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# THE DEVELOPMENT OF HEPATITIS-SAFE FACTOR VIII CONCENTRATE BY THE SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

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## 1. INTRODUCTION

1.1 The most significant advances in the treatment of haemophilia A have been:

- The provision of Factor VIII concentrate
- The provision of HIV-safe Factor VIII concentrate
- The provision of hepatitis-safe Factor VIII concentrate.

1.2 Scotland is believed to have been the first country in the world to become self-sufficient in the provision of Factor VIII concentrate obtained from unpaid volunteer blood donors.

1.3 Scotland is believed to have been the first country in the world to be able to provide sufficient HIV-safe Factor VIII concentrate for all of its people with haemophilia A.

1.4 Scotland is believed to have been the first country in the world to be able to provide sufficient hepatitis-safe Factor VIII for all of its people with haemophilia A.

How this was achieved is outlined below.

## 2. FACTOR VIII

2.1 Factor VIII is a plasma protein which is necessary for blood to clot normally. Individuals deficient in Factor VIII suffer from Haemophilia A, a disorder which can result in a painful crippling condition and early death, if left untreated.

2.2 Factor VIII concentrates for the treatment of Haemophilia A became available from the early 1970's and revolutionised the lives of haemophilia sufferers who with this treatment were able to lead a relatively normal life for the first time.

2.3 As soon as the benefits of this treatment were appreciated, the demand for Factor VIII increased beyond all expectations.

2.4 The preparation of Factor VIII is a highly specialised activity which was initially attempted by only a small number of commercial pharmaceutical manufacturers, based largely in the USA, and some blood transfusion services.

2.5 In the UK this activity was undertaken by the NHS blood transfusion services. Production of Factor VIII concentrate took place in centres in Edinburgh (The Protein Fractionation Centre), Oxford (The Plasma Fractionation Laboratory) and Elstree (The Blood Products Laboratory)The PFC operated within SNBTS and PFL/BPL operated under the aegis of the blood transfusion services of England and Wales.

2.6 At this time,(during the 1970's) Factor VIII was identifiable only by its ability to correct the defective coagulation of haemophilic plasma (ie. its biological 'activity'). Little was known of the molecular, physical and chemical characteristics of Factor VIII. In addition, Factor VIII activity was unstable and tended to co-purify with Fibrinogen and Fibronectin, which are particularly difficult proteins to deal with in pharmaceutical processing because of their poor solubility and adherent nature.

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2.7 Most methods for preparing Factor VIII concentrates were based on work that had been carried out during the 1960's at New York University Medical Center, under the direction of Dr Alan J Johnson[1]. SNBTS (PFC) collaborated with Dr Johnson in order to introduce this technology into the UK.

2.8 Despite assistance from Dr Johnson, the product was found to be extremely difficult to manufacture, because of the instability of Factor VIII activity and the poor processing characteristics of the other proteins present. Consequently processing was always problematic, Factor VIII yields were low, capacity was very limited and there was insufficient Factor VIII available to meet patient needs.

2.9 Manufacturers world-wide experienced similar problems, however commercial companies increased their output by purchasing increasing quantities of plasma from paid donors, a practice which was favoured in the USA where limits on the volumes of plasma that could be taken from an individual donor were much more lenient than in Europe.

2.10 As a result, the NHS requirement for Factor VIII concentrate was met increasingly by commercial products imported from the USA.

2.11 In order to increase its output of Factor VIII, the SNBTS undertook a programme of R&D aimed at resolving the scientific and technical problems which were restricting output and also sought to obtain more plasma for fractionation by changing the way in which blood donations were being used clinically.

2.12 From this research, we discovered the cause of Factor VIII instability in the PFC process[2-4] and why yield was being lost[5-7]. New equipment was designed and constructed and other technical improvements made, resulting in a substantial increase in both yield and capacity[8-10].

2.13 These advances enabled Scotland to have available, from its own blood donor population, sufficient Factor VIII for the treatment of all people in Scotland with haemophilia A according to UK clinical practice (ie. to be self-sufficient in Factor VIII concentrate derived from unpaid blood donors).

2.14 The knowledge obtained from this work also provided the foundation necessary for future developments in virus inactivation and Factor VIII purification.

## 3. HEPATITIS AND FACTOR VIII

3.1 The risk of hepatitis transmission has been associated with the clinical use of human blood products since their inception over 50 years ago. A specific screening test for hepatitis B infection was introduced for blood donors in the early 1970's, following the identification of the hepatitis B virus, which was believed to be the agent responsible for post-transfusion hepatitis.

3.2 By the late-1970's it became evident, from liver function tests, that haemophiliacs were contracting another form of hepatitis[11-13] which became known as non-A, non-B hepatitis (NANBH). Usually there were no clinical symptoms and the illness was

generally regarded as mild and non-progressive[14,15]. However, by the mid-1980's, there was growing evidence that NANBH may be a more serious disease[16,17].

3.3 It was not until 1989 that the hepatitis C virus was identified[18] and appropriate screening tests were developed subsequently.

3.4 SNBTS worked throughout the 1970's to try and remove the risk of hepatitis from coagulation factor products, collaborating on research into methods for removing viruses from Factor VIII[19] and Factor IX concentrates[20-22].

3.5 This work was superseded in the early 1980's by research into heat treatment, as soon as we became aware of developments in this area[23].

4. HEAT TREATMENT OF FACTOR VIII

4.1 A heat treatment process (pasteurisation of the solution at 60°C), whereby Human Albumin products could be made hepatitis-safe was developed in the 1940's in the USA and was employed by SNBTS for its Albumin products. However, Albumin was considered to be unique amongst plasma products in its ability to withstand heating to this degree[24].

4.2 Factor VIII concentrates were highly sensitive to damage by a variety of mechanisms. The notion that conditions might be obtained under which Factor VIII could be heat treated to inactivate hepatitis virus(es) was a concept which only emerged in the early 1980's, when two different approaches to the heat treatment of Factor VIII were reported, one from Germany and one from the USA.

4.3 Research in Germany by Behringwerke involved pasteurisation at 60°C (ie. heating as a liquid) of a more highly purified form of Factor VIII, which had been partially stabilised using a high concentration of sucrose, which then had to be removed to make the product suitable for administration to patients[25].

4.4 There were two major problems evident. Firstly, although experiments carried out in chimpanzees indicated that hepatitis B infectivity had been eliminated, it was not clear if this was due to removal of virus by the purification process or inactivation of virus by pasteurisation. Whether or not the process would be effective against the agent of NANB hepatitis was not known.

4.5 The second problem concerned the need to separate Factor VIII from the added stabilisers once pasteurisation had been completed. This was necessary in order to be able to provide the final product in a dose form which was pharmaceutically acceptable. The procedures used initially for this purpose were technically difficult and very inefficient resulting in a high loss of Factor VIII, with the overall yield[26] being less than 25% of that being achieved at PFC at that time.

4.6 Although the Behringwerke process did not appear to be viable immediately (because of the very low yield) and despite uncertainty over the effectiveness of the heating procedure, we believed that the possibility that heat treatment could be applied to

Factor VIII deserved very serious attention. Therefore, to resolve these problems, the SNBTS began in 1981 to undertake research on the pasteurisation of Factor VIII, as soon as we became aware of the progress being made in Germany.

4.7 A second approach to the heat treatment of Factor VIII emerged in August 1982 and concerned heating of the product after it had been freeze dried. It was reported at a meeting in Hungary, that 50% of the Factor VIII activity could survive heating at 80°C for 10 hours[27], but the product had such a poor solubility that it was suitable for clinical use only when heated at lower temperatures (eg. 60°C)[28]. No information was available on the ability of this procedure to inactivate hepatitis viruses or any other viruses.

4.8 Differences between Factor VIII products prepared by different manufacturers meant that the degree of 'dry' heat treatment that a product was able to tolerate varied from manufacturer to manufacturer (eg. from 60°C for 24h for Factor VIII manufactured by Alpha, to 68°C for 72h for Factor VIII manufactured by Bayer)[29].

4.9 Some USA manufacturers reported data from chimpanzee studies that claimed to show a reduction of hepatitis infectivity following 'dry' heat treatment[30,31]. However, such products continued to transmit hepatitis in clinical use[32,33], suggesting that none of them could be considered to be hepatitis-safe.

4.10 Uncertainty over the findings of studies in animals[34] meant that the hepatitis-safety (or risk) of a product could only be determined following detailed evaluation in patients. In 1984, concern over the validity of such studies led to a protocol (the ICTH protocol) being drawn up for this purpose by an international committee of experts. This required the assessment of up to 10 batches of a product in up to 20 susceptible patients who had not been treated previously with a blood product; with each patient being monitored for evidence of sub-clinical NANBH, at frequent intervals, for up to 6 months[35].

## 5. INITIAL SNBTS R&D ON HEAT TREATMENT OF FACTOR VIII

5.1 To achieve self-sufficiency in the supply of Factor VIII from unpaid donors, the SNBTS Factor VIII concentrate at that time (named 'NY') was a high yielding product which was consequently somewhat less purified than most of the commercial products. We found that NY could withstand dry heat treatment for up to 24 hours at 60°C or for up to 2 hours at 68°C before becoming insoluble.

5.2 Because of the lack of evidence concerning the ability of dry heat treatment to inactivate hepatitis and the relatively low tolerance of the NY concentrate to this type of treatment, the SNBTS R&D programme remained focused on pasteurisation, for which there was preliminary evidence from studies in animals and patients that it might be effective against hepatitis[36].

5.3 At PFC a number of discoveries were made in our attempt to develop pasteurisation of Factor VIII into a viable process[37-39] and, although there were considerable difficulties remaining, sufficient progress was made during 1983 that we were able to

prepare a pilot batch of pasteurised Factor VIII for clinical evaluation. Unfortunately the first patient treated suffered an adverse reaction, the clinical study was abandoned and we had to revise our R&D programme.

5.4 Our prototype pasteurised product (named 'ZHT') was less purified than that being trialled in Germany and we decided that further purification was needed both to avoid reactions in patients and to resolve the major technical problems being encountered on scale-up of the process.

5.5 Therefore, we began to undertake R&D on a high-yielding chromatographic method for the purification of Factor VIII in collaboration with Dr Alan J Johnson at New York University Medical Center[40], in the belief that a higher degree of purification would improve the pasteurisation process and perhaps enable a much greater degree of heat treatment to be applied, should this be needed to inactivate hepatitis viruses.

5.6 We learned much later that Behringwerke had experienced similar processing problems to ourselves which had severely restricted their ability to manufacture pasteurised Factor VIII. These problems were partially resolved by the incorporation[41] of a novel formulation procedure to stabilise Factor VIII, which had been discovered as a result of R&D at PFC, and a chromatographic procedure similar to that invented by Dr Johnson. In addition, we are aware of one major USA manufacturer (Bayer) who took seven years to develop a similar process for the pasteurisation of Factor VIII[42], which was later abandoned[29].

## 6. AIDS AND FACTOR VIII

6.1 In mid-1982 it was reported that two haemophiliacs in the USA had contracted a new illness, which subsequently became known as AIDS. By early 1983 further cases had occurred in recipients of Factor VIII and it seemed possible that this disease may be being caused by a blood borne virus.

6.2 As AIDS was occurring predominantly in the USA, the continued use of Factor VIII concentrates imported from the USA was a major concern. The use of locally produced Factor VIII was seen as a first line of defence, but with a recognition that the disease might be caused by a blood borne virus and that if so, it may just be a matter of time before the UK blood supply became contaminated.

6.3 It was a matter for conjecture whether or not this putative 'AIDS virus' might be inactivated by any of the procedures being studied for the inactivation of hepatitis viruses.

6.4 HIV was isolated in the USA during 1984 and this enabled an HIV screening test to be developed, as well as sufficient stocks of virus to be grown for laboratory experiments to be undertaken on the heat inactivation of HIV in the presence of Factor VIII.

6.5 During October 1984, in one of the first applications of the new HIV screening test, samples were tested from haemophiliacs being treated at the Edinburgh Centre. We were quickly informed that a number of Scottish haemophiliacs who had only ever

been treated with SNBTS products were HIV positive, indicating that contamination of the Scottish blood supply with HIV was already taking place.

6.6 Studies on the effect of heat treatment on HIV were being carried out in the USA by the Center for Disease Control, in conjunction with commercial manufacturers. Preliminary results were first reported on 2nd November 1984 at a meeting in the Netherlands at which SNBTS scientists were present.

6.7 The data presented demonstrated that a substantial degree of inactivation of HIV was obtained after 'dry' heating Factor VIII at 68°C for 1 hour; we already knew from our own studies that the SNBTS NY product could tolerate heating at 68°C for 2 hours.

6.8 PFC production had been suspended during the period October-December 1984, in order to complete a previously planned upgrade of the facility. Therefore, we decided to 'dry' heat treat at 68°C for 2 hours, all of the SNBTS Factor VIII already manufactured in order to have an immediate supply of product which would be HIV-safe. By heat treating the existing stocks of product, representing almost 12 months supply, we were able to ensure that all Factor VIII issued by SNBTS from December 1984 onwards would be HIV-safe. Furthermore, in this way sufficient heat treated, HIV-safe Factor VIII was available to treat all patients in Scotland.

6.9 At the same time, further R&D led us to discover how to prepare Factor VIII in a manner that would allow 68°C heat treatment to be extended beyond 2 hours, to provide a greater margin of safety. Experiments were undertaken using samples retained from our earlier studies on Factor VIII stability[4], resulting in a change to the formulation of NY being discovered that allowed heating at 68°C to be extended from 2 hours to 24 hours.

6.10 This work was completed in time for 24 hour heat treatment of FVIII to be introduced as soon as PFC production was begun again in January 1985.

6.11 At the same time, studies were being undertaken on the 'dry' heat treatment of Factor II, IX & X concentrate (named 'DEFIX'), which was used to treat haemophilia B. Changes to the DEFIX process were discovered which enabled the product to be modified to withstand heating at 80°C for 72 hours. However, as Factor IX concentrates were known to carry a risk of causing thrombosis, it was necessary to carry out suitable safety studies in animals[43,44] prior to infusing the new heat treated concentrate into humans. This precaution, delayed the clinical trial and introduction of heat treated DEFIX until October 1985.

6.12 Some years later, as the result of an HIV 'look-back' study it was discovered that two of the first batches of NY heated in November 1984 and two of the first batches of modified NY heated in January/February 1985, had each been prepared using a donation infected with HIV. Contaminated batches were subsequently found to have not transmitted HIV[45], confirming the effectiveness of the heat treatment processes used and the critical importance of introducing 68°C heat treatment immediately.

## 7. THE DEVELOPMENT OF 80°C HEAT TREATMENT OF FACTOR VIII

7.1 NHS colleagues at PFL Oxford were investigating the ability of a variety of preparations of Factor VIII to withstand different heat treatment procedures. During 1984, they discovered that one of their experimental preparations was able to withstand 'dry' heat treatment at 80°C for 72 hours.

7.2 This was a unique achievement, which was expected to provide a greater margin of safety against the risk of HIV transmission[46]. The preparation was some 10-times more purified than the SNBTS NY product and this was believed to be the reason why the PFL product (named '8Y') was able to withstand heat treatment at 80°C.

7.3 At this time there was no information to indicate if 80°C 'dry' heat treatment would have any effect on hepatitis viruses. By contrast, there was strong evidence from clinical studies, as well as from animal studies, that the pasteurisation process developed by Behringwerke might be effective against hepatitis viruses[36,47] (although these studies did not comply with the ICTH protocol and had to be repeated[48]).

7.4 Consequently SNBTS continued to work on the development of pasteurisation, with studies at this stage focusing on increasing Factor VIII purity to resolve the problems that had been encountered earlier (an approach which we now know that Behringwerke also took at this time).

7.5 Our work using chromatography to increase the purity of Factor VIII was already well underway resulting in material some 150-times more pure than NY. By the Autumn of 1985 we were able to prepare sufficient of this highly purified Factor VIII to begin studies on the freeze drying of this type of material.

7.6 We discovered that the standard method used to freeze dry Factor VIII was inappropriate for such a highly purified product and a new method of freeze drying had to be devised. However, once we had determined how to freeze dry this highly purified material, we discovered that it did not withstand 'dry' heat treatment at 80°C.This suggested that increased purity might not be the reason why 8Y could tolerate heating at 80°C.

7.7 By contrast, samples of the relatively impure NY product, that had been included in this set of experiments as controls, were found to withstand heat treatment at 80°C.

7.8 It became clear from these experiments, that it was the nature of the freeze drying process rather than the purity of the product *per se* which was critical to achieving 'dry' heat treatment at more severe conditions[49]. We therefore shelved our work on increasing purity and concentrated instead in adapting our existing technology to be able to introduce 80°C 'dry' heat treatment to Factor VIII to increase the margin of safety with regard to HIV, as this remained the overriding concern at this point in time[50-52]. This change in strategy was endorsed by SNBTS Management in February 1986.

7.9 The new freeze drying cycle that we had devised took much longer to complete than the standard cycles used in production therefore, to make this process practicable it was necessary to reduce the volume of solution per vial by introducing a degree of purification and concentration into the product. Although we were able to adapt

methods which we had already researched, these required to be fine-tuned and production equipment had to be designed, purchased and evaluated.

7.10 In September 1986, preliminary clinical data were reported by PFL/BPL[53] providing evidence that their 80°C 'dry' heat treated 8Y product had a reduced risk of hepatitis transmission and recommending that this pilot study be followed by a formal prospective clinical trial with a stricter protocol.

7.11 At PFC we had already decided to cease manufacture of 68°C/24 hour heated NY, so that the introduction of SNBTS 80°C heated Factor VIII (named 'Z8') could be accelerated by making production resources and facilities available to assist completion of the development work. We did so, knowing that we had sufficient stocks of heat treated HIV-safe NY to ensure continuity of supply while we worked on the new product. Consequently, the first full-scale production trial batches of Z8 were processed in August 1986.

7.12 On transferring Z8 to the production freeze driers a further key discovery was made concerning the importance of the crystalline structure of the product after freezing. A special freezing technique was devised to enable the uniform crystal structure required to be achieved reproducibly in all vials throughout all of the different production freeze driers[54,55].

7.13 Further fine-tuning of the process was required at full production scale, as some of the initial batches of Z8 were unable to tolerate heating at 80°C and were instead heated at 75°C for 72 hours.

7.14 The development of 8Y at PFL Oxford was undertaken using an early model of freeze drier which operated in a unique manner. In retrospect it is possible to see that the particular composition of 8Y, together with its FVIII content, specific activity, dose size and vial size, resulted in a volume of solution which when processed in this particular freeze drier, achieved both the necessary ice crystal structure and the appropriate drying conditions required for the product to then withstand 80°C heat treatment.

## 8. DIFFERENCES BETWEEN SNBTS (Z8) AND BPL (8Y) PROCESSES

8.1 The Z8 process developed by SNBTS[54] was essentially a simplified version of the 8Y process developed at PFL Oxford[56], which had itself been derived from the earlier ZHT (para 5.4) pasteurisation process being developed by SNBTS[37-39].

8.2 In both the 8Y and Z8 processes Factor VIII was prepared from cryoprecipitate, followed by a precipitation step to remove contaminating proteins. This step was followed by the concentration and formulation of Factor VIII prior to freeze drying and heat treatment.

8.3 In the 8Y process the first precipitation step used a relatively high concentration of heparin as precipitant[56] whereas in the Z8 process we used zinc combined with a low concentration of heparin[57]. There were two main reasons for this:

Firstly heparin, at high concentrations, interferes with the Factor VIII assay method used by PFC at that time and additional development of assays would have caused a significant delay.

Secondly, and most importantly, we had discovered that the degree of purification obtained by the 8Y process was not necessary for 80°C 'dry' heat treatment to be achieved. Therefore, by using the zinc/heparin precipitation procedure, with which we were already familiar, we were able to avoid a major area of additional work that would have been needed to implement 80°C heat treatment at PFC.

8.4 In the 8Y process, Factor VIII was concentrated by precipitation/centrifugation and the recovered precipitate resuspended then formulated using gel filtration. We had studied the same precipitation procedure during our work on pasteurisation but had found ultrafiltration to be a superior technology for this purpose, both in performance and ease of operation.

We had no experience of gel filtration of Factor VIII but, as formulation could also be achieved using ultrafiltration, our preference for ultrafiltration at the concentration step obviated the need for the extra stage in the process using unfamiliar gel filtration technology.

8.5 We judged, therefore, that rather than begin work on a new product with new process steps, we could introduce an 80°C heat treated product more rapidly by adapting existing SNBTS developments for this purpose.

8.6 In early 1985, there was no readily available equipment that could be purchased immediately for the heat treatment stage. At PFC, equipment which we had designed for the pasteurisation of Albumin at 60°C was able to operate at up to 70°C and this was utilised to enable the heat treatment of Factor VIII at 68°C to be introduced promptly.

8.7 During this period, PFL Oxford developed a specialised heat treatment oven for heating dried products, in conjunction with a manufacture experienced in this technology. PFC collaborated in this development and purchased equivalent ovens from the same manufacturer as soon as they became available.

## 9. INTRODUCTION OF 80°C HEAT TREATED FACTOR VIII BY SNBTS

9.1 Full-scale production of Z8 was begun at PFC during the Autumn of 1986. However, before the product could be issued routinely it was necessary to undertake a clinical evaluation to ensure that the product was effective and well tolerated.

9.2 Although 8Y appeared to be well tolerated, Z8 was a less purified product. There were concerns in the medical literature that heat treatment of Factor VIII may cause adverse reactions in patients[58] which, taken with our earlier experience of pasteurisation (see para 5.3), meant that freedom from adverse reactions could not be assumed. In addition, careful evaluation of the pharmacokinetics of heat treated concentrates was strongly advised[59]. Therefore, a clinical trial to establish the tolerability and effectiveness of Z8 was regarded as critical before the product could be issued routinely.

9.3 Before the clinical trial of Z8 could be undertaken, it was necessary to complete the fine-tuning of the process at full-scale (see para 7.13) and then to prepare a number of batches of the definitive product for clinical evaluation (with each batch taking about 2-3 months to complete manufacture and testing).

9.4 The clinical evaluation of tolerability and effectiveness of 80°C heated Z8 was undertaken in March-April 1987, with satisfactory results enabling the product to be available for routine clinical use from April 1987.

9.5 During 1987, a number of batches of Z8 were prepared which could not withstand heating at 80°C and were heated at 75°C instead. A thorough investigation discovered the problem to be related to the use of plasma which had been held in a temporary cold storage facility. Further work was undertaken to adjust the Z8 process conditions to make the product more robust to variations of this type.

9.6 Additional data on the safety of 8Y were published in 1988[60] and these were consistent with the interim results reported in 1986[53]. Further clinical studies have since confirmed both 8Y and Z8 to have been free from the risk of hepatitis transmission[61-64].

## 10. CONCLUDING REMARKS

10.1 The development of 8Y was a major achievement by NHS colleagues in England. This was the first 80°C heat treated Factor VIII product in the world and a number of patients in the UK were the first to benefit from this advance.

10.2 SNBTS scientists worked closely with their colleagues in England throughout this period, co-operating on the development of both Factor VIII and Factor IX concentrates

10.3 Although the development of 8Y was described at a number of international conferences during 1985/86, we believe that PFC was the first manufacturer other than PFL/BPL to have been able to achieve 'dry' heat treatment of Factor VIII at such high temperatures. We are aware of at least two other manufacturers who attempted and failed to achieve 80°C heating of Factor VIII before the key method that we devised for freezing and freeze drying of the Factor VIII solution was reported[54].

10.4 Many countries continued to use 60-68°C heated Factor VIII concentrates up to the early 1990's. Analysis of patient data has suggested that the use of such products reduced the incidence of HCV(NANBH) infection in haemophilia patients by about 75% in France[65], 83% in Finland[66] and 94% in Italy[67].

10.5 In the USA, these early heat treated products accounted for 90% of the Factor VIII usage in 1987 and some were still available in late-1989[68].

10.6 In 1986/87, commercial imports (which were predominantly heated at 60-68°C) accounted for about 70% of the Factor VIII used in England & Wales. By contrast there was little or no imported Factor VIII used in Scotland.

10.7 An imported Factor VIII concentrate, which had been 'dry' heat treated at 60°C, was withdrawn from the UK market in October 1986, following the transmission of HIV to a number of patients in the UK[69] and elswhere[70,71].

10.8 When a specific test for HCV became available, plasma and Factor VIII concentrates were found to have a much greater frequency of contamination with HCV when obtained from paid USA donors rather than UK donors[72-74].

10.9 In 1987, the use in England & Wales of Factor VIII prepared by PFL/BPL fell by about 25%, co-incident with the introduction of 8Y and there was an increased use of commercial imports commensurate with this.

10.10 Factor VIII concentrates imported into the UK during this period continued to be associated with hepatitis transmission[75,76].

10.11 Most commercial manufacturers exporting plasma products to the UK did not achieve hepatitis-safe FVIII before 1988-1990[29].

10.12 In Scotland, hepatitis-safe Factor VIII concentrate was introduced by SNBTS in April 1987 without any disruption to Factor VIII supplies.

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