

Addendum

to

Self-Sufficiency and the Supply of Blood products in Scotland (with Particular Reference to the Treatment of Haemophilia A) [PEN.013.1125]

1. Introduction

i) At the oral hearings of the Penrose Inquiry, Lord Penrose invited me to revise my SNBTS paper on self-sufficiency [PEN.013.1125] (transcript 10th May 2011, page 153, lines 20-23).

ii) In response to this invitation, I have prepared an addendum to the paper, to provide the Inquiry with additional information which may be of assistance.

iii) Two aspects are considered;

- the supply of Factor VIII to Glasgow, and
- adverse reactions to SNBTS Factor VIII concentrate,

as these were reasons that were given to explain why commercial Factor VIII concentrate was used at Yorkhill Hospital Glasgow, rather than the Factor VIII provided by the SNBTS.

iv). In his evidence to the Inquiry (6th May 2011) Professor Hann stated that Dr Willoughby:

"felt that he had been let down with regard to supplies" and that commercial supplies meant *"you don't get let down at the last moment"* (transcript, 6th May 2011, page 28, lines 12-16),

and that Dr Willoughby was also concerned about :

"significant problems with reactions, infusion related reactions". (transcript, 6th May 2011, page 28, lines 24-25)

iv). Therefore, as a result of these comments, both the supply of SNBTS Factor VIII concentrate to Glasgow and the impact that adverse reactions to SNBTS Factor VIII concentrate might have had on achieving self-sufficiency in Scotland have been examined further.

2. Supply of SNBTS Products for the Treatment of Haemophilia

2.1 Supply of SNBTS Factor VIII Concentrate

i) During the oral proceedings the use of commercial Factor VIII concentrate in Glasgow in the early 1980s was questioned in comparison with Edinburgh, where much less Commercial Factor VIII concentrate was used. Inadequate supply of SNBTS Factor VIII concentrate to Glasgow, in terms of availability when needed as well as quantity, was indicated as one of the reasons why commercial concentrate was used.

ii). As little commercial Factor VIII concentrate was used in Edinburgh, the supply of SNBTS Factor VIII concentrate to Edinburgh must have been adequate enough to largely avoid use of commercial Factor VIII concentrates in that region.

iii). It may therefore be helpful to compare the amount of SNBTS Factor VIII concentrate issued to Edinburgh with that issued to Glasgow, to determine if Glasgow received significantly less than Edinburgh.

iv). In order to make this comparison it is necessary to take into account the different numbers of patients being treated in each region, their medical circumstances and treatment needs at any point in time, including situations where a greater volume of treatment was required.

v). SNBTS does not hold this patient information. Therefore, supplies of SNBTS Factor VIII concentrate to Glasgow and Edinburgh have been compared according to the size of the population encompassed by the respective Regional Transfusion Centres.

vi). The population figures used in this analysis are 2.718 million for the Glasgow region and 1.135 million for the Edinburgh region. These figures were the populations covered respectively by the West of Scotland RTC at Law Hospital and the Edinburgh & South East of Scotland RTC at the Royal Infirmary of Edinburgh in 1992, and are the figures nearest to the period of interest which I have been able to obtain from the SNBTS. Although the period examined (1976-1983) was some 10 years earlier, there was little change in the population of Scotland over this time; therefore the 1992 figures should be adequate for this comparison.

vii). SNBTS Factor VIII concentrate was distributed from the PFC to the SNBTS Regional Transfusion Centres, all of which held stocks from which supplies were issued to clinical users. To the best of my knowledge, supplies were issued from the RTC at Law Hospital to either the Haematology Department at Glasgow Royal Infirmary (GRI), where stocks were held and then issued to clinical users or, from Law Hospital directly to other hospitals in the Glasgow region, such as Yorkhill Hospital. In Edinburgh, Factor VIII concentrate was issued to clinical users directly from the stocks held at the Regional Transfusion Centre.

viii). To the best of my knowledge, records are no longer available for the issue of SNBTS Factor VIII concentrate from the RTC at Law Hospital to the Haematology Department at GRI, or to clinical users directly from either the RTC at Law Hospital, the Edinburgh RTC or the Haematology Department at GRI.

vix). By contrast, records are available on the supply of Factor VIII concentrate from the PFC to all of the SNBTS RTCs. These records include the original, signed batch issue sheet for every batch issued from 1979 onwards, which records the quantity issued, the date of dispatch and the RTC destination.

x). Data have been assembled for 1976-1983, to encompass the period when commercial Factor VIII concentrate was used in Glasgow. However, batch issue sheets prior to 1979 have not been retained by the SNBTS and only quarterly figures are available for the period 1976-1978. The quarterly and annual figures for 1977-1978 are given in Table A1.

xi). The original batch issue sheets have been reviewed to obtain the amounts of Factor VIII concentrate issued to the RTCs at Glasgow (Law Hospital) and Edinburgh each month for the years 1979-1983. These data are also listed in Table A1, together with the data for 1976-1978, in which the relative quantities issued are also expressed on a population basis. Comparisons between Glasgow (Law Hospital) and Edinburgh (expressed as a ratio) are given both quarterly and annually for the period 1976-1984.

Table A1. Issue of SNBTS Factor VIII Concentrate from PFC to SNBTS Regional Transfusion Centres in Glasgow (Law Hospital) and in Edinburgh, 1976-1983.

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop Ratio Glasgow/Edinburgh
	Glasgow	Edinburgh	Glasgow	Edinburgh	
1976					
Q1 '76	142600	97800	52465	86167	0.61
Q2 '76	74800	62400	27520	54978	0.50
Q3 '76	112800	47400	41501	41762	0.99
Q4 '76	221800	72800	81604	64141	1.27
<u>YEAR '76</u>	<u>552000</u>	<u>280400</u>	<u>203091</u>	<u>247049</u>	<u>0.82</u>
1977					
Q1 '77	245200	119000	90213	104846	0.86
Q2 '77	253600	47600	93304	41938	2.22
Q3 '77	235800	67400	86755	59383	1.46
Q4 '77	189600	20400	69757	17974	3.88
<u>YEAR '77</u>	<u>924200</u>	<u>254400</u>	<u>340029</u>	<u>224141</u>	<u>1.52</u>
1978					

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop
	Glasgow	Edinburgh	Glasgow	Edinburgh	Ratio Glasgow/Edinburgh
Q1 '78	120800	79400	44444	69956	0.63
Q2 '78	253200	39400	93157	34714	2.68
Q3 '78	295600	142000	108756	125110	0.87
Q4 '78	159600	36200	58720	31894	1.84
YEAR '78	829200	297000	305639	261674	1.17
1979					
Jan '79	91240	nil			
Feb '79	58840	7870			
Mar '79	115390	12810			
Q1 '79	265470	20680	97671	18220	5.36
Apr '79	94260	44850			
May '79	132830	21000			
June '79	67450	21000			
Q2 '79	294540	86850	108366	76520	1.42
July '79	146340	32970			
Aug '79	77600	21850			
Sept '79	136880	24120			
Q3 '79	360820	78940	132758	69551	1.91
Oct '79	165260	72600			
Nov '79	174350	nil			
Dec '79	137730	nil			
Q4 '79	477340	72600	175622	63965	2.75

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop
	Glasgow	Edinburgh	Glasgow	Edinburgh	Ratio Glasgow/Edinburgh
<u>YEAR '79</u>	<u>1306930</u>	<u>259070</u>	<u>480843</u>	<u>228256</u>	<u>2.11</u>
1980					
Jan '80	103890	nil			
Feb '80	161380	44720			
Mar '80	108470	47120			
Q1 '80	373740	91840	137506	80916	1.70
Apr '80	127260	112600			
May '80	192890	75700			
June '80	158420	94580			
Q2 '80	478570	282880	176074	249233	0.71
July '80	226050	17220			
Aug '80	100160	81360			
Sept '80	254370	99600			
Q3 '80	580580	198180	213606	174608	1.22
Oct '80	127930	203850			
Nov '80	161390	159600			
Dec '80	94070	258660			
Q4 '80	383390	622110	141056	548115	0.26
<u>YEAR '80</u>	<u>1816280</u>	<u>1195010</u>	<u>668241</u>	<u>1052873</u>	<u>0.63</u>
1981					
Jan '81	101800	55100			
Feb '81	212760	10290			

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop
	Glasgow	Edinburgh	Glasgow	Edinburgh	Ratio Glasgow/Edinburgh
Mar '81	142830	108640			
Q1 '81	457390	174030	168282	153330	1.10
Apr '81	155700	9500			
May '81	136490	54560			
June '81	388290	97200			
Q2 '81	680480	161260	250361	142079	1.76
July '81	245160	52040			
Aug '81	535150	135920			
Sep '81	236750	140180			
Q3 '81	1017060	328140	374192	289110	1.29
Oct '81	295690	88200			
Nov '81	347810	79910			
Dec '81	260450	85820			
Q4 '81	903950	253930	332579	223727	1.49
YEAR '81	3058880	917360	1125416	808247	1.39
1982					
Jan '82	147200	nil			
Feb '82	85440	160330			
Mar '82	177174	99600			
Q1 '82	409814	259930	150778	229013	0.66
Apr '82	339500	58000			
May '82	nil	107400			

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop
	Glasgow	Edinburgh	Glasgow	Edinburgh	Ratio Glasgow/Edinburgh
June '82	399010	nil			
Q2 '82	738510	165400	271711	145727	1.86
July '82	292970	88200			
Aug '82	211820	127710			
Sept '82	nil	42120			
Q3 '82	504790	258030	185721	227339	0.82
Oct '82	113670	149800			
Nov '82	274400	84580			
Dec '82	259230	99590			
Q4 '82	647300	333970	238153	294247	0.81
<u>YEAR '82</u>	<u>2300414</u>	<u>1017330</u>	<u>846363</u>	<u>896326</u>	<u>0.94</u>
Jan '83	nil	151620			
Feb '83	433030	24000			
Mar '83	455310	194650			
Q1 '83	888340	370270	326836	326229	1.00
Apr '83	422130	74000			
May '83	329810	89700			
June '83	279340	252000			
Q2 '83	1031280	415700	379426	366255	1.04
July '83	575540	75000			
Aug '83	540720	54000			
Sept '83	637690	222000			

Date	FVIII Issued (IU)		FVIII Issued (IU/m. pop)		FVIII Issued per m. pop
	Glasgow	Edinburgh	Glasgow	Edinburgh	Ratio Glasgow/Edinburgh
Q3 '83	1753950	351000	645309	309251	2.09
Oct '83	314300	125000			
Nov '83	1139360	629950			
Dec '83	662970	277720			
Q4 '83	2116630	1032670	778745	909841	0.86
<u>YEAR '83</u>	<u>5790200</u>	<u>2169640</u>	<u>2130316</u>	<u>1911577</u>	<u>1.11</u>
<u>1976-1983</u>	<u>16778104</u>	<u>6390210</u>	<u>6172960</u>	<u>5630141</u>	<u>1.10</u>

xii). It can be seen that supplies of SNBTS Factor VIII concentrate were dispatched to Glasgow RTC every month throughout the period 1979-1983 except for 3 months; May and September 1982 and January 1983. By comparison, there were 6 months when Edinburgh RTC received no supply; January, November and December 1979, January 1980, January 1982 and June 1982. In most instances, relatively high amounts of Factor VIII were distributed in one of the adjacent months, suggesting that RTC stocks were sufficient to enable the RTC to meet clinical demand during the month in question.

xiii). Edinburgh RTC did receive greater quantities of Factor VIII than Glasgow in the 2nd and 4th Quarters of 1980; the former may relate to the introduction of home treatment in Edinburgh (PR, 10.76), whilst the latter may relate to a marked increase in demand as a result of surgery on a number of patients in Edinburgh (PR 10.83). However, from mid-1976 onwards, Glasgow generally received greater supplies than Edinburgh.

xiv). Apart from the markedly higher distribution to Edinburgh in Quarter 4, 1980, there appears to be no evidence that supply to Edinburgh was generally higher than

that to Glasgow; indeed, for most of the period examined, supply of SNBTS Factor VIII concentrate to Glasgow exceeded the amount distributed to Edinburgh.

2.2 Supply of Cryoprecipitate by the SNBTS

i) The SNBTS provided cryoprecipitate, as well Factor VIII concentrate, for the treatment of haemophilia A. Therefore, it is necessary to determine whether or not any differences between Glasgow and Edinburgh in the use of cryoprecipitate might have impacted on the amounts of Factor VIII concentrate required.

ii) Records of the issue of cryoprecipitate for the period in question have not been retained by the SNBTS RTCs. However, the annual amounts of cryoprecipitate that were issued by each RTC for the period 1978/79 to 1983/84 are available from the SNBTS report that was prepared for the annual meeting of the Haemophilia Directors and the SHHD that was held in March 1985.

iii) The amounts of cryoprecipitate issued by the West of Scotland RTC (Law Hospital) and by the Edinburgh & South East Scotland (RIE) are given in Table A2 for the financial years 1978/79 to 1983/84 expressed as both the number of donations issued each year and the number issued per million population.

iv) Although cryoprecipitate was issued for the treatment of other medical indications, it is assumed that most of the cryoprecipitate issued at this time was primarily for the treatment of haemophilia A.

Table A2. Issue of Cryoprecipitate by SNBTS Regional Transfusion Centres in Glasgow (Law Hospital) and in Edinburgh, 1978/79 to 1983/84.

YEAR	Cryoprecipitate Issued (number of donations)		Cryoprecipitate Issued (no. donations per m. pop.)		Ratio G/E
	Glasgow	Edinburgh	Glasgow	Edinburgh	
1978/79	19922	13329	7330	11744	0.62
1979/80	12568	15735	4624	13546	0.34

1980/81	6551	17358	2410	15293	0.16
1981/82	7065	9221	2599	8124	0.32
1982/83	5187	7558	1901	6659	0.28
1983/84	7930	3423	2918	3016	0.97

v) These data indicate that the use of cryoprecipitate in the Glasgow region was much lower than in the Edinburgh region prior to 1983/84, with the greatest difference occurring in 1980/81.

2.3 Potential Impact of Cryoprecipitate

i) To assess the impact that cryoprecipitate might have had on the need for Factor VIII concentrate, it is necessary to combine the amount of factor VIII provided by cryoprecipitate with that provided by concentrate.

ii) This has been done for the years 1978/79 to 1983/84, in order to match the issue of Factor VIII concentrate by the PFC with the issue of cryoprecipitate by the RTCs. These data assume that one donation of cryoprecipitate contained 100 IU of factor VIII activity and that one vial of concentrate contained 200 IU of factor VIII activity.

Table A3. Issue of Factor VIII (Cryoprecipitate and Concentrate) by the SNBTS to the Glasgow and Edinburgh Regions, 1978/79 to 1983/84.

Year ^a	Total FVIII Issued (IU) ^b		Total FVIII Issued (IU/m. pop)		Ratio G/E
	Glasgow	Edinburgh	Glasgow	Edinburgh	
1978/79	3966070	1571180	1091269	1384300	0.79
1979/80	2672000	1867730	983076	1645577	0.60
1980/81	2555030	3196680	940040	2816458	0.33
1981/82	3717804	1925360	1367845	1696352	0.81

1982/83	3297640	1883470	1213260	1659445	0.73
1983/84	6343230	2714950	2333786	2392026	0.98

^a Financial year, April to March.

^b Total obtained by combining cryoprecipitate with Factor VIII concentrate, assuming 100 IU per donation of cryoprecipitate.

iii) The figures in Table A3 indicate that the greater use of cryoprecipitate in the Edinburgh region had a significant impact on overall Factor VIII supply, with more Factor VIII in total being issued by the SNBTS to Edinburgh than to Glasgow prior to 1983/84.

iv) The greatest difference in supply was in 1980/81 and coincided with a particularly high demand for concentrate in Edinburgh to treat surgical patients (PR 10.83).

v) The results in Table A3 are in contrast to those in Table A1, which concerned the issue of concentrate only and where the supply to Glasgow was generally higher than to Edinburgh.

vi) Therefore, it is possible that the greater utilisation of cryoprecipitate in Edinburgh may have reduced the need for concentrate in Edinburgh in comparison with Glasgow.

3. Conclusions (Supply)

i). There is no evidence that supply of SNBTS Factor VIII concentrate to the West of Scotland RTC (at Law Hospital) was generally lower than to the South East Scotland RTC (Edinburgh RIE) from mid-1976 to 1983; except for the period September – December 1980, when extra supplies were issued to Edinburgh when the impact of surgery influenced demand (PR 10.83).

ii) When the supply of cryoprecipitate is taken into consideration, the overall provision of Factor VIII by the SNBTS was greater to Edinburgh than to Glasgow each year from 1978/79 to 1982/83 inclusive.

iii) It would appear that, in addition to SNBTS Factor VIII concentrate, the total usage requirement for the treatment of haemophilia was made up in Edinburgh by the use of cryoprecipitate, whereas in Glasgow it was made up by the use of commercial Factor VIII concentrate. This difference may relate to clinical circumstances, such as the numbers of patients being treated at home.

iv) This is consistent with a conclusion in my original briefing paper:

"If cryoprecipitate is accepted as having been suitable for the treatment of haemophilia A when there was a shortfall of Factor VIII concentrate, then sufficient factor VIII was supplied by the SNBTS to provide treatment at the average UK level throughout the period from 1975/76 to 1989/90, except for 1982/83 when only about 90% of the UK level was supplied (Table 15), although reserve stock was available (Table 17)." [PEN.013.1125] (page 73).

v) Although the provision of Factor VIII concentrate by the SNBTS did not always match average UK use, it seems unlikely that the treatment of children should have been constrained by this, as factor VIII is administered by body weight and the quantities required to treat children should have been modest in comparison to the treatment of adult patients.

4. Adverse Reactions to SNBTS Factor VIII Concentrate

i). It has been a requirement since 1964 that an adverse reaction to a 'Prescription only Medicine' should be notified to the regulatory authority by the clinician concerned.¹

ii). Whenever the SNBTS was informed of a possible adverse reaction to one of its products, an appropriate assessment or investigation was undertaken.

iii). The SNBTS has retained records of possible adverse reactions to PFC products of which it was notified.

iv). These records have been analysed for any reactions to SNBTS Factor VIII concentrate during the period 1975-1983, excluding reports of viral infection.

v) There were three reports of reactions to SNBTS Factor VIII concentrate in the period 1975-1983:

a). Report CFA1 75-01².

This report concerned severe pyrogenic type reactions in two patients treated in Glasgow and was reported to the PFC on the 3rd of September 1975. The key points to note are:

- The patients concerned each received a different batch of SNBTS Factor VIII concentrate, but both experienced their reaction on the same day.
- In both cases the product was prepared for administration by staff in the Haematology Department at GRI, using a commercial supply of water-for-injection to reconstitute the Factor VIII concentrate.
- Both batches were recalled by the SNBTS; the SHHD advised that SNBTS Factor VIII concentrate should not be used for home therapy whilst the reactions were being investigated and Glasgow RTC (at Law Hospital) ceased the issue of SNBTS Factor VIII concentrate whilst the incident was being investigated.
- Both batches of Factor VIII concentrate had been used in the treatment of other patients in Edinburgh and in Glasgow, without any adverse reactions.
- Treatment with SNBTS Factor VIII concentrate was resumed without incident following the investigation, although no conclusion on the precise cause of the reactions was documented.
- As the implicated batches had been used to treat other patients without incident it is highly unlikely, in my opinion, that the Factor VIII concentrate was the cause of these reactions. The fact that both patients reacted on the same day points, in my opinion, to a common source of bacterial infection associated most probably with either the reconstitution or the administration of the product at GRI.

b). Report CFA1 78-01³

On 27th March 1978, the PFC Director was notified of a reaction in one patient in Inverness following treatment with SNBTS Factor VIII concentrate.

This type of reaction was not untypical of treatment with Factor VIII concentrate and appears to have been so minor that it did not merit further investigation.

c. Report CFA1 83-01⁴

The SNBTS received reports in October 1982 and in January 1983 from Dr Forbes of GRI concerning epileptiform reactions associated with the administration of SNBTS Factor VIII concentrate. The key points to note are:

- Although the SNBTS was originally informed that two recipients of Factor VIII had experienced reactions, it was subsequently confirmed that only one patient had reacted not two, and that this particular patient had reacted on 3 occasions.
- The implicated batches of Factor VIII concentrate were withdrawn by PFC pending investigation of the reactions and the Medicines Control Agency was notified.
- Following a thorough investigation it was concluded that the reactions were caused by the product being infused too rapidly by the patient concerned, rather than being due to a fault with the product.
- The implicated batches of SNBTS Factor VIII concentrate were re-issued and used without incident.

5. Conclusions (Adverse Reactions)

- i). PFC hold no reports of adverse reactions at this time that were received from either Dr Willoughby or from the Yorkhill Hospital Glasgow.
- ii). Report CFA1 75-01, did concern severe reactions in two patients in Glasgow. Although the SNBTS Factor VIII concentrate was not found to be responsible for these reactions, it is possible that the temporary hold on product supply by the West of Scotland RTC (Law Hospital), of about 3 weeks, may have brought the matter to the attention of Dr Willoughby (if he had not already known about it).

References

1. McIntosh RV. The regulation of the manufacture of medicinal products derived from blood plasma and the preparation of blood and blood components by the Scottish National Blood Transfusion Service. SNBTS report, October 2011. (already supplied to the Inquiry)
2. File CFA1 75-01
3. Report CFA1 78-01
4. File CFA1 83-01

Dr Peter R Foster

8th November 2011.