Confidence when scaling up

By using a structured, analytic approach under simulated process conditions at the experimental stage, it is possible to accurately predict filter performance at cGMP level. Parker domnick hunter explains more...

Results gleaned during initial experiments to determine the most appropriate bioprocess can be scaled up to cGMP production – so long as a robust design is initally adopted.

Take, for example, a case study for determining the correct sizing for a filter involved in an utomated final bulk-fill system for biopharmaceutical product.

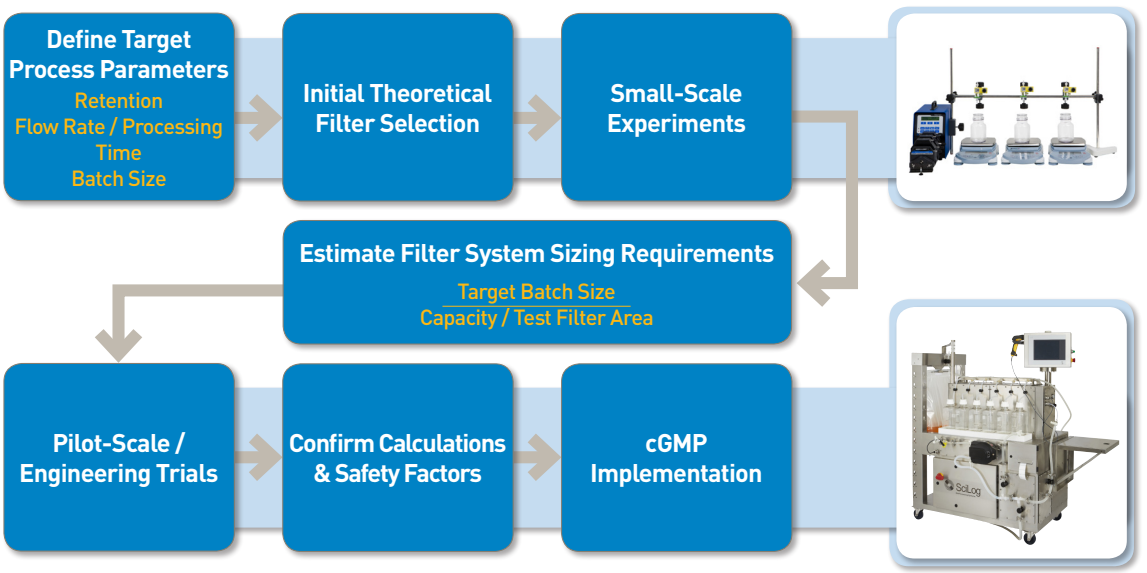
Methodology

The process for successful scale-up (Figure 1) begins with the manufacturer identifying a target product and the process parameters which a bioprocess must work within to the ensure quality of the final product.

Small-scale experiments using a theoretical selection of filters will allow the manufacturer to estimate filter system sizes, which can then be tested in pilot-scale and engineering trials.

Because the capacity is directly proportional to the filter area, data from the smaller scale experiments can be scaled up to determine the required system size for the target process. ▸▸

Figure 1: *The process for successful scale-up*

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Experimental variability can also be introduced through differing filter formats, drug products batches or process equipment at a pilot-scale or during full engineering trials to confirm the initial findings.

To ensure scale-up predictability, sizing should be performed using a scale model of the target process. Ideally, processing time should remain constant, and the flow rate should be adjusted as a function of test batch volume.

The SciLog® FilterTec system measures differential pressure across a filter during testing, allowing real-time assessment of filter blocking characteristics and further optimization through the use of prefiltration stages. Constant flow testing is performed until the differential pressure across the filter reaches a defined, predetermined end point.

Scale-up testing

For this case study, to match the requirements of large-scale manufacturing, sterilization filtration of a high-potency drug was required. The process was defined by the maximum batch size of 25 L of bulk product and an upstream pressure limit of 2 barg (29 psig).

Mid-batch filter blockage or damage to the single-use manifold resulting from overpressure was not acceptable because of the hazardous nature of the drug product.

Small-scale disc testing was performed on Parker domnick hunter's PROPOR HC at a target flow rate of 10 mL/min, with a pressure limited to 1.6 barg (23.2 psig), which gave a 20% safety factor.

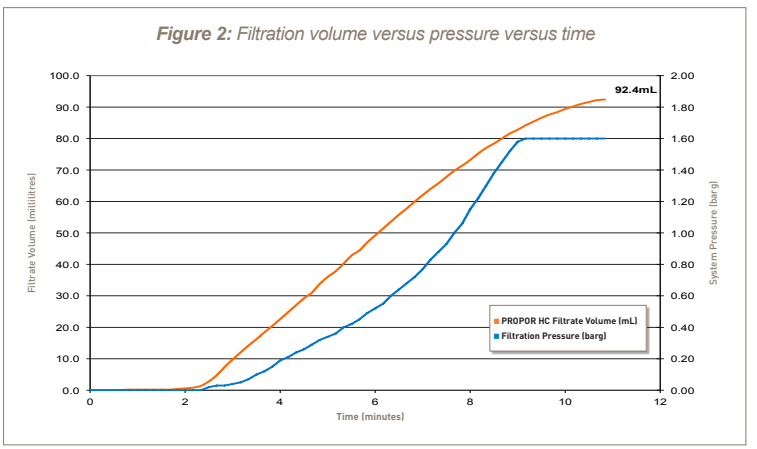

Figure 2: Filtration volume versus pressure versus time

This established a capacity of 92.4 mL of solution for a 47 mm PROPOR HC disc at an actual flow rate of 8.5 mL/min (Figure 2). Scaled-up relative to effective filtration area, this is the equivalent to 35 L of bulk product through a 10 inch (250 mm) filter capsule, which is capable of processing a 25 L batch while incorporating a 40% safety factor in capacity.

Confirmation of this analysis through the use of a pilot-scale trial provides further assurance that the results are repeatable on a larger scale and that the batch could be processed without the risk of filter blockage.

A structured analytic approach creates confidence when scaling up. Furthermore, the use of automation during this process allows increased accuracy through the removal or potential operator variability. ■