Summary
Due to its unique lubricating and moisture holding properties and its natural presence in many body tissues, Hyaluronic Acid (HA) is used in an ever increasing number of applications in pharmaceuticals, cosmetics and medical devices. One area in particular is ophthalmic lens care and prescriptive drug formulations.

This expanding market has also led to the development of new production methods of raw HA based on Bacillus Subtilis fermentations, which are reported to sterile filter more easily. However, even at low concentrations, sterile filtration of solutions containing HA can present challenges due to their high viscosity.

Parker domnick hunter can work with you to increase the efficiency and economy of your sterile filtration system by maximising throughput, minimising filtration trains and limiting downtime.

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Key Filtration Requirements:

- **No alteration to solution characteristics**
  Any effect of filtration the properties of HA in the solution will have an adverse effect on the efficacy of the final product.

- **High throughputs**
  It is important for process economy that the sterile filtration system is able to process the viscous HA solution without blockage.

To aid in choosing a sterile filtration system, Parker domnick hunter have conducted a study to evaluate the effect of HA concentration and molecular weight, on filtration throughput for different filter types.
The Effect of Filtration on Solution Characteristics

The relationship between HA concentration and viscosity for solutions of HA with two different molecular weights - 760 kDa from Bacillus Subtilis and 1.1 MDa from Streptococcus - is shown in figure 1. It can be seen that the solutions of the two different molecular weights have similar viscosities up to a concentration of 0.2%. At this point the trends diverge and the viscosity of the 1.1 MDa HA solutions increase more sharply with concentration, making them more viscous than the 760 kDa solutions at an equivalent concentration.

The direct relationship between concentration and viscosity means that viscosity can be used as an indication of a change in the characteristics of the HA before and after filtration. To determine if filtration has any effect on the properties of the HA solution, the viscosity was measured before and after filtration of the 760 kDa HA at different starting concentrations. The results, represented in figure 2, show that the viscosity of the solution is not significantly changed after filtration.

Filterability Studies

Constant flow filterability studies were conducted with a selection of filter media on samples of HA with molecular weights of 760 kDa and 1.1 MDa over a range of concentrations to investigate the effect on throughput.

To ensure a close representation of actual commercial products, the solutions were made up in 1% PBS (Phosphate Buffered Solution). The HA was fully dissolved by continually stirring for 18 hours at 400 rpm. All testing was conducted at 25 °C (77 °F). The filterability studies were conducted on Parker domnick hunter’s 0.2 µm PROPOR SG single layer and 0.2 µm PROPOR HC dual layer PES products; a competitor’s 0.2 µm single layer PVDF product was also tested for comparison.

Figures 3a to 3c show differential pressure against throughput for 760 kDa and 1.1 MDa HA solutions at concentrations of 0.025% and 0.2%. At constant flow, filter blockage is shown by an increase in differential pressure. Generally, it can be seen that the PROPOR HC dual layer filter significantly extends throughputs compared to single layer products for all of the HA solutions tested.
Low molecular weight HA solutions
The testing showed that lower molecular weight HA solutions (figure 3a) are filtered more easily than higher molecular weight solutions (figures 3b and 3c) and the total throughput was greater.

Even at relatively high concentrations, the dual layer PROPOR HC outperformed both of the single layer products, achieving high throughputs and maintaining a constant low pressure.

High molecular weight HA solutions
The solutions of higher molecular weight HA proved more difficult to filter (figures 3b and 3c) and, as the concentration increased, it became increasingly difficult for the single layer products to pass any of the HA solution through.

Figure 3c shows that, at higher concentrations, the single layer products are unable to process the solution at all; however, the solution was able to pass through the dual layer PROPOR HC product.

These results demonstrate that, through use of a dual layer membrane product, sterile filtration can still be considered as an option, even for solutions that are unable to pass through single layer products. This avoids reliance on other methods of sterilisation such as heat and radiation which may damage vital biological or proteinaceous components in the final product.

Variation in filterability
The results of the study showed that the filterability of different HA solutions can vary considerably from one to the next. For this reason, Parker domnick hunter recommends that small scale filterability studies are conducted on an individual basis to ascertain the optimal filtration system for any given product. Our Technical Support Group (TSG) can assist in this.
**Conclusion**
Studies conducted by Parker domnick hunter into the filtration of hyaluronic acid based solutions have shown:

- The viscosity of HA solutions is directly related to the concentration and higher molecular weight HA is more viscous than lower molecular weight at concentrations over 0.2%.
- The viscosity of an HA solution is not affected by filtration and, therefore filtration does not have an impact on the characteristics of the solution.
- The higher the concentration and molecular weight of the HA, the more viscous and difficult to filter the solution becomes, eventually becoming too viscous to be processed by single layer filter products.
- Dual layer PES out-performs the single layer products for throughput of HA based solutions.

**Filtration choice**
Parker domnick hunter’s PROPOR HC dual layer PES filter incorporates a highly asymmetric prefilter layer which allows it to cope well with highly viscous solutions. During this study, it has been shown to perform very effectively when filtering hyaluronic acid based solutions and can increase throughputs to up to 10 times that of single membrane products. Using the PROPOR HC for sterile filtration of products containing hyaluronic acid can reduce downtime due to frequent filter changes and decrease system size for greater process economy.

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**Product Selection**
The right product for your application

<table>
<thead>
<tr>
<th>Product</th>
<th>Membrane</th>
<th>Main Feature</th>
<th>Cost Saving Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>TETPOR HP</td>
<td>Hydrophilic PTFE</td>
<td>Zero binding of preservatives</td>
<td>Filling can begin immediately without preconditioning of filters to eliminate product wastage.</td>
</tr>
<tr>
<td>PROPOR SG</td>
<td>PES</td>
<td>Very high flow rates</td>
<td>Faster processing for minimal batch turnaround time.</td>
</tr>
<tr>
<td>PROPOR HC</td>
<td>PES plus PES prefilter layer</td>
<td>Increased capacity</td>
<td>Economical filtration of difficult to filter solutions with a high concentration of viscosity enhancer.</td>
</tr>
</tbody>
</table>

N.B. This table is for guidance only. Filterability can vary from one solution to the next and Parker domnick hunter recommends that filterability studies are conducted on an individual basis to ascertain the optimal filtration system.
**Products**

**Sterile Liquid Filtration**

- **PROPOR SG**
  - 0.2 micron
  - Polyethersulphone
  - High Flow
  - Low preservative binding

- **PROPOR HC**
  - 0.2 micron
  - Polyethersulphone
  - High capacity
  - Low preservative binding

- **PROPOR LR**
  - 0.1 micron
  - Polyethersulphone
  - Retentive to diminutive organisms
  - High flow rates

- **TETPOR HP**
  - 0.2 micron
  - Hydrophilic PTFE
  - Elimination of preservative binding

- **PORECHECK IV**
  - Integrity Testing
  - Bubble point testing
  - Diffusional flow / pressure decay testing
  - Water intrusion testing

**Liquid Filtration**

- **PROPOR BR**
  - 0.2 micron
  - Polyethersulphone
  - Bioburden reduction
  - Maximum throughput

- **PROCLEAR PP**
  - 0.6 - 100 micron
  - Polypropylene
  - Particulate removal
  - Robust to withstand aggressive chemicals

- **PROCLEAR GP**
  - 0.5 micron
  - Glass Fibre / Polypropylene
  - High capacity
  - Maximum protection of downstream membrane

- **Housings**
  - A full range of stainless steel housings specifically designed for pharmaceutical applications

**Sterile Gas Filtration**

- **TETPOR AIR**
  - 0.2 micron
  - PTFE
  - Validated by liquid and aerosol challenge

- **HIGH FLOW TETPOR II**
  - 0.2 micron
  - PTFE
  - Unrivalled flow rates
  - Validated by liquid and aerosol challenge

- **HIGH FLOW TETPOR HT**
  - 0.2 micron
  - PTFE
  - Continuous use at high temperatures
  - Validated by liquid and aerosol challenge

- **TETPOR PLUS**
  - 0.2 micron
  - PTFE
  - Resistant to chemical attack
  - Ideal for venting of ozonated water tanks

- **VALAIRDATA II**
  - Integrity Testing
  - Aerosol challenge testing
  - Integrity testing of gas filters

- **Housings**
  - A full range of stainless steel housings specifically designed for pharmaceutical applications
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