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MEMORANDUM

TO: Mr. John G. Watt	FROM: P. Foster
SUBJECT: <u>R &amp; D PROGRAMME FOR PTC CONCENTRATES</u>	DATE: 6th April, 1983

1. INTRODUCTION

A rough summary of the current PFC situation is:-

1.1 Routine Products1.1.1 PPSB

The only routine product containing an appreciable quantity of FVII. Carries a potential risk of infection and a risk of thrombogenicity at high doses. Unattractive to manufacture for various reasons.

1.1.2 DEFIX

Successful product, but carries a risk of infection. Maybe thrombogenic at high doses. Maybe effective for treatment of FVIII inhibitors in the short-term.

1.2 Development Products1.2.1 Supernine

Reduced risks from infection and thromogenicity. Poor yield at present (e.g. 20% from DEFIX).

1.2.2 FVII

Scale-up problems under investigation. Risk of infection. Thrombogenic risk uncertain.

2. OBJECTIVES

Clearly our aim is to be achieve non-infective, non-thrombogenic products in reasonable yield. However, the advent of heat treatment has increased the number of options available. These would seem to be:-

2.1 Supernine

The infectivity risk has not been tested and the preparation may already be non-infective.

2.2 Heated DEFIX

Heating seems to be more respectable than PEG for removing infectivity. Thrombogenicity would need to be assessed. Results so far suggest that FIX/

FIX yield may be higher than present Supernine process.

### 2.3 Heated Supernine

Double attack on virus but thrombogenicity would need to be evaluated. Yield would be extremely low.

### 2.4 Supernine from Heated DEFIX

Another double attack on virus, but less effective than 2.3. May have a lower thrombogenicity risk than 2.3, but yield equally poor.

### 2.5 Heated FVII

Potential for pasteurisation still to be studied.

## 3. PROPOSALS FOR R & D PROGRAMME

### 3.1 Supernine

Recent experiences in Production suggest that further study should be carried out to optimise yield vs thrombogenicity (in vitro tests). I am planning to introduce this programme as FVIII studies wind down.

### 3.2 Heated Supernine (or SIX from Heated DEFIX)

If heat is used to cope with the virus then process conditions could be reassessed to maximise yield, with thrombogenicity as the only boundary condition.

### 3.3 Heat Treated Preparations

There will be a need to develop preparative methods for all of the potential products. Only when these have been determined can the properties of the various materials be seriously assessed.

## 4. ANIMAL STUDIES

Most of the decisions concerning preparative methodology should be taken according to in vitro tests (e.g. NAPTT, Tgt5<sup>0</sup>). However there is a good case for subjecting potential products to some in vivo assessment to confirm (or otherwise), the validity of the in vitro work. If confirmation is achieved then routine QA could continue to rely on the standard in vitro tests. The animal model would then be of little interest to PFC.

If there is a discrepancy between in vitro and in vivo results there would be a need for further research. This would seem to be a continuation of Chris Prowse's studies and would be best handled by him.

If we can achieve satisfactory products then I foresee little PFC interest in on-going animal work. Those interested in researching mechanisms of thrombogenicity may want to pursue longer term studies and it would be up to them to organise the facility.

## 5. POTENTIAL PRODUCTS

If I had to make a 'stab' at a future range of products I would go for:-

### 5.1 Heated DEFIX

Virus-free, reasonable yield, dose limited by thrombogenicity.

## 5.2 Heated Supernine

Low yield, for high dose use.

## 5.3 Heated FVII

## 6. ANOTHER POSSIBILITY

The approach being pursued by ARC is the preparation of "pure FIX", apparently on the grounds that "thrombogenicity" is due to excess FII.

The recent clinical experience with Supernine tends to act against this theory. However, there is probably a case for a low priority project to look at the methods so that we have something on file in case we need to go this way. Ron McIntosh has already done some preliminary reading to cover this.