PRODUCT DEV. GROUP. (Factor VIII)

FACTOR VIII DEVELOPMENT PROPOSAL

C PROWSE - April 1990

0031

REQUIREMENTS

I am convinced, given clinical expectations, that we must develop a virally inactivated factor VIII concentrate of specific activity >50 iu/mg and yield from plasma ≥200 u/kg within the next two years (to clinical trial). I take this to mean we have 12 months at most to establish a process suitable for pilot scale production and that the latter will provide material suitable for clinical trial 12 months thereafter.

VIRAL INACTIVATION

Given the yield losses incurred by use of dry or wet heat treatment, our current problems in routine application of severe heat treatment (due to the critical limits in terms of freeze drying for success using this technique) and Jim Smith's statement that severe heat treatment of products under 10 mg/ml protein is very difficult to achieve, I believe that we will need to adopt established solvent detergent technology. However, recent in-house data on heat treatment of the Lille product (attached) suggests it may be possible to retain in excess of 70% VIII activity at a specific activity of ~100u/mg. Thus we should not abandon terminal treatment, but should continue to work on this as a 'belt and braces' approach.

PROCESSING

As current precipitation technology does not consistently yield products in excess of 10 iu/mg, to achieve a specific activity 10 - fold more than this I am convinced a chromatographic process is necessary. In view of work by Eibl et al on identifiable immunosuppressive effects in FVIII concentrates this should ideally yield a product with a minimal IgG content.

Given the time limits to develop the product we do not have time to develop, in the first instance, an entirely novel process. Thus we should:

a. Seriously consider sub-licensing an established technology, such as that of Lille. This should be initiated now.

b. It is highly desirable in terms of clinical trial base and consistency within the UK, at least, to develop a product of comparable specification for the whole UK. I

therefore suggest that we pursue the option of developing a collaborative development with the CBLA.

The aim of this should be a formal comparison of the processes currently under development at PFC and BPL and the Lille process:

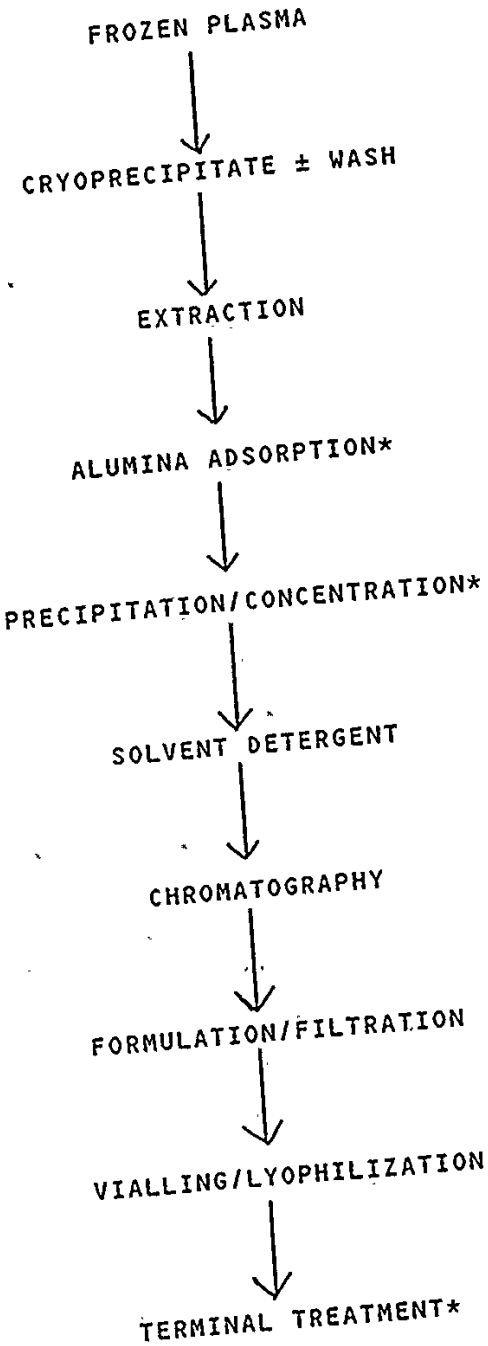
1. QAE - Sepharose chromotography
2. BPL - Chromotography process developed from AH Sephorose

Disclosures will be necessary and some further developments necessary (eg. choice of column feedstock, removal of prothrombin) before such a comparison can be made but we should aim for such a comparison in about 12 months time.

c. Longer term, better chromotography processes are possible (see D Pepper proposals) and in the interim we should continue to work on these. However as gels for these are unlikely to be commercially available now, and we have no impetus in this area at present, this option is unlikely to provide a viable pilot scale process within 12 months. This option would include appraisal of the Dutch gel and any arising from the Link proposal with Biotechnology Processes Ltd.

VON WILLEBRAND'S TREATMENT

There will be a continuing demand for a product to treat Von Willebrand's disease, which is currently being met by importing the 8Y product from BPL. This source cannot be regarded as secure in the long term. A product with a RiCof/vWf specific activity of 0.8 is required. It has already been proposed that, as an approach to these, available process fractions be screened for suitable fraction from which to develop a vWf product. There is also the possible option of obtaining the Lille process.



* Possibly optional step

0032

IN CONFIDENCE

HAEMOGLOBIN

D Pepper and S McDonald, NSL

A cross-linked pyridoxal modified stroma free haemoglobin product is under development at laboratory scale. The intended specification of this product is:

Haemoglobin (g/dl)	14-18
COP (torr)	20-25
p50 (torr)	20-28
Free tetramer (%)	<2
Met haemoglobin (%)	<10
Half-Life (h)	>6
Phospholipid (mg/dl)	<0.5
Virus removal	≥5 log at one step

To date the process allows production of a stroma and phospholipid free haemoglobin. Current work is aimed at minimising the content of free tetramer and endotoxin and incorporating a virucidal step. In vivo model studies have shown the current product has minimal vasoactivity due to the removal of adenine nucleotides.

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