oxford (PFL) had established a convincing sub-pilot scale pasteurisation process for factor VIII, with optimisation of the many complex process steps necessary to establish the shift to pilot scale. Unfortunately, yield considerations, and the expectation of difficulties in maintaining downstream process integrity from re-infection if the process were transferred to the ageing manufacturing facility at Elstree, argued against proceeding down this route. Subsequent events proved the emphasis on dry heat-treatment to have been correct but, at the time, there was much regret at the abandonment of a very significant achievement.

36. Between May and October 1984, the activities leading to the establishment of the 8Y process began in earnest – almost as a sideline to the pasteurisation work just described. By August 1984 the basic process had been established. Terminal dry heat treatment and solvent-detergent were identified as possible virus inactivation mechanisms, and were under preliminary evaluation by October 1984. Pilot-scale batches were run in October (50kg) and November (150kg). Product from this second run was used to evaluate a range of dry heat treatment conditions. Heating at 80°C for 72 hours (conditions coded "HT3") was found to be the most severe conditions consistent with an acceptably small yield/quality penalty. Material from this batch, heated at 80°C for 72 hours, was the first clinical trial material released in April 1985. A significant consideration in the choice of dry heat treatment was the fact that virus inactivation in the sealed final container rules out subsequent re-infection of the product.

37. This intense new product development programme was paralleled by evaluation (and clinical supply) of heated variants of the existing factor VIII products. A set of conditions coded "HT1" (60°C for 72 hours) was applied to some batches of product (8CRV) made at PFL, Oxford, but quickly gave way to a modification (coded "HT2", 70°C for 24 hours) applied to both the Oxford (8CRV) and Elstree (HL) factor VIII

concentrates. First issues of HT2-heated factor VIII were made in February 1985; after May 1985 all factor VIII issued by BPL/PFL had been heated under at least HT2 conditions.

38. Neither 8CRV, nor HL, was especially suited to terminal dry heating – they had not been designed with heating in mind, and parameters such as moisture content, protein content, containers sealed under vacuum, were not favourable. We established pragmatic criteria for acceptability after heating (>200iu per vial, soluble within 20 minutes) and undertook trial heat runs on vials from each batch. A modification to the HL formulation, which involved addition of 1% sucrose as a stabiliser, was evaluated and proved useful. This was incorporated into the last series of HL batches made during 1985. We were aware that even this low level of sucrose might protect virus as well as the product, but had no way of confirming this with the time and resources available. (Subsequent studies on 8Y indicated that these concerns were almost certainly unfounded.)

39. After September 1985 all issues of factor VIII were subjected to HT3 heat treatment conditions. The product (coded "8Y") was made at both Oxford and Elstree. The manufacturing conditions established at the time remain essentially unchanged to date.

40. There was no formal recall of unheated factor VIII. The progression from unheated to heated product was a complex continuum, with product in short supply at all times. Some UK haemophilia specialists took the decision to continue to use unheated NHS concentrate, in preference to heated (US) commercial concentrate, until such time as 8Y was readily available. I think it unlikely that any unheated BPL factor VIII concentrates were administered after July 1985.

41. BPL was more cautious in the evaluation of heat treatment on our Factor IX concentrate (the unheated concentrate was coded "9D", the heated product "9A"). Although the programme of work began at the end of 1982, the heated product 9A was only released for clinical trial in selected centres in July 1985, three months after the first trial batches of 8Y. We were especially concerned to rule out the potential for thromboembolic sequelae that might be caused by activated factors produced on heat treatment of the 9D product. Prothrombin complex concentrates in general had a history of association with problems of this sort and we were concerned that the risk might be increased by heating the concentrate. These concerns were allayed by *in vivo* studies in dogs (performed in Edinburgh, in collaboration with SNBTS) to ascertain whether there were such side

effects from the heated product. A protocol for these studies was agreed with PFC in November 1984, and was implemented jointly.

42. As with factor VIII, BPL evaluated both pasteurisation and dry heat options but, perhaps surprisingly, factor IX appeared more susceptible to denaturation by wet heat than factor VIII. Dry heating studies performed in the second half of 1984 established 80°C for 72 hours as the most severe conditions consistent with good recovery of factor IX. A tendency to thrombin formation during heat treatment was recognised, but it was established that addition of antithrombin (also manufactured by PFL) to the formulation prior to drying, countered this effect. The time taken to recognise, and then correct this tendency, contributed to the delay in issuing heated factor IX. Heated factor IX (9A) was first issued in July 1985 (this was a limited clinical trial of safety and efficacy only). All factor IX issued after 2 October 1985 was type 9A, subjected to HT3 heat treatment conditions.

43. During the first nine months of 1985, although heat treated US Factor IX products were available (though perhaps not in sufficient quantity to satisfy all requirements), most treatment centres in the country continued to use the BPL unheated product. I recall that there was general concern that the effects of heat treatment on factor IX were not properly understood – and fatal thromboembolic sequelae to treatment with (US) commercial factor IX concentrates had occurred sufficiently recently to be well remembered. The organisation of UK haemophilia directors issued an advisory document on 9 January 1985 recommending continued use of NHS factor IX concentrates, both for untreated, and for previously treated, severely-affected factor IX deficient patients. It is a fact that the NHS product, in contrast to the US concentrates, was (and always had been) supplied free to hospitals; I have no way of determining the extent to which this may have influenced physicians in their individual decisions to use the NHS product. There is evidence to suggest that centres continued to use the unheated BPL factor IX up to October 1985, when unheated product was formally recalled.

44. In contrast with the circumstances obtaining for factor VIII, there was sufficient delineation between last availability of unheated factor IX (9D) and first availability of heated factor IX (9A), for recall to be effectively and usefully implemented. The recall was greatly facilitated by the fact that factor IX issues had always been made direct to individual haemophilia specialists (rather than via regional transfusion centres, as was the practice for factor VIII). At various times in the history of supply of factor IX, product

had been in short supply and it had always been considered prudent to maintain the main stock-holding at BPL (originally at PFL), supplying "on request" to a haemophilia specialist. Recall took the form of a single communication (7 October 1985) to each specialist (my memory is that there were about 120 identified) advising availability of heated product (9A) and instructing return of unheated product (9D).

45. In June 1985 Craske indicated that a small number of NHS Factor IX treated patients were HIV antibody positive and one or two had developed symptoms of AIDS but there had been no transmission in the haemophilia B patients in Edinburgh although they had been exposed to Factor IX produced from the same starting plasma pool as that implicated in the transmission of HIV to haemophilia A patients. He recommended changing to heat treated NHS Factor IX concentrates as soon as possible, but made no recommendation about the use of heated US products.

46. The annual returns for 1986 indicate a significant reduction in NHS Factor IX usage in 1985 – only 8 million IU used, compared to 12 million IU in 1984; commercial Factor IX usage increased to 3 million IU. This reflects, in 1985, a discontinuity of supply from BPL, with no unheated factor IX released for sale after June and the first batches of heated factor IX for regular issue not released until September. Unheated factor IX continued to be issued, but in diminishing amount, until October, when the heated product was launched and the unheated product was recalled. Commercial product filled the gap .

47. At the time of all of these events, and until April 1991, BPL as part of the National Health Service (and thus a Crown undertaking) had Crown immunity. One of the implications of this was that BPL was not subject to a formal licensing regime, although the facility was subject to MCA inspection, and BPL's factor VIII and factor IX concentrates were licensed from February 1977. It is my view that, if BPL had been subject to a more formal licensing regime, and if our products had been subject to the full (documentary) rigour of the licensing process, there would have been inevitable delay to development and introduction of 8Y and 9A.

48. The 8Y and 9A processes were established without the formality of present day clinical trials, but in accordance with best practice obtaining at the time, including follow-up at least to the spirit of the ICTH protocol previously described. The effectiveness of the virus inactivation process could not be validated before first clinical use, but evidence

was obtained for product safety in other respects. Certainly it was reasonable to assume that heated products would carry no greater risk of infection than their unheated precursors.

49. By July 1985 BPL was able to issue a product information sheet on 8Y stating "clinical trials at six Haemophilia Centres are in progress to gain evidence of reduction or elimination of viral transmission, and several patients have safely passed the point at which first evidence of NANBH virus transmission would normally occur with unheated Factor VIII". In May 1986 BPL presented updated clinical trial data showing continued freedom from NANBH transmission and followed this up in September 1986 with an interim report (to UK Haemophilia Directors) recommending follow up with a formal prospective clinical trial to a stricter protocol. To date neither product is associated with reports of transmission of hepatitis viruses or HIV.

Contacts between PFL/BPL and BTSB

50. There were contacts between PFL/BPL and BTSB in the 1980s. These involved both advice (and testing for BTSB) in support of quality control (for which I was the contact) and on virus safe process development (for which Dr Jim Smith – PFL, Oxford – was the contact). I do not have information on the advice provided by Jim Smith, to BTSB, in respect of their Factor IX product. Analysis of the BTSB product presented few problems to us - the process used in Dublin was sufficiently similar to that used by BPL/PFL and we had a well-established quality control department, with capacity for additional testing. In 1983 the fractionation unit of BTSB asked us about (sterilising) filtration of Factor IX and we also supplied details of our product leaflet inserts. Cecily Cunningham spent a week visiting Elstree and Oxford in late October 1983. I believe that she combined this visit with attendance at a scientific meeting (on "Natural blood products and synthetic substitutes" hosted by the Pharmaceutical Society of Great Britain, which dealt with the current status of factor concentrates - her attendance arose because I was unable to attend and I offered her my invitation).

51. In late 1984 and early 1985, Ms Cunningham asked us some questions about heat treatment and we gave her all the help we could. We discussed with her the then still unresolved worry about possible thrombogenicity resulting from heat treatment of Factor IX. I do not recall discussions with BTSB about the type of heat treatment that BTSB intended to use. I do not believe that it would have been practicable for BTSB to heat at

80 degrees centigrade for 72 hours without extensive and time-consuming redevelopment of their manufacturing process and without commissioning the construction of special ovens and associated equipment. Such activities demand considerable committed development resource which, to my knowledge, was not available to BTSB at the time.

52. We did a certain amount of quality control assay work for BTSB over the years in relation to batches of heat treated BTSB Factor IX product. This was to measure the components of the final product and to test for contaminants and viruses in that final product. We didn't charge for this initially (it was a tiny fraction of our own testing commitment) but later charging arrangements were agreed. We continued to assay samples of heat treated BTSB Factor IX during 1986, and again when the Factor IX was produced by Armour (and heat treated by BTSB) from 1988 to 1989.

53. I have been asked to comment on the safety record, as then known by fractionators, of the method of heat treatment employed by BTSB in respect of its Factor IX product (fractionated by Armour) in the late 1980s. This method was dry heat at 60 degrees centigrade for 144 hours. Whilst the robustness (reliability) of the process would have been very dependent on the precise characteristics of the product to which it was applied (protein content, moisture content, stabiliser content, vacuum or nitrogen fill, container/closure characteristics), it was and is reasonable to assume complete effectiveness against HIV. There was sufficient evidence of breakthrough NANBH infection from products heated at lower temperatures for shorter periods of time (Colombo et al, 1985; Preston et al, 1985) that effectiveness against NANBH would have needed to be proven (though heating for 144 hours would certainly have been more effective than a shorter period of heating). I am not aware that Hyland *Autoplex* and *Proplex*, subjected to such a heat treatment regimen, were ever reported to have transmitted NANBH.

54. SD technology, pioneered in the New York Blood Centre by Horowitz in the early to mid 1980s, appears to have been as effective in respect of HIV, HBV and HCV as the HT3 heat treatment applied by BPL to 8Y and 9A. The safety of both these technologies in application to coagulation factor concentrates became generally accepted from late 1988 onwards, and was subsequently confirmed when HCV testing became available from mid 1990 onwards. (Application of SD technology to other plasma fractions – immunoglobulins for example – presented practical challenges, and was not common until the 1990s; dry heat treatment regimens have not found general use beyond

coagulation factor concentrates.) The adoption of solvent detergent technology from early 1990 by the BTSB was consistent with, or in advance of, other national fractionators. BPL introduced an SD-treated factor VIII (under licence from Baxter Healthcare) in March of that year.

HTLV-111/HIV ("HIV") Testing

55. BPL, as the national fractionator, received plasma exclusively from blood centres in England and Wales. BPL was not involved at any time in the recruitment of donors. Policies on donor selection and screening were determined at national level by the organisation of Transfusion Centre Directors, in liaison with the UK Health Departments. BPL's only role in this regard was in ensuring that the plasma supplied to BPL complied with the minimum requirements defined in the UK (in the "Guidelines for the Blood Transfusion Services in the United Kingdom" – known as the "Red Book") and, later, in Europe.

56. Transfusion Centres in England & Wales undertook HIV-Ab testing on individual plasma donations from October 1985. The implementation date was determined by decision at a national level, after the evaluation of the available test kits for sensitivity and specificity. The lag time, from test implementation at donor level, to guaranteed availability of product from donations exclusively screened for HIV-Ab, was different for each product type. The last dates of issue of concentrates manufactured from unscreened plasma are as follows:

a. Factor VIII type 8Y … November 1996

b. Factor IX type 9A … April 1987

57. Transfusion Centres in England & Wales undertook HCV-Ab testing on individual plasma donations from September 1991. Again, the implementation date was determined by decision at a national level, after the evaluation of the available test kits for sensitivity and specificity. A position statement from the European Committee on Proprietary Medicinal Products (CPMP) defined the deadline for products from unscreened plasma to be placed on the market as 1 January 1993 (in the case of the UK, 16 months post implementation of testing). BPL complied with this requirement.

58. Donor screening contributes to the assurance of product safety but, given the effectiveness of the virus inactivation procedure, there is no reason to assume that

product manufactured by the 8Y and 9A processes before introduction of either screening test was anything but safe. This is supported by the long record of use of both products without evidence of virus transmission.

Self Sufficiency

59. BPL produced 25% or less of the national (England and Wales) demand for Factor VIII throughout the 1970s, the bulk being supplied as frozen cryoprecipitate or commercial concentrate (at 50% by the end of the decade). Throughout the same period it produced almost all of the factor IX (or PCC) that was used.

60. In 1975, and again in 1978, injection of central funding allowed BPL's output of factor VIII to be increased. By 1984 BPL was manufacturing 50% of the factor VIII used in England and Wales (though this proportion subsequently fell, primarily as a consequence of the lower yields for virus inactivated products). The limitations at this stage were manufacturing capacity at BPL and supply of plasma from the National Blood Transfusion Services. By 1988, with the new manufacturing unit at BPL fully operational, BPL was again manufacturing 50% of the national requirement.

61. Whilst the National Blood Services in England and Wales were regionally organised (and funded), an arrangement existed by which factor VIII concentrate was returned to transfusion centres on a pro rata basis, depending on the amount of plasma that these centres had supplied for fractionation. This meant that a local haemophilia director wishing to increase the availability NHS factor VIII would have had to persuade their regional transfusion centres to increase their supply of plasma to BPL. No such constraint applied to factor IX, which was always distributed directly from BPL (or PFL) to Haemophilia Centres.

62. I have been asked to comment on whether BPL would have been able to process Irish plasma to have made an equivalent product to 8Y or 9A from Irish plasma on behalf of BTSB. We might have been able to do this by 1988, but not earlier. One of the difficulties, even after 1988, would have been the logistics of segregating Irish and UK plasma (unless an arrangement for mixing plasma could have been mutually agreed, and this would probably not have been feasible). I believe that BPL was asked to give an indicative cost for supply of product to BTSB. I have no knowledge of the detail of any discussions that might have taken place. No arrangement was ever implemented.

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Table 1. **Factor VIII and Factor IX products manufactured by BPL (and PFL) and supplied for the treatment of Haemophilia in England & Wales**

Product description	Period of manufacture	Produced where/brand	Product characteristics
Blombäck factor VIII (ethanol precipitate of fibrinogen & factor VIII from plasma)	1968 – 1974	BPL & PFL	Relatively insoluble; Low potency & specific activity; Low yield; No virus inactivation
Johnson factor VIII (cryoprecipitate extract)	1974 – 1984	BPL (HL) & PFL (8CRV)	Improved solubility; Higher potency & specific activity; improved yield; No virus inactivation
Factor VIII type 8Y (cryoprecipitate extract, further purified by heparin and glycine precipitation)	1985 to date	BPL (8Y) & PFL (8Y)	Solubility, potency & specific activity further improved; Virus inactivation by dry heat (80°C for 72 hours); Acceptable yield penalty on heating
Method M factor VIII (cryoprecipitate extract, purified on a factor VIII monoclonal antibody gel column – technology licensed from Baxter)	1990 to date	BPL (originally called 8SM, then branded "Replenate")	High purity factor VIII (virtually homogeneous but human albumin added for stability); Virus inactivation using proprietary solvent-detergent ("SD") process; Yield lower than 8Y but still acceptable for a state-of-the-art, high purity product
Factor IX type C (a four factor Prothrombin Complex Concentrate ("PCC"), containing factors II, VII, IX and X)	1961 – 1974	PFL	A much valued alternative to fresh frozen plasma, but a difficult process to maintain & reproduce; Heparin added as a stabiliser; No virus inactivation
Factor IX type 9D (a three factor PCC, made by DEAE-cellulose adsorption of cryosupernatant)	1972 – 1984	PFL, then BPL	The absence of factor VII necessitated the production of a separate factor VII concentrate; No virus inactivation
Factor IX type 9A	1985 – 1999	BPL & PFL	As 9D, but with virus inactivation by dry heat (80°C for 72 hours)
High purity factor IX (Metal chelate gel column)	1994 – 1997	BPL (originally called 9MC, then branded "Replenine")	High purity, single factor, factor IX concentrate; Virus inactivation using proprietary solvent-detergent ("SD") process
High purity factor IX (Metal chelate gel column) with virus filtration	1997 to date	BPL, branded "Replenine-VF"	As Replenine, but with virus filtration to remove non-enveloped viruses like Hepatitis A virus and Parvovirus B19