FUTURE PREPARATION OF PLASMA PROTEIN FRACTIONS BY NBTS:

A Reassessment of Requirements

MEMORANDUM BY THE DIRECTOR, BLOOD PRODUCTS LABORATORY

SEPTEMBER 1979

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The following paper contains an analysis of the future requirements of blood product manufacture presented as a background introduction and followed by a framework of strategic proposals relating to NBTS.

INTRODUCTION

Two major problems which exist within the transfusion service are:

(1) The failure to meet NHS requirements for blood and (in particular) certain blood products derived from human plasma fractions

(2) The serious predicament of BPL following recent sharp criticism of the unsatisfactory manufacturing conditions by Medicines Division inspectors.

In both instances, the deficiencies can be resolved only by a co-ordinated joint approach based on two fundamental premises: first, the essential relationship between raw material supply and manufacture in which RTCs control the collection of raw materials (fresh human blood and plasma) and BPL manufactures the therapeutic plasma protein fractions; second, the quality control of the process being a continuous process involving RTCs and BPL. The two parts of the service are necessarily inter-related by balanced production capacity and quality control of product. It follows therefore that implementation of Medicines Division recommendations at BPL will have a complex feedback on RTCs: equally, failure to review the current position of RTCs will effectively limit the success of any attempted improvements at BPL either in its present state or conceivably in a future redevelopment.

The problems that exist now in the NBTS are not new, but have been accumulating in severity over several years in both regional transfusion centres and at BPL. The difficulties have been accentuated by the growth in requirement during the 1970s of plasma products, an exercise in production maintained without adequate planning, co-ordination or finance from the outset.

Thus the recent visit of Medicines Division inspectors to BPL has resulted in a timely acute focus of attention on this complex situation. It is timely because it coincides with the incipient reorganisation of the Health Service following publication of the Royal Commission Report. In spite of its own great need for reorganisation, it is significant that at no place does NBTS feature in the Royal Commission Report. For this reason, however, it is now appropriate that experts within NBTS with its interests in mind and with working knowledge of its needs make the strongest recommendations on the most suitable form of organisation to sustain an efficient service in the 1980s and beyond.

1. Blood Products: Provision to NHS

Protein fractions fall into two groups: those which are prepared at BPL and for which alternatives are not imported at present (e.g. anti-D immunoglobulin) and those which have readily available commercially manufactured alternatives (e.g. factor VIII and albumin). Commercial products, without exception, are highly expensive and imported i.e. they originate from plasma donated outside U.K.

Where BPL has traditionally supplied sufficient product, there has been no pressure to import material and no restriction on clinical use based on supply or cost to NHS: equally, product quality has been clinically acceptable and adequately controlled. Where BPL has failed to supply sufficient product, the deficit has been made good in several notable instances by imported commercial material (factor VIII, albumin and anti-tetanus immunoglobulin, for example), but at considerable and increasing expense to NHS.

Commercial cost to NHS of albumin cannot be accurately assessed, but it would be considerably increased if the price, per se, did not substantially restrict justifiable clinical use. With factor VIII (antihaemophilic globulin), a significant increase in use has been sustained over a 4-year period, current growth in use being maintained solely by extra imported factor VIII. It is likely that 60-65 M iu factor VIII were used in 1978, of which approximately 30 M iu were imported at a cost approaching £3 million (twice the BPL entire operating budget). In addition, this amount of imported factor VIII can be attributed to plasma from foreign (paid) donors equivalent to 900,000 to 1 million standard blood donations. In essence, more plasma was originated from paid donors abroad for factor VIII than was made available for all protein fractionation at BPL by NBTS during the same period.

In principle, this worsening situation is contrary to WHO recommendations, but, equally important, it is financially damaging to NHS and inevitably restrictive on clinical management. That the NBTS has deteriorated in its efficiency represents an untenable position both financially from the viewpoint of accountability and morally from the aspect of our responsibility to the voluntary blood donor.

The deficiencies lie within the NBTS and its administration since

it has been shown that, freed from constraints, the NBTS could make NHS self-sufficient in blood and blood products. Proposals seeking to correct these faults should relate to the blood transfusion service as a whole: they should seek to sustain and promote the voluntary blood donor programme and aim to co-ordinate blood collection, blood product manufacture and the requirements of the clinician. Proposals should also provide for full accountability and cost-effectiveness of operation.

Blood Products Manufacture: BPL

The list below shows the output of major products (1978) and marks with an asterisk those which provide for NHS self-sufficiency (1977 figures in brackets).

Coagulation factors:			
	Factor VIII concentrate 250 iu	62236	(52507)
*	Factor IX concentrate 600 iu	13085	(11495)
*	Fibrinogen 2g	1945	(1527)
Plasma:			
*	Dried human plasma 400 ml	14796	(10046)
Albumin:			
	Plasma protein fraction 400 ml (18g)	132471	(130847)
	100 ml (4.5g)	5259	(1381)
	Albumin 25 g dried	4102	(6292)
	20 g solution	1662	(—)
* Normal Immunoglobulin:			
*	250 mg	63000	(42895)
	750 mg	37050	(43360)
*	Anti-D 50 µg	30306	(29885)
	100 µg	88373	(76105)
*	Anti-tetanus 250 iu	35000	(1000)
*	Anti-hepatitis B 500 mg	1130	(1422)
*	Anti-rabies	1365	(531)

Factor VIII production, essentially static since April 1977, is at present deficient by some 30 M iu per annum. This deficiency will increase in 1979 and beyond.

Factor IX: meets current demands.

Fibrinogen: meets demands and is not imported. (There is no equivalent alternative product.)

Dried plasma: demands are approximately met but these originate mainly from a deficiency in purified albumin.

Plasma protein fraction and albumin preparations: all fall far short of requirements. Imports occur but are not accountable. No true value for clinical need currently exists.

Normal immunoglobulins) Specific immunoglobulins) Self-sufficiency is complete excepting anti-tetanus immunoglobulins which should become complete over the next two years.

The best estimate of commercial equivalent value of BPL products is in excess of £10 million per annum; at the level of NHS self-sufficiency, this would be nearer to £30-40 M p.a. by 1985.

This background indicates the essential nature of BPL plasma fractions and establishes the need to maintain BPL in production. It also underlin the urgency for expansion of BPL manufacture before clinical use of blood products becomes firmly orientated round the commercial market and before the extent of reliance on foreign paid donor plasma becomes generally known and there is an erosion of confidence in the NBTS voluntary donor organization.

Medicines Act 1968
Inspection Report on the Blood Products Laboratory

In summary, 'the burden of the report is that the shortcomings (of the laboratory) are so serious that continued production can be tolerated only because of the essential nature of the products and only if immediate improvements are introduced'.

There are two immediate forms of response to this report:

1. Within the existing laboratory there are limited additions, improvements, modifications etc. which should be made. These are interdependent in that each improvement on its own provides marginal benefit, whereas the package gives a significant increase in product safety. The need for co-ordinated improvements influences the cost: the programme includes increased staff and equipment, procedures and documentation, maintenance and environmental quality control. Much of the Stop Gap development was complementary to increased product safety.

These requirements should not be confused with others which would have been incurred anyway in the replacement of ageing plant and increasing maintenance of fabric in order to secure production reliability in status quo i.e. before BPL was inspected.

These requirements above are short-term based on maintaining production at its existing level.

Immediate planning should commence to redevelop the production process areas in new buildings by 1983/84 at levels of production outlined elsewhere in the 'Phased Redevelopment Initial Project Design' paper (Ref).

2. The second response is that, contrary to the recommendations of Medicines' Division, it is not realistic to hold production of factor VIII and albumin at existing levels until new process areas are commissioned. Without growth at BPL in the interim period, by 1984 the projected demand for factor VIII will be such that BPL's contributions will have become insignificant and unlikely to feature in the main stream programme of home therapy for haemophilia. Patients will be established by habit on commercial products and pack presentation.

There must be limited growth at BPL to assist the laboratory in a more gradual transition to a new large production unit. Thus staff will benefit from experience of new production systems and increased process capacity before taking over a new plant.

Particularly important during the interim is the determination of raw material supply from RTCs at the increased process level of a new plant. A large step-up in fresh plasma supply cannot be made suddenly. Between now and the commissioning date of a new production laboratory, the whole administrative and financial programme on which plasma supply is based would need reorganisation and time for gradual phased introduction.

The Central Defect in NBTS Organisation

In spite of the Medicines Division report, it is questionable whether BPL could make a substantial increase in factor VIII output at present because of the fall-off in frozen fresh plasma supply during 1979. Financial restrictions at RTCs are only part of the problem. Inability to co-ordinate the plasma programme is a central defect in NBTS organisation.

The considerable discrepancies between different regions with regard to how much support the RTC receives suggests that, even at regional level, the transfusion service has been neither clearly nor uniformly represented. For many years, the relationship between RTCs and BPL has existed only in an irregular manner, raw material supply being on a 'grace and favour' basis from regions. The pressing need for plasma protein fractions during the past 5 years has mercilessly exposed the organisational dichotomy

within NBTS whereby DHSS controls and funds BPL (the producer) and RHAs fund RTCs. At no time has there been an integrated administration capable of executive co-ordination of the NBTS programme.

Following Medicines Division Inspectors' visit to BPL and coincident with the publication of the Royal Commission Report on the Health Service, this is an opportune moment to provide NBTS with the type of structure and administration it needs to enable the whole blood transfusion programme to be efficiently managed in the future.

Reorganisation of NBTS

The NBTS is not mentioned at any point in the Royal Commission Report. This omission allows for experts in the transfusion service to outline the type of organisation needed independently of reorganisation of the rest of the NHS. Success in the future will depend on efficient management structure and a financial system compatible with efficient production and growth.

Special Health Authority. An SHA should be proposed and set up in keeping with special powers of Secretary of State. The NBTS would still comprise the 14 regional centres and the two central laboratories. Control would be through a board including special skills in finance, production, scientific/technical and personnel matters etc.

Services provided by RTCs would continue to relate to population zones now served by RHAs although the organisation of health authorities could change.

BPL would deal with RTCs on a pro-rata basis i.e. a highly controlled documented source of contracted plasma supply with return of attributable products at defined yields. The basis for inter-laboratory cost-accountancy would be established.

The transfusion centres directors would be part of the management board represented in a form similar to the new supraregional system plus central laboratories.

Financing

Within NBTS there have been limitations on ways whereby DHSS policy for NBTS could be centrally financed with capital and implemented peripherally without transgressing RHA's financial control of regional spending.

Additionally, the financial state of the Health Service suggests that, in the future, a proportion of future growth in health care will be supported by pay-beds organised through Medical Health Insurance.

If the NBTS is to maintain growth equivalent to entire health care needs, it will have to receive a disproportionate share of NHS funds or generate income from the private sector.

Equally the suppliers of plasma (RTCs) and the manufacturer of plasma products (BPL) must be on the same financial administrative basis.

Logically funding for NBTS should be taken completely out of the present system. NBTS instead should generate its own revenue, R & D income and capital through service charges made to health authorities and other health care systems on an equal basis.

The service must be fully cost-accountable with performance based on and compared with normal commercial practice. The aim would be to pass on to the health services the economies of the voluntary donor system (free plasma) coupled with the absence of marketing and sales promotional costs. The main benefit would be that of controlling blood products within NBTS rather than being progressively more vulnerable to policies of overseas commercial operators. However, the cost of NBTS products to NHS should be realistic, and allow for an adequate capital growth of the service.

Working Group to plan implementation of Inspectors' Report

DHSS has proposed that a working group is formed urgently to respond to the Medicines Division Report. This group should be sufficiently representative to make positive proposals on

(1) Short term changes at BPL and estimated costs

(2) Phased redevelopment of BPL as an urgent matter

(3) Reorganization of NBTS structure, administration and management to form an integrated unit comprising regional centres and central laboratories.

It is stressed that no valuable contributions to the future of BPL can be taken out of context of the NBTS as suppliers of raw material and receivers of finished products. In accordance with the Medicines Division requirements, documentation and quality control of human plasma must be uninterrupted from the donor to the manufactured final product.

The Working Group should make immediate proposals on financial reorganisation that will protect NBTS from the constraints of the present budgetting system.

R. S. LANE,
19 September 1979.

Reference: Annex 5, "The Function of Stop Gap and Phased Redevelopment of the Blood Products Laboratory". STC (79)5, Scientific and Technical Committee on 7 June 1979.