Scale-Up Capsule Filtration of Oligonucleotide Solutions for cGMP Use

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Abstract

Oligonucleotide production in cGMP facilities typically involves large volumes of product (> 20 L) that require sterilization-grade filtration prior to lyophilization in order to remove potential contaminants. To streamline the current practice, a pump-driven filtration was performed using a pre-sterilized capsule filter with a 0.45/0.2µm pore size PES filter. This approach increased efficiency of the filtration process with no measurable impact on product integrity as well as eliminated the cumbersome use of 1 L sterile vacuum filter flasks. Here, we show that capsule filtration is an easy scalable process as it was successfully applied to multiple manufacturing campaigns (up to 30 L). Additionally, it is as robust as the sterile single-use filtration systems, but significantly more efficient with less potential for contamination and less burden on operators.

Materials

Equipment

- Peristaltic pump
- Pressure gauge
- Balance
- Ring stand and clamps

Materials

- Sterile tubing
- Sterile hose barb union tee
- Sterile hose barbs
- Sterile capsule filter, PES (0.45/0.2µm)
- Sterile HDPE collection containers

Methodology

Pump-driven filtration was performed at a constant flow rate of ~600 mL/min allowing filtration of the entire product volume in one single run.

Filtration was monitored throughout via a pressure gauge located upstream of the filter to ensure integrity of the membranes shown in **Figure 1**.

All components of filtration apparatus are pre-sterilized and single-use, decreasing the overall risk of bioburden and endotoxin contamination.

A balance is used to determine when ~1.5 L of product has been filtered to ensure Lyoguard trays are not overfilled.

WFI is used to rinse the system and filter following the filtration of the entire oligonucleotide solution (300-400 mL).

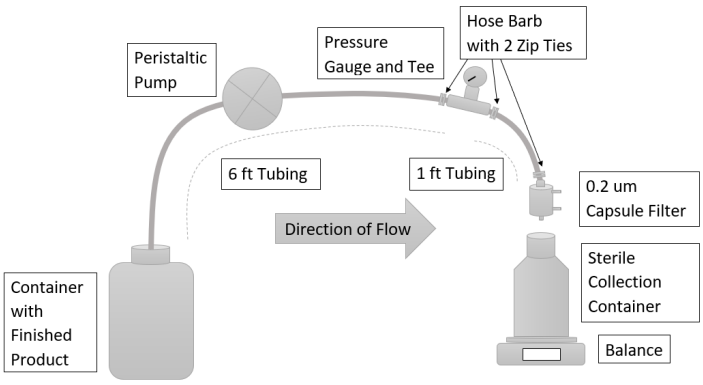

Figure 1. Diagram of pump-driven filtration setup with capsule filter.

Results

Quantitative recoveries were observed following capsule filtration with no measurable impact on product integrity.

Particulates were not observed within the sterile packaging of the separate pieces or the filtered oligonucleotide solution.

Table 1. Summary of results comparing capsule filtration and filter flasks

Volume Filtered	Bioburden Results Post-Filtration	Time to Filter Using Capsule Filter (including set up)	Time to Filter Using Filter Flasks (estimated)
4 L	0 CFU/g	30 min	60 min
6 L	0 CFU/g	45 min	90 min
20 L	<20 CFU/g	75 min	200 min
30 L	0 CFU/g	90 min	300 min

Conclusions

Capsule Filtration

- More time efficient
- Lower risk of contamination
- Ease of process
- Ease of burden on operators
- No impact on final product
- Comparable recoveries to filter flasks
- No particulates have been observed in filtered solutions

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