THE SPEYWOOD GROUP

P.P.D.S.

APPLICATION

Chancel House, East Street, Bingham, Nottingham NG13 8DR, England
Telephone: Bingham (0949) 38665-6 Telex 377138

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APPLICATION

SPEYWOOD POLYELECTROLYTE FRACTIONATION

Application for assistance under the Product and Process Development Scheme

Speywood Laboratories Ltd.

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In early June 1979 in the hope of obtaining a Product and Process Development grant, we submitted to the Department of Health a general statement of our plans for the development of a new plasma fractionation process, the costs of the development and a timetable for the development. This memorandum elaborates on that statement and on the costs involved.

Specifically it covers:

I. An introductory overview of what it is we are trying to accomplish and how the different elements of the programme inter-relate.

II. Details of the fixed capital investment required for pilot plants.

III. Details of the operating and overhead costs required to run the pilot plants.

IV. Details of external research costs.

V. Details of anticipated clinical trials and licensing costs.

VI. Cost Summary.

Appendices covering

A. Technical papers

B. External research programmes

C. Factory plans.

I. INTRODUCTION

For over two years Speywood Laboratories Ltd has been researching into the fractionation and purification of animal (porcine) and human blood fractions using polyelectrolytes. The initial work which has concentrated on Factor VIII has been very successful. Moreover, the laboratory results show that polyelectrolytes can be used for a total blood fractionation process producing purer fractions with better yields at lower capital and labour costs than can be obtained with the traditional Cohn process. This discovery could have a significant impact on the Department of Health's plasma fractionation costs, it will generate substantial foreign exchange earnings from exports and licence fees, and it will increase employment. This introduction explains the process and programme required to turn a laboratory discovery into commercially producable licensed products.

1. THE PROCESS

To make the various potential products a reality Speywood Laboratories is working through what is in effect a three stage process:-

a) Stage 1 - Production Research:- After a fraction has been isolated at the basic research stage we examine whether it will be feasible to produce relatively large quantities of the material economically and without loss of quality. At this stage an experimental laboratory manufacturing process is evolved and tested.

b) Stage 2 - Small Scale Production:- The laboratory process is taken and scaled up. In the process of scaling up parameters are changed and many refinements are made. At the end of this stage it is possible to design a pilot plant confidant that the pilot plant and the process have been optimized.

c) Stage 3 - Pilot Plant Production:- This plant produces material for clinical trials and licensing. It also enables Management to eliminate minor manufacturing problems before further substantial investment is made.

Because of the size of the Company, its personnel, laboratory equipment and research facilities, much of the work in Stage 1 is either sub-contracted to outside laboratories, or is carried out by Speywood's staff in outside laboratories. Two laboratories are of particular importance to us:

- Dr. Alan Johnson's laboratory in New York. Dr. Johnson was the first man to realise the possible potential of polyelectrolyte fractionation.

- Dr. Jean-Pierre Allain's haemostasis and coagulation laboratory at the C.N.T.S. in Paris.

Other laboratories where specific parts of the work will probably be carried out include Dr. Richard Lane's laboratory at the Lister Institute, Prof. Arthur Bloom's laboratory in Cardiff and Dr. Preston's laboratory in Sheffield. Proposed programmes of work with these various laboratories are outlined in Appendix B.

At Stage 2 all the work is drawn together at Speywood. In the future this work will be done in the area shown as "Research and Development" on the proposed Wrexham factory plans in Appendix C.

Stage 3 pilot plant production facilities are also shown in Appendix C.

2. THE PROGRAMME

The Company's intention is to develop the existing polyelectrolyte fractionation process to a point where the Company can produce itself a range of animal fractions and can licence others to produce human fractions. The fractions envisaged and their stages of development are as follows:

	Animal		Human
Stage 3	Factor VIII:C	Stage 3	Factor VIII:C
			Von Willebrand Factor
Stage 2	Fibrinogen	Stage 2	Factor VIII:R.A.G.
	Albumin		Albumin
	Animal Globulins		Immune Serum Globulins
	Haem		Factor IX
	P.A.F.		Factor X
		Stage 1	Factors II and VII
			Anti-thrombin III
			Plasma Proteinase Inhibitor
			Fibronectin

The way this programme fits together is shown diagramatically on page 6 . The importance of these fractions can be established quite quickly through discussions with the Department of Health. Many of the fractions have not been isolated before, and none of them with the purity that can be obtained using the Speywood polyelectrolyte process.

PROGRAMME FOR GETTING ELEMENTS OF THE NEW PLASMA FRACTIONATION PROCESS TO PILOT PRODUCTION

	1980	1981	1982	1983
STAGE 3 PILOT PLANT (Wrexham)	PORCINE VIII:C HUMAN VIII:C vWf			
STAGE 2 SMALL SCALE PRODUCTION (Wrexham)	FIBRINOGEN ALBUMIN ANIMAL GLOBULINS HAEM PAF HUMAN VIII: RAG. ALBUMIN ISG FACTORS II, VII, IX, X			
STAGE 1 PRODUCTION RESEARCH (Largely external)	PLASMA PROTEINASE INHIB FIBRONECTIN		NEW POLYELECTROLYTES DERIVATIZED PORCINE VIII SOLID PHASE ANTIBODY FOR IMMUNO ASSAY	

II CAPITAL INVESTMENT

The factory plans included in Appendix C show the lay-out of the proposed new facility at Unit No. 9, Wrexham Industrial Estate. The lay-out has been designed in such a way that the porcine plasma fractionation pilot plant can be scaled up easily once licenses have been obtained (1981).

The Department of Health has authorised the use of one sterile area for both pilot plants, and has given permission for several items of equipment to be utilized in both the human and animal plasma fractionation processes. This has resulted in savings over previous cost estimates.

The detailed costings are as follows:-

1. Essential basic structural modifications to standard Advance Factory lay-out (incl. changes to drains etc.)

   £12,000

2. Research & Development Laboratory:

- Structure	£2,000
- Refridgerated store	4,000
- Laboratory fittings	8,000
- Laboratory equipment	15,000

   £29,000

3. Pilot Plants:

a)	Central block clean area to class 10,000			£90,000
b)	Services including heat, light, filtered air, pyrogen free water, steam and 3-phase electrics			40,000
c)	Quality control structure, office and equipment			27,000
d)	Equipment			
		Animal	Human	Common
	Sharples	6,000	6,000	
	Wrights Cols	3,000	3,000	
	Stainless Steel Ware	2,000	2,000	
	Oven			6,000
	Autoclave			15,000
	Plasmabank			10,000
	Ref Store			4,000
	Chemical Store			1,000
	Wash area equipment			5,000
	Storage racking			10,000
				73,000
				230,000
	Total of 1,2 and 3			271,000
	Contingency of 10 per cent			27,000
			Estimated capital cost	£298,000

The timing of these costs is (1) November - December 1979; (2) and (3) some deposits November - December with balances April - June 1980.

III OPERATING AND OVERHEAD COSTS

The company plans to obtain licences by July 1981, i.e. within one year of the commencement of pilot plant operation. Between now and July 1981 the Company will have very substantial operating costs with only a small return from limited sales of Porcine VIII:C on a named patient basis. These costs are itemized below at constant 1979 prices.

	One off	Monthly (18months)	Total
1. Polyelectrolytes			
- Lab production	£10,000		£10,000
- Regular supplies (incl. supplies for external research)		£10,000	180,000
2. Cryoprecipitate		1,000	18,000
3. Other consumables		500	9,000
4. Operating charges			
- Heat,Light and Power		150	
- Filling charges		200	
- Post and Telephone		50	
- Depreciation		2,000	43,200
5. Salaries			
- R & D (Stages 1 and 2)		1,300	
- Pilot Plant (Stage 3)		2,200	63,000
6. Management and overhead charges @ 10%		1,750	31,500
TOTALS	£10,000	£19,150	£354,700

IV EXTERNAL RESEARCH COSTS

In the introduction we explained how some research is "sub-contracted" to outside laboratories, because of the Company's lack of suitable equipment and specific technical expertise. Generally this research is Stage 1-type work, but it can occur in Stages 2 and 3 to resolve particular problems. At the moment Speywood is completing a phase of work with Dr. Alan Johnson's laboratory in New York, and a further phase is planned to start in January 1980. Four other sub-contracted research programmes are also envisaged in order to enable the Company to complete its total fractionation process. These proposed programmes are all detailed in Appendix B. In summary they can be described as follows:-

1. Dr. Alan Johnson: Research to determine the best methods of obtaining large quantities of Plasma Proteinase Inhibitor. (Small quantities have already been obtained by affinity chromatography). Other work will be done to scale up methods for isolating Cold Insoluble Globulin (Fibronectin) by changing affinity procedures from Sepharose gel supports to supports with less internal volume.

   £63,660

2. Dr. Jean-Pierre Allain: Research into the scaling up of vWf fractionation, and the refinement of a new RIA Factor VIII assay.

   £50,000

3. Dr. Richard Lane: Finalisation of procedures for the fractionation of Human Factor VIII.

   £12,000

4. Professor Arthur Bloom: Development of a new assay technique for Porcine VIII:C

£5,000

5. Dr. Preston: Work to raise anti-bodies in rabbits for testing products prior to clinical trials and development of diagnostic products.

£12,000

V. CLINICAL TRIAL AND LICENSING COSTS

The final activities in which substantial costs will be incurred prior to being able to market the products are clinical trials and licensing.

1. CLINICAL TRIALS

Our intention is to carry out thorough clinical trials in the U.K, France and the U.S.A., supplementing these with limited trials in other countries, where necessary. With the data generated in these major countries we will be able to obtain product licences anywhere. The costs of carrying out clinical trials for animal Factor VIII and vWf will be borne entirely by Speywood. Clinical trials on other human fractions generally will be organised in conjunction with overseas partners. Estimated monthly and total costs for a six month programme are as follows:-

	£	
Porcine Factor VIII		
- Free product	£5,000	
- Consultant fees	1,000	
- Staff Costs	750	£40,500
vWf		
- Free product	1,500	
- Consultant fees	500	
- Staff Costs	250	£13,500

	£	
Human Factor VIII (UK)		
- Polyelectrolytes	(already budgeted)	
- Staff Costs	1,000	£6,000
Human Factor VIII (Overseas)		
- Polyelectrolytes	(already budgeted)	
- Staff Costs (incl. travel)	2,500	£15,000
	Total	£75,000

2. LICENSING

In the U.K. the costs of obtaining product licences will be determined by the Department of Health at the time applications are submitted. A rough estimate of this cost is £2,650. In addition we will retain the services of a firm of consultants to prepare the documentation for all countries at a cost of £26 per hour. For the first three products worldwide this is likely to amount to £50,000.

SPEYWOOD POLYELECTROLYTE FRACTIONATION PROCESS

(£000)

COST AREAS	1979	1980				1981		TOTAL
	OCT-DEC	JAN-MARCH	APRIL-JUNE	JULY-SEPT	OCT-DEC	JAN-MARCH	APRIL-JUNE	
II CAPITAL INVESTMENT								
- Building Structure	13.00							13.00
- R & D Lab	3.00	14.00	15.00					32.00
- Pilot Plants	25.00	100.00	128.00					253.00
III OPERATING COSTS								
- Polyelectrolytes	10.00	30.00	30.00	30.00	30.00	30.00	30.00	190.00
- Cryoprecipitate		3.00	3.00	3.00	3.00	3.00	3.00	18.00
- Other Consumables		1.50	1.50	1.50	1.50	1.50	1.50	9.00
- Operating charges		7.20	7.20	7.20	7.20	7.20	7.20	43.20
- Salaries		10.50	10.50	10.50	10.50	10.50	10.50	63.00
- Overhead alloc.		5.25	5.25	5.25	5.25	5.25	5.25	31.50
IV EXTERNAL RESEARCH								
- Dr. A. Johnson		10.37	10.37	10.37	10.37	11.09	11.09	63.66
- Dr. J. P. Allain		8.00	8.00	8.00	8.00	9.00	9.00	50.00
- Dr. R. Lane		3.00	3.00	3.00	3.00	-	-	12.00
- Prof. A. Bloom		1.25	1.25	1.25	1.25	-	-	5.00
- Dr. Preston		2.00	2.00	2.00	2.00	2.00	2.00	12.00
V CLINICAL TRIALS								
- Clinical Trials		27.00	37.50	10.50	-	-	-	75.00
- Licensing		10.00	10.00	10.00	12.65	10.00	-	52.65
TOTAL	51.00	233.07	272.57	102.57	94.72	89.54	79.54	923.01