Adsorptive Pre-filtration to Increase Virus Filter Performance and Overall Process Robustness in Blood Derived Processes

Volker Thom, Björn Hansmann, Jörg Hoss, Benjamin Schneider
Sartorius-Gebäude Biotech GmbH, Göttingen, Germany, Membrane R&D

Adsorptive pre-filters

The evaluation of virus filters is not confined only to its capacity to retain viruses. Indeed, selection of a virus filter is influenced by numerous factors. One factor gaining increased importance is process economics. Different adsorptive pre-filters have been introduced to the market for capacity increase of virus-retentive filters. Today’s established adsorptive pre-filters are compared in the table below.

<table>
<thead>
<tr>
<th>Filter Configuration</th>
<th>CEX Membrane</th>
<th>Virosart® Max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High flux to low flux</td>
<td>High flux to low flux</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Performance independent from process conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Performance independent from process conditions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced cross flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced cross flow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrity test available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrity test available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrity test available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Integrity test available</td>
</tr>
</tbody>
</table>

Characteristics of Virosart® Max

Working principle
- Combination of adsorptive capacity and size exclusion leads to removal of virus filter foulants
- Aggregates and (or) small hydrophobic molecules are typical virus filter foulants

Filter Configuration
- Material: Optimized polysaccharide
- Pore size: 0.1 μm (nominal)
- Format: Double-layered elements
- Size: Available from 5 cm² to 30 cm² elements

Higher capacity through aggregate reduction
The impact of Virosart® Max on the filtration of different IVIG concentrations (5, 10 and 20 g/L) through Virosart® HC, 20 cm² virus filter (5 cm² Minisart® devices) was analysed. Filtrations have been performed with and without the use of Virosart® Max at 2 bar 30 psi filtration pressure. Results were compared at 90% flow decay.

As a result, filtration capacity scales with solution concentration because the concentration of membrane fouling impurities scales accordingly.

Robust against process conditions
The effect of different pre-filtration strategies was evaluated for IVIG (5 g/L) in different buffer conditions at varying pH and ionic strength using Virosart® HC 20 cm² virus filter (5 cm² Minisart® devices) at 2.0 bar 30 psi.

As a result, the use of Virosart® Max results in lowest performance spread by varying process conditions.

Implementation

Cartarpon cartridges and capsule format of the filter allows flexible process implementation:
- Stainless steel housing setup
  - Robust setup
  - Steam sterilization and pre-use integrity testing possible

Single-use setup
- Ease of use
- Flexible
- Pre-use integrity testing limited under fully-contained sterile conditions

Automated setup
- Customized set-up
- High level of automation

Spiking studies

Binding curves have been obtained for a wide range of therapeutic monoclonal antibodies using a range of both adherent and suspension cell lines with examples presented in Figure 4. Each assay run includes cells stained with the secondary antibody alone and unstained cells as controls to determine background fluorescence signal.

Preferred Option:
- Off-line pre-filtration (decoupled)
  - Product is pre-filtered off-line and afterwards virus spike is added to the product feed
  - Pressure (flow) adaption over pre-filter
  - Low capacity of virus filter by highly fouling feed streams
  - Common approach in the industry
  - Pre-filtration before validation to restore sample

Alternative 1:
- In-line pre-filtration (coupled)
  - Pre-filter and virus filter are run in-line and virus spike is added in-line
  - Virus retention by pre-filter not tested as robust
  - Possible if pre-filter is tested independently for virus retention

Alternative 2:
- In-line pre-filtration with in-line spiking
  - Pre-filter and virus filter are run in-line, but the virus spike is added in-line after the pre-filter
  - Complex setup
  - Difficult control of feed titer

Alternative 3:
- Spiking virus selection
  - Validation via a retentive filter for paroviruses (PPV, MVM) and imply sufficient LRIV for larger viruses (MUL, INK)
  - Accepted by regulatory authorities

References