**Introduction**

The cost of filtration and separation stages within the production of pharmaceuticals has been increasing along with the increased complexity of final drug products. The PROPOR HC, developed in partnership with a major pharmaceutical manufacturer, has been shown to overcome significant processing problems associated with their production of a drug intermediate. The previous costly requirement to reprocess batches due to difficulties in filtration has effectively been eliminated. The increase in throughput performance of the PROPOR HC compared to competitive products, is the result of newly developed Parker domnick hunter PES membrane technology. This technology has also been shown to provide significant benefits with other protein based solutions such as serum free CHO-K1 medium and a 0.5 mg/ml protein concentration of dust mite serum.

**Contact information:**

At Parker domnick hunter we believe that application driven new product development is intrinsic to competitive advantage and customer satisfaction. Our commitment was tested through a collaboration with a multinational pharmaceutical manufacturer on the filtration of a particularly troublesome high value drug solution. This led to the extremely rapid development of a high capacity sterilizing grade membrane filter capable of substantially increasing product throughput. The development process, from the initial filterability trials performed by the Parker domnick hunter Technical Support Group and the customer, through to on-site tests of the full scale product and full product validation was achieved within 6 months. The rationale behind the configuration of the filter is explained along with the actual performance benefits benchmarked against competitive products in this and subsequent applications.
The problem
Fit for purpose filtration

The production of drug products by fermentation and cell culture can be an unpredictable science due to the complexity of the components and processes. This may lead to variation in product characteristics during the manufacturing process which can significantly impact the product filterability.

In this instance the drug intermediate was being manufactured via a microbial fermentation. The downstream processing of the product involved multiple crystallization steps which in some cases produced an intermediate that proved extremely difficult to filter. It became impossible to guarantee that a batch of product could be processed through the existing sterile filtration stage. This led to a need to accommodate change out of filters mid-batch and in some cases having to quarantine a complete batch because it could not be processed.

The cause of the filtration variability was identified as the production of small fibrils during the crystallization stages. Whilst analysis of the final product showed that the fibrils did not affect the drug quality, the processing difficulties were substantially impacting shipments and revenues. An urgent solution was required of the site manufacturing team. An international team from Parker domnick hunter were seconded to the company and together they identified the root cause of the problem and developed small-scale solutions that were subsequently used on a production scale.

Membrane polymer
Making the right choice

Polyethersulphone membrane was chosen because of its inherent low protein binding coupled with exceptional flow rates. Typical binding properties are shown in figure 1.

Parker domnick hunter PES provides substantially lower protein binding than nylon, polypropylene or polysulphone membranes. This can significantly improve product throughput with proteinaceous solutions.

Filterability trials
Testing the application

Samples of problematic batches were tested in conjunction with the customer at the Parker domnick hunter laboratory facilities. After re-constituting the product using the customers pre-defined protocol, small-scale filterability studies were conducted to ascertain the optimum filtration train and membrane configuration.

The filtration studies included the evaluation of our recently developed highly asymmetric membranes specifically designed to maximize throughputs on complex protein solutions. Extensive studies showed that a dual layer construction incorporating a prefiler and a sterilizing grade membrane provided substantial performance advantages. Figure 2 shows some examples of the performance seen with three of the tested configurations. This illustrates the importance and value of addressing filter configuration to specific application requirements through a systematic and collaborative approach.

Innovation
At the core of product development

These performance advantages were achieved by the combination of expert optimization and the use of our new range of leading edge PES membranes. As shown in Figures 4-6, these membranes combine a highly asymmetric structure with a very well controlled retentive layer on the downstream face of the membrane.

A new filter has been successfully developed to solve a particular processing problem on a drug intermediate in a very short time frame. The key ingredient in the development of the PROPOR HC filter has been the close relationship between the customer, their application problem and personnel from Parker domnick hunter Technical support group (TSG), R&D and sales teams.

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The large amount of testing required to support the production release of this new product was handled through Parker domnick hunter’s ‘Stage Gate’ process. The flexible team approach adopted throughout ensured that the product could be released to the customer with full validation guide within the 6 month time frame.
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The comprehensive filterability studies conducted at small-scale proved to be invaluable in ensuring the filter configuration was optimized. The dual layer membrane construction incorporating a highly asymmetric prefilter layer has been shown to increase throughputs of proteinaceous solutions by up to ten times. The significant benefits have also been realised with other protein based solutions such as serum free CHO-K1 medium and a 0.5 mg/ml protein concentration of dust mite serum. In both cases throughputs of proteinaceous solutions by up to ten times. The significant benefits have also been realised with other protein based solutions such as serum free CHO-K1 medium and a 0.5 mg/ml protein concentration of dust mite serum. In both cases system size was reduced more than 4 fold. The efficacy of the membrane prefilter also allows the possibility of simplifying filter trains by replacing a discrete prefilter stage, thus providing further economic and processing benefits.

Conclusion

The large amount of testing required to support the production release of this new product was handled through Parker domnick hunter’s ‘Stage Gate’ process. The flexible team approach adopted throughout ensured that the product could be released to the customer with full validation guide within the 6 month time frame.
### 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

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

#### PoreCheck IV
- Integrity Testing
- Polyethersulphone
- 0.1 micron
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#### Liquid filtration

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

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

**PROCLEAR GF**
- 0.6 - 10 micron Glass Fibre
- High capacity
- Maximum throughput

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

#### Sterile gas filtration

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

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

**HIGH FLOW TETPOR II**
- 0.2 micron PTFE
- Unrivaled flow rates
- Validated by aerosol challenge

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

**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

### Application Note

**Technical Application Publication**

Optimized sterile filtration of pharmaceutical solutions

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