F VIII file 0041

M E M O R A N D U M

TO: Mr. J. Watt H.O.D.'s A. Dickson J. Sinclair	FROM: Dr. P. Foster
SUBJECT: Plant Capacity for FVIII Production	DATE: 29th December, 1980

The new full-scale thawing tank will be ready early in the New Year. This will remove the present limit on our scale of operation, other factors will then become limiting.

1. PACK STRIPPING

Recent work in the Process section has established that the plastic pack can be removed (with difficulty) at temperatures higher than about -20°C. We already know that the optimal procedure before crushing (in terms of FVIII yield) is to allow the plasma to warm from -40°C to about -15°C by leaving the plasma at +4°C for about 6 hours. As it also seems that additional warming/cooling procedures may adversely affect FVIII recovery then we should aim for only 1 cycle of freezing/thawing. Hence the plastic should be removed during the single warming phase when the plasma lies between -20°C and -15°C. There would then be no requirement for additional heating (eg dip in warm ethanol), though washing with a cold solution may still be desirable to minimise microbial contamination.

The rate at which plastic can be removed from the packs now becomes a crucial parameter and this varies markedly with pack size. For single donor packs and manual stripping (4-5 operators) a rate of only about 70 l/hr has been achieved. Even this number of operators is probably too high to maintain cleanliness hence, if single packs are to be received at all, an automatic (or at least semi-automatic) process must be introduced. Otherwise this will become the limiting factor as soon as the new thawing tank is operational.

For large packs manual stripping is possible at a rate of about 200 l/hr.

2. CRUSHING AND THAWING

With plasma at -15°C the crusher operates at a rate of 200 to 250 l/hr while the new thawing tank has been designed to operate at about 200 l/hr. (This latter point will need to be confirmed in practice).

The limit of these operations is essentially time. If the whole process is to be completed within an 8.30 am - 5.00 pm working day then the cryoprecipitate should be available for extraction by about 1.30 pm at latest. With about 4 hours available for crushing and thawing then the maximum pool size will be about 700 - 800 l plasma. Larger pools will necessitate an earlier start to the stripping/crushing/thawing operation

3. CRYOPRECIPITATE COLLECTION

The Westfalia BKA6 has a capacity of 4.0 - 4.5 kg cryoprecipitate (see memo 19/11/79). This is equivalent to about 450 litres plasma. For larger pool

sizes the BKA25 should be considered. Though we have not used this machine for cryoprecipitate recovery the capacity will certainly be in excess of 10 kg (ie 1000 litres plasma pool).

Clean removal of the paste is likely to be even more difficult with the BKA25, hence provision of a proper facility for this must be a priority item.

4. FVIII EXTRACTION

The vibromixer agitator (E2) operates in the range 10-150 litres. The extract volume is approximately 4.2 litres/100 litres plasma, hence capacity here is substantial.

5. Al(OH)3 ADSORPTION

The key point here is removal of the gel. This is done by centrifugation and filtration. Five bucket centrifuges are available for this, but with only a 15 minute centrifugation time then the machines could be sequenced for multiple use. With appropriate phasing of these centrifuges and the clarifying filtration then about 40 litres of extract could be handled in the time available (Note: a reduction in the extraction time from 30 mins to 5 mins seems likely with the E2 agitator). Extra equipment (eg bell filters) may be needed to cope at this scale (eg 950 litres plasma).

6. FILTRATION AND DISPENSING

15 litre containers are currently in use (350 litres plasma) and 20 litre and 30 litre vessels are available. It should be possible to provide larger containers if necessary.

The time taken for these operations may become an important factor. This totals approximately 1 hour/10 litres of product for a 30 ml fill.

7. FREEZE DRYING

7.1 Leybold Heraeus

The limit here is a condenser capacity of 12 litres. This limit has been reached with the current pool size (300 kg plasma, gross) giving almost 12 litres of solution dispensed.

7.2 Usifroid

With the current 100 ml vial then space is the limiting factor. About 650 vials can be accommodated giving a maximum dispensed volume of 19.5 litres for a 30 ml fill. This would result from a plasma pool volume of about 450 litres.

If the PFC vial is replaced by the Elstree vial and if 2 extra shelves can be fitted then 950 vials could be accommodated from 28.5 litres of solution and a plasma pool volume of about 650 litres.

7.3 DRYING CYCLE

The current cycle is 3-4 days. The moisture content of the product must be less than 2% (E.P. monograph) however we do not know the lower limit necessary for stability. We do not know our routine moisture levels from our current cycle. To achieve full use of the driers the optimal moisture content (and drying cycle) should be determined.

8. CONCLUSION

The limiting factor on both plasma pool size and frequency of processing will be freeze drying capability.

The Leybold Heraeus is limited to a plasma pool of 300 kg (gross) while the Usifroid will meet a pool size of about 500 kg (gross). The smaller FVIII vial may allow the pool size to be increased to 700 kg (gross) for the Usifroid.

The drying cycle of 4 days is a major limitation and the best that can be achieved may be 6 loads per drier per month. Allowing 3 loads for FIX concentrate (and FVII) then perhaps only 6 Usifroid and 3 Leybold loads will be possible per month for FVIII. Even this may have to be reduced if holding of the dispensed vials at -40°C (in G86) is to be avoided.

Hence with the present vial, PFC capacity is limited to 975 kg plasma/week for Factor VIII recovery; this could be increased to 1275 kg/week if the smaller vial is introduced. This would give an annual capacity of 50-55,000 kg/year FFP. To meet the Scottish trends (66,000 kg/year) plus NBTS FFP we therefore require to increase both the number and size of our freeze driers. A partial solution to this problem would be to achieve a smaller fill volume (eg 200 iu FVIII in a 10 ml fill using 30 ml vials); this option would involve a yield penalty and would require a development decision by SNBTS (and NBTS).