

0032

MINUTES OF MEETING OF FACTOR VIII STUDY GROUP HELD IN HEADQUARTERS UNIT
ELLEN'S GLEN ROAD ON WEDNESDAY, 2nd FEBRUARY, 1983

Present:

Dr J D Cash (Chairman)
Dr C V Prowse (Secretary)
Dr F E Boulton
Dr P Foster
Dr R J Perry
Mr J G Watt (morning only)
Dr D S Pepper
Mrs B Griffin
Mr A Farrugia
Dr G S Gabra

1. INTRODUCTION AND APOLOGIES FOR ABSENCE

There were no apologies for absence.

2. MINUTES OF MEETING HELD ON 14th OCTOBER, 1982

There were no objections to the minutes of this meeting.

3. MATTERS ARISING

(a) Report of Factor VIII Yield WP (Dr Foster)

(i) Plasma Quality

VIII assays on plasma snow (3 samples) are now a part of routine QA at PFC. Complete data on 1982 batches were presented and showed mean results of approx. 0.60 VIII:C u/ml and 0.84 VIIIIR:Ag for FR and 0.51 VIII:C and 0.79 VIIIIR:Ag for FR18. VIII:CAG on a few batches averaged 0.93 u/ml for FR and 0.76 for FR18. Preliminary FpA results on one batch were higher than expected. Doubt was expressed about the validity of the higher values for VIII:C in 1979 plasma but the fact that PFC produced more concentrate from such plasma supports the assay values. Due to the variability of the Laurell VIIIIR:Ag assay attempts have been made to set up RIA and IRMA assays but these have not been successful to date. Vials of the new International Plasma Standard for VIII:CAG will be obtained and will hopefully improve long-term standardisation of the CAG assay. Dr Prowse will request information on sampling plasma for FpA during plasma processing from Dr Pflugshaupt in Switzerland and Dr Perry has already written to Dr Myllyla for similar information from Finland.

The above results are from plasma mixed from various centres except for some which are wholly from Glasgow. FR and FR18 are processed separately. It was suggested that some consideration should be given to determining VIII:C in plasma from various regions separately in view of the current English mode of pro rata distribution of VIII concentrate.

Current QA on plasma at regional centres was reported at about 0.72 u/ml VIII:C in Edinburgh (sample at pooling), 0.60 in Glasgow (on sacrificed packs) and 0.35-1.4 in Inverness. Current input plasma to Elstree was said to contain 0.8 u/ml and it would be worth investigating how English centres have achieved this through Jim Smith and possibly by local visits.

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(ii) Plasma Processing

The study on preventing loss of VIII:C following extraction of cryoprecipitate is now virtually complete. Optimal results are obtained with citrate/calcium or phosphate/saline/maltose, the former being preferred as it is closer to the current process. FpA assays suggest calcium addition does not cause thrombin generation.

Stability studies on a batch of 3 ml vials of the current VIII concentrate were undertaken to provide baseline data for any new product. Initial results were difficult to interpret in view of doubts about the potency of the zero time sample. Further studies will be done, including assessment of library samples from all outdating (3 year) batches.

The use of zinc precipitation to produce a high purity concentrate is now ready to go to full scale production. A factor IX immunoassay is still needed to follow the fate of this protein. Experiments by Dr Bier and Dr Pepper show the process does not reduce HBsAg titres but good progress has been made on the heat treatment (60°C, 10 hours) of the product. Data from Dr Boulton showed a highish zinc-insulin using diabetic may take on 1.6 mmol/Zn/year. For a haemophilic using 10⁵ VIII units/year this load would be obtained with a Zn content of 4 µmoles/250 u. vial concentrate, i.e. 0.2 mM for a 20 ml. vial.

(b) Report of Factor VIII Safety Action Group (Dr Pepper)

Due to possible problems with neoantigens and toxicity following chemical treatment, heat treatment remains the method of choice, particularly as it is known to work. However Immuno have reported two chemical methods for viral inactivation, one used at 4°C may involve diethyl pyocarbonate; the other is novel and requires 37°C and may be revealed by patent search. Modelling of the antiviral effects of radiation awaits development of the appropriate virus target cell systems which will also be used to provide back-up data on other processes, e.g. heat treatment. Use of ¹²⁵I-HBsAg (22nm particle) has shown a 1-log reduction in titre during cryoprecipitation but little effect on zinc precipitation, Cuno filtration, polymer-aided cold precipitation or immunoabsorption with solid phase polyclonal or monoclonal antibody. Any further work on detergent treatment would require training of personnel in the DNA-polymerase assay. This is not planned for the moment.

Infectivity Models

Results of intramuscular injection of agent H or R Hopkins' putative marker in marmosets have been negative to date. Further work may be done but reports from other groups suggest very variable results in this model. A quote received for chimpanzee studies is for \$35,000 for 2 animals for six months (\$55,000 for twelve months). If, as is possible, this work would be done in the States, it would be subject to the new FDA Committee regulating such studies. There is also strong competition for both animals and titred inocula for such studies. Reports from the recent Athens meeting suggest that infectivity is dramatically affected by administration route and that viral DNA is considerably less infective than intact virus. In view of the above it would appear that the optimal infectivity model will probably be high risk human patients.

(c) Quality of Plasma WP (Dr Gabra)

Dr Gabra's report was, in general, accepted but the following comments were made:

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PFC felt that quality was more important than quantity of plasma now and also that they received a higher proportion of ACD plasma than indicated by the tables. The general mood was also that regional QA of VIII:C in FR was preferable to assay by a central laboratory.

7.4 would be difficult to implement

7.7 and 7.8 may be outwith the remit of the Technical Evaluation Group

7.9 : It was stated prototype design of the tear bag should be delivered soon. These have been chosen to have a 700 ml. capacity and a maximum frozen depth of 25 mm.

9A3 : remove 'individual'

Tables : will require updating in future.

Dr Gabra and his group were asked to:

- (1) Produce a formal report based on data obtained on current FR production in Scotland for the Regional Directors, as soon as possible.
- (2) Produce a specification for FR specification (Gabra, Boulton, Perry) to be attached to (1) if possible.
- (3) Recommend quality assurance tests and sampling frequency in relation to (2).
- (4) Produce a literature review presenting evidence for optimal conditions for the various stages of plasma production (Boulton).
- (d) Assays and Standards WP (Dr Prowse)

Supplies of substrate plasma and standard have been produced. The latter has been calibrated against the National plasma standard but further assays are required from Glasgow and hopefully NIBSAC before final assignment of potency. A workshop is being arranged in Edinburgh for Dundee and Aberdeen staff on 17th March. It is estimated fresh standard will be required annually although formal degradation studies have not been done. Consideration should be given to the long term production of substrate plasma (B Griffin to supply R Perry with final method of production), and to provision of quality control samples twice a year to centres using this assay (C Prowse).

4. DATE OF NEXT MEETING

Thursday, 15th September, 1983 at 10.00 a.m.