

How Four-Piston Diaphragm Pumps Can Optimize TFF Processes

Achieve gentle product handling in tangential flow filtration activities with PSG® Biotech pumps

By Dr. Andreas Frerix



Introduction

At its most basic, the manufacturing of biologics for the creation of biopharmaceuticals, medicines and therapeutics can best be defined as a process that enables the consistent, reliable and safe completion of a series of unit operations. One of the most common and critical of these unit operations is tangential flow filtration, or TFF, which is also known to some as “cross-flow filtration.”

TFF is a filtration process in which the biologic feed stream is passed across the filter membrane tangentially at positive pressure relative to the permeate side. As the biologic feed stream passes over the membrane, the liquid stream with molecules that are smaller than the membrane’s pore size flows through the membrane (called the “permeate”) while the molecules or particles that are larger than the pore size remain on the feed side of the membrane and is called the “retentate.”

During the filtration process, a portion of the molecules or particles that will not pass through the membrane will form a gel layer on the membrane. Over time, this gel layer will get larger and thicker, and will ultimately restrict the flow through the membrane before it eventually blocks the pores. The overriding advantage of TFF is that this gel layer, or the substances that remain on the filter that can blind the filter, are washed (retained in flow) away during the filtration process, allowing higher efficiency and operation time for the filter.

By comparison, dead-end/normal-flow filtration – a process in which the feed stream is passed through the membrane – can be susceptible to clogging caused by high concentrations of larger solids becoming trapped on the filter. Therefore, TFF is a cost-effective and efficient method to remove impurities from product feed streams, in the process of creating a highly concentrated retentate that is ready to be used in the biologic-manufacturing process.

In this white paper, we will look at the operational variables inherent in creating a successful TFF operation, the challenges that must be overcome in optimizing these variables and illustrate why Four-Piston Diaphragm Pumps from PSG® Biotech can be the optimal choice for ensuring TFF success, resulting in the creation of biologics that are safe and efficient for human administration.

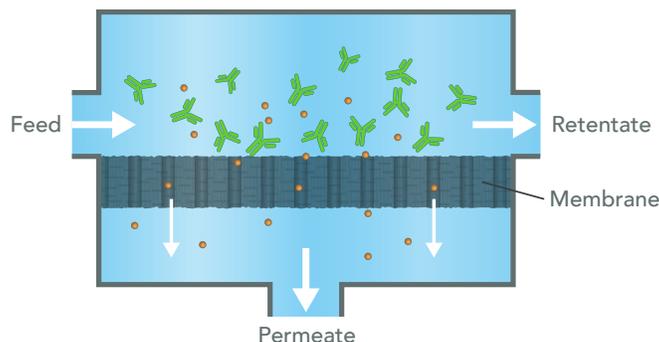
The Challenge

The creation of an effective TFF process requires the adequate control of two significant operational variables:

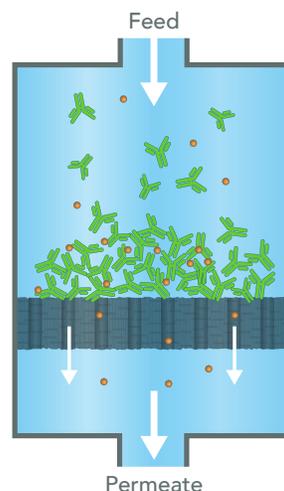
1. **Recirculation Rate:** This is the “cross flow” that helps give TFF its name. Optimized recirculation or cross-flow rate is required to minimize the formation of the gel layer on the membrane and keep the filtration functioning properly. The cross-flow is directly controlled by the flow rate that is created by the pump. The recirculation rate needs to work in sync with the second operational variable...
2. **Trans-Membrane Pressure (TMP):** TMP is the average amount of pressure (between the pump inlet and outlet) deducting the permeate pressure. This positive pressure is the active force that is applied to the membrane and which pushes the permeate liquid stream through the membrane. Maintaining a constant TMP is critical because if it is too high it can contribute to gel-layer formation and potential membrane blockage that cannot be removed by recirculation and if it is too low it can result in unacceptably low filtration (permeate) flow rates that will reduce process efficiency and lower yield outputs. The TMP or backpressure is controlled by a control valve in the retentate line.

Both recirculation/cross-flow rate and TMP are critical parameters that need to be maintained in a narrow operational window throughout the whole TFF process. Helping ensure that the recirculation/cross-flow rate and TMP remain in their desired ranges can necessitate the use of a pumping technology that delivers gentle product handling and low-pulsation flow characteristics, which will decrease the risk that fluctuations will occur within these operational variables.

So, which types of pump technologies are most commonly used in TFF applications? Two common technologies used in TFF processes are centrifugal and peristaltic (hose) pumps, however, both have operational



As the biologic feed stream passes across the filter membrane during the **tangential flow filtration (TFF)** process, the permeate (molecules smaller than the membrane’s pore size) flow through the membrane while the retentate (molecules larger than the pore size) are collected on the feed side of the membrane.

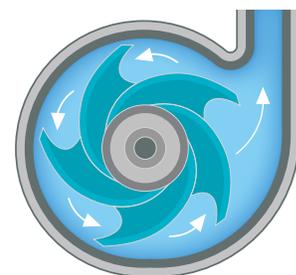


Retentate that remains on the filter during **dead-end filtration** processes can create gel buildup that will blind, or plug, the filter. The advantage of TFF is that any potential filter-blinding retentate that remains is washed away during the filtration process, which improves efficiency and extends filter service life.

shortcomings that can compromise the effectiveness and reliability of the TFF operation.

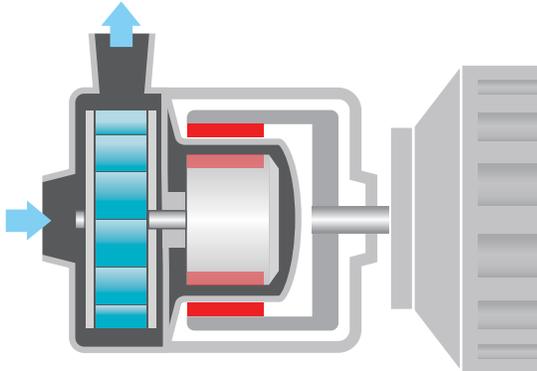
Centrifugal pumps can struggle in TFF applications because they are not positive displacement (PD) pumps. This means that their method of operation – rotating impellers that use mechanical energy to “throw” the pumped product toward the discharge outlet – can result in poor flow control and unstable flow rates at varying pressures.

Depending on the pressure and type, centrifugal pumps can also be prone to creating shear within pumped liquids, which can undermine end-product integrity. Centrifugal pumps are susceptible to excessive heat buildup at higher pressures during their operation because of operational inefficiencies when compared to PD pumps.



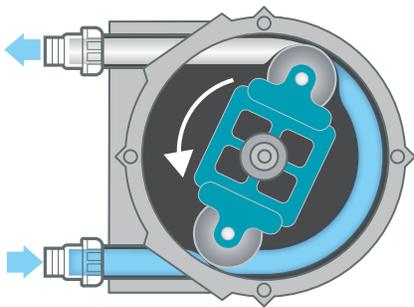
Centrifugal pumps struggle in TFF applications because of potential heat generation at higher discharge pressures and poor flow control at varying pressure conditions.

A final concern to be aware of when considering centrifugal pumps in TFF applications is that some models are magnetically driven. There are two potential disadvantages here: 1) magnetically driven pumps can generate heat, which can affect product integrity and 2) instead of mechanical seals, the pumps are coupled and driven by a motor and magnet combination. In increasingly popular single-use biologic-production applications, disposing of the pump's magnets can raise environmental issues.



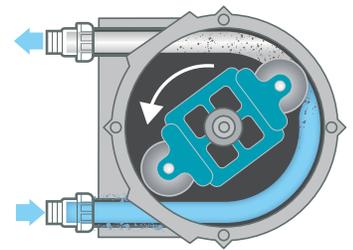
Centrifugal pumps are oftentimes driven by a motor and magnet combination. This can be problematic when the pumps are featured in single-use production applications because **disposing of the magnets** can create environmental concerns.

Peristaltic (hose) pumps' main deficiency in TFF applications is also the most apparent: their method of operation – rotating rollers that compress a hose or tube, creating vacuum that draws the liquid through the hose or tube – will undoubtedly produce pulsation within the feed stream, and liquid pulsation is undesirable in biologic manufacturing. Peristaltic pumps also have limited flow and pressure-handling abilities. Additionally, mechanical deformation of the hose or tube during the pumping process can result in inconsistencies in the peristaltic pump's flow rate and performance.



By their very method of operation, **peristaltic pumps** create pulsation in the fluid stream, which can affect overall product consistency.

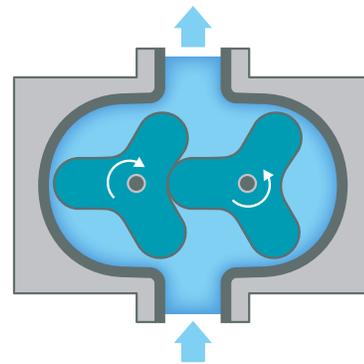
Finally, peristaltic pumps can also release or shed small quantities of hose or tube material – in a process known as “spalling” – into the pumped feed stream, which can compromise product integrity and purity. This raises the risk that the spalled hose material could make its way into the final biologic product, which will compromise its integrity and potentially harm the consumer.



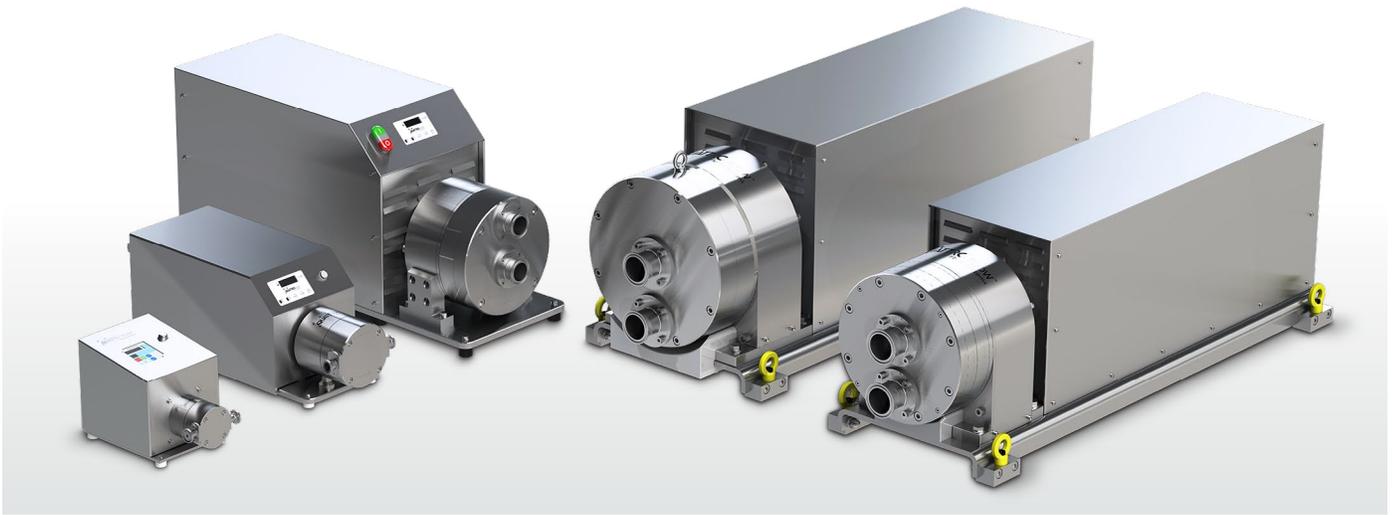
A disadvantage of **peristaltic pumps** is their tendency to shed, or “spall,” small quantities of hose material, which can compromise the purity of biologic products.

One additional technology that has also been known to be used in TFF applications is the lobe pump.

Lobe pumps are not a good match for TFF application because excessive product slip, which is caused by the gap between the rotating lobes and the pump housing, can occur during their operation, which can result in increased product shear damage and heat generation. Lobe pumps also have mechanical seals, which essentially produce a controlled leak that does not promote full product containment unless special seals and seal barriers are used. Since sterility, or at least bioburden control, is required in all forms of biologic handling, no outside contaminants should be introduced into the purification process, which is something that pumps with mechanical seals cannot reliably ensure, unless specific precautions are taken. These special seals can prove costly to both acquire and maintain, and are liable to be damaged during transportation, all while adding to the pumping system's complexity.



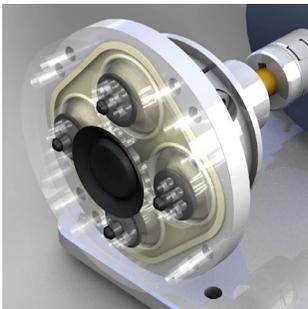
Lobe pumps are not a good fit for TFF applications because excessive product slip can occur, which results in increased shear damage and heat generation.



The heart of any biopharma operation, Quattroflow® Four-Piston Pumps from PSG® Biotech feature a method of operation that allows them to securely and gently convey aqueous solutions and biologic products that are shear-sensitive, such as those handled in TFF applications. Quattroflow Four-Piston Pumps are available in both multi- and single-use configurations with a total flow-rate range from 0.06 L/min to 267 L/min (0.02 gpm to 71 gpm).

The Solution

As noted earlier, an effective pumping solution for TFF applications that addresses the operations concerns of centrifugal, peristaltic, lobe and piston pumps, can be the Four-Piston Diaphragm Pump models manufactured by PSG Biotech product brand Quattroflow®, Duisburg, Germany. In the 25 years since Quattroflow pumps were introduced to the biologics-manufacturing industry they have earned a trusted reputation and leading position in the market. This is based on a method of operation that allows them to gently, safely and securely convey biologic materials with low pulsation.



The four-piston design of Quattroflow pumps does not require any mechanical seals or wetted rotating parts, which helps ensure total product containment while minimizing shear, pulsation and particulate generation.

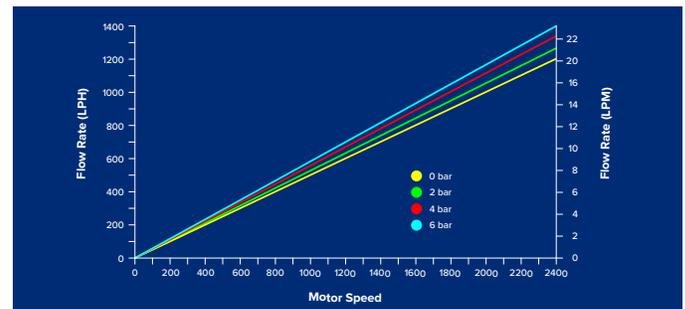
Quattroflow pumps excel in TFF applications because their four-piston design does not require any mechanical seals or wetted rotating parts, which helps ensure total product containment while helping to minimize the generation of shear, pulsation and particulate. The pump's method of operation also offers risk-free dry-running, self-priming capabilities and high turndown ratios.

A self-priming pump technology with high turndown ratios allows for the creation of a broad flow range, especially in regard to changing viscosities. In other words, in TFF applications

self-priming Quattroflow pumps deliver consistent, low-shear and low-pulsation flow control that is essential for stable and consistent process controls.

The Quattroflow pump's characteristics also allow it to produce a linear flow-performance curve, the benefits of which include:

- Proportional flow characteristics and low impact of pressure changes on the flow rate that help to maintain constant cross-flow
- In comparison, pressure changes in a centrifugal pump cause significant changes in flow rates, which makes achieving stable process control very difficult. Even a small increase in the TMP can cause a significant reduction in the cross-flow rate, which can contribute to membrane blockage
- Quattroflow pumps require up to 50% less energy to operate than a lobe pump: less energy = less heat input = less shear stress = less product damage = higher yields



The operating characteristic of Quattroflow pumps enable them to produce a linear flow-performance curve, which means that any pressure changes during the TFF process will not adversely affect the cross-flow rate.

In today's evolving biologic-manufacturing processes, Quattroflow pumps are the first-choice technology in popular single-use production setups. Put simply, a single-use pump with a replaceable pump head/chamber enables biologic manufacturers to eliminate the cost of cleaning and revalidating their pumps. The result is not only quicker production and changeover processes, but ones that deliver preferred levels of product integrity, purity and sterility with no chance for cross-batch or cross-product contamination.

Other advantages of Quattroflow pumps in TFF applications include:

- A unique form of operation, specifically designed for bioprocessing, that mimics the human heart
- Fluid-contacting pump head/chamber is safely disposed
- Easy replacement of product wetted parts
- Ability to use multi-use or single-use pump chambers on the same drive
- Pump chamber can be replaced in a short time, eliminating excessive downtime
- Lower hardware, cleaning and validation costs
- Useable when cleaning in place (CIP) or steam sterilization is not practical or possible
- Easy scalability from 0.06 L/hr up to 16m³/hr over a selection of pump sizes and drives, enabling the use of the same technology from product development to production

Additionally, PSG Biotech's Quattroflow team has recently engineered the Q-Control Integrated Pump Controller. Q-Control has been designed to replace the difficult installation and setup of a separate programmable logic controller (PLC) through the integration of a proportional-integral-derivative (PID) controller within the pump itself, which gives the pump the ability to directly interface with pressure and flow sensors. This minimizes the need for manual intervention in process applications as the pump can automatically adjust its motor speed to meet desired flow and pressure conditions or, in extreme instances, automatically stop the pump's operation when a high-pressure event occurs thanks to the presence of an internal-alarm function.

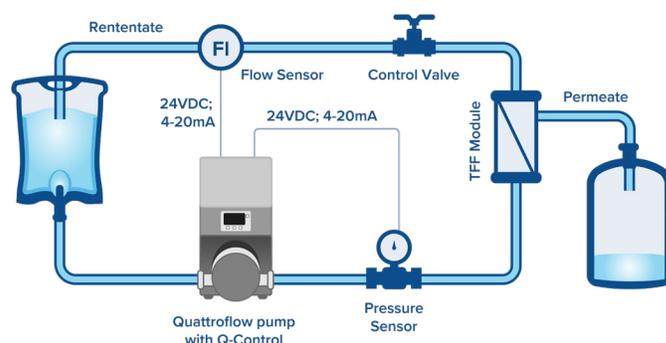


The Q-Control Integrated Pump Controller is a proportional-integral-derivative (PID) controller that is positioned within the pump, which gives the pump the capability to interface directly with the TFF system's pressure and flow sensors.

The Q-Control offers several different operational modes that can be used as needed in different biologic-processing conditions, including an integrated autotune function. This function makes it easier to find and set the correct parameters to configure the PID controller. Another feature of Q-Control is its process alarm, which can define a specific alarm for every connected sensor so that if the pressure exceeds a certain setpoint, the pump will automatically cease operating.

The Q-Control pump controller can also provide user-programmed automatic dispensing that helps ensure that defined volumes of product can be repeatably filled, while a manual control option allows operational parameters like motor speed to be manually set by the operator so that calculated flow rates can be maintained with no need for the addition of an external sensor.

FLOW AND PRESSURE CONTROL IN TANGENTIAL FLOW FILTRATION (TFF)



Q-Control provides user-programmed automatic dispensing that produces defined volumes of product and features a manual-control option that allows the operator to manually set the motor speed so that calculated flow rates can be maintained.

Finally, Q-Control can monitor trend data and alarm logging, while also allowing remote operation. During all of Q-Control's different operational modes, trend data like pump speed and sensor readings is logged into a historical file that can be reviewed later by the operator from anywhere in the world. This easy access to all important operational data gives the user an easy-to-access overview of the pump's operational history.

Conclusion

The importance of achieving and maintaining an optimized TFF unit operation within biologic manufacturing is unquestioned. That's why it is so significant that the proper pumping technology be identified and incorporated into the TFF process. While many pump technologies – most notably centrifugal, peristaltic, lobe and piston – have found some acceptance among biologic manufacturers, the simple truth is that all of them feature some level of operational imperfections – chief among them the inability to produce low-shear and low-pulsation flow rates – that affect their capacity to facilitate a fully optimized TFF process.

Four-Piston Diaphragm Pumps, on the other hand, have been designed to reliably deliver low-shear/low-pulsation operation. Specifically, PSG Biotech offers its

Sartorius Sartoflow® 4500 single-use tangential flow filtration system using a Quattroflow QF5050SU as recirculation pump and Quattroflow QF1200SU as transfer pump



TFF is a critical application in biologic production, which is what makes its optimization so important. Quattroflow Four-Piston Pumps from PSG Biotech hit the sweet spot in TFF optimization because they possess the operational features – reduced shear, low pulsation, consistent flow rates and total product containment – to reliably and safely deliver the desired outcome.

Quattroflow brand of four-piston diaphragm pumps, with all models possessing the operational features that can lead to optimized TFF performance, resulting in the creation of biopharmaceuticals, medicines and therapeutics that are safe for human consumption and contribute to advancing the human condition.

About The Author

Dr. Andreas Frerix is the Product Manager Quattroflow® for PSG® Biotech and can be reached at andreas.frerix@psgdover.com. PSG Biotech, Oakbrook Terrace, IL, USA, is dedicated to "Caring For Every Drop" by being a leading provider of specialty flow-control solutions, including pumps, sensors and flow meters, that have been designed to safely transfer and precisely meter the most delicate life science biologics, medicines and therapeutics, all while increasing yield, throughput and speed to market. PSG Biotech is a brand of PSG®, a Dover company, Oakbrook Terrace, IL, USA. You can find more information on PSG Biotech at psgdover.com/biotech.

ABOUT PSG®

PSG® is the global pump, metering and dispensing-solution expert, enabling the safe and efficient transfer of critical and valuable fluids that require optimal performance and reliability in applications where it matters most. Additionally, PSG is a leading provider of flow meters designed to reduce waste and downtime while accurately measuring, monitoring and controlling the distribution of fluids. Headquartered in Oakbrook Terrace, IL, USA, PSG is comprised of several world-class brands, including Abaque®, All-Flo™, Almatec®, Blackmer®, Ebsray®, em-tec®, Griswold®, Hydro™, Malema™, Movex®, Neptune®, PSG® Biotech, Quantex™, Quattroflow® and Wilden®. PSG products are manufactured on three continents – North America, Europe and Asia – in state-of-the-art facilities that practice lean manufacturing and are ISO-certified. PSG is part of the Pumps & Process Solutions segment of Dover Corporation. To learn more about PSG, please visit psgdover.com. **PSG: Where Innovation Flows.**



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