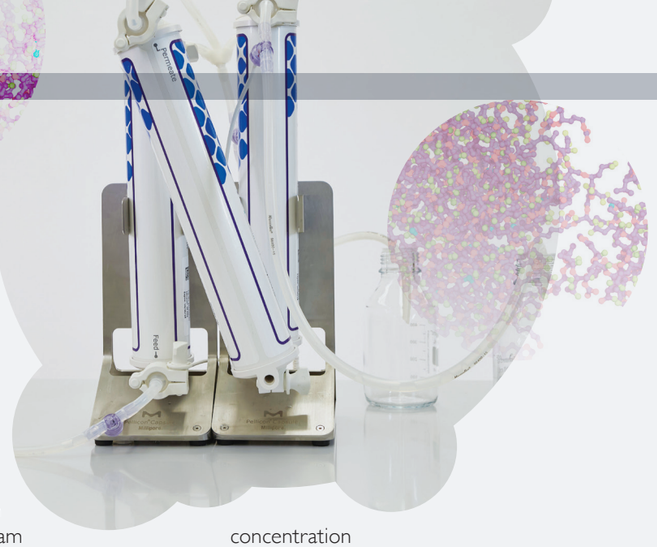
Adding Versatility with Single-Pass TFF

Single-pass TFF is a convenient means of reducing volumes, column sizes and hardware costs, as well as eliminating tank bottlenecks – and can be powerfully combined with single-use technology.

By Emily Peterson

In the early days of the biopharmaceutical industry, the costs of production received little attention given that profit margins on lifesaving drugs often tipped over 100 percent (1). But as the number of blockbuster drugs slowed and competition in the sector increased, the industry began to think hard about how to reduce manufacturing costs. Facilities in those days exclusively used inflexible, hard-piped equipment and stainless steel bioreactors and tanks. More recently, single-use technologies have emerged, presenting an attractive alternative that allows companies to eliminate cleaning validation requirements, while reducing the risk of cross contamination. Plus, faster turnaround between campaigns and the reduced time for new facilities to become operational are a good match for companies with several products in the pipeline – and the figures bear this out.

In 2006, 21 percent of bioreactors were single use, but by 2017, the number rose to 80 percent (2). There has also been a similarly rapid growth in the adoption of single-use mixing systems, which increased by 58 percent over the same period. The growth in the adoption of some new(er) single-use equipment, such as membrane adsorbers and perfusion/tangential flow filtration devices, has been slower (37 percent and 38 percent, respectively), but these technologies do mesh well with the industry's shift away from batch processing.



Single-pass tangential flow filtration is one such technology that I see in an increasing number of applications, including for processing monoclonal antibodies (mAbs), vaccines and plasma. Tangential flow filtration (TFF) is widely used for downstream processing applications and involves concentrating product through volume reduction, followed by buffer exchange via diafiltration to achieve high yields. Traditional TFF requires multiple passes through a system, using a pump to drive feed through a filter and sending the retentate back to a tank for another pass through the system.

Single-pass TFF, on the other hand, does not recycle the retentate because the TFF sufficiently concentrates the product after a single-pass through the filter assembly. This results in a much smaller footprint in any unit operation you want to use it with. For example, imagine bringing in a new molecule and the tank doesn't have sufficient capacity to hold the volume. You may decide to implement a volume-reduction step, and single-pass TFF is a great option here because you can reduce volume before reaching the tank capacity without adding additional stainless steel piping to your existing manufacturing line.

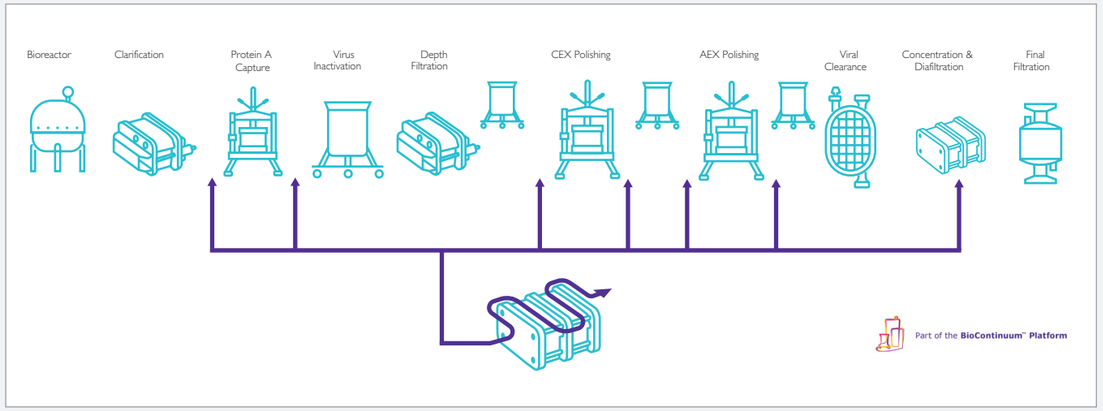
Single-pass TFF can also be used in process intensification; specifically, to intensify your chromatography and filtration steps. This is simply a case of doing a concentration prior to loading onto a column. This way, you can increase the dynamic binding capacity of your resin, which allows you to use less resin in your process step. This will greatly reduce the cost, column size and buffer usage – everything that goes along with larger feed volumes.

Another great application is for high-concentration formulations. Single-pass TFF typically runs at much lower cross-flow rates when compared with traditional batch TFF – in the region of one L/min/m² or lower, as opposed to the 4-6 L/min/m² you get with batch. This eliminates the need for larger pipes and pumps, resulting in significant equipment cost savings. And because there isn't as much dilution at the end of the process, it can be much easier to achieve higher concentrations when compared with batch TFF.

Finally, single-pass TFF also offers safety benefits. For example, with batch TFF you're repeatedly concentrating – passing a volume of fluid over and over again with multiple passes – which introduces the chance of damaging your molecule. Single-pass TFF is a much gentler operation, which can be a big bonus if your molecule is shear-sensitive.

Single-pass TFF and single use

Single-pass TFF can be powerfully combined with single-use technology. Traditional TFF is hardware driven – you have to install devices and holders and there's some cleaning and pre-use work that's related to traditional TFF. There are also a lot of stainless components that restrict moving and scalability for platforming. In addition, once you're done processing, you have to disassemble the units, clean them and discard them. This certainly goes against the overall industry trend towards disposable, more flexible, systems.



Single-pass TFF can be accommodated anywhere in a process where volume reduction is needed.

There are single-pass TFF options, such h as Merck's Pellicon® capsule, which come holderless and pre-sterilized – reducing setup time and eliminating cleaning altogether. There are also no diverter plates, so to get started, you simply connect capsules in a series: retentate to feed, feed to retentate. Essentially, you plug it into your process and you're ready to go. At the end of your process run, you throw the capsule away so you don't have to worry about bioburden or operator safety.

Single-pass TFF is easy to get started with in that there's no need for pre-cleaning or pre-conditioning – you just have to flush the water that's been there for shipping purposes. Then, it's simply a case of finding the right conditions (although granted this can be a little tricky for someone who has never done it before). The biggest variable is figuring out the correct back pressure, which is feed specific and, therefore, depends on your starting concentration – this can sometimes involve a little experimentation to find the optimal pressure. Next, it's a case of running your feed flux excursion at the different flow rates. Usually, I start out at one L/min/m² and decrease from there. By decreasing the cross flow rate, you increase your conversion rate, which allows you to dial in the kind of conversion you're looking for.

One great advantage of single-pass TFF is that you can collect data over multiple sections to figure out how many sections you'll need in the end. For example, if you want more time to consider, you can decrease your area and increase your time by turning down the cross flow rate. Once you have your back pressure and desired cross flow rate based on conversion or volumetric concentration, you just have to increase your area based on process volume and desired process time. Essentially, once you know your cross flow rate, scale-up volume, and time that you want to process (depending on how much area you use), you're looking for the same number of sections and the same pressure profile across the devices.

Once you've overcome these steps in process development, single-pass TFF is simple to use. And for companies looking to reduce volumes and column size – especially in existing facilities where space may be limited – as well as eliminate tank bottlenecks, it's a great option. It's also an enabling technology for companies looking to transition towards more continuous and single-use processes, where high product quality, speed to market, resource conservation, and safety are paramount. The biopharmaceutical industry is clearly trending in this direction, and I believe we'll see newer technologies, such as tangential flow filtration systems, become more widely adopted over the next few years – as mixing systems and bioreactors have. From a personal perspective, having worked in TFF for just under four years – and the industry as a whole for almost two decades – customers seem very positive about the technology and I see a growing interest in combining single-pass TFF with single use for a number of applications.

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The life science business of Merck operates as MilliporeSigma in the US and Canada.

References

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2. *American Pharmaceutical Review, "Top trends in single-use biomanufacturing", (2017). Available at: https://bit.ly/2PZMAGe.*