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Novel Concept for Production of mAbs

Reduce Costs and Increase Flexibility with High-Productivity, Single-Use Technologies

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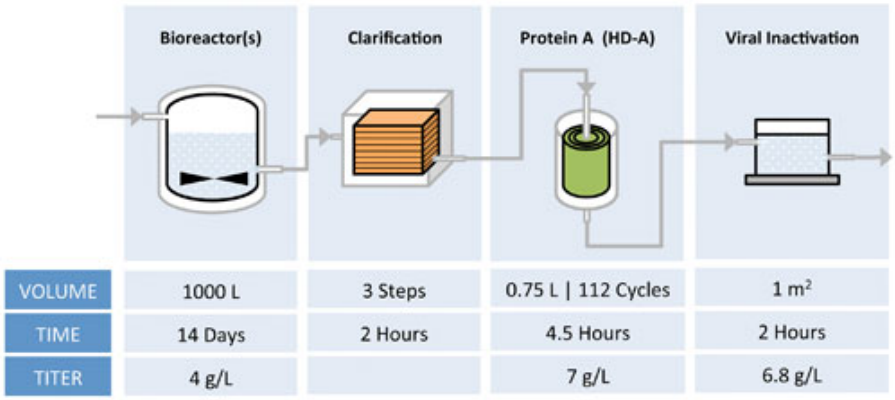


Current market dynamics have created the need for new manufacturing facility designs that are more flexible and have high productivity, enabling large variations in scale in a small footprint at lower investment cost.

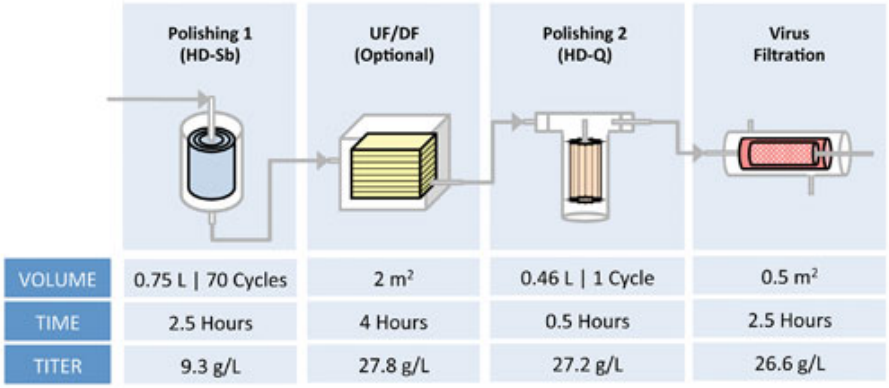
Traditional monoclonal antibody manufacturing plants are most cost-efficient when the infrastructure is large-scale and fully utilized. This is partially due to designs based on equipment that is of fixed configuration, thereby making it difficult to economically accommodate varying scales of operation.

Expenses related to environmental monitoring and quality control incur at these fixed facilities even when batches are not being manufactured. Full capacity utilization with higher flexibility and cost-

efficiency can be achieved by designing manufacturing facilities that employ scale-flexible, state-of-the-art multiproduct technologies.

A new flexible fed-batch manufacturing concept is presented in *Figures 1* and *2* and discussed in detail in this tutorial. The hypothetical example presented shows production capacity of 2.5 kg per batch. The entire high-capacity downstream processing could be completed in approximately 24 hours. This capacity could be economically scaled linearly up to 16 kg per week to meet market demand or for clinical-stage requirements.

Fully Flexible Facilities



Single-use bioreactors are good and well-accepted options for this flexible fed-batch manufacturing process. In the schematic provided in *Figures 1–2*, these reactors produce 4 kg of mAb in 14 days, and multiple single-use reactors can be added as the cell culture volume requirements increase with product demand.

For example, in order to increase manufacturing out to 16 kg mAb per week (up to 800 kg per year), production from 6 to 7 bioreactors would be linked to the one downstream processing train in *Figures 1–2*.

One of the key advantages of this manufacturing scheme is that a single downstream processing train could be sufficient to process feed streams from multiple bioreactors, with the harvests staggered to leverage the high productivity of the downstream process and maximize throughput of the facility. This simple and flexible downstream purification train would be enabled by relatively inexpensive single-use membrane chromatography capture and polishing technologies.

In contrast to expensive resin columns and centrifuges, inexpensive single-use membranes and filters allow for complete utilization of the media in a single batch.

Technologies chosen for these unit operations would share critical attributes, i.e., high-performance (productivity and selectivity) and robust single-use configurations.

For example, rather than clarifying with a traditional large, capital intensive centrifuge, the purification train would employ modern disposable filters to create a continuous process that steadily feeds the subsequent chromatographic steps. For UF/DF applications, disposable single-pass tangential flow filters (SPTFF) would be appropriate. SPTFF is capable of achieving 2–30 fold concentrations in a single pass by eliminating the iterative recirculation loop path that is common in conventional TFF units, creating a simplistic and time-efficient UF/DF operation. These SPTFF modules are also easy to scale, enable continuous manufacturing, and are available in compact sizes that optimize facility footprint.

Natrix Separations' hydrogel membranes were chosen for chromatography operations since they are available in compact and single-use per batch formats, are easily scalable, and have higher (or similar) binding capacity with faster processing times than chromatography resins in stainless steel columns.

Modern resins offer adequate selectivity only at slower flow rates due to slow mass transfer kinetics stemming from long and restricted diffusional flow pathways.

Moreover, unlike single-use-per-batch membranes, chromatography resins and column hardware are expensive, labor-intensive, large in size and cannot be conveniently adjusted to different production scales. These resin columns need to be amortized over many batches to be cost-effective and are often underutilized.

For the affinity chromatography capture step, a new Protein A hydrogel-based membrane, which is currently in development at Natrix, would be applied in the presented process. Lab studies with prototype Protein A membrane materials have demonstrated 45 g/L binding capacity with 6 seconds residence time with 95% yield (data not shown).

As a hypothetical example, a 1 L Protein A membrane column would be rapidly cycled over 100 times to match the upstream mAb production rate in *Figure 1* and enable completing the entire downstream process in approximately 24 hours.

The Protein A membrane capture step could be followed by Natrix' hydrogel-based HD-Sb (cation exchange, CEX, and perhaps optional depending on aggregation) and HD-Q (anion exchange, AEX) chromatography membrane operations (*Figure 2*). These compact ion exchange (IEX) membrane options are high-capacity polishing tools that would fit well in small footprint facilities.

In the concept presented, a less than 1 L HD-Sb membrane column used in bind-and-elute mode for less than 100 cycles in approximately 3 hours would be sufficient to process the Protein A membrane eluate, and the HD-Q column would be used to process the HD-Sb purified stream in a single 30-minute flow-through due to a high loading capacity.

Increase Productivity in Smaller Footprint

Manufacturers can increase overall productivity and decrease the footprint associated with storage bags in this process by “staggering” downstream unit operations. For instance, earlier eluates of the capture step could be processed through the cation exchange polishing step while latter cycles continue.

The productivity of the entire process could be further increased by replacing one or more of the single-use fed-batch reactors with a single-use high-density perfusion bioreactor, and running the entire process in a quasi-continuous mode using multicolumn configurations. The fast processing features of the single-use purification technologies discussed above would allow the downstream purification process to run continuously.

The conceptual process in *Figures 1–2* would be capable of manufacturing up to 800 kg of mAb per year by coupling 6 to 7 single-use fed-batch bioreactors to one high-productivity downstream train. This manufacturing output can be readily and economically increased by adding single-use fed-batch reactor trains and coupling them with more downstream purification trains.

With the exception of matching the run rates of the bioreactor operations to match the increased output, no other changes would be required. Manufacturing processes designed with these modern technologies are very flexible and can easily be adapted and scaled to changes in product demands.

Unlike with traditional facilities where scale-up or scale-down is unfeasible due to the upfront cost of capital equipment, these high-productivity and disposable technologies enable flexible manufacturing without wasting capacity, incurring less capital expense, and minimizing operational expense. These flexible, single-use technologies are also appropriately sized to be operated in relatively smaller manufacturing facilities.

Finally, since exactly the same scale process trains could be used for both clinical and commercial manufacturing, a streamlined regulatory filing would be possible, bringing additional benefits including faster approval times and much reduced associated costs.