

CAL36 (180412)

Clinician's perspective on availability and use of clotting factor concentrates for treating haemophilia in Scotland in the context of

Chapter 10 of the Penrose Inquiry Preliminary Report

Professor Christopher Ludlam

1. From the 1970s onwards there was a desire to treat those with severe haemophilia with concentrates of clotting factors because it was possible to administer an exact dose of treatment (labelled potency on the bottle), it was easier to administer than cryoprecipitate, adverse allergic reactions were less common than with cryoprecipitate and home therapy could only safely be given with concentrate.
2. In Scotland, because of the limited availability of factor VIII concentrates, much more cryoprecipitate was used than elsewhere in the UK in the late 1970s and early 1980s. This focused treatment in hospital rather than at home.
3. In addition in the late 1970s and early 1980s, there was a great deal of very understandable pressure from patients in Scotland to be given home treatment especially because this was less available than in England.
4. Home therapy critically depends on a ready and reliable supply of concentrate. Whereas hospital treatment can adapt to a reduction in the availability of concentrate, by substituting cryoprecipitate, for those at home this is not an option. If there is a lack of concentrate for home treatment then home therapy has to be discontinued. This is very disturbing and disruptive for patients (and their families) and should therefore be avoided if at all possible. Thus once a patient has been started on home therapy every possible effort is made to maintain this.
5. In Scotland the amount of SNBTS VIII concentrate was entirely dependent upon a supply of fresh frozen plasma (FFP) being delivered from the Regional Transfusion Centres (RTCs) to PFC. In return each RTC received an amount of factor VIII in proportion to the amount of FFP sent (a pro rata arrangement). The yield of VIII from FFP was at least 200 i.u per litre (kilogram) FFP.
6. The amount of FFP from each RTC sent to PFC varied quite considerably over the years as is illustrated in the Table on page 363 of the Preliminary Report. As a consequence the amount of concentrate which each RTC could expect would also varied to very significant extent each year. In addition some VIII concentrate had to be added to the national stock. There was an attempt by SNBTS to try to 'smooth out' the consequences of varying FFP supply between regions by redirecting concentrates to areas where an acute relative shortage appeared to develop.
7. As is clearly set out in the Preliminary Report Chapter 10 there were production difficulties from time to time at PFC for a variety of reasons. These had a very direct effect on the availability of concentrate to treat patients.
8. **Para 10.112 describes an example of the difficulties which arose when PFC was unable to deliver the anticipated amount of factor VIII concentrate.**

This paragraph describes in detail some of the meetings and correspondence in relation to availability of factor VIII concentrate in Edinburgh over the period 1981-1983. The description, however, is incomplete and therefore, unintentionally, does not encapsulate how the difficulty

CAL36 (180412)

arose, nor whether Dr Ludlam's expectations of the amount of factor VIII delivery from PFC to Edinburgh were reasonable. In the text quotations are given from two letters; Letter of 10th May 1982 from Dr Boulton to Dr Ludlam (SNB.001.5199) and a letter from Dr Ludlam of 1st September 1982(SNB.001.513).

What is not apparent in para 10.112 is that at the meeting between Dr Ludlam and Dr Boulton on 13th November 1981 (SNB.001.5195) it was clear - from the Minutes of the meeting but not quoted in the Preliminary Report - that PFC was at that time receiving FFP at the rate of 6000 litres per year from Edinburgh RTC and it would therefore be reasonable to have expected in return 1.32 million units of factor VIII concentrate per annum. The Minute concludes by making reference to a 'developing shortage of storage space' at the Edinburgh RTC for factor VIII. It thus appears in late 1981 that there would be a supply of VIII at the rate of about 1.32 million units per year and that there appeared to be a reasonable stock in the Edinburgh RTC. On this basis, Dr Ludlam calculated that on a conservative basis that Edinburgh could expect about 500 bottles of VIII per month (1.32M units FVIII/year gives a little over 100,000 units/month which equals about 500 bottles - the Minutes (SNB.001.5195) also indicate that there might be an increased amount of 1.65M units/year if certain production criteria were met).

Subsequently, in 1982, serious production difficulties arose and further anticipated at PFC as described by Mr Watt in his letter of 17th February 1982 to Dr Cash (SNB.007.2951). This letter was not seen by Dr Ludlam until recently and he does not have any memory of the situations described being discussed with him at the time. It illustrates in detail the difficulties arising in processing plasma early in the year and suggests that part of the reduction in deliveries of concentrate to Haemophilia Centres was due to Mr Watt using part of the FVIII output to build up a stock of FVIII to cover anticipated down time in 1983 (Preliminary Report 10.124 and Mr Watt's letter of 17th February 1982). These were again recorded in a Minute of a meeting 6 months later between Dr Boulton and Dr Ludlam on 23rd August 1982 (SNB.001.5207)). Professor Ludlam does not recall knowing about the plan to stock pile FVIII being discussed with him until this meeting, although it is evident from Mr Watt's letter that the plan was in place by February 1982. As a result of these various factors, the supply of concentrate at this time had to be reduced to 380 bottles per month and in addition there was to be a further reduction to 330 bottles per month in October 1982.

A major difficulty, therefore arose as a result of the stockpiling of Factor VIII by PFC, meaning PFC was no longer able to provide Edinburgh with the expected 500 bottles per month.

That this 500 bottles per month was a reasonable expectation by Dr Ludlam was strongly supported by Dr Cash in a letter to Mr Watt of 28th October 1982. Dr Cash in his letter of 28th October 1982 (SNB.007.3264) wrote ;

' there is no doubt that Chris Ludlam had, by the time we had our Pro Rata meeting (April 22nd.1982) started a very large number of 'new' patients on home treatment. He had done this on the basis that he knew by 31st March, 1982 the Edinburgh Centre had sent >6,000 kg FFP to PFC in that year. He did his sums and concluded on a pro rata basis he could look forward to a monthly issue, beginning of April 1982, of at least 500 bottles/month (assuming a 200 i.u./kg yield).

You will not be surprised to learn that Chris is on Schedule- his monthly consumption is exactly 500 bottles! Unless something can be done then he will have to switch some of his Home therapy patients to commercial concentrate'

CAL36 (180412)

The letter goes on to mention the then current industrial action at PFC. Dr Cash concludes by considering how it might be possible to continue to allocate 500 bottles per month of factor VIII to Edinburgh.

This example illustrates the great difficulty faced by clinicians who made plans for home treatment based on reasoned expectations of SNBTS supply (in this case 500 bottles per month) and then find potential serious logistic difficulty in treating patients when there is a shortfall in the amount actually delivered (down to 330 bottles per month).

Para 10.112 continues by drawing attention to Dr McClelland's letter of February 1983 to Dr Cash (SNB.001.5194) which is inaccurate in stating that 'one cannot readily accept the implication that Chris was inadequately informed of the supply situation'. Dr Ludlam was well aware of the then current situation (see above and the meeting at St Andrew's House of 21st January 1983) but there was a difficulty because he had started additional patients on home therapy in the spring of 1982 on the understanding that PFC was receiving 6000 litres of FFP from Edinburgh (equivalent to 500 bottles factor VIII) but subsequently this was reduced to 330 later in the year due to production difficulties at PFC (see above).

9. Fortunately after this time the supply of FFP to PFC improved, manufacturing arrangements improved at PFC and consequently the amount of concentrate available improved markedly during 1983 so that Scotland became self-sufficient in 'intermediate purity' factor VIII concentrate in this year.

See letter of 10th May 1983 (Dr Ludlam to Dr McClelland) and further correspondence from Dr McClelland of 15th May 1984 and reply from Dr Ludlam of 23rd May 1984. (copies attached – letter of 10th May 1983 retyped by CLO as original was poor quality carbon copy (with minor handwritten amendment to copy by Dr Ludlam in last paragraph of first page)

10. Logistics of supply, distribution and use of SNBTS Concentrate in Scotland.

There were three principal components which contributed to the difficulties in maintaining patients on SNBTS VIII concentrate

1. **The variable output of factor VIII concentrate from PFC.** The amount produced was dependent on the delivery of FFP to PFC (and this varied significantly over time as referenced above) and the ability for PFC to process it into VIII concentrate (which was interrupted periodically for a variety of logistic reasons including staffing difficulties at the manufacturing facility, the need for upgrading the facility periodically and even the supply of factor VIII deficient plasma for assaying the content of the final product).
2. **The extensive distribution and multiple 'storage' sites for the factor VIII concentrate.** Factor VIII concentrate was stored at many sites including RTCs, Haemophilia Centres, a variety of other hospitals across Scotland (so that they could provide emergency treatment for patients presenting with bleeds) and the homes of all patients who were on the Home Therapy programme. The number of patients starting on home therapy in the early 1980s was considerable and each one required a stock of concentrate and this was a drain on the supply (although it had not actually been infused to treat bleeds). An example of the distribution arrangements for the East of Scotland is set out in Figure 1 (attached) which illustrates the variety of multiple sites. It must be borne in mind that the size of the stock at the different sites was very different (e.g. the Edinburgh Royal Infirmary was a single site which attempted to hold a relatively large stock which would be sufficient for a month's requirement of the Haemophilia Centre, whereas there were multiple stocks in the many homes of patients on home therapy).

CAL36 (180412)

3. **The very variable requirement for factor VIII concentrate to treat patients.** Today large numbers of patients are treated with regular doses of prophylactic therapy. This has two advantages - it prevents bleeds and it is relatively easy to predict patient use of concentrate. In the 1970s and 1980s prophylactic therapy was uncommon and the majority of patients were treated when they bled, i.e. on demand therapy. This was completely unpredictable and consequently use of concentrate was therefore highly variable over time. This variability in use is illustrated by the monthly use of factor VIII in Edinburgh Haemophilia Centre which in 1982 varied from a low of 58,000 units (October) to high of 267,000 units (March); in one of the high using months it was therefore readily possible to exceed the 'monthly' allocation and strain the stock levels at the RTC (copy of original monthly usage record for 1982 attached – Figure 2).

As this variability and increasing use appeared to be a very serious contributor to the difficulty in maintaining a continuity of supply we undertook a systematic study of the situation by a University of Edinburgh statistician Dr Robin Prescott (Reader in Medical Statistics) who supervised a year-long project by Dr Hamid (attached – Reference 1).

11. Use of Commercial factor VIII concentrates in Scotland

Commercial factor VIII concentrates have been used in Scotland for the following reasons

- a. Uncertainty and inadequacy of supply of SNBTS concentrate (e.g. especially in the 1970s and early 1980s in Glasgow).
- b. Commercial concentrates were of higher purity and they were used either if patients in receipt of PFC concentrate developed a hyperviscosity haemorrhagic state after surgery (because of the low purity of the SNBTS product) or to cover surgery because it was anticipated that hyperviscosity might arise. This was a problem encountered in Edinburgh.
- c. Treatment of haemophilia A patients with an anti-factor VIII antibody requiring treatment of a bleed with a large doses of factor VIII concentrate.
- d. For the treatment of unusual haemostatic difficulties, or other 'exceptional situations' arising in patients with haemophilia A (occasional patient). This occurred in Edinburgh (details given in Reference 2: Table of Commercial Human Factor VIII Use' - attached)

It was generally agreed that the then current FPC concentrate was of a relatively low purity and that it was appropriate to consider that 10% of total use would need to be of high purity (PR page 357 para 10.99 and 10.101, and in SNBTS documents (SGF.001.0316, SGF.001.0257 and DHF.001.1268). As SNBTS did not manufacture a 'high purity' factor VIII concentrate at this time it was necessary to purchase this from a commercial supplier.

See correspondence of 26th November 1984 from Dr McClelland to Dr Ludlam and Dr Ludlam's response of 30th November 1984 related to commercial factor VIII purchases (attached)

Commercial Factor VIII statistics for Scotland 1974 to 1990

CAL36 (180412)

- a. Annual commercial factor VIII use by patients at each of the Haemophilia Centres was reported to the UKHCDO database. A summary of the annual returns for each commercial concentrate (and all other concentrates) at each Haemophilia Centre was set out in the Preliminary Report (Appendix 1 of PR). This Appendix is in the process of being updated particularly to add data prior to 1980.
- b. In Chapter 10 the Preliminary Report describes the history of collecting data on FFP supply from RTCs, the manufacture of clotting factor concentrates by SNBTS, their use in patients and the purchases of commercial concentrates. The report indicates that 'the data provided in Scottish documents tend (also) to be in consistent and unsatisfactory'. The exact source of information in the SNBTS documents is not explicit (SNB.002.3479 and SGF.001.0953). It might be helpful to set out some of the reasons why the data appears to be unsatisfactory.
 - a. UKHCDO concentrate use statistics at this time were recorded by **calendar year** whereas commercial purchases data was collected for **financial years**. It is also important to note that UKHCDO statistics record use of products by patients, whereas the statistics for commercial concentrates represent purchases. Concentrates may have been purchased in one year and used in the following one.
 - b. The information in the SNBTS documents appear incomplete, e.g.in a table entitled SNBTS; Purchases of Commercial Blood Products (SNB.002.3479) (Para 10.109 ref 135) there is no information given for Glasgow in 1982 – no reason is given for this – presumably this information would have been available from GRI.
 - c. It is unclear where SNBTS acquired its information about commercial purchases. Some was acquired from hospital pharmacies, which tended to operate on a financial year bases. But it was apparent to haemophilia physicians working in the hospitals that the information given by pharmacies was sometimes erroneous. For example it is unclear what SNBTS requested from hospital pharmacies – was it commercial total factor VIII purchases or commercial *human* factor VIII purchases (it was likely to the former); the former would, however, include porcine factor VIII concentrate. That this probably occurred is illustrated by the Edinburgh data for 1984 where in the calendar year 35,000 units of commercial human factor VIII was given to a patient (see Appendix 1 of PR) but the SNBTS summary (SNB.002.3479) states that in the financial year 1984 108,059 units of factor VIII were purchased. The discrepancy between these two numbers of about 73,000 units (108,059-35,000) was probably due to the purchase and use of porcine factor VIII in the calendar year 1984. The use of porcine in this calendar year was 91,000 (and 45,000 units porcine VIII was also used to treat patients in the subsequent year 1985).

A further example of a difficulty was when the pharmacy was compiling their data to give to SNBTS they may not have distinguished between different blood products and merely added the units of all products together (presumably thinking that they were all human factor VIII) – this led on occasions to factor VIII units being added to FEIBA units (this is basically a concentrate of factors II, IX and X which only contains traces of factor VIII).

CAL36 (180412)

The situation where human and porcine factor VIII appear to have been confused is illustrated in the above paragraph.

- d. One aspect of good therapeutic practise in haemophilia is to keep each patient on the same 'brand' of concentrate and not to chop and change concentrates from different suppliers. This was for two principal reasons, to limit the patient to different donor pools and to reduce the chance of developing an anti-factor VIII antibody. When there was a critical shortage of SNBTS concentrate at a particular Haemophilia Centre, SNBTS attempted to augment the stock at this Centre by moving product either from PFC or other BTS held-stocks. Occasionally a Haemophilia Centre, short of SNBTS concentrate and unable to maintain its patients on such a concentrate, would purchase commercial concentrate which would be exchanged for SNBTS concentrate held at another Haemophilia Centre where it would be given to patients maintained on a commercial concentrate. This system of exchange only happened occasionally but it certainly potentially explains another mechanism by which purchases of concentrate in some Centres may not equate with use. There are discrepancies in table SNB.002.3479 between what was apparently purchased in Edinburgh in 1982 (725,524) (SNB.002.3479) and used to treat patients (7000)(Appendix 1 of PR) and again in 1983 there as a purchase (of 463,868) and use (of 151,000) (data from Appendix 1 of PR). Detailed records of 'swaps' do not appear to be available but certainly occurred between Belfast and Edinburgh in the early 1980s. See letter of 30th December 1983 from Dr McClelland to Dr Ludlam referring to the arrangement with Belfast and indicating that the 'stock level is low' but 'the total stock level within SNBTS is at present very healthy' (attached). This highlights one of the challenges faced in ensuring a sufficient supply. See also Dr Ludlam's response of 11th January 1984 (attached) – related to 'exchange of commercial for PFC factor VIII with Belfast'. One or more relatively small exchanges occurred between Edinburgh and Belfast, where there were many patients already maintained on commercial factor VIII. There was also agreement in principle to have an exchange between Glasgow and Edinburgh but it seems unlikely this ever took place (copies of letters available).

List of attachments

- 1 Letter from Dr Ludlam to Dr McClelland 10th May 1983 (retyped by CLO)
- 2 Letter from Dr McClelland to Dr Ludlam 30th December 1983
- 3 Letter Dr Ludlam to Dr McClelland 11th January 1984
- 4 Letter from Dr McClelland to Dr Ludlam 15th May 1984
- 5 Letter from Dr Ludlam to Dr McClelland 23rd May 1984
- 6 Letter Dr McClelland to Dr Ludlam 26th Novmeber 1984
- 7 Letter Dr Ludlam to Dr McClelland 30th November 1984
- 8 Figure 2 - Edinburgh Monthly use of blood products 1982
- 9 Reference 1 - Consumption of factor VIII (FVIII) concentrates in Scottish haemophiliacs (1989-2003) by Eisa Hamouda Hamid (submitted to University of Edinburgh as part of M.Sc project)
- 10 Figure 1 – Flow chart of blood product distribution in East of Scotland
11. Reference 2 - Table of Commercial Human Factor VIII Use'