10

PETER REYNOLDS FOSTER

BSc, MSc, PhD, CS, CSci, CEng, FIChemE.

I would like to thank you for inviting me here today and I hope that I will be able to assist you with your investigations. I would like to comment on a number of topics; to give you background information as well as describing my personal experiences. In particular I would like to say something about:

- licensing of plasma products,
- self-sufficiency and the supply of Factor VIII, and
- the development of heat treatment.

I will begin by introducing myself.

INTRODUCTION

I am a chemical engineer by profession and I specialised in biochemical engineering, completing a PhD in 1972 concerning technology for the separation of proteins. I joined the Protein Fractionation Centre (PFC) of the Scottish National Blood Transfusion Service (SNBTS) in January 1973 as a research scientist. PFC is where SNBTS manufactured plasma products, such as Factor VIII and Factor IX concentrates for the treatment of haemophilia, as well as other products such as albumin for the treatment of casualties and a range of antibody products known as immunoglobulins. At that time PFC was situated beside the Regional Blood Transfusion Centre at the Royal Infirmary of Edinburgh. Planning of a new facility on the outskirts of Edinburgh was underway. This was commissioned in 1975 and operated routinely from 1976. Staffing arrangements for the new centre were drawn up in April 1974 and I was appointed head of Research & Development, reporting to the Director of PFC; which is essentially the position I hold today. I have been involved with the whole range of plasma products, but problems with factor VIII came to dominate my work from 1976. Factor VIII concentrate was an extremely difficult product to manufacture and my research was aimed initially at increasing output to try to achieve national self-sufficiency. The knowledge gained from this work provided a foundation for the development of technologies aimed at eliminating risks of infection. Before I say more about

these problems, I would like to say something about the licensing and regulation of blood plasma products.

REGULATION AND LICENSING

Plasma products are Prescription-only-Medicines (POM) and for legal purposes they come under the UK Medicines Act of 1968. The Government body responsible for enforcing this act is the Medicines and Heathcare products Regulatory Agency (the MHRA) which was formerly called the Medicines Control Agency (the MCA). There are two principal types of licence awarded by the MHRA, a Manufacturer's Licence, which demonstrates that the premises and their operation are suitable for the manufacture of pharmaceutical products, and a Product Licence (sometimes known as Marketing Authorisation) which demonstrates that a product has been judged to be suitable for the clinical use specified.

Within the MHRA, advice on Product Licensing was given by the Committee on Safety of Medicines (the CSM). As well as considering clinical information, such as data on clinical effectiveness and on side-effects and other complications, the CSM also considered issues such as the product quality, the product composition and the method of preparation, including labelling & packaging. With regard to packaging, all pharmaceutical products must carry warnings of potential side-effects or adverse reactions and the warnings and the wording must be approved by the MHRA (MCA) before a licence is awarded.

For example, SNBTS was first granted a Product Licence for Factor VIII concentrate in 1978. The packaging contained five warnings concerning the risk of hepatitis, two warnings on the outer carton, two warnings in a patient information leaflet and one warning on the label attached to each vial. The wording for all of these warnings was submitted with the application for a Product Licence and was approved by the MCA when the Product Licence was granted.

Commercial Factor VIII concentrates were first licensed in the UK in 1973. To the best of my knowledge all coagulation factor concentrates carried warnings concerning hepatitis. I presume that these warnings, and the wording used, were approved by the MCA. I should point out that pharmaceutical manufacturers do not deal with patients directly and depend on the doctor who is treating the patient to ensure that individuals are informed of risks associated with their treatment.

CROWN IMMUNITY

The regulation of products manufactured within the NHS was complicated by the existence of Crown Immunity, which allowed the manufacture of pharmaceuticals within the NHS to be legally exempt from provisions in the 1968 Medicines Act. There were three NHS facilities in which blood plasma products were manufactured, the Blood Products Laboratory (BPL) at Elstree just north of London (now known as the BioProducts Laboratory), the Plasma Fractionation Laboratory (PFL) at Oxford (which was administered by BPL and which carried out coagulation factor research for BPL) and the Protein Fractionation Centre (PFC) in Edinburgh. I was not directly involved with licensing, but will try to explain the situation in Scotland.

The first Director of PFC (Mr John Watt) was a member of the CSM and he strongly advocated that the new PFC facility should be subject to the Medicines Act. Differences between Scots law and English law meant that there was uncertainty over the application of Crown Immunity to Scotland and he was therefore authorised to apply for a Manufacturer's Licence. This was granted in 1976 for a period of five years. Applications were also made for Product Licences for Factor VIII and Factor IX concentrates both of which were granted in 1978 for a period of five years.

In 1981, when PFC's Manufacturer's Licence was due for renewal, further legal advice was taken by the Common Services Agency (CSA), the body that administers SNBTS. Fresh legal opinion now held that Crown Immunity did apply in Scotland. No application was made for renewal of PFC's Manufacturer's Licence. Mr Watt, who had been the Director of PFC since

1966, left SNBTS at the end of 1983. Before leaving he submitted applications for renewal of the Product Licence for Factor VIII and for a Product Licence for intravenous immunoglobulin, a new product which we had developed. In both instances, Product Licences were granted for five years. Thereafter, no further licence applications were made by SNBTS until Crown Immunity was removed in 1991. Despite the provisions of Crown Immunity, PFC continued to interact with the MCA, encouraging informal inspections and acting on the advice given.

There is one implication of Crown Immunity that should be noted. Normally, when a product or its method of preparation are modified, an application must be made to vary the Product Licence; if a substantial change is made, a new Product Licence application may have to be submitted. When SNBTS introduced heat treatment to remove risks of infection from coagulation factors it did so by informal consultation with the MCA. If we had been required to apply for licence variations or for new Product Licences then the administrative formalities alone would have delayed the introduction of heat treatment considerably. In these circumstances more patients in Scotland would almost certainly have been infected with HIV. We believe that freedom to make changes rapidly at this critical time did benefit people with haemophilia.

Contrary to what you have been told, PFC has never had any of its licences suspended or withdrawn by MHRA. Nor has PFC been closed by the Medicines Inspectorate. PFC currently holds a Manufacturer's Licence and a Good Manufacturing Practice (GMP) certificate as well as Good Laboratory Practice (GLP) accreditation and underwent a satisfactory inspection as recently as two weeks ago. PFC holds 19 Product Licences, 15 of which are for plasma products, and in this respect is one of the most successful manufacturer's of protein pharmaceuticals in the UK.

However, it is considered that PFC is no longer economically viable as a supplier to the Scottish Health Service and a policy decision has been taken by Scotland's former Health Minister that Scotland will obtain its blood plasma

products elsewhere. A novel clinical product is still being manufactured at PFC for the Ministry of Defence. This contractual obligation is expected to be fulfilled within the next 6 months, after which PFC will close.

SELF-SUFFICIENCY AND SUPPLY OF FACTOR VIII

I would now like to comment on the issue of self-sufficiency and the supply of Factor VIII concentrate. I will begin with the international situation. The 1975 World Health Assembly recommended that all countries should aim to meet their medical requirements for blood and blood products from their own population using unpaid volunteer donors. Ten years later, 70% of the world's plasma products continued to be derived from commercial plasma collected in the United States. Today, that figure is 65%, demonstrating that progress towards national self-sufficiency has been limited. The main reason why the United States has been so dominant, in my opinion, lies in the volume of plasma that can be taken from a donor in the USA, which is considerably more than in other countries.

In the United Kingdom, a commitment to national self-sufficiency was first announced by the Government in January 1975. A few months earlier, a number of senior haemophilia doctors and the Haemophilia Society had urged the Government to fund the purchase of commercial Factor VIII concentrates, on the grounds that 90% of patients were receiving inadequate treatment. It is important to note that at this point in time in the UK, life-expectancy was 42 years for a person with haemophilia A and 34 years for a person with haemophilia B. Commercial Factor VIII concentrates were purchased under a central supply contract administered by DHSS with only Haemophilia Directors or their nominees having authority to purchase. This centralised arrangement ended in March 1979 and individual Health Authorities were advised to make their own arrangements for purchase thereafter, with only Haemophilia Directors or their nominees authorised to purchase commercial products. I would like to stress that the UK blood transfusion services did not purchase commercial products nor did they import commercial plasma at that time.

To achieve self-sufficiency, the UK transfusion services had to supply the amount of plasma needed and fractionation facilities, with the capacity to process this volume of plasma, had to be provided. Planning for this was dependant on two crucial figures; the amount of Factor VIII required for the treatment of haemophilia in the UK and the quantity of factor VIII that could be extracted from each litre of plasma (ie. the yield of factor VIII). I think you are aware that the use of Factor VIII concentrate exceeded all projections and the Reverend Tanner has told you of the impact this had on the treatment of haemophilia from his personal experience. Although the annual requirement was initially estimated to be about 40 million units of factor VIII, actual use reached 80 million units by 1984. This did not level-off, and reached 160 million units in 1994 and 280 million units by 2004. I mention these figures to give you some indication of how little treatment was being provided in the 1970s. In my experience assumptions on factor VIII yield also turned out to be wrong, with the actual yield in large-scale manufacturing being much lower than had been assumed in 1974 by the MRC working party. There are a number of technical reasons for this, mainly associated with the difficulty of manufacturing Factor VIII concentrate and the instability of factor VIII during processing, but also to changes in the way factor VIII was measured in concentrates, which was changed in 1976. The wrong assumptions used for planning in the early 1970s meant that requirements for the supply of plasma and for its processing were underestimated considerably.

I will now describe what happened in Scotland. Initially the same planning assumptions were used as in England and it was expected that sufficient Factor VIII could be obtained as a by-product of albumin production, which was the plasma product in most demand at the time. When it was realised that this would not be the case, considerable efforts were made to increase the output of Factor VIII concentrate. The amount of extra plasma required could not be obtained by recruiting more donors. Instead plasma had to be separated from blood soon after donation, leaving hospitals to use red cells instead of whole blood for transfusion – a concept known as component therapy. This was a major change to established medical practice. To encourage hospital doctors to make this change SNBTS medical staff

embarked on a process of education and persuasion and SNBTS eventually stopped issuing whole blood altogether, unless approved by an SNBTS doctor. Whilst this was taking place I was working on factor VIII yield and we managed to increase this by about 60%. I will try to explain how this was done. I said earlier that Factor VIII concentrate was a very difficult product to prepare. The amount of factor VIII present physically in blood is very small, I am talking here about the blood of a normal person not someone with haemophilia. Factor VIII is a protein and it accounts for about 0.0006% (ie. 6 parts per billion) of the protein in human plasma. Treatment of haemophilia with plasma had limited success because it was not possible to give enough factor VIII without overloading the patient's circulation. To treat haemophilia properly, factor VIII had to be concentrated into a much smaller volume – hence the term Factor VIII concentrate. There were a number of things that had to be done technically to achieve this. Proteins which would not dissolve in such a small volume had to be removed, proteins which could damage factor VIII also had to be removed, as did proteins such as immunoglobulin and albumin which were needed to treat other patients. After all of this had been done, any bacteria that might be present had to be removed. This was done by filtering the factor VIII solution through membranes with tiny holes, holes so small that bacteria could not get through, something that had not been possible with cryoprecipitate or with earlier types of Factor VIII concentrate. The Factor VIII was then put into vials and because it was unstable it had to be freeze dried. After this it could be stored at 4°C and used immediately when needed. The first step in the manufacturing process involved the preparation of cryoprecipitate, a substance that you have heard about already. Cryoprecipitate is a thick, sticky residue of protein which forms when frozen plasma is melted and which dissolves as the plasma warms up. Most of the factor VIII in plasma goes into this residue, but is still only a tiny proportion of the protein present. Factor VIII could be concentrated by separating the cryoprecipitate from the rest of the plasma and then dissolving it in $1/10^{th}$ or less of the original volume of plasma. Further processing was then carried out on this concentrated protein solution. None of this was easy, mainly because most of the proteins which make up cryoprecipitate are

'sticky', do not dissolve easily and tended to block the filters used to remove bacteria. Factor VIII itself is very fragile and tended to disappear for no obvious reason. That is why yield was such a problem. To deal with this it was necessary to be able to track what was happing to the factor VIII – where was it going, how was it being damaged? In the 1970s, knowledge of factor VIII was very limited and the scientific tools available were rudimentary by today's standards. There was no way of detecting factor VIII directly and it could only be tracked by its activity – that is its ability to clot plasma from a haemophiliac. These tests had to simulate the blood clotting process and were very complicated. They had to be performed in specialist laboratories – even then accuracy was poor, even in the most expert laboratories. There was also a type of damage to factor VIII – called activation – that would give exaggerated readings in the clotting test, indicating that a lot of factor VIII was present when really there was very little there. Because of these problems, experiments had to be repeated many times and even then it could be difficult to interpret the results. It was also hard to get plasma for research as priority was given to making Factor VIII for patients. At one point we had so little plasma available that PFC staff volunteered to donate their own plasma to allow our research to continue. As well as doing experiments in the research laboratory, I also examined the production process carefully because the production situation is very different to small-scale laboratory experiments and findings from the lab could not always be reproduced in production. I began by looking at the first step in the production process, the preparation of cryoprecipitate at large-scale. The yield at this step was much lower than expected. It was not clear how Factor VIII was being lost – one theory was that factor VIII was being damaged during the time taken to melt the frozen plasma, another theory was that factor VIII was dissolving back into the melted plasma because the temperature had become too warm. These possibilities were not mutually exclusive, so both had to be addressed. But there was a contradiction; how could the melting of frozen plasma be speeded-up and the temperature reduced at the same time? I designed equipment to solve this problem. This involved continuously feeding particles of frozen plasma to a small heated container from which the plasma could flow away from the heated surface, as soon it had melted. This worked well,

the yield was increased by 45% and the cryoprecipitate was much easier to dissolve than before. I also fine-tuned the other process steps and, most importantly, was able to identify why factor VIII was unstable during processing. I was able to correct this by adding a small amount of calcium, which helped to protect factor VIII from an anti-coagulant that had to be added to prevent clotting. This addition of calcium to stabilise factor VIII later became important in the development of heat treatment, both at BPL and at PFC, and is widely used today in the preparation of both recombinant Factor VIII and Factor VIII derived from plasma.

By the early 1980s the supply of plasma to PFC had increased about 3-fold. Despite this large increase, PFC still had sufficient capacity to process the extra plasma, as plans to process English plasma had not come to fruition, leaving PFC with spare capacity. Because of the extra plasma and the increased yield, SNBTS was able to supply sufficient Factor VIII for the treatment of all patients in Scotland in 1983, making Scotland one of few countries ever to have achieved self-sufficiency using donations from unpaid volunteers and, as far as I am aware, the first country to do so.

In 1998, the use of UK-donor plasma for the preparation of plasma products was banned as a precaution against the theoretical risk from variant CJD. This effectively ended the UK policy objective of self-sufficiency. The Department of Health has since purchased a commercial plasma supply company in the United States, to safeguard plasma supplies to BPL, and the United Kingdom now depends on the USA commercial plasma system for its plasma products.

HEAT-TREATMENT

I would now like to talk about the development of heat treatment for coagulation factors. There are two types of heating that I will describe; in one method, called pasteurisation, heating was carried out on a solution of factor VIII after it has been dissolved in a lot of sugar; in another method, known as dry-heat treatment, heating is applied to Factor VIII after it has been freeze dried and is sealed in its final container. Initially, the objective with both of

these approaches was to discover heating conditions that could destroy viruses responsible for non-A, non-B hepatitis. Later this also encompassed the virus responsible for AIDS. The problem of hepatitis was not new. The possibility that human blood plasma products could transmit hepatitis had been known since the 1930s. Hepatitis was a major challenge to transfusion science and a considerable amount of research was undertaken to try and eliminate this risk. Hepatitis infection in haemophiliacs in the UK was first described in 1963. In 1967, international experts advised that recipients of Factor VIII concentrates should be monitored for evidence of hepatitis. Two different types of hepatitis were recognised, one with a shorter incubation period and another with a longer incubation period. These became known as hepatitis A and hepatitis B respectively. It was the second of these viruses, hepatitis B, that was implicated in infections by transfusion. The virus responsible for hepatitis B was identified in 1967 and the virus responsible for hepatitis A was discovered in 1973. Screening of blood donors for infection with hepatitis B was introduced by SNBTS in 1970. When I joined PFC in 1973 research was still being carried out to try and find a way to remove the hepatitis B virus from coagulation factors, because it was appreciated that the screening test for hepatitis B was not sensitive enough to detect all infected donations. Later we learned that hepatitis B was not the only problem as there were patients with hepatitis which could not be accounted for by either the hepatitis A virus or the hepatitis B virus. This type of hepatitis was called non-A, non-B hepatitis (NANBH).

NANBH in haemophiliacs was first reported by doctors to a meeting of the World Federation of Hemophila (WFH) in 1975; the WFH is an international body which represents patients and to which the UK Haemophilia Society was a founder member. Research was begun, including research at SNBTS, to try and discover the cause of NANBH, which was presumed to be due to one or more viruses. We know now that NANBH was caused by the hepatitis C virus (HCV) which was discovered in 1989 by researchers in the USA. We also know now that hepatitis C accounted for 90% of the hepatitis transmitted by blood and blood products, even in the 1960s. Whilst the search for the virus was going on, the problem that we and other fractionators faced was how to

design a technology to remove a virus that had not yet been discovered, without damaging fragile coagulation factors. It was in 1981 that I learned that a company in Germany was pasteurising Factor VIII to try and destroy hepatitis viruses. This was being done by using a thick sugar solution to stabilise the factor VIII, with the sugar having to be removed after the heating had been completed. The main problem was that the yield from this process was extremely low, partially because of damage to factor VIII during heating but also because of losses that were incurred when the sugar was removed. Because the yield was so low, relatively few patients could be treated. Most of the Factor VIII produced by the company was not heated and most of the Factor VIII used in Germany was imported from the USA. In our research to increase yield I have already mentioned that I had identified why factor VIII was unstable during processing. I thought that it might be possible to use this knowledge to increase yield over pasteurisation, so we began work using this approach. There was considerable scepticism over the idea that factor VIII might survive heat-treatment. I remember one doctor who was convinced that it would all turn out to be a mistake and that pasteurised Factor VIII would not work in patients. We continued our research despite these views and made sufficient progress that we were able to prepare some pilot production batches of pasteurised Factor VIII in 1983 to determine its effectiveness in patients. The product was given to three patients. Two tolerated the product well, but one experienced an allergic reaction, which his doctor judged to be unacceptable. The recovery of factor VIII in his circulation was normal and it was concluded that some other protein in the product must have been damaged by the heat treatment and had caused this reaction. We decided that the purity of the product needed to be increased considerably and we began research on this in collaboration with scientists in the USA who were devising technology for this purpose.

The second approach to heating coagulation factors, dry-heat treatment, emerged in 1982. Researchers in the USA had found that freeze dried Factor VIII could withstand heating at temperatures in the range 60-68°C. Freeze drying is used widely to stabilise biological products, such as vaccines, so

viruses would be expected to be more stable to dry-heating as well as factor VIII. This turned out to be the case and patients receiving commercial products that had been treated this way continued to be infected with non-A, non-B hepatitis. There was concern that heating might damage factor VIII in a way that would cause patients to develop antibodies which would stop the factor VIII from working and that they would be harmed as a result. This did actually occur later in Europe where two pasteurised factor VIII products had to be withdrawn. Because of this fear, there was a reluctance to use heated Factor VIII concentrates without some evidence that viruses were being destroyed. The adverse reaction to our pilot batch of pasteurised Factor VIII heightened this concern. Attention was now being directed towards AIDS as well as hepatitis.

HIV, the virus responsible for AIDS, was discovered in 1984. Contrary to the claim by the Haemophilia Society, heating experiments with HIV and Factor VIII were first performed in Autumn 1984 by scientists at the Centres for Disease Control (CDC) in the USA in conjunction with the plasma fractionation company Bayer. They discovered that HIV that had been added to Factor VIII could be destroyed by dry-heat treatment at 68°C. Their results were not published in a peer-reviewed journal until August 1985, but the findings were so important that CDC summarised the results in its Morbidity & Mortality Weekly Report (MMWR) that was published on 26th October 1984. PFC subscribed to MMWR, but its distribution was slow, so we first heard of these findings on 2nd November 1984 when they were presented at a conference in the Netherlands which I and some of my colleagues were attending. A speaker from CDC reported that HIV infectivity that had been added to Factor VIII was reduced 10,000-fold after dry-heating for 1 hour at 68°C. Our Factor VIII could withstand dry-heating for 2 hours at 68°C. By this time we had managed to establish a 12-month stock of Factor VIII, because of increased supplies of plasma and the yield improvements that I described earlier. We decided to dry-heat our stock of Factor VIII at 68°C for 2 hours to provide heat-treated Factor VIII as quickly as possible; this enabled us to recall unheated Factor VIII and meant that factor VIII that had been prepared

from blood donations collected as early as October 1983 could be subjected to dry-heating, effectively back-dating heat-treatment by over 12 months. As a result, SNBTS was able to distribute sufficient heat-treated Factor VIII for all patients on 10th December 1984. I believe Scotland was the first country in the world to move over completely to heat-treated Factor VIII, even discounting the 12-month 'back-dating' that was gained by heating our stock of Factor VIII. There were still concerns that factor VIII would be damaged by heating and would cause patients to develop antibodies that would stop factor VIII from working. One senior haemophilia doctor wrote to us to complain that we had introduced heat treatment too quickly. Other experts wrote to the Lancet to argue against heat-treatment, believing that it would do more harm than good. SNBTS considered these views carefully but stuck to its position; we know now that if we had not done so, many more patients in Scotland would almost certainly have been infected with HIV. In my research I had been studying the effect of various additives on Factor VIII to try and increase the yield even more. I used samples that were already available to see if dry-heating at 68°C could be extended beyond 2 hours. I discovered that it if a small amount of sugar was added, heating could be extended to 12 hours. We made this change immediately and the sugar was added to all batches of Factor VIII that were newly prepared enabling these to be dry-heated at 68°C for 12 hours.

I should point out here that the claim by the Haemophilia Society that infectious batches of Factor VIII could have been detected in 1983 by an HIV-screening test is quite wrong. SNBTS did screen all of its batches of Factor VIII for evidence of contamination once an HIV-test was commercially available, but the original screening test (which detected antibodies to HIV) was not sensitive enough to detect contamination in concentrates. This did not become possible until 1991, after a more sensitive analytical technique had been developed.

Following the advice of October 1984 from CDC, most countries moved to heated concentrates during 1985 to prevent HIV transmissions. A vaccine was available to protect individuals at risk from hepatitis B (including staff at

fractionation centres), but the problem of non-A, non-B hepatitis had still to be solved. Research was progressing internationally on a number of fronts. Despite its low yield, the pasteurised product in Germany was the only approach so far in which patients had remained free from hepatitis, although international experts did not regard their results as definitive. We were aware that our NHS colleagues at PFL/BPL had made a breakthrough in their research and had managed to prepare a Factor VIII concentrate that could withstand dry-heating at 80°C for 72 hours. This was a remarkable achievement. It had been done with a new preparation of Factor VIII (called 8Y) that was 5 to10-times more pure than established products and this greater purity was thought to be the reason why 8Y was exceptional in being able to withstand this very high temperature. However, unlike pasteurisation, there was no evidence available that hepatitis might be destroyed by dry-heat at 80°C. We continued our research to increase purity as this was consistent not only with improved pasteurisation but also with the view that greater purity was the key to dry-heating at 80°C, or at even higher temperatures if that was needed to destroy hepatitis viruses. A number of things then happened later in 1985 which caused us to change this strategy. First, as a result of experiments done at PFC by my colleague, Dr McIntosh, we discovered that it was the method that had been used to freeze dry 8Y, rather than its purity, that had enabled heating at 80°C to be tolerated. This had not been realised by scientists at BPL and the method used to freeze dry 8Y had not been included in their patent application. This explained why other manufacturers had failed to reproduce the process. We went on to discover that it was the structure of the ice crystals that had formed during the freezing stage that was critical. The ice had formed a particular structure in 8Y because of a chance combination of circumstances, so we designed a special freezing procedure to deliberately cause this precise crystal structure to form uniformly in every vial of Factor VIII. 8Y was introduced routinely by BPL in September 1985 and, although it was not known if hepatitis viruses would be destroyed, they went on to show that routine large-scale manufacture was possible and that the product was well tolerated. Also in late-1985, we began to hear from the

USA that dry-heating might be less effective against HIV than had been believed.

We wanted to be sure that patients would be safe from HIV. Now that we knew how to develop a product that would withstand dry-heating at 80°C, we decided to shelve our research on high-purity Factor VIII, to focus instead on developing a product similar to 8Y. This could not be done by modifying our existing Factor VIII concentrate and required a new product to be developed and a new manufacturing process to be installed. In pharmaceutical manufacturing, it normally takes many years for a new product to go from research through to routine production. We began large-scale production of our new Factor VIII (which we named Z8) in August 1986, just 8 months after taking the decision to go down this route. About two months later, in October 1986, a preliminary report from BPL was presented to the UK Haemophilia Centre Directors which suggested that 80°C dry-heat might be effective against non-A, non-B hepatitis. These preliminary results were not confirmed until 1988. Z8 was available for clinical trial in December 1986 and was released routinely from April 1987. Throughout this period we worked in collaboration with scientists at BPL, assisting them with problems in the manufacture of 8Y and undertaking laboratory studies with viruses on their behalf. Although BPL was first in the world to achieve this advanced technology, most Factor VIII concentrate used in England & Wales prior to 1988 was imported and was not heated at 80°C. PFC was second in the world to master this technology and was able to supply sufficient Z8 to treat all patients in Scotland. I estimate that this enabled Scotland to be about three years ahead of any other country in having sufficient Factor VIII concentrate for all patients that was safe from hepatitis C.

I would also like to say something about Factor IX concentrates that are used for the treatment of haemophilia B. The UK was self-sufficient with respect to factor IX because there are fewer people with haemophilia B and because Factor IX concentrate was less difficult to manufacture than Factor VIII. However, like all coagulation factors, factor IX is sensitive to processing and

can be damaged easily. Factor IX can be very dangerous when it is damaged – it can become what we call 'thrombogenic', basically it can be far too active, causing the blood to clot too much. This problem emerged in the 1970s when some patients in the USA died from this type of complication. Research was undertaken to devise tests that could be used to screen batches of factor IX to avoid this problem. SNBTS was at the forefront of this research. This coincided with research that was taking place at PFC that was aimed at removing hepatitis viruses from Factor IX. An experimental preparation of Factor IX concentrate from PFC that had been processed to remove viruses was found to be highly thrombogenic in animals. The method also failed to remove hepatitis B completely. By contrast, in a comparative study of different products, our standard factor IX concentrate was found to be the least thrombogenic. This thrombogenic risk was taken very seriously, so when we came to examine the effects of heat treatment on Factor IX it was one of the issues that had to be considered. When we subjected our Factor IX to heat treatment, it failed one of the lab tests that was used to screen batches for thrombogenicity. Although we discovered a way of modifying the product so it passed this test, it was decided that safety from thrombogenicity needed to be confirmed in animals. These safety studies were complicated and very difficult to perform and were undertaken jointly with BPL, with whom we were collaborating closely. The animal safety study was competed successfully in July 1985 at which point Factor IX concentrate, dry-heated at 80°C for 72 hours, was issued for clinical evaluation. Earlier in 1985 a commercial heat treated Factor IX concentrate from the USA had become available and had been purchased by Haemophilia Directors in Scotland. Consequently SNBTS stopped supplying its unheated Factor IX in May 1985. We began to issue 80°C heat-treated Factor IX concentrate routinely from August 1985, and all of our unheated Factor IX concentrate was recalled as soon as our heated product had been distributed. I think that the timescales in England were similar. Dry-heating at 80°C for 72 hours was later shown to destroy HCV as well as HIV, putting the UK some years ahead of the rest of the world in being able to provide haemophilia B patients with a Factor IX concentrate that was safe from infection with hepatitis C as well as HIV.