Tovey Ad Hoc.

MEMORANDUM

TO: DR. R.S. LANE

FROM: DR. J.K. SMITH

DATE: 29TH APRIL, 1981.

SMALL-POOL FREEZE-DRIED CRYOPRECIPITATE AND OTHER SMALL-POOL PRODUCTS

At the meeting with representatives of the NBTS and DHSS on 23 April, 1981, representatives of the Haemophilia Centre Directors stated their preference for I.P. concentrate as the major component in national supply of factor VIII, but asked for up to 10% as high purity (not discussed here) and up to 10% as freeze-dried cryoprecipitate. From discussions with Dr. Gunson and Dr. Tovey on 24th April, I have the impression that the 10% had not been thought through but was a general indication of an upper limit. Clearly, they do not intend mass production of freeze-dried cryoprecipitate e.g. in the interests of factor VIII yield, but 10% of 100 million i.u. is still comparable with BPL's present output and means 150,000-250,000 donations per year! I find it hard to believe that this amount will be necessary for treatment of e.g. von Willebrand's disease (assuming nothing more specific comes along), carriers or very mildly affected haemophiliacs. Criteria and indications should be agreed before the availability of such an expensive product leads to abuse. It is also hard to believe that it will constitute a steady 10% of growing demand, since any growth will come only for the severe haemophiliac. The Working Party agreed that it would be prudent to retain a modest level of production of frozen cryoprecipitate in a few RTCs, for strategic reasons and, I would add, scientific reasons.

Product specification. How should we "design" this product in response to the stated needs?

(1) Safety. Most adverse reactions are associated with residual plasma in the cryoprecipitate. We would therefore aim at a hard-packed cryo with maximum removal of plasma and possibly a wash stage.

(2) Pool size. This has to be really significantly less than the 500-1,000 donations in large pools made in France and Belgium. A less rigid approach to "donor exposures" is suggested below.

(3) Unit dose. I see no reason to aim at more than the present 200-250 i.u. dose, since there is no indication for self-treatment or heavy dosage.

(4) Freeze-drying. A major problem of freeze-dry cryo is the large volume of dilute factor VIII to be dried, usually approached by spin-freezing. I don't know of any good way to include spin-freezing in the final bottle in a clean system (you may remember a debate with LV on the subject) and I am driven to the view that we should get the volume down to less than 40 ml to avoid spin-freezing, at whatever cost in overall yield and freeze-drying time.

(5) Yield and potency. These should be of lesser importance in this context than in the argument over the dominant national product. I suggest lower limits of 200 iu/kg and 5 iu/ml to the patient.

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Plasma sources. We are now obviously talking about plasmaphereis as a major source of plasma for factor VIII. One pattern which we might borrow from Belgium (even if it is not the main one) is the small panel bled at 10 litres per annum. One begins to play with the idea of counting intensively monitored donors, rather than donations, in much the same way as we treat the more elaborately accredited donors for FC. One could surely think about six month collections from 10 donors yielding batches of 50 kg plasma, given at least some plasmapheresis stations set up for intensive bleeding and equipped with additional freezers.

Whether donor exposures are minimised by pooling only about 2 kg plasma or up to 50 kg plasma, it is attractive to speculate on the comprehensive use of such "accredited" plasma for other products which cannot normally be considered safe from transmitting hepatitis.

(a) FC will, alas, probably increase rather than decrease, and will amount to a tax on factor VIII production unless we can develop it from cryosupernatant.

(b) FB (70% clottable) would best be recovered from this source, and the volume should be adequate.

(c) Factors II, IX, X concentrate could be used for a wider range of potential applications if it were not a hepatitis risk. One thinks of carriers, II or X deficient patients, reversal of warfarin therapy, liver biopsy, etc. The volume of production is about right.

(d) Factor VII. Again, the required volume of product may be about right.

(e) Factor XIII (possibly fibronectin?). This will probably alternate with FB, i.e. not recoverable from the same Fraction I. The volume required is likely to be very small.

(f) Antithrombin III. At least for the moment, the volume required for cautious clinical trials might well be covered by small-pool supernatants.

(g) Non-Cohn IgG, unpasteurised albumin; perhaps these are not to be dismissed. Also, non-production staff might be happier working with plasma carrying a greatly diminished risk of transmitting hepatitis.

Fractionation technology. Two main kinds of approach are suggested:

(a) Small-volume pools e.g. ≃ 2 kg or 10 donations.

The need to remove all the plasma from cryoprecipitate really means making, centrifuging, dissolving and pooling single-donation cryoprecipitates, i.e. pre-pooling of plasma in e.g. 2 kg or 3 kg packs is virtually ruled out. We are then condemned to a cottage-industry or "multiple" operation employing many labour-intensive aseptic transfers. If demand were small enough, I would recommend thaw-siphoning as giving the best yield of factor VIII per kg plasma and potentially the highest potency, to eliminate spin-freezing, but this would need even more hands than conventional cryoprecipitation. I also believe we would be required to do an expensive sterilising filtration, however well we organised aseptic transfers. The preferred product might therefore be a 4 or 5-donation pool giving ≃ 250 i.u. in 30-40 ml. Such a product would have to be quality controlled on a statistical basis, since the final product would

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be destroyed in sampling and testing. The prospect does not enthral me.

(b) Larger pools, 50-100 kg.

With the dispensations argued above, we could handle 50-100 kg pools from 10-20 donors in autoclaved equipment, virtually as PFL have been doing for years. Even with cosmetic improvements, the system would be conceptually more "open" than small-pool work, but would still offer a much better risk than 5,000-donor pools. The ensuing batch of 50-100 vials would be homogeneous and offer opportunities for respectable quality control. Sterilising filtration would be reasonably economical.

This approach is dependent on the kind of intensive plasmapheresis programme operated in Belgium, and some dilution of the current concept of "accredited" pools, but would approximate more closely to a defensible process for central fractionation.

GRO-C

J.K. SMITH

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