HoD F
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GRO-C

0008

LIMITATIONS IN THE SYSTEM OF INTERMEDIATE F VIII PREPARATION

1.0 Seven sub-systems exist in or are associated with the production line of F VIII.

1.1 Plasma storage.

1.2 Cryoprecipitate recovery.

1.3 Albumin production capacity to absorb supernatant.

1.4 Cryo rework.

1.5 Product filtration.

1.6 Product filling.

1.7 Product drying.

Each sub-system comprises a number of activities which to a lesser or greater extent can influence the ability of the centre to successfully process the supply of suitable plasma to acceptable product. A brief discussion of the constraints prevailing is presented.

1.1 Plasma Storage

Plasma storage was discussed in an earlier document (26.2.81) with specific reference to freeze drying capacity. The points made are still broadly true.

1.2 Cryoprecipitate Recovery

Cryoprecipitate recovery entails the following:

(a) Plasma pack stripping is possible using current methods with rates depending upon temperature and pack size.

At -5° to -8°: 200 - 300 kg/hr of 5 1/2 l packs.

120 - 160 kg/hr single donations.

(b) Crushing using the extructor is dependent upon the size and temperature challenge and the reliability of the machine.

At any given temperature the single donation packs crush more quickly than 2 - 5 l as they require no pre-breaking and are of ideal dimensions for the machines.

Plasma at -8° to -12° is limited to 200 - 250 kg/hr. At -4° to -8° 300 - 400 kg/hr is possible.

The reliability of the mechanical components has been close to 100%, the only difficulties being re-setting of bearings following complete strip-down (for painting). The electrical reliability record is less satisfactory, particular difficulties having been experienced with the starter (third now in operation) and the fact that the motor is under specified for the load and transmission type. (Present 2 Hp, 4 Hp now recommended).

(c)/

(c) The thawing apparatus has only been in operation for two months, accordingly reliability is unknown but both helix drive and plasma transfer pump seem the weakest elements. The heat exchanger supply is dependent upon the adequate supply of steam, the acceptable performance of the circulating pump and the pneumatic controller. Engineering may be able to assess reliability in this area.

The thawing rate is in the range 200 - 350 kg/hr and as such is unlikely to be limiting.

One feature of the thawing system so far has been the accumulation of cryoprecipitate around the helix and should this phenomena persist it may be that the mass of such material may restrict batch size. (Developments so far have reduced this effect from 2 kg to 0.6 kg).

(d) The centrifugation of the thawed liquor to collect the precipitate is limited in resolution by (a) the thaw rate and consequently in-rotor residence time, (b) the supply of refrigerated coolant and (c) the capacity within the bowl for solids.

At present the Westfalia BKA6 machine is employed for collection of cryo solids as a spare machine is available and has proven to fulfil the necessary requirements for flow rates of 200 to 250 l/h and 450 kg of plasma, however, there are indications that its limit is being approached. The use of a BKA25 machine would necessarily limit the flexibility of other product lines, but would satisfy the need for greater capacity and residence time. The thermal performance may not be so impressive.

1.3 Albumin Production Capacity to Absorb Supernatant

As indicated earlier (26.2.81) the capacity of the albumin production lines using existing equipment and current staffing levels (20) is of the order of 1 200 litres/week and this will of course include plasma types from which F VIII is not derived.

1.4 Cryo Rework

The rework of the cryoprecipitate involves:

Paste Wash
Tris Extraction
$Al(OH)_3$ Absorption
Centrifugation
Filtration
Buffer Addition

which can cope with volumes equivalent to 450 kg plasma. Increased frequency of product pool processing could be accommodated with little difficulty. An increase in pool size would require larger containers and a longer turn-round but could not be considered a severe limiting factor.

1.5 Product Filtration

Filtration is carried out in two stages;

(a)/

(a) Clarifying, which is estimated with an 18 l challenge to be at 50 - 60% capacity with adequate flow rate: 18 l/10 mins.

(b) Sterilising, which is estimated to have a 30 l capacity and is at present passing 18 l in 10 minutes.

and is followed by collection in a holding vessel - current item 22 l capacity.

1.6 Product Filling

Filling of sterile products into final containers is presently carried out at 10 vials/min and its duration is dependent upon (a) the total volume to be filled and (b) the volume per vial.

1.7 Product Drying

In the case of freeze driers the capacity of the Usifroid is limited by the shelf space available up to 30 litres which is the condensor capacity.

The Leybold has spare shelf capacity with the existing vial size but the condensor is limited to 12 litres.

Both driers require a four day cycle for drying F VIII at present filling levels of 30 to 40 ml - reduction in this quantity would shorten the cycle.

Reduction of the vial height should permit an extra shelf to be fitted to the Usifroid but this will only increase the product pool maximum volume to 22 litres.

Recent events, during which the Leybold was unserviceable due to failure of the printed circuit board, demonstrate that our capacity to to reliably process fresh plasma for the production of F VIII is most crucially constrained by our freeze drying capacity - failure of the Usifroid for any period of time would immediately mean that we were receiving more fresh plasma per unit time than we could process using current procedures which would highlight the chronic deep-freeze storage problem and could result in over-flow of non-fresh plasma to the cold store. (This situation of course has already arisen at the end of 1980).

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