NOTES FOR HAEMOPHILIA DIRECTORS MEETING MAY 1988 (SCOTLAND ONLY)

1. FACTOR VIII CONCENTRATES

1.1 Supply 1987/88

There exists a clear upward trend in the use of FVIII during 1987. This trend is substantial overall but perhaps most significant during the last quarter of 1987/88.

Estimates of RTC issues to Haemophilia Centres are derived as follows:

<table>
<thead>
<tr>
<th>RTC Stock</th>
<th>RTC Stock</th>
<th>PFC Issues</th>
<th>RTC Issues</th>
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<tbody>
<tr>
<td>March 87</td>
<td>March 88</td>
<td>1987/88</td>
<td>87/88 (estimated)</td>
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<tr>
<td>$1.9 \times 10^6$ IU</td>
<td>$0.9 \times 10^6$ IU</td>
<td>$9.56 \times 10^6$ IU</td>
<td>$10.56 \times 10^6$ IU</td>
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These figures compare with previous years as follows:

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<tbody>
<tr>
<td>IU</td>
<td>4.97</td>
<td>6.07</td>
<td>7.15</td>
<td>5.83</td>
<td>7.32</td>
<td>10.56</td>
</tr>
</tbody>
</table>

Thus issues of FVIII in 1988 represent an 81% increase over 1986 and a 44% increase over 1987. These figures represent a major and unplanned escalation in demand.

These increases coupled with manufacturing/technical difficulties (resulting in low process yields) at PFC have resulted in supply difficulties toward the end of 1987/88.

Whilst these technical problems associated with the introduction of the new Z8 product have now been substantially resolved, their effect combined with increased demand has led to a major depletion of National product stocks. In addition there has been a reduction in plasma intake during 1987/88 (51,200 kg vs 54,775 kg in 1986/87).

1.2 Production/Supply Planning 1988/89

The above supply/demand position is now imbalanced and whilst SNBTS Directors are urgently exploring options to increase output of FVIII to meet the unexpected escalation in demand, it is appropriate to forecast supply situation for 1988/89 based on:

(a) existing plasma supplies.

(b) existing process yields.
Estimates indicate that SNBTS can manufacture approximately $10.00 \times 10^5$ IU FVIII (Z8).

Directors are asked to address the possibility that supplies to Scottish Haemophilia Centres will be restricted to a maximum of $3 \times 10^6$ IU in 1988/89.

1.3 FVIII Development Plans

The PFC has established a two stage development strategy for FVIII products. The basic underlying policy is to concentrate on product virus safety, more appropriate dose size and National self-sufficiency. An emphasis on product purity per se is considered inappropriate at the present time. Directors may wish to note that 'new generation' commercial concentrates (immunopurified, solution heated etc) diminish process yield (approximately 25%–35% of PFC yields) and as a result are substantially more expensive. Moreover, there is emerging a major concern that yield penalties of these new processes are leading to product shortage in both the US and Europe.

The PFC development strategy is:

(a) Development of 'Classical' high purity concentrate utilising 'spin off' technology from the Z8 process. It is planned to manufacture this product in late 1988 for supply in January 1989. Product characteristics will be:

- Specific activity 2–3 IU/mg
- Dose size 250 IU and 500 IU
- Solubility Improved (less than 10 minutes)
- Heat treatment 80°C/72 hrs (dry)
- Yield 250–300 IU litre plasma

(b) Development of 'High Purity' concentrate (50 IU/mg) within the next 2–3 years. This product will probably result in a yield penalty of approximately 25% and will require to be phased into routine use over an extended period. This development is being pursued as a collaborative development with New York Blood Centre and Dr Alan Johnson (New York University).

2.0 FACTOR IX CONCENTRATES

There is a continued escalation in demand for FIX (DEFIX). PFC issues to RTC's since 1983 are as follows:

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<tbody>
<tr>
<td>IU</td>
<td>1.05</td>
<td>1.31</td>
<td>1.59</td>
<td>1.17</td>
<td>2.09</td>
<td>2.65 ($x 10^6$)</td>
</tr>
</tbody>
</table>

Improvements to process reliability and increasing processing scale have led to improved product availability and elimination of chronic supply shortages which have been apparent for some years. However, further unplanned escalation in demand will lead to a recurrence of supply problems.

PFC has planned to manufacture approximately $3.25 \times 10^6$ IU FIX in 1988/89.
Directors are asked to advise on:

(a) whether there is likely to be a further increase in demand for Factor IX during 1988/89.

(b) the proportion of FIX used for Haemophilia B and Haemophilia A (inhibitor patients) respectively.

(c) whether heat treated Factor IX has a comparable efficacy to non-heat treated FIX in the treatment of inhibitor patients.

2.2 FIX Product for Inhibitor Patients

The PFC is developing a FIX product for the treatment of inhibitor patients.

This product will possess the following characteristics and pilot batches for clinical trial are planned for Autumn of 1988.

- Increased specific activity and dose size.
- Removal of Anti-Thrombin III.
- Modified freeze drying conditions and formulation to conserve biological activity over dry heat treatment.

It is important (for planning purposes) to establish the likely demand for this product. Directors are asked to advise on the current distribution of product usage between Haemophilia B and Haemophilia A (inhibitors).

2.3 FIX for Acquired Haemophilia

The PFC has been approached by the British Society of Haematology to advise on the availability of coagulation factor concentrates for the treatment of acquired (coumarin induced) haemophilia. Directors are asked to advise on the likely demand for a FIX product in such situations.

3.0 VIRUS SAFETY OF COAGULATION FACTORS

Clinical evidence is accumulating to indicate that dry heat treatment of coagulation factor concentrates (80°C/72 hrs) is capable of providing non-infective products (HIV, NANB and HB). Whilst this data is derived primarily from studies of BY (BPL product) model virus studies at PFC indicate that the SN8TS product (28) has a comparable level of virus inactivation. Model virus studies have also established that dry heat treatment (80°C/72 hrs) is comparable in virucidal efficacy to "new generation" solution heated commercial products. HIV inactivation data is not yet available. Transfer of this work to PFC (subject to SHRO approval) is imminent. It is anticipated that 80°C/72 hrs dry heat treatment will be shown to be highly effective in HIV inactivation.

4.0 PRODUCT LICENSING

Submissions to DHSS have now been assembled. However, DHSS have indicated that HIV inactivation data is an essential component of these submissions and thus formal submission for the grant of product licence variations (FVIII and FIX)
has been delayed pending the availability of HIV data.

Directors may wish to note that PFC has recently appointed a person to assume responsibility for regulatory and product licencing activities of PFC.

5.0 NEW PRODUCTS

AT III AND FVIII

The development of a FVIII and AT III concentrate have been delayed during 1987/88 due to more pressing problems elsewhere in the PFC product range (FVIII, FIX, Albumin). It is hoped that FVIII and AT III pilot batches for clinical trial will be available within the next 9 months.

FVIII and FIX Deficient Substrates

Pilot batches of FVIII and FIX deficient substrate (manufactured by immunodepletion) are now being produced at PFC. Haemophilia Directors are asked to advise on:

(a) whether they would wish to receive supplies of this material in due course.
(b) the likely scale of demand.

DR R J PERRY
19 April 1988