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Dear Brian,

I have discussed the question of the microbiological quality of pooled plasma from Edinburgh with Bruce and it seems that we do not have much data specific to Edinburgh. However, Bruce has already started to collect data and we should have some hard facts in a few weeks time.

My initial reaction to the claim that PFC FVIII concentrate is of poorer quality than commercial "intermediate-purity" products is that this is probably fair comment. Our overriding aim has been to maximise yield to meet the philosophy of national self-sufficiency. Because of the inverse relationship between yield and quality this policy does mean that quality suffers. Our manufacturing process is designed to achieve a minimal quality commensurate with GMP (eg that the product will pass through a 0.2 μ filter and have a reasonable stability). Because of this our yield is relatively high (I do not know of a fractionator with a higher yield).

Obviously the commercial manufacturers do not have to worry about yield to the same extent and are therefore able to tailor their products to make them more attractive than the products of those who are attempting to be self-sufficient. While "hepatitis-free" FVIII is the extreme example (Beringwerke's published yield is 8%) this situation also exists within the "intermediate" range of products. A trade-off between yield and quality can be made by marginal changes in manufacturing protocols. For example PFC, Elstree and Oxford all use slightly different manufacturing methods even though our philosophy is the same (i.e. maximise yield). Neither BPL nor PFC have been able to filter their products when prepared ostensibly by the PFC method. They have therefore added an extra process stage (slightly different at each centre) giving a slight increase in purity to allow successful filtration; but that has entailed a yield penalty of 10-15%. Similar balancing cuts take place within the commercial houses with their different emphasis on yield showing through in the quality of the final products.

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Another point which should not be underestimated is the importance of feedstock quality. We believe that the commercial fractionators have a massive head-start simply because their FFP (plasmapheresis donations frozen to -40°C within 2 hours, stored at -40°C and fractionated within 2 weeks) is superior to ours (frozen at questionable temperatures up to 18 hours after donation, stored at questionable temperatures, up to 2-3 months before fractionation).

We appreciate that this situation can put the individual clinician in something of a dilemma and our present research programme therefore has 2 main objectives:-

(i) To increase yield further (we have identified the last major loss mechanism in-process and are well on the way to achieving a solution - that still leaves plasma quality as a problem).

(ii) To improve quality with little or no lossoof yield (we are making good progress in developing a method for a low-fibrinogen, high-yield product).

To return to your request for data, we have recently looked at a range of commercial products kindly supplied by Dr. Ludlam. I have enclosed some of the relevant data.

According to Jim Smith's definition of intermediate-purity (clinics in Haematol 8 (1), 183-206, 1979 - key page enclosed) the quality of the PFC product is in the middle of the range (ie about 0.35 iu/mg and 50-60% fibrinogen) but our yield is high (see Vox Sang 42, 180-189, 1982). Only 2 of these commercial products appear to fall within Jim's intermediate definition (i.e. Armour C + Alpha A) and I believe that we would achieve similar figures if we used the commercial "specification" for FFP noted above. There are a number of other products which fall into the lower end of Jim's high-purity range (Hyland A & C, Armour B, Immuno A & B) and it is conceivable that these may have been marketed as intermediate purity products.

Interestingly, some of the better quality high-purity products (eg Armour A and Cutter A) still have a high fibrinogen level measured as % total protein. This suggests that the fibrinogen load has been reduced by removing total protein (rather than fibrinogen specifically), hence the low FVIII yield.

I hope that these comments and the data will be of some help though I'm afraid that we will probably never win the quality "race" simply because we operate under ph philosophical and moral constraints which are different to thos of the commercial manufacturers.

Best wishes.

PETER R. FOSTER