Ad Hoc Working Party on Trends in Blood Transfusion

PLASMA SUPPLY FOR SELF-SUFFICIENCY IN BLOOD PRODUCTS

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INTRODUCTION

Factor VIII intermediate concentrate reached its peak production rate at BPL in March 1977 at 15M units p.a. This was obtained from approximately 60-70 tonnes (1 tonne = 1000L) FFP p.a., equivalent to 350,000 donations of plasma. With no planning or finance forthcoming, this rate of production has not changed. During this period, use of factor VIII has approached 60M units p.a., achieved largely at the expense of imported product.

Since self-sufficiency in blood and blood products obtained free of any commercial persuasion is now increasingly advocated (WHO, ISBT Code of Ethic, etc.) the problem of meeting of meeting adequate plasma supply becomes the main central problem of NBTS during this decade. Immediate considerations are, therefore, the future requirements of the regional transfusion services to increase plasma supply and the need to improve fractionation capacity. It is evident that the needs and objectives of regional plasma suppliers and the fractionation laboratory are inter-related and complementary - a point to remember in all future planning.

To increase fractionation capacity to self-sufficiency levels, a new facility at Elstree is needed urgently. The interim period must be spent, however, defining past deficiencies, establishing new policies and organisation and making headway in production.

STATEMENT OF REQUIREMENTS

A. Interim programme

Factor VIII capacity 30M units coming on-line between mid-1981 and mid-1982. Capital investment approved; work and planning in progress and on schedule. Plasma requirement 140 tonnes = 740,000 donations (190ml). This level of FFP can be obtained from approximately 40% of the total whole blood donated p.a. (see below). Current effective input of FFP is 65 tonnes p.a.

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B. The plasma requirement to operate a new fractionation facility at self-sufficiency

The ultimate target is 90M units factor VIII derived from 410 tonnes of FFP at a nominal 220 units per litre.

A new laboratory would commission at 250 tonnes p.a.

Following commissioning, there would be phased targets.

(1)	Commission	250 tonnes p.a.
(2)	Self-sufficiency 1980 levels (65M units factor VIII)	300 tonnes
(3)	Full capacity 90M units factor VIII	410 tonnes

The deficits of the current programme are:

At commissioning (1) 250-65 = 185 tonnes

At 65M units VIII (2) 300-65 = 235 tonnes

At 90M units VIII (3) 410-65 = 345 tonnes

NB 1 tonne = 1000L = 5260 donations (190 ml) = 2000 x 0.5L plasmapheresis donations.
or 5550 donations (180 ml)

FFP from existing blood programme may be realised as follows:

% utilisation of 1.93M donations	plasma tonnes p.a.
20	73.3
40	146.6
60	219.9
80	293.2

FFP from an expanded donor programme (2.5M donations p.a.) may be realised as follows:

% utilisation of 2.5M donations	plasma tonnes p.a.
20	95
60	285

Thus the objectives, maintaining the maximum economic use of the voluntary blood donor programme are:

(1) Intermediate target of 140 tonnes, requiring the plasma from approximately 750,000 donations.

(2) Self-sufficiency later in the decade with three targets on a phased programme:

At commissioning, plasma from 1,300,000 donations.

At 65M units factor VIII, plasma from 1,650,000 donations.

At full capacity, plasma from 2,255,000 donations.

All plasma referred to is frozen fresh plasma (FFP) since the controlling parameter is factor VIII production. From the plasma provision for

factor VIII, sufficient plasma protein fraction (and other Cohn fraction V derivatives) may be realised.

INCREASED FFP COLLECTION FOR FRACTIONATION

There is a primary need for an NBTS policy statement on projected growth that embraces plasma producers, fractionation facilities and clinical use of products and enables the collective financial implications to be assessed.

In this respect two questions require an answer:

(1) How much of each product is needed? The driving force of 90M units of factor VIII for self-sufficiency in the late 1980's has been based on current usage of the product. This figure has been set for a redeveloped fractionation facility but the projection has been made largely without consideration of the implications for plasma production.

(2) Over what time-scale does the production policy extend? This is not determined although the requirements for NBTS growth is urgent since commercial inroads on the therapeutic blood product market are growing rapidly. If one accepts (1) above, then the ultimate growth required in output of plasma for fractionation is approximately six times the current level. Within the next 5-7 years, however, a level of 300 tonnes p.a., 4.5 times current output of FFP, is a reasonable target.

The secondary need is for NBTS to determine the extent and distribution of its growth requirements to provide for:

(1) an intermediate target of twice the present production of FFP.

(2) an ultimate target of a six-fold increase in FFP.

Since growth in any one part of the blood programme influences most other parts, an assessment of the variables and interacting factors is essential.

Main product variables are:

Whole blood
Red cell concentrates
Platelets
Therapeutic FFP
Cryoprecipitate
FFP for fractionation

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Main product requirements may vary primarily through clinical demand or as a result of the requirement of fractionation; e.g. the commitment of FFP for fractionation appears in diametric opposition to the clinical need for platelets and cryoprecipitate.

As a secondary phenomenon, the clinical use of plasma products (e.g. factor VIII) disturbs the product variables through increased needs for FFP for fractionation.

Undesirable cyclical effects may become superimposed, e.g. high FFP demands produce a high clinical usage rate of concentrated red cells, which in turn provokes increased use of plasma protein fraction. The drive to high collection rates of FFP may be economically self-defeating.

The inability to alter a single variable without having significant effects on others represents the inflexibility in the operation of the blood programme caused by having the whole blood donation as the common source of feedstock to meet all product demands. Any consideration of major growth in a single product therefore threatens to push the programme into imbalance unless there are ways of offsetting the effect. FFP supply for fractionation can be decoupled from the whole blood donor programme by using plasmapheresis, and some importance must be attached to this possibility (the same benefits of plasmapheresis may allow platelet collection to be decoupled from whole blood collection as the prime source).

Planned growth of plasma supply in the 14 regions will allow for special regional differences and requirements to be considered. It is likely, on various grounds, that it will be found that some regions will be better suited to collect FFP in bulk. An overall view of the expansion programme within the NBTS, with detailed input from each region will enable the consideration of different options each with their cost implications. It is clear that this cannot be achieved without co-ordination between regions, and is an important task for the proposed Advisory Committee on the NBTS.

Finally, financial aspects cannot be ignored. At present 350,000 donations of whole blood become time-expired per year together with a proportion of red cell concentrates. This immediately produces a loss of 15M units of factor VIII worth £1.2 -1.5M but the cumulative effect means that the efforts of three transfusion centres are limited to the production of plasma for PPF and normal immunoglobulin. The cost of such materials, per unit, must be high.

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The most economic manner for collecting FFP has to be considered. For example, it is believed that plasma collection from whole blood is less expensive than collection by plasmapheresis; there are no detailed costings to support this notion, but, were it so, would it remain economic to extend plasma collection from whole blood donations even though the red cells were not required? If so, to what degree?

OPTIONS AVAILABLE FOR INCREASED PLASMA SUPPLY

(1) Intermediate target

It can be seen from the data above that the intermediate target can be achieved by separating the plasma from approximately 40% of the existing donations. As stated previously 350,000 donations of blood become time-expired each year so that their potential value is lost to factor VIII production. In many countries it has been established that the use of red cell concentrates well in excess of 40% can be readily implemented and this target should be an urgent aim for the U.K. In many instances separation of plasma within 18 hours of blood collection will only anticipate removal after expiry so that the proportion of time-expired plasma should fall to a small proportion of the total.

Cryoprecipitate continues to be produced at many R.T.Cs. (in excess of 8.5M units in 1979), and it is important to consider how this product should continue to be used in the treatment of haemophilia. The well-known disadvantages of this product restrict its use and limit its value in many instances, but consideration should be given to the question of a freeze-dried small-pool preparation of cryoprecipitate to supplement the intermediate factor VIII concentrate. It should be borne in mind that the apparent higher yield of cryoprecipitate compared with that of factor VIII concentrates will be dependent on the pool size since yield will be lowered due to the necessity for obligatory tests for quality assurance in accordance with the B.P. and Medicines Act. Also losses will be incurred on freeze drying.

The production of cryoprecipitate in R.T.Cs. only relates to the intermediate target in as far as it prevents the separation of an adequate quantity of FFP. With pro-rata distribution of blood products each region will have to consider how its own programme can best be achieved and such considerations embrace several parameters, e.g. the total requirement of the various blood products, the financial implications and the staffing and space available for preparation of FFP, cryo., etc.

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(2) Self-sufficiency in blood products

(a) Maintain whole blood collection in NBTS at the present level and collect all excess plasma requirements by plasmapheresis;

(b) Increase whole blood donations to (say) 2.5M p.a. and collect excess plasma requirements by plasmapheresis;

(c) Applicable to (a) and (b) above, (i) examine advantages of collecting platelets by platelet pheresis, (ii) study the effects on the blood programme of increasing red cell storage time with CPD Adenine or with Saline-Adenine-Glucose;

(d) All FFP to be obtained from whole blood with discard of excess red cells.

Whichever option is acceptable, the effects of its implementation on regional services and NBTS organisation need full consideration. At self-sufficiency it will be vital for plasma supply to be guaranteed to BPL. The intermediate target is 40% utilization of whole blood for FFP production. It could be argued that this could be raised to 60%.

At this level, 100% capacity will be:

(a) present blood collection: 1,158,000 donations of plasma (220 tonnes)

(b) at collection of 2.5M: 1,600,000 donations of plasma (290 tonnes)

It is not realistic to base the supply on 100% capacity since many factors adversely affect its achievement. A more reliable working factor is 75% of total capacity. The above figures are then reduced to (a) 165 tonnes and (b) 217 tonnes FFP p.a. respectively. This gives a considerable shortfall on self-sufficiency and to achieve the required volume of FFP from whole blood on this basis would require the collection of some 4.7M donations.

These facts confirm those given previously that during the interim period of development of a new fractionation laboratory a source of plasma supply alternative to the use of whole blood donations will need to be investigated, planned and implemented. This will have considerable impact on the blood donor and donor organisation, since phlasmapheresis of one form or another seems to be the most applicable.

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New technology also has a bearing on the planned growth of plasma production. Thus:

(a) Increased red cell preservation with adenine

(b) Improved plastics and their effect on increasing platelet survival.

(c) Use of plateletpheresis.

(d) Cyrstalloid additives for red cell suspensions (saline-adenine-glucose).

(e) Single plasma pack development. This is now under trial in three regional centres and it is hoped that it will be introduced into other regions during 1981. The use of the single plasma pack has certain advantages for regional centres:

(i) the collection of the plasma is in a closed system and sets aside the need to meet Medicines Division's requirements for handling open systems;

(ii) it eliminates the time-consuming pooling of plasma;

(iii) it allows for the more rapid freezing of plasma;

(iv) there is a positive identification of each donation until immediately before fractionation.

The single plasma pack is designed for automated opening at BPL and whilst a facility for opening both 5 l. and single packs will be available for some time to come, consideration should be given to the handling of the packs at regional centres and the impact that they will have on staffing levels and facilities required per "unit volume" of plasma produced.

(f) Plasmapheresis

(i) Conventional manual procedure

The problems associated with this procedure, such as the time taken to complete, the need for refrigerated centrifuges, and the potential confusion of donor red cells are well known. The requirement for supervision at all stages is high. The combination of 450 ml. plasma and one donation of concentrated red cells is a possible variant to reduce the time factor.

(ii) Hemonetics Model 50. This machine is rapidly gaining favour and allows 500 ml. plasma to be separated in 35 minutes and an R.T.D. Working Party is considering the Code of Practice which should be applied to its operation. The chosen anticoagulant (4% citrate) is not well suited to factor VIII fractionation and the manufacturers aim to change this, probably to CPD. The plasma contains up to 30,000 platelets/ul but a 75 Kg pool recently fractionated at BPL presented no special problems although complete details are awaited.

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The cost of plasma harvested by this method is reportedly high but the manufacturer's estimate should be available in October and it can then be compared with other forms of collecting FFP.

(iii) Membrane Pheresis - should be available within 12-18 months. Potential advantages are cell-free plasma without centrifugation.

One main advantage of the single plasma pack and plasmapheresis for harvesting FFP is that it should result in the preservation of plasma of a uniform high quality since the donation is committed to FFP for fractionation at the time of blood collection from the donor. This should be reflected in the quality of the finished product, both in coagulation factors and Cohn fractionated proteins.

Other technological developments may have an effect on plasma supplies for fractionation, e.g. better methods of fractionation with improved yields, a better understanding of non-A, non-B hepatitis, and the means of removing this virus from the product, etc. It is important that all developments are closely monitored in order that selective advantages can be taken into account.

CAPACITY OF THE NBTS TO EXPAND FFP PRODUCTION

This is a complex problem which requires consideration in depth. There are several key areas, e.g. capital requirements for buildings and equipment, revenue consequences, management of donor organisation and administration. Important questions for resolution are:

(a) Within the 14 regions there exists a considerable variation in the potential to expand. What are the basic capital needs of individual R.T.Cs. to expand plasma production?
   (i) by increasing blood donations
   (ii) by increasing blood donations plus plasmapheresis
   (iii) by plasmapheresis alone

(b) Is it appropriate to consider all 14 regions as equi-potential for the expansion programme?
   Distribution of an expanded plasma production pro-rata to need throughout the 14 regions will stimulate growth in each and justify additional capital expenditure already much needed in certain regions. This approach allows the pro-rata supply of blood products to operate and authorities will find individual savings on the purchase of the commercial products.

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Assuming that there is the requirement in certain regions for increased red cells (say to an overall national level of 2.5M per year) and the remainder of the plasma required will be obtained by plasmapheresis, the collection of 200-250 tonnes of plasma by plasmapheresis may not be appropriately and economically distributed between all 14 regions. Areas of low population density may be less well suited to plasmapheresis than major urban centres. If certain regions undertake plasma collection surplus to their own requirements then pro-rata supply of blood products cannot operate successfully unless these regions can defray expenses by cross-charging. This important aspect must be fully considered and each region needs to answer the following questions:

(i) What is the most economically effective rate for plasma production within the region?

(ii) What is the maximum amount of plasma supply that can be undertaken by the regional service?

(iii) Is it advantageous to purchase the equivalent amount of plasma from another region to satisfy requirements rather than collect the plasma?

The calculations clearly must include, in addition to revenue implications, the capital cost of extensions to buildings and equipment. In the latter category the cost of storage facilities is important and must be correlated to the frequency of deliveries. The case for BPL taking over the entire collection of plasma is of interest, particularly if this can be combined with delivery of various products.

Staffing levels will need to be revised in the light of the targets set for increased plasma and blood collection. The impact on staffing levels in view of the newer developments in data handling will need to be assessed. For an expanded BPL to succeed economically, it is important that not only a guaranteed supply of plasma be provided by regions, but that the plasma conforms to agreed quality assurance and that the data generated by the regional centres can be successfully transferred to BPL. The introduction of data handling systems would need to be considered early in the planning of a new fractionation laboratory and this must be an urgent consideration within the regions.

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Donor organisation will be an important area for consideration. The collection of additional plasma will inevitably require more donors and this burden can be alleviated to some extent if plasmapheresis is part of the overall programme, since one donor may contribute 8-10 litres of plasma p.a. However, the distribution and management of plasmapheresis donors will present special problems. It is suggested that a working party should be formed at the earliest opportunity to examine the way in which a new plasmapheresis donor population is to be set up and maintained and how it should interact with the existing donor panels.

FINAL COMMENT

It is not suggested that this document is an exhaustive review of the problems of plasma supply which exist in the NBTS at present. Other factors will undoubtedly be high-lighted as discussions proceed. It is hoped, however, that this will be received by the divisions within the NBTS and discussed so that initially comments can be received by the Advisory Committee for the NBTS. Such comments can only be regarded as an initial approach to the problem since the present devolved administrative structure of the NBTS, which is likely to continue unchanged, requires detailed consideration at regions.

For the targets of both the intermediate target and later self-sufficiency in blood products to succeed it is important that there is a close co-ordination between regions so that the timing of the development of a new fractionating laboratory can coincide with an adequate supply of high quality plasma for fractionation.

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