

NOTES ON FEASIBILITY EXERCISE PERFORMED AT PROTEIN FRACTIONATION CENTRE (PFC)
LIBERTON, TO TEST THE CONTINUOUS SMALL VOLUME MIXING (CSVM)
FRACTIONATION SYSTEM UNDER CONTINUOUS OPERATION

(2)

The CSVM fractionation system was developed for the continuous fractionation of human plasma and was brought into use at PFC in 1976. Since then its use has been confined to the production of Albumin products for clinical use but operation has not been on a truly continuous basis, the length of each fractionation run being approximately 8 hours.

Two main reasons have prevented continuous (i.e. 24 hour per day, 5 days per working week) operation, these being:

- (a) Shortage of plasma
- (b) Administrative problems which have prevented the operation of a shift system of working.

Disadvantages of discontinuous CSVM operation

To operate the CSVM system discontinuously is said to be inefficient because:

- (i) Time is wasted in stopping and starting each day, leading to lost production and wasted effort by the staff.
- (ii) Housekeeping losses are accentuated by frequent stopping and starting and contribute to reduced yield.
- (iii) Optimum fractionation conditions have to be re-established daily. To operate continuously for long periods using optimum precipitation conditions should result in improvements in yield and possibly purity.

Feasibility Exercise to test the process capability of the CSVM system

To demonstrate both the efficiency of the CSVM system free from the disadvantages of (i) to (iii) above, together with its ability to endure the rigours of continuous operation it was decided that for a limited period the problems presented by (a) and (b) above should be overcome on a temporary basis. This was achieved by:

- (a) Deciding to fractionate a large quantity of time-expired plasma received from BPL Elstree between February and June 1977.
- (b) By agreement between the Employing Authority (the Common Services Agency, CSA) and the Trades Unions representing PFC staff.

Summary of Agreement allowing PFC Staff to work during Feasibility Exercise

In summary the agreement was as follows:

- (i) The Feasibility Exercise was to be conducted from the 12th October to the 18th December.
- (ii) During this period, staff working at PFC would be paid, in addition to the normal hourly payments, one or two disturbance allowances. These allowances were referred to as A and B.

Disturbance Allowance A was to be paid to all staff for all hours worked during the duration of the Feasibility Exercise.

Disturbance Allowance B was an additional allowance paid to staff working between 5 and 8 a.m.

The rate for both allowances was 80 pence per hour.

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1458

38/42

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Structure of Feasibility Exercise

Although the exercise was planned to last for a 10 week period (from the 12th October to 18th December) continuous operation of CSVM system would cover a period of 10 working days, divided into two weeks of five days each.

The additional eight weeks of the exercise would include one week for preparation for the exercise together with seven weeks for progressing fractionated material through the rest of the production system.

The exercise can be shown diagrammatically thus:-

Weeks	1	2	3	4	5	6	7	8	9	10
<u>Basic Operations</u>										
Setting Up										
CSVM Fractionation										
Bulk finishing and Aseptic Filling										
Incubation, Storage and Quality Control										
Final Inspection, Labelling etc										

The exercise was to test not only the ability of the CSVM system but also the ability of the other production and back-up sections within PFC to process the products of continuous fractionation. It is important to note however that at no time during the study was PFC subjected to "all systems go" operation; such a situation being approached only during five days in week three.

Deployment of Staff during the Feasibility Exercise

- (i) Extra staff were not employed during the Feasibility Exercise.
- (ii) The 24 hour period was divided into two shifts of 12 hours. 8 hour shifts were considered to be impossible because staff would be spread too thinly. (Excepting the maintenance section which did work 8 hour shifts).
- (iii) Staff worked one or other of the shifts, from 8 a.m. to 8 p.m. or vice versa, with possibly a change-over during the second week. It was apparent that some staff not directly involved with production did not work the full twelve hours.

BPL staff at PFC

Two members of BPL staff (Mr.M.Tucker and Mr.E.D.Wesley) were present at PFC during week three, thereby allowing participation and observation of both the CSVM fractionation and Bulk Finishing and Aseptic Filling.

Production during week 3

I CSVM Fractionation (Processing)

- (i) Starting Material: time expired plasma stored at -25°C in 5 L volumes in polythene packs.

20,000 Litres were sent between February and June 1977 from BPL to PFC.

Approximately 10,000 Litres were fractionated previously and the residue formed the starting material for the Feasibility Exercise.

38/43

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(ii) Batch Size

For 8 hour CSVN, batch size constituted the products prepared from plasma fractionated during the period.

For continuous operation batch size cannot easily be defined. During the feasibility exercise a batch constituted material produced during each 24 hour period. There was no formal break in processing at this point and it is unclear how differentiation between the end of one batch and the start of the next was achieved with precision because it may be assumed that some degree of mixing occurs at the end and beginning of each 24 hour session.

(iii) Fractionation Programme

During the Feasibility Exercise the CSVN system was programmed to produce Fraction IV - 4 + V. This is the product normally prepared during 8 hour fractionation, representing the starting material for Stable Plasma Protein Solution (SPPS).

(iv) Plasma Pooling

5 Litre pools were softened overnight at approximately 10 - 15°C. The following day the plastic pack was stripped from the still frozen block of plasma which was then broken into approximately 1 L lumps which were fed into the plasma crusher. The finely divided plasma produced by the crusher was fed into a thawing tank where the plasma was thawed and run off into a holding vessel. This equipment is normally used for the production of cryoprecipitate and its supernatant. It has a capacity of 400 L plasma per hour and was therefore capable of thawing the daily target plasma volume of approximately 1000 Litres within 3 hours.

After thawing, pools of plasma was stored at approximately +4°C, awaiting Fraction I batch precipitation.

(v) Fraction I precipitation

Fraction I was separated by batch-wise precipitation using conventional equipment, as the CSVN system at present is unable to fractionate whole plasma.

Having separated the Fraction I the supernatant was stored awaiting its introduction into the first stage of the CSVN system.

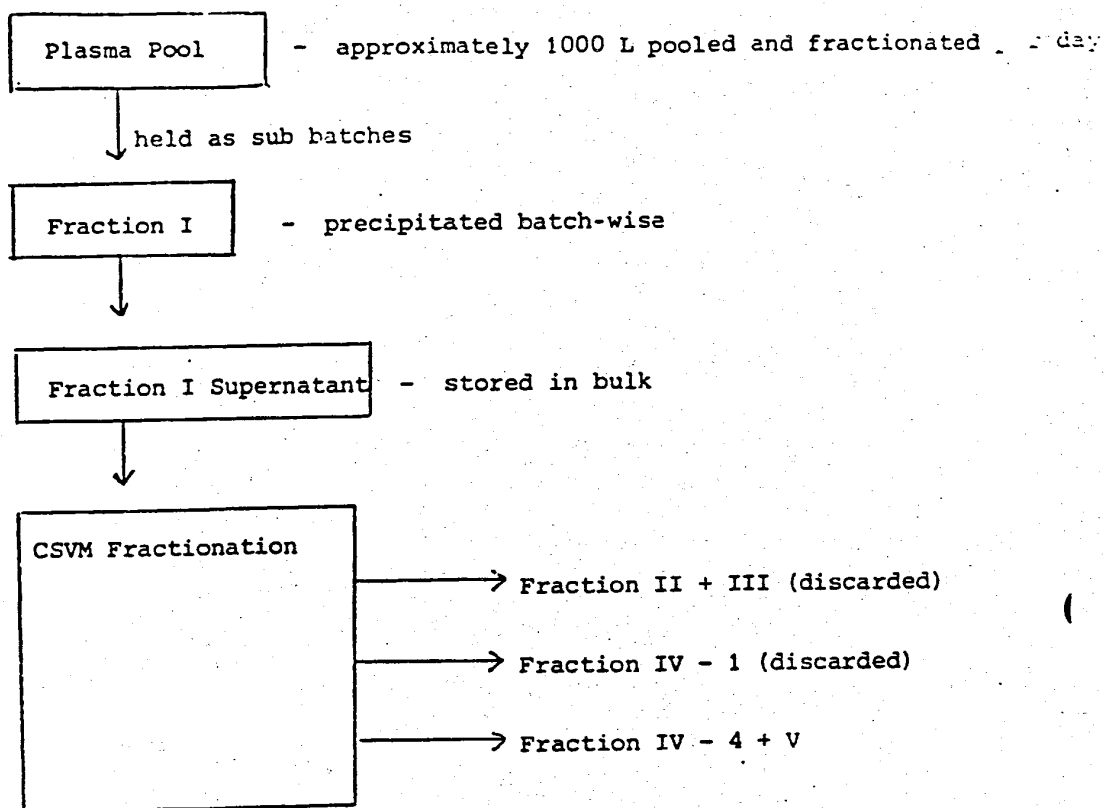
This method of operation, i.e. pooling plasma and holding in bulk both before and after Fraction I separation appears to reduce one of the advantages of CSVN, that being that frozen plasma can be converted to frozen Fraction IV - 4 + within a matter of hours, thereby reducing the opportunity for microbial growth.

It was said that work is being conducted to allow the CSVN system to process whole plasma.

(vi) CSVN Fractionation System

24 hour work schedule

38/44



Fractions II + III, IV - 1 and IV - 4 + V were precipitated using CSVM trolleys and Westfalia BKA 25 centrifuges were used to separate the precipitates.

The quantity of plasma fractionated per 24 hours during the Feasibility Exercise varied between 800 and 1000 Litres. The limiting factor is the capacity of the CSVM trolleys, this being approximately 45 Litres per hour.

The total volume of plasma fractionated during the 10 day period was approximately 8500 Litres.

(vii) Yield and Purity of Fraction IV - 4 + V

One reason for performing the Feasibility Exercise was to demonstrate the improvements in yield which would accrue from continuous CSVM fractionation.

During week 3, no data was available on yield and purities achieved and it was said that this information would not be available until the end of the study, i.e. 18th December.

It may be argued that the starting material is unrepresentative of the usual material fractionated and that as a consequence, figures obtained for purity and yield will not be comparable. It has been the experience at BPL that when fractionation time expired plasma and fresh frozen plasma the purity and yield of the time expired product is as good as that prepared from the fresh frozen plasma. It may be argued that time expired plasma is more suitable as lipoproteins may be more easily removed from the end product.

39/45

(viii) Reliability of CSVM Fractionation System

In addition to demonstrating improvements summarized in (viii) above, the exercise was also intended to demonstrate the ability of the CSVM system to endure the rigours of continuous operations for up to 120 hours.

Adequate spare trolleys and centrifuges appear to be available and were substituted when equipment malfunctioned or required cleaning. During both weeks of the Exercise no major problems were said to have arisen in Fractionation, and providing sufficient plasma and fractionation staff were available the system could have operated for longer.

The ability of the CSVM system to operate continuously could be predicted from the experience gained during 6 years operation for 8 hours per day (it may be argued that discontinuous operation may present more rigorous conditions. It is difficult to see what circumstances would arise which (given adequate spares) could prevent continuous fractionation.

Similarly, there is no reason to believe that the BPL could not also be operated on a 24 hour system almost indefinitely, provided a suitable formula can be found for staff employment.

(ix) Production of other Fractions during the Feasibility Exercise

(a) Immunoglobulins: specific and normal

These fractions for clinical use are prepared using batch fractionation equipment. During the exercise the batch fractionation equipment was in daily use for Fraction I precipitation and so no immunoglobulin was fractionated at all during week 2 and 3.

(b) Salt-Poor Albumin

This material is also produced in the batch fractionation equipment. For the reasons given in (a) above, no salt-poor albumin could be produced.

(c) Factor VIII

The "usual" quantity of Factor VIII was produced on each of the two weeks during the exercise. This amounted to the equivalent of 400 Litres of fresh frozen plasma per week.

II Bulk finishing during week 3

Each batch of Fraction IV - 4 + V, produced during each 24 hour period of fractionation, was processed through Bulk Finishing Filling to a batch of Stable Plasma Protein Fraction (SPPF) maintaining the batch identity, as far as possible, of the starting plasma.

The 24 hour working dayⁱⁿ this section was divided as follows:-

- (a) Paste resolution, ethanol removal and protein concentration by vacuum distillation during the evening and throughout the night.
- (b) Bulk finishing, sterilization and aseptic filling during the early morning through to noon.
- (c) Heat-treatment of the filled batch from late afternoon to the following morning.

38/46.

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- 5 -

Except for minor problems during vacuum distillation no production problems occurred in Bulk Finishing during week 3.

The quantity of IV - 4 + V paste available from the fractionation section did not unduly stretch the aseptic bottling capacity, batches of over 1000 bottles being processed daily. The section appeared to have the capacity to handle more material although constrictions caused by vessel capacity may lead to limitations in batch size.

III Support Services

- (i) Pyrogen-free water and reverse-osmosis water production.
More than adequate supplies were said to be available during week 2 and 3, and should not be a limiting factor.
- (ii) Cold room and process refrigeration
More than adequate supplies were said to be available during week 2 and 3, and should not be a limiting factor.
- (iii) Quality Control
A 24 hour service was provided for those control functions required by production sections.
- (iv) Incubation and ambient storage
The incubation (2 weeks at 30°C) and ambient storage facilities appeared to be over stretched even before the arrival of the increased volume of material resulting from fractionation during week 2 and 3.

Bottled SPPS was stored in plant space under totally unsuitable conditions and for long term continuous operation additional storage space would be required outside PFC.

The problems at BPL which have prevented increased production and are now in the process of being rectified are mirrored at PFC.

(v) Inspection, Packing and Despatch

The existing facilities appeared unsatisfactory and inadequate for the normal quantity of SPPS being processed. The increased quantity available as a result of the Feasibility Exercise could most probably be handled by longer working hours but under conditions which do not meet GMP.

(vi) Ethanol Reclamation

The ethanol reclamation plant was said to be adequate to handle the increased volume of IV - 4 + V supernatant. During week 3, problems did arise which caused the discarding of large volumes of ethanolic waste. It was not clear if this problem arose because of the increased demands made as a result of the Feasibility Exercise, or because of a reduced level of supervision due to 24 hour operation, or just by chance.

(vii) Maintenance

This section appeared totally capable of dealing with the maintenance problems experienced during week 3. It was not clear to what extent levels of routine preventive maintenance were reduced during the Feasibility Exercise.

Conclusions

1. The CSVM system is capable of continuous operation for periods of at least 120 hours and there is no reason to believe that the system could not be operated permanently for such periods, with 48 hour breaks at weekends for maintenance etc.

38/47

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2. There is no data at present to indicate how purity and yield of the product are effected by truly continuous CSVM fractionation.
3. With the present bulk-fractionation equipment available, continuous fractionation would prevent the production of immunoglobulins and salt-poor albumin.
4. During the Feasibility Exercise, Factor VIII production was limited to the normal quantity. No evidence is available therefore from the Exercise to suggest what increase could be made to factor VIII production by the fractionation of large volume of fresh frozen plasma.
5. With the exception of Quarantine storage through to Inspection and Despatch, all support sections appeared to have the capacity to handle the product from 1000 Litres of time-expired plasma per day.
6. Storage space throughout the whole of PFC was at a premium and increased production as achieved during week 2 and 3 will probably place a even greater strain on what is already an overloaded system.

The production of Stable Plasma Protein Solution, from the plasma storage through to the release of the finished material, relies heavily on each link in the chain functioning correctly. Because of limited in-process storage capacity what may appear at first to be a minor problem, overcome without undue difficulty under normal conditions, may develop because of "knock-on effects" into a much more serious situation when dealing with the products of continuous CSVM operation.

The capability of PFC to withstand this type of problem was not challenged at the Feasibility Exercise.

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E.D.Wesley
15th December 19

38/48