

FVIII 2.167

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## M E M O R A N D U M

TO: Mr. J. Watt

H.O.D.'s

FROM: Dr. P. FosterSUBJECT: Heat Treatment of  
FVIII. A StrategyDATE: 3rd May, 1983

Until very recently the objective of our heat treatment programme was to cope with the hepatitis problem in haemophiliacs.

Because severe haemophiliacs have already been heavily exposed to untreated products then only mild and moderate haemophiliacs could benefit from a treated product (in the foreseeable future). It was estimated that the mild/moderate group could use up to 30% of the total FVIII. This estimate, plus the fact that these patients are presently likely to be treated with single donor cryoprecipitate have determined our present strategy i.e. that we will.

- (1) Plan for 4-6 pilot-scale lots during 1983.
- (2) Design a full-scale plant to handle 30% production for 1984/85 at the earliest.
- (3) Mild and moderate haemophiliacs can continue to receive single donor cryo meanwhile.

The possibility that another more serious infectious agent (AIDS) is now involved suggests that we may need to review this strategy. In the new scenario:-

- i) The haemophiliacs most at risk are the severes rather than the mild and moderates.
- ii) There is already evidence of a panic recourse to cryoprecipitate.

In the absence of any hard data, heat treatment (of everything) looks at the moment to be the most likely possibility that we have to face up to. If this is so then we will have to plan to pasteurise all of the FVIII (rather than 30%) and we may also want to review the timescales noted above.

Timing may become crucial for a number of reasons:-

- i) The publicised view that FVIII is infectious and that there may be a long incubation period (i.e. 3 years). We may argue that this has not been proven but hard data (one way or the other) could take years to achieve. Meanwhile decisions will probably be taken according to a "worst case" hypothesis.
- ii) There are some who would find a move back to cryo attractive and if this gathers momentum (it would only need 1 suspected case from NHS FVIII) we could see our FFP disappear overnight.

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There may therefore be a case for accelerating our heat treatment programme. While I do not disagree with point (2) above it may be possible to introduce an intermediate stage, still using the pasteurisation cabinets. We probably have most of the equipment to allow us to do this already.

i.e. Consider a 1000 kg pool of FFP.

- i) Zinc-Supernatant. This would be approximately 50 litres.
- ii) Sorbitol-Addition. The final volume would be about 110 litres. The old batch thawing vessels (150 l) are available and could be suitable for this stage. A new stirrer would need to be manufactured.
- iii) Pasteurisation. The spray cabinets are only used for 20 hours per week. Hence there is substantial capacity available for bottled fluids. The full scale FVIII batch could result in 220 x 500 ml bottles.
- iv) Dilution. At the moment we would expect to dilute the 110 litres of sorbitol-FVIII to 440 litres using a Tris/citrate/CaCl<sub>2</sub> buffer. This could be done in one x 500 litre vessel or two x 300 litre vessels.
- v) Ultrafiltration. The 440 litres should be concentrated to about 10 litres and this solution (15% sorbitol) should be diafiltered x 5 volumes. The total volume involved equals 480 litres (ie 430 + 50).

The Amicon DC30 can be extended to take 7 cartridges. The initial test of the air-driven pump suggests that a throughput of 7 litres/hr per cartridge is possible. Hence a complete unit (DC 70) could give 50 litres/hr.

The ultrafiltration time will therefore be about 10 hours but some time will also be needed for pre-filtration (prior to ultrafiltration), final filtration and dispensing. Hence the total finishing time could be about 15 hours. However, because FVIII is stable in the presence of sorbitol it would be possible to do the finishing over two days.

A tentative programme might be:-

- Day 1 (Monday) - Prepare cryo; zinc fractionation; add sorbitol; pasteurise overnight.
- Day 2 - Pre-filter; concentrate 440 litres to 100 litres.
- Day 3 - Concentrate 100 litres to 10 litres; diafilter, sterile filter etc. (10 ml fill).  
Repeat day 1 also
- Day 4 - Repeat day 2
- Day 5 - Repeat day 3 finishing.

This option would require the purchase of ultrafiltration equipment, some other minor items (eg stirrer) and perhaps some extra staffing, but it would enable us to cope with 2000 kg FFP per week as an interim solution pending a fully engineered process design.

Of course the in vivo recovery and FVIII yield would have to be adequate and information on this should be generated as quickly as possible.