

# Application Note

## Effective Filtration of Hyaluronic Acid Based Solutions



### 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.**



### Contact Information:

Parker Hannifin Ltd  
Parker domnick hunter  
Process Division  
Durham Road  
Birtley  
Co. Durham DH3 2SF

phone +44 (0)191 4105121  
fax +44 (0)191 4105312  
dhprocess@parker.com

[www.domnickhunter.com](http://www.domnickhunter.com)

#### 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.



ENGINEERING YOUR SUCCESS.

# 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.

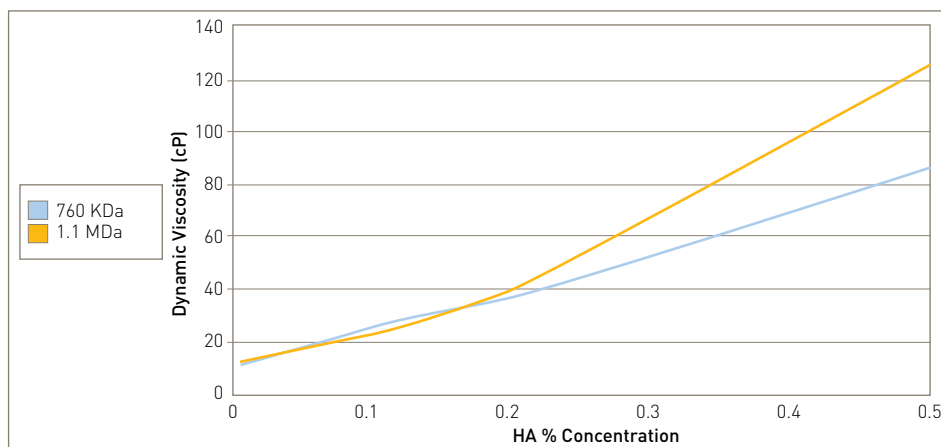


Figure 1 - Effect of HA concentration on solution viscosity for two different molecular weights

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.

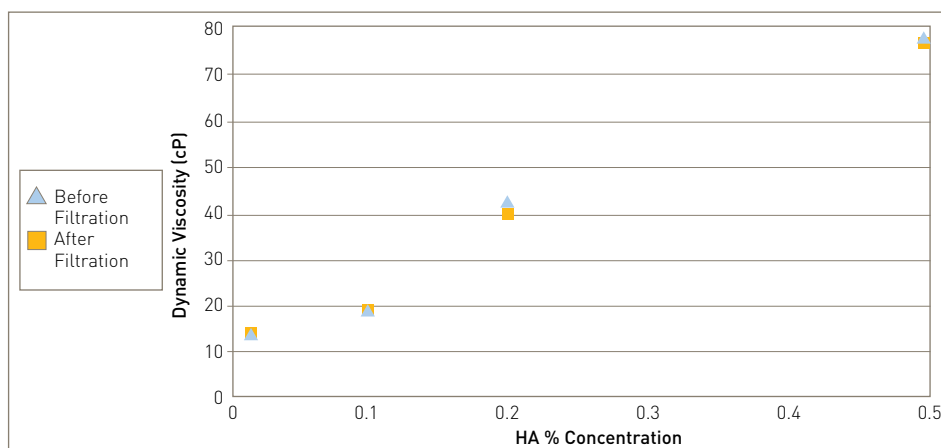


Figure 2 - Effect of filtration on solution viscosity for 760 kDa HA

## 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 out-performed 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.

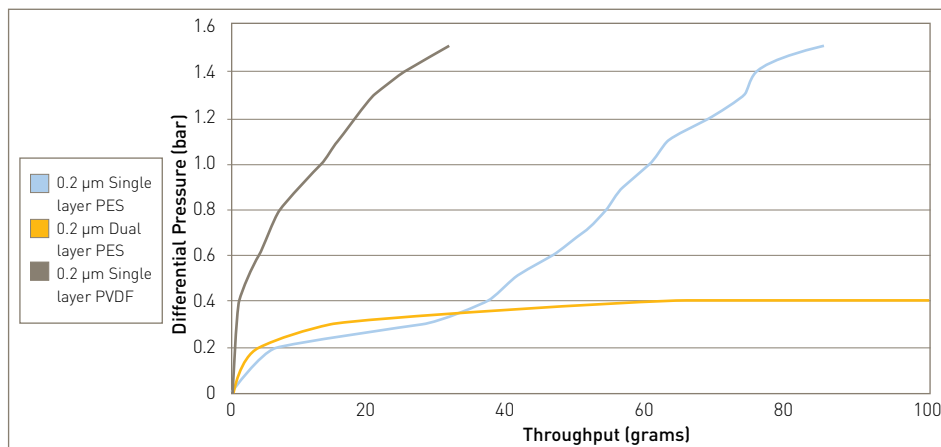


Figure 3a - Differential pressure against throughput for 70 kDa molecular weight HA at 0.2% concentration

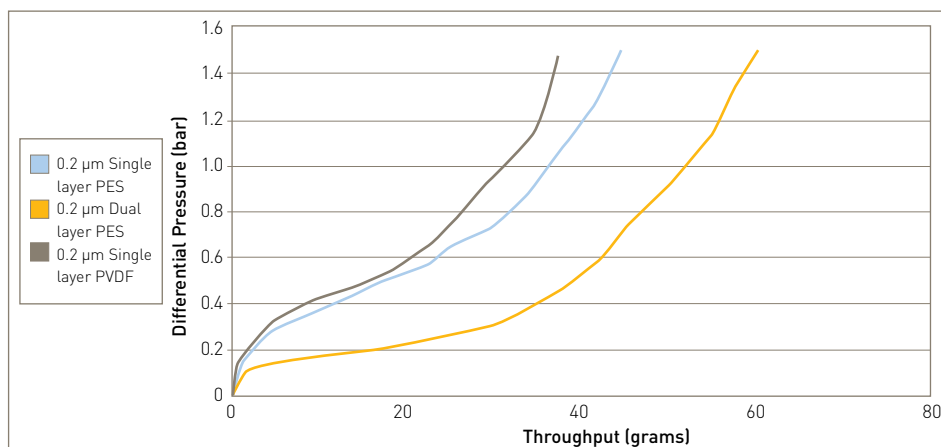


Figure 3b - Differential pressure against throughput for 1.1 MDa molecular weight HA at 0.025% concentration

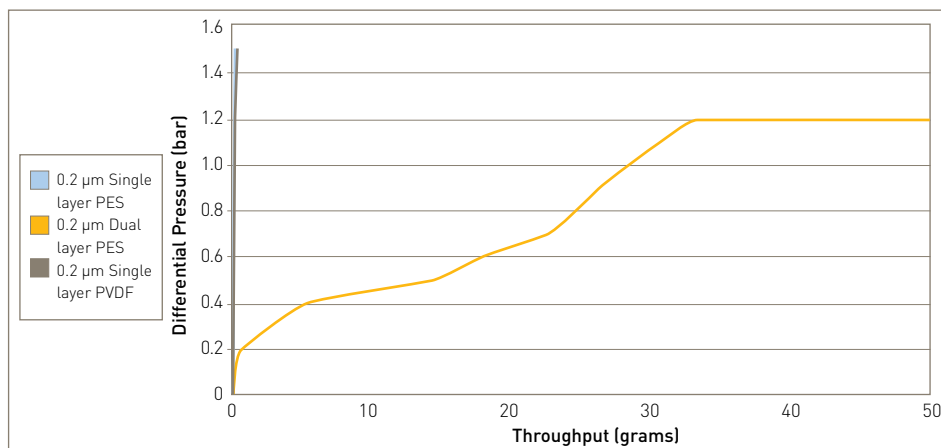


Figure 3c - Differential pressure against throughput for 1.1 MDa molecular weight HA at 0.2% concentration

# 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.

# Product Selection

The right product for your application

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

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

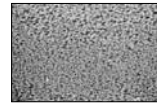


Polyethersulphone

- High Flow
- Low preservative binding

### PROPOR HC

0.2 micron

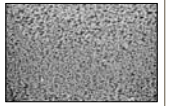


Polyethersulphone

- High capacity
- Low preservative binding

### PROPOR LR

0.1 micron

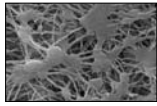


Polyethersulphone

- Retentive to diminutive organisms
- High flow rates

### TETPOR HP

0.2 micron



Hydrophilic PTFE

- Elimination of preservative binding

### PORECHECK IV

Integrity Testing

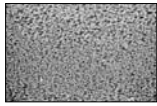


- Bubble point testing
- Diffusional flow / pressure decay testing
- Water intrusion testing

## Liquid Filtration

### PROPOR BR

0.2 micron

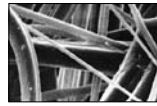


Polyethersulphone

- Bioburden reduction
- Maximum throughput

### PROCLEAR PP

0.6 - 100 micron

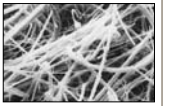


Polypropylene

- Particulate removal
- Robust to withstand aggressive chemicals

### PROCLEAR GF

0.6 - 10 micron

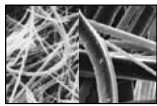


Glass Fibre

- High capacity
- Maximum throughput

### PROCLEAR GP

0.5 micron



Glass Fibre / Polypropylene

- High capacity
- Maximum protection of downstream membrane

### Housings

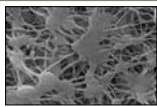


- A full range of stainless steel housings specifically designed for pharmaceutical applications

## Sterile Gas Filtration

### TETPOR AIR

0.2 micron

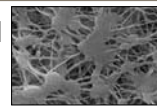


PTFE

- Validated by liquid and aerosol challenge

### HIGH FLOW TETPOR II

0.2 micron

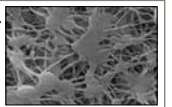


PTFE

- Unrivalled flow rates
- Validated by liquid and aerosol challenge

### HIGH FLOW TETPOR HT

0.2 micron

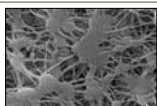


PTFE

- 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

# Sales Offices Worldwide

AE – UAE, Dubai  
Tel: +971 4 8127100  
parker.me@parker.com

AR – Argentina, Buenos Aires  
Tel: +54 3327 44 4129

AT – Austria, Wiener Neustadt  
Tel: +43 (0)2622 23501-0  
parker.austria@parker.com

AT – Eastern Europe, Wiener Neustadt  
Tel: +43 (0)2622 23501 900  
parker.easteurope@parker.com

AU – Australia, Castle Hill  
Tel: +61 (0)2-9634 7777

AZ – Azerbaijan, Baku  
Tel: +994 50 2233 458  
parker.azerbaijan@parker.com

BE/LU – Belgium, Nivelles  
Tel: +32 (0)67 280 900  
parker.belgium@parker.com

BR – Brazil, Cachoeirinha RS  
Tel: +55 51 3470 9144

BY – Belarus, Minsk  
Tel: +375 17 209 9399  
parker.belarus@parker.com

CA – Canada, Milton, Ontario  
Tel: +1 905 693 3000

CH – Switzerland, Etoy  
Tel: +41 (0) 21 821 02 30  
parker.switzerland@parker.com

CN – China, Shanghai  
Tel: +86 21 5031 2525

CZ – Czech Republic, Klecany  
Tel: +420 284 083 111  
parker.czechrepublic@parker.com

DE – Germany, Kaarst  
Tel: +49 (0)2131 4016 0  
parker.germany@parker.com

DK – Denmark, Ballerup  
Tel: +45 43 56 04 00  
parker.denmark@parker.com

ES – Spain, Madrid  
Tel: +34 902 33 00 01  
parker.spain@parker.com

FI – Finland, Vantaa  
Tel: +358 (0)20 753 2500  
parker.finland@parker.com

FR – France, Contamines/Arve  
Tel: +33 (0)4 50 25 80 25  
parker.france@parker.com

GR – Greece, Athens  
Tel: +30 210 933 6450  
parker.greece@parker.com

HK – Hong Kong  
Tel: +852 2428 8008

HU – Hungary, Budapest  
Tel: +36 1 220 4155  
parker.hungary@parker.com

IE – Ireland, Dublin  
Tel: +353 (0)1 466 6370  
parker.ireland@parker.com

IN – India, Mumbai  
Tel: +91 22 6513 7081-85

IT – Italy, Corsico (MI)  
Tel: +39 02 45 19 21  
parker.italy@parker.com

JP – Japan, Tokyo  
Tel: +(81) 3 6408 3901

KR – South Korea, Seoul  
Tel: +82 2 559 0400

KZ – Kazakhstan, Almaty  
Tel: +7 7272 505 800  
parker.easteurope@parker.com

LV – Latvia, Riga  
Tel: +371 6 745 2601  
parker.latvia@parker.com

MX – Mexico, Apodaca  
Tel: +52 81 8156 6000

MY – Malaysia, Shah Alam  
Tel: +60 3 7849 0800

NL – The Netherlands, Oldenzaal  
Tel: +31 (0)541 585 000  
parker.nl@parker.com

NO – Norway, Ski  
Tel: +47 64 91 10 00  
parker.norway@parker.com

NZ – New Zealand, Mt Wellington  
Tel: +64 9 574 1744

PL – Poland, Warsaw  
Tel: +48 (0)22 573 24 00  
parker.poland@parker.com

PT – Portugal, Leca da Palmeira  
Tel: +351 22 999 7360  
parker.portugal@parker.com

RO – Romania, Bucharest  
Tel: +40 21 252 1382  
parker.romania@parker.com

RU – Russia, Moscow  
Tel: +7 495 645-2156  
parker.russia@parker.com

SE – Sweden, Spånga  
Tel: +46 (0)8 59 79 50 00  
parker.sweden@parker.com

SG – Singapore  
Tel: +65 6887 6300

SK – Slovakia, Banská Bystrica  
Tel: +421 484 162 252  
parker.slovakia@parker.com

SL – Slovenia, Novo Mesto  
Tel: +386 7 337 6650  
parker.slovenia@parker.com

TH – Thailand, Bangkok  
Tel: +662 717 8140

TR – Turkey, Istanbul  
Tel: +90 216 4997081  
parker.turkey@parker.com

TW – Taiwan, Taipei  
Tel: +886 2 2298 8987

UA – Ukraine, Kiev  
Tel: +380 44 494 2731  
parker.ukraine@parker.com

UK – United Kingdom, Warwick  
Tel: +44 (0)1926 317 878  
parker.uk@parker.com

US – USA, Cleveland  
Tel: +1 216 896 3000

VE – Venezuela, Caracas  
Tel: +58 212 238 5422

ZA – South Africa, Kempton Park  
Tel: +27 (0)11 961 0700  
parker.southafrica@parker.com

