CD. APPENDIX I

NATIONAL BLOOD SERVICE (Or UK?) - INFORMATION SHEET FOR HOSPITALS ON FRESH FROZEN PLASMA

DRAFT 2 -9/5/97

You may be aware that a pooled, licensed fresh frozen plasma (FFP) preparation virally treated by the solvent detergent (SD) method is now available (Octaplas, produced by Octapharma). The UK Blood Transfusion Services are committed to providing an SD FFP product from UK donor plasma, in collaboration with Octapharma. Production of standard single donor FFP will also continue. As a licenced product, Octaplas will be supplied with a data sheet outlining its specification. This information sheet is intended to provide comparative data for single unit FFP, with specific emphasis on viral and other risks. It is not intended to cover dosage or indications for FFP, for which users should consult BCSH Guidelines [1].

STANDARD FFP

Presentation and content.

A unit of FFP contains approximately 200-300 ml of plasma from a single donor containing 40-60 ml of anticoagulant nutrient mixture. The plasma may be derived from either whole blood or apheresis donation, and in either case is frozen to -30° C or below within 8 hours of collection.

Plasma proteins in FFP are present in similar concentrations to those in normal plasma. National quality requirements demand that >70% of units have a factor VIII content of >0.7 iu/ml [2].

Donor selection and testing.

All blood donors in the UK are accepted under the Medical Assessment of Donors Guidelines [2]. These are designed to exclude donors who are likely to be at particular risk of acquiring viruses which may be transmitted by transfusion. As a further safety enhancement, FFP is manufactured only from donors who have tested negative for anti-HIV 1+2, anti-HCV, hepatitis B surface antigen and syphilis in the preceding 6-24 months, as well as in the current donation. In addition, most of the plasma currently collected from regular, multiply screened apheresis donors, is directed towards FFP production.

From **?April?exactly when** samples from FFP units will also be tested in 'mini-pools' for HCV RNA. FFP units will not be released for issue till the results of such testing are known.

Infectious risks.

Despite the above measures, there remains a small but definite risk of an infected unit entering the blood supply. The approximate theoretical risks of viral transmission from single donor blood components from previously tested donors have been calculated from data collected in England and Wales[3]. These are:-

HIV 1+2	0.19 / million donations (95% confidence interval 0.05-0.55)
Hepatitis C	2.40 / million donations* (95% confidence interval 1.6-3.7)
Hepatitis B	Data to come

*Calculated prior to implementation of HCV RNA screening.

Theoretically, single unit FFP can also transmit hepatitis A and parvovirus B19. contamination. An expected incidence of asymptomatic B19 viraemia in blood donors of 1 in 16,000 has been estimated[4]. No figures have been calculated for transmission of HAV or B19 **(Kate Soldan may be able to provide theoretical risks)** but there have been no such notifications to the NBS/PHLS reporting system which has been collecting data for 2 years. Similarly, no confirmed cases of bacterial contamination of FFP have been reported.

Other side effects.

Acute mild allergic reactions to FFP are common (up to 1%), and severe reactions rare (0.1%). The risks of red cell haemolysis due to passive transfer of anti A,B are minimised by prescribing ABO compatible FFP (group AB is the 'Universal Donor'), and by testing group O donors for high titre anti -A,B.

Rarely, the presence of potent anti-HLA or anti-granulocyte antibodies in the donor may give rise to transfusion-related acute lung injury (TRALI)[5], with clinical features resembling adult respiratory distress syndrome. Similarly, severe thrombocytopenia due to passive transfer of platelet antibodies has been reported.

FFP contains intact and fragmented red cells, leucocytes and platelets. These may be responsible for some of the side effects. Because of the red cell content, children and women of childbearing age who are RhD negative should receive FFP from RhD negative donors.

SOLVENT DETERGENT FFP[6]

Presentation, content and efficacy

SD FFP is manufactured from UK plasma collected by the Transfusion Services, with the same donor selection criteria as standard FFP. Pools of 380 litres (up to 1300 donations approximately) are subjected to solvent-detergent (SD) treatment. The solvent (1% Tri N-butyl phosphate, TNBP) and detergent (Triton X-100) are then removed by chromatography, leaving residual levels of 2ug/ml and 5ug/ml respectively. Toxocological studies indicate that no clinical problems should result from these concentrations. The plasma is refrozen in 200 ml aliquots, such that each unit in the batch is identical with respect to clotting factor levels. A minimum of 0.5 IU/ml is obtained for each clotting factor.

The clinical indications for SD FFP are identical to those for standard FFFP, except that SD FFP is ~~not licenced~~ unsuitable for neonates. SD FFP is effective when used in plasma exchange procedures for thrombotic thrombocytopenic purpura.

Infectious risks

In addition to the donor selection and screening procedures described above, from **?April?exactly when** samples from FFP units will also be tested in 'mini-pools' for HCV RNA. Plasma will not be sent for viral inactivation until the results of such testing are available.
The plasma pools and finished product are also tested for HBsAg, anti-HIV 1 +2 and anti-HCV (?sensitivity). The solvent detergent method provides reliable inactivation of lipid coated viruses such as HIV, HBV and HCV. Non lipid-coated viruses such as hepatitis A, parvovirus B19 and other non-lipid-coated viruses are not specifically inactivated by the method. Therefore the risk of transmission of such viruses may be greater than with single donor FFP. Plasma pools for SD FFP manufacture contain potentially neutralising antibodies to HAV (at a specified minimum level shown to neutralise a predicted viral load) and B19, but the possibility of transmission cannot be excluded.
Parvovirus B19 may cause hydrops fetalis/fetal loss if administered during pregnancy, and may precipitate aplastic crises in patients who are immunocompromised or with underlying haemolysis. Therefore SD FFP should only be given to such patients if strongly indicated, and in all recipients, the risks of HAV and B19 should be weighed against the benefits of inactivation of HAV, HCV and HIV. **Wording of exclusion of neonates - up to what age? Unclear at present.**

For patients likely to receive repeated exposure to FFP, vaccination against HBV and HAV should be considered.

Non-infectious risks

Allergic reactions are not abolished by SD treatment. However, side-effects attributable to passive transfer of red cell, leucocyte or platelet antibodies are likely to be minimised, due to the dilution effect of the pool.
Because cellular debris is removed by the SD process, immunisation to red cell antigens is precluded. Therefore SD FFP pools contain both RhD positive and negative units and no specific product is required for RhD negative patients.

Lorna Williamson 9/5/97

References.

1. BCSH Guidelines for the use of fresh frozen plasma. Contreras M et al. Transfusion Medicine 1992;2:57-63.

2. UK Blood Transfusion Services/National Institute for Biological Standards and Control Guidelines. 2nd Edition 1994.

3. Soldan K, Barbara JAJ. Manuscipt in Preparation.

4. Prowse C, Ludlam CA, Yap PL. Human Parvovirus and Blood Components. Vox Sanguinis 1997;72:1-10.

5. Popovsky MA, Chaplin HC Jnr, Moore SB. Transfusion-related acute lung injury: a neglected serious complication of haemotherapy. Transfusion 1992;32:589-592.

6. Octaplas - data sheet. Kindly supplied by Keith Lawson, Octapharma.