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IN CONFIDENCE

Minutes of Coagulation Factor Study Group Meeting
held on 14 October 1986

Present:

Dr J D Cash (Chairman)
Dr F E Boulton
Dr B Cuthbertson
Dr J Dawes
Dr G S Gabra
Dr R J Perry
Dr C V Prowse (Secretary)
Dr D S Pepper
Mrs E Porterfield (Minutes)
Dr P Foster

1. INTRODUCTION AND APOLOGIES FOR ABSENCE

Dr Cash welcomed all members to the meeting.

2. MINUTES OF THE PREVIOUS MEETING

The minutes of the meeting held on 23 June 1986 have been circulated and with the undernoted amendments were agreed as a true record:

Minute 3 (c) (v): Urinary FpA studies should appear under the Aberdeen plasmapheresis study, not E/W developments.

Minute 3 (f) (ii): Change "1½" to "½ and 1".

3. MATTERS ARISING

a. FFP Specification

(i) Alterations to reporting format

(ii) RTC Validation results

There was a wide ranging discussion of the data collected for the first 8 months of 1986 which demonstrated inexplicable differences between centres in the mean FVIII:C content of all plasma collected. While 70% of plasma from Inverness,

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Aberdeen, Dundee and Edinburgh had met or exceeded the specification (0.7iu/ml) the Glasgow plasma had consistently fallen below specification. There was no apparent reason for this and it was agreed that Dr Gabra should continue to monitor the situation and in due course produce a report, for Directors, based on 12 months data with appropriate recommendations. GSG

(iii) Platelet Studies

Dr Prowse reported that comparison of frozen and unfrozen "spiked" plasmas frozen once and twice had produced no variation in results.

(iv) Follow-up of discrepancies: PFC/SEBTS FVIII Assays

Dr Prowse reported the results of the repeat studies which showed losses of about 5% on small freezing 2 ml amounts and 14% in universal containers. The problem was thought to be due to different methods of processing between SE and PFC. It was recommended that in future assays should be done only in PFC. ?→20ml

b. Centralised Assay System

Full information was not yet available on Glasgow/Edinburgh sample exchange study. This would therefore be included in the report for Directors being prepared by Dr Gabra. It was noted that it would be necessary for all centres to participate in the system and it was felt the Director, NIBTS would welcome the opportunity to do so. GSG

(Note - The draft manuscript for submission to Vox Sanguinis would be sent to Dr Cash for comment).

c. Fractionation Update

(i) Virus Inactivation

Dr Cuthbertson summarised the findings contained in his report (which had been tabled) on the ongoing heat inactivation studies on

1. Old FVIII Product (NY)
2. DEFIX
3. Z8 (Formulation 1)
4. BPL 8Y

(ii) Phase III Product

Update (Z8)

Dr Foster reviewed the background to the studies undertaken as follows:

1. Process — Cryoppt
Zinc Purification (also A1 on 3)
Concentrate/diafiltration
Slow Freeze-drying

2. R & D Studies — Cryo extract taken from production and further processing carried out in R & D Laboratory.
Freeze dried in pilot plant freeze drier to make 3 lots (50, 600 and 1,800 vials FVIII).
The losses on heating (80°/72) were 10–15% with a solubility time of 5 minutes (50 vials).

3. Introduction to Routine Production (Z-8-80)

Lot 1: ¼ scale, 200 vials on small production drier (600 vial).
Results were the same as those found in R & D.
Dr Dawes was currently engaged on assays and Dr Cuthbertson on "spiking" data.

Lot 2: ¼ scale, 600 vials on large production drier (1,800).
Results showed a 50% loss of FVIII:C (80/72) with a solubility time of 8 minutes.
(Note - during production a mechanical/electrical fault developed which was repaired and studies continued; see below)

Lot 3: Full scale, large production drier.
Results showed a 35% loss of FVIII:C (80/72) with a solubility time of 40 minutes.

In view of the above modifications were made to the freeze drying cycle.

Lots 4-8: Full scale, large production drier, various stages.
Results showed losses of 30–70% FVIII:C

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(80/72) with solubility times ranging between 35-40 minutes.

Failure at full scale production was due to varying performance of the freeze drier and a change in product composition (increased fibronectin) at batch 4.

In an effort to overcome these problems work was continuing in the following areas:

1. Modifications to procedure to improve extraction.
2. Establishment of freeze drying parameters to cope with "worst case" scenario.
3. Reduction of weight of cryo/L plasma to 1984 levels.

It was thought that it was unncessary to heat at 80°/72 hours and studies on product heated at 75°/72 hours had yielded approximately 300iu FVIII/L plasma (current yield was 200iu).

After further discussion of the difficulties inherent in the production and issue of a 75°/72 product it was agreed that Dr Cash would write to Dr Boulton (copy to Dr Ludlam) seeking the co-operation of Haemophilia Directors in a small study (approximately 4 weeks) of recovery and t½ of this product. Dr Cuthbertson would send Dr Boulton the analytical profile of the product, when available.

Dr Dawes reported on the studies undertaken on Phase III product (Lot 1 above) which had shown an increase in aggregates greater than in any previous studies. It was noted, however, that studies on 8Y (2273) and NY (2268) product had produced results never seen before: peaks on heated and non-heated product similar; fibronectin was removed; constituents could not be identified and more sensitive assays were required. A comparative estimate of aggregate content between 8Y and NY was currently being assessed.

It was agreed that further comparison of these results with commercial products (eg 2 vials Immune, Alpha, Hyland and Cutter Products - PFC to purchase via FEB) would be helpful. Dr Boulton agreed to contact Dr Eric Preston who might be able to assist; failing this approach product would be purchased. (See above)

FEB

(iii) Phase IV Product

Due to the diversion of effort to Z8, recent staffing changes and the realisation that cryoppt was of a poorer quality than previously there was no progress to report. However, all

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necessary equipment had been received and it was hoped to commission this in the near future.

(iv) Citrate Studies

These studies were progressing well and a report summarising the current position would be issued very soon by Dr Prowse. -see gallups

Studies were now in progress on autologous infusion using ½ and full strength citrate.

Dr Foster was asked to consider minimum batch sizes for fractionation.

(v) Plasmapheresis Study

Dr Prowse showed graphs of the recent results which demonstrated higher levels of FpA than those previously seen. It was not clear what had caused this phenomenon which might be attributable to differing freezing rates because of technical failure (freezer broke down).

Dr Perry explained the difficulties encountered in collecting plasma pools as planned (250 kg of Haemonetics/Dideco/PRP/Recovered) in order to assess comparative differences on fractionation. It was now proposed to include Haemascience plasma in the study and NE BTS would collect plasma (using Haemascience machines) for comparison with that collected using Haemonectics machines. Notwithstanding the cost implications of these studies Dr Perry emphasised the importance of continuation and after further discussion Dr Perry was advised to contact Dr Morgan, WBTS (where Haemascience machines were already in regular use) to seek her co-operation in plasma collection. RJP

(vi) E/W Developments

A. Small Scale Models

FVIII

Dr Smith had now concluded that the variable temperature of plasma from pool to pool before thawing and crushing affected cryoprecipitate quality and this had now been controlled.

FIX: There was no progress to report.

B. Core Protocol: The paper prepared by Dr Smith was tabled.

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d. Lots 4013 and 4014 - Cardiff Studies

OFF AGENDA

e. Virocidal Options (see above)

f. Assay Group

(i) QA Exercises

Dr Prowse presented the results of exercise 86/2. It was agreed that he should send to JDC in January 1987 a precise report which would be sent to Directors along with the report from Dr Gabra (see above). CVP

(ii) Immunodepleted Plasma

Dr Prowse spoke to an overhead slide showing data on recent batches of congenital/monoclonal substrate plasma, neither of which had met the required stability/performance standard.

Dr Perry had, as agreed, considered with his staff the possibility of undertaking production within PFC and had asked Mr McQuillan to liaise with Dr Prowse regarding the necessary technology etc and handover or production. Mr McQuillan had now done so and discussions were taking place within PFC. In the meantime a further batch would be made in SE.

g. Dog Studies - DEFIX

Dr Dawes summarised the results following infusion of Lot 4-012 (unheated) and the comparative data with Lot 4-015 (heated). It was concluded that this batch was thrombogenic and could constitute a risk if issued for use by inhibitor patients.

h. Phosholipid/VIII Complexes - OFF AGENDA

i. FIX Concentrates - Clinical trials

This project was now of a lower priority.

j. Heat induced damage to proteins (see above)

k. Thrombogenicity of Surfaces

Dr Pepper had carried out a study of membranes supplied by Sydney Pugh (Bellhouse Medical Products). While he had found the project of interest he would not wish to pursue this area further unless it was decided it was in the best interests of the Service.

It was agreed that this matter should be considered further with Bellhouse and the Group would be kept informed of developments, if any.

Note: Dr Pepper's report on the study would be sent to those members of the Group who requested it.

4. DATE OF NEXT MEETING

11 February 1987 at 10 am in HQ Unit.