Evaluation of Prion Reduction Filters.
UK + Irish Blood Services
Prion Removal Working Group

• To be the primary point of contact within UKBS for manufacturers developing prion removal technology.
• To provide expertise and advice to manufacturers on the laboratory and clinical development requirements for prion removal systems.
• To liaise with manufacturers regarding in-house operational evaluations.
• To liaise with JPAC and SAC’s on all matters regarding approval of prion removal systems for UKBS use.
• To ensure that appropriate decision-making bodies are kept appraised of the technology.
How great a reduction in infectivity is needed to be clinically useful?

- Assumes red cell concentrates in OAS, with prior LD and 10-30 ml residual plasma
- Assumes that total residual infectivity $>2$ ID$_{50}$/whole unit will transmit for certain
- Assumes prion removal mainly from plasma
## Prion reduction filters

<table>
<thead>
<tr>
<th>Infectivity ID</th>
<th>residual leucocytes</th>
<th>residual plasma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD alone</td>
<td>0.2</td>
<td>130</td>
<td>130.2</td>
</tr>
<tr>
<td>1 log</td>
<td>0.2</td>
<td>13</td>
<td>13.2</td>
</tr>
<tr>
<td>2 log</td>
<td>0.2</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>3 log</td>
<td>0.2</td>
<td>0.13</td>
<td>0.33</td>
</tr>
<tr>
<td>4 log</td>
<td>0.2</td>
<td>0.013</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Prion reduction filters

- 1-2 logs - of limited value
- 3 logs - 75-90% reduction in incidence of secondary transmission
- further reduction in residual plasma could augment reduction in infectivity and incidence of secondary transmission
- any further affect on cell-associated infectivity could be of significant additional benefit.
Prion reduction specification

- 3 log reduction by spiking to be demonstrated by Western blot and bioassay.
- Reduction in endogenous infectivity up to limit of model which must be capable of demonstrating at least a 1 log reduction - demonstrated by Western blot and bioassay.
- Process variables (4°C and ambient temp) by Western blot once validated.
- Companies have been asked to propose surrogate markers for process monitoring.
In-process quality monitoring - what would be a suitable marker?

- Direct measurement of infectivity levels not possible.
- Need to demonstrate parallelism in reduction/removal of surrogate marker across prion removal filter.
- Possible surrogates: Factor IX, PrPc.
- Challenging because so little plasma in SAGM red cells.
Component quality specification

- In vitro as per UK Guidelines to day 42
- In vivo- volunteer red cell survival studies using radio-chromium-recovery must be 75% at 24 hours -also red cell survival
- Red cell membrane changes
  - expression of common red cell antigens
  - alteration in band 3 protein
  - CD47 expression
  - interaction with large panel of normal sera / plasmas
Independent evaluation study

• Requested by SEAC, MSBTO and UK Blood Service.s
• provide independent substantiation of some of the key data provided by the companies
• where possible extend that data to more clinically informative models
• Initially probable spiking studies with
  – 263K brain homogenate / microsomal / sonicated assessed by Western blot and bioassay
  – 301V spleen assessed by Western blot and bioassay.
  – Endogenous infectivity studies
• Trade off between comprehensiveness and time-lines
Clinical studies

- Primary aim of clinical studies is to look for adverse events and immune responses
- Study 0: exposure of patients to 1,2,3 units
- Study 1: complex cardiac surgery- 300 patients, all receiving PRF-treated RCC.
- Study 2: transfusion dependent (probably MDS) randomised: PRF-treated vs control RCC - 150 in each arm.