

*Ms Legge**Spec for Dr Maycock*

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MINUTES OF A MEETING HELD AT THE DEPARTMENT OF HEALTH AND SOCIAL SECURITY
ON 11 MARCH 1976 TO CONSIDER FACTOR VIII PRODUCTION

Present:	Dr J C A Raison	(Chairman)
	Dr Ethel Bidwell	PFL Oxford
	Dr Drummond Ellis	BPL Elstree
	Dr W d'A Maycock	BPL Elstree
	Mr J G Watt	PFC Edinburgh
	Dr A D McIntyre	SHHD
	Maj Gen H C Jeffrey	National Director, Scottish NBTS
	Dr Sheila L Waiter	}
	Dr J A Holgate	
	Mr P Jones	
	Mr T E Dutton	
	Mr R P Cleasby	DHSS

cc Those present
 Mr Draper
 Mr R N Roberts SHHD
 Mrs S G Evans WO

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Papers : Members had before them (i) a Memorandum by Dr Waiter surveying commercially-produced and NHS-produced Factor VIII concentrates
(ii) a note on the purchases of commercially-produced concentrates by NHS authorities

1. The Chairman opened the meeting by explaining that the Minister of State, who was taking a particular interest in the production of Factor VIII within the NHS had recently reaffirmed the intention to achieve NHS self-sufficiency by the middle of 1977. He was anxious that there should be maximum co-operation between the production units in England and Scotland both in achieving the target figure and reversing any preference which some users might have for one or more commercial products.
2. Dr Maycock said that if the expected volume of plasma was made available by NBTS the present annual rate of output of about 30,000 containers of AHG concentrate each of 250 International units (i u.) from BPL Elstree and PPL Oxford together would rise to a combined annual output of approximately 55,000 vials (a total of about 14 million i u. approximately). Several Regional Transfusion Centres had not yet been able to begin to work towards their individual targets for plasma production. He confirmed that there was an increased demand for cryoprecipitate in some areas. In the Birmingham region the increase appeared to be caused by the introduction of regimes of treatment which used larger doses of cryoprecipitate. Major General Jeffrey said that there had also been a rise in the use of cryoprecipitate in Scotland but demand was now levelling off. Mr Watt said that in Scotland half the current requirement of Factor VIII was being met with cryoprecipitate. The Scottish target figure for Factor VIII availability was 4.5 million i u. a year, making a combined target of $18\frac{1}{2}$ million i u. for Great Britain. Dr Maycock drew attention to the fact that the UK target was set by the Expert Group on the Treatment of Haemophilia in March 1973, and that there were those who now thought that the target should be considerably higher.

3. Papers were tabled showing -

- (i) the recovery of Factor VIII as dried product (Intermediate) EDINBURGH
- (ii) characteristics of 24 batches of Factor VIII concentrate produced at EDINBURGH
- (iii) characteristics of 12 batches of Factor VIII concentrate produced at OXFORD
- (iv) characteristics of 8 batches of Factor VIII concentrate produced at ELSTREE

It was explained that in order to equate the figures of international units

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of Factor VIII per ml for the English and Scottish products and express both figures in terms of activity of the reconstituted material, the Scottish figures (which referred to the volumes as filled) would have to be doubled. Mr Watt said that the general practice was to dissolve the concentrate in a sufficiently small volume to allow a 20ml syringe to be used. Both the Oxford and Elstree products were filled in a volume of 100 ml in a 400 ml BT bottle for freeze drying and was reconstituted in 50 ml.

When discussing the question of yield per litre of plasma, Dr Bidwell explained that the Oxford figure had been expressed in terms of gross yield. This figure, less the quantity used in testing, gave the net yield figure. Dr Maycock said that the Elstree net yield was about 200 iu per litre of plasma. Dr Maycock and Dr Bidwell confirmed that their aim was to produce a concentration of 10-12.5 units per ml eventually.

It was agreed that reconstitution at a temperature of 30°-37°C would reduce solubility time very considerably.

Mr Watt confirmed that the pH values for batches of concentrate prepared at the Protein Fractionation Centre, Edinburgh, referred to the reconstituted material. There was some evidence for the view that pH had some bearing on the stability of the product between time of reconstitution and use. In his experience, maximum stability was achieved when the pH was about 7.2.

4. Dr Waiter's memorandum "A Survey of commercially-produced and NHS-produced Factor VIII concentrates" was then considered. Mr Watt, referring to the statement on page 1 about yield in the 30-35% range, said that the aim at Edinburgh was to achieve a 70% yield. The yield at present was 35-40% but was rising. The gross yield in terms of units recovered per litre of plasma was running at 350-375 iu per litre. He agreed that the reference to a yield of 30-35% was previously correct. In order that results should be comparable it was agreed that yield should be expressed as gross and net yields in terms of International Units per litre of plasma, the gross yield being the total number of units recovered/litre and the net yield the total number of units/litre available for clinical use after removal of samples for testing, reference samples and inspection rejects. Dr Holgate referred to the statement on page 2 that three other firms had applied for product licences and said that two would probably be issued; 1 application had been withdrawn.

Dr Ellis suggested that the viscosity of the final product might be included

amongst the significant factors listed on page 3. If the solution was too viscous, usually because of excess fibrinogen, it became difficult to inject.

It was confirmed that production rates are increasing at the 3 NHS units. All could process more than the plasma at present available to them.

Regarding the cost of the NHS product, Mr Watt thought the figure stated, 6 pence per iu was too high. The Edinburgh figure was 4.2p per unit as issued, including water for reconstitution, and with some allowance for research. Dr Maycock said that the Elstree and Oxford products were being costed.

5. Dr Bidwell and Dr Maycock said that their products would shortly be available in a smaller container and require less water for reconstitution. There was discussion on the number of International Units which should be provided in each container taking into account clinical preferences. Dr Bidwell reported that the clinicians she supplied favoured two levels of iu per container and would accept 125 iu and 500 iu for a period of trial to assess the most economical "fill". It was agreed that the aim should be to meet the clinicians needs while avoiding the waste which would result if there were more units in a container than a patient needed. In discussion on solubility times, it was pointed out that the European Pharmacopoeia draft monograph stipulated solution within 15 minutes but it was agreed that the aim should be solution at 30°-37°C in about 5 minutes.

6. The effect of fibrinogen content on frothing was considered. Mr Watt pointed out that it was relatively easy to remove fibrinogen but only at the expense of Factor VIII yield. He felt that it was not always an advantage to be able to dissolve the concentrate in a small volume of water: a patient could find a syringe smaller than the 20ml size difficult to handle.

It was agreed that any other comments on the paper should be sent directly to Dr Waiter.

7. The Chairman concluded that the general view was that it was desirable for NHS products to be closely comparable, particularly in regard to purity, solubility and range of dose sizes (ie number of iu per container), bearing in mind the clinical and economic advantages of having a range of dose sizes. It was agreed that if the solution was too concentrated it might cause local irritation if injected too quickly and that the more experienced Haemophilia Centre Directors should be asked for their views on dosage and syringe sizes

preferred. Dr Bidwell pointed out that there was a high wastage rate in testing bottles which contained a large number of units per bottle.

It was agreed that to have too few alternatives in the NHS products range was undesirable because it would lead to the preferences of fewer clinicians being met.

8. It was agreed that the users' views should be obtained on what accessories, such as filter needles, administration needles, syringes, should be supplied in addition to the concentrate and distilled water. It was wasteful to include an administration needle and syringe with each package.

9. The impact of the Medicines Act on NHS production of AHG was discussed. Dr Holgate explained that the National Institute for Biological Standards and Control was currently testing commercial products and would shortly begin to subject NHS products to the same criteria. It was anticipated that the NHS manufacturers would effectively cope with Medicines Act requirements.

Any other business

There was no other business.

Date of next meeting

It was agreed to consider whether a further meeting of producers should be held when the views of users had been obtained.

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May 1976

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