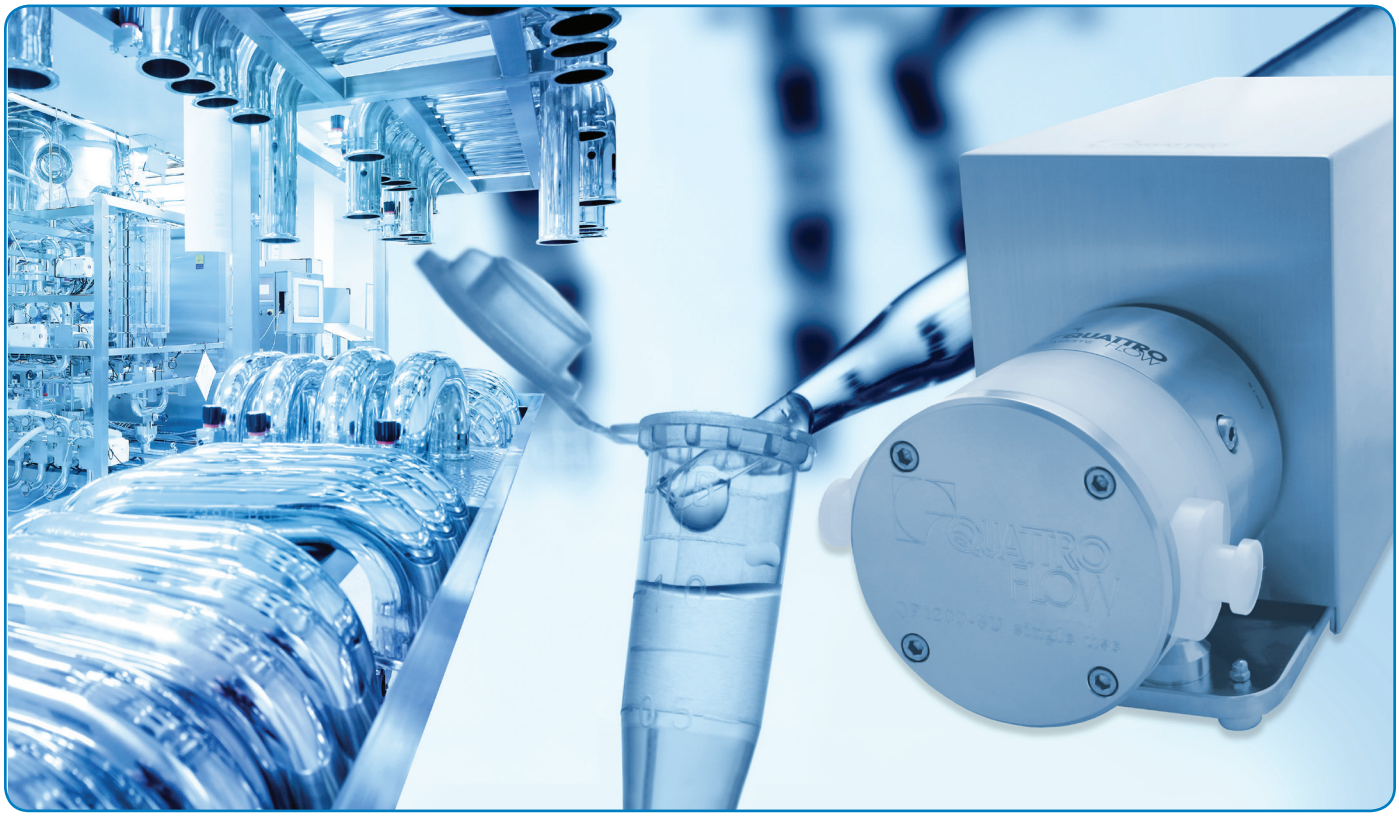
Single-Use Pumps Take Center Stage

Single-use quaternary diaphragm pump technology from Quattroflow™ meets the speed-to-market challenges of biologic-based drug manufacturing

By Wallace Wittkoff



Biologics-manufacturing operations take place in extremely sterile and time-sensitive conditions. Pump technology like that found in single-use quaternary diaphragm models from Quattroflow® are able to satisfy the product containment and speed-to-market requirements that are paramount in these types of operations.

Introduction

In the multi-billion-dollar global biopharmaceutical industry, a further emphasis is being placed on the development and manufacture of advanced biologically derived drugs (termed here as biologics). These biologics offer exciting potential for the development of blockbuster drugs that can provide as-yet-unknown treatments for a wide array of diseases. While pharmaceutical drugs are derived from more traditional chemical processes and reactions, biologic-based drugs are the result, as the name implies, of biologically induced processes, such as intra-cell growth processes (mammalian cells, bacteria, viruses and such), and the subsequent harvesting and purifying of target substances, such as proteins, molecules and enzymes. These substances are then used to create drugs, vaccines or antitoxins. In essence, cells are used as miniature process vessels to create new substances.

The development of new biologically derived drugs, however, is just one opportunity for manufacturers. Another equally important goal is to commercialize these products as early as possible in the typical 20-year patent window. Patent submission needs to occur during the drug-development process. Following a patent filing, much occurs, including further product development, toxicity checks and clinical trials. Hopefully, Food & Drug Administration (FDA) approval also occurs during this period. Following FDA approval, the developers need to take all the necessary steps to properly produce the product in commercial scale and execute the market–introduction plan. If the drug's development takes additional time after patent approval, the patent may run through a good portion of its window of protection before the drug has a chance to be commercialized. In some

cases, there are only about seven years left on the patent for the product when it goes to market. Every year a drug is covered by its patent can be worth billions of dollars in sales, so every day that the development process can be accelerated means that much more to the bottom line.

From a process-equipment standpoint, permanent and single-use quaternary diaphragm pumps, such as Quattroflow™ pumps, represent a growing technology that both helps enable the efficient development of new biologic drugs and then facilitates the speed to market of the end-product. Single-use pumps, such as those using disposable pump chambers, feature replaceable wetted parts, meaning that no cleaning and validation process is needed during a product-development process that can require multiple trials. This is a great advantage for drug manufacturers who are looking to maximize their production operations through the implementation of cutting-edge pumping technology.

"The biopharm industry is adopting disposables faster than the general population is trying to recycle," said Mark Sitcoske, who heads High Purity New England, Smithfield, RI, USA, a company that specializes in single-use pump technology.

Essentially, the driving force in the process to create these target products is to promote growth of biologic material in a highly controlled, sterile environment with adherence to strict operational parameters, such as the correct pH (acidity) level, temperature, oxygen level and nutrient feed. An imbalance in any of these parameters can cause unwanted biologic processes to occur, such as the formation or growth of competing and undesirable organisms, or it could cause the target biologic process to not occur at all. Once the raw biologic product is produced, the desired target components (proteins, molecules, etc.) can be purified by using a number of techniques. These techniques include filtration (such as tangential/cross flow and chromatography), separation (through a centrifuge) or certain chemical reactions.

The critical issue in these target-component extraction techniques is that biologics are extremely sensitive to change or damage from outside influences, such as shear, temperature changes and light. That means the extraction process that these target components are subjected to requires a type of pump that can reliably deliver the following desired operational characteristics:

- High purity and sterility
- Very low volume and surface area exposure; 15 ml/73.5 cm2 in the smallest pump
- Low levels of leachables and extractibles
- No mechanical spalling/shedding of contact materials
- Controlled/constant flow, as needed
- Low shear, slip and collateral effects
- Low pulsation
- Self-priming and negative suction lift
- Controlled pressure
- No heat addition
- High volumetric efficiency

This white paper illustrates how one type of pump technology—positive displacement quaternary diaphragm—has become one of the preferred pumps to incorporate in critical biologics-handling applications.

The Challenge

The harvesting and purification of biologic target materials is accomplished using separation and filtering processes. There are generally three purification processes (that can also be used in combination) as follows:

- **Tangential Flow Filtration** (TFF)—Also known as cross-flow filtration. For this process the biologic feed stream flows horizontally with positive pressure across the filter membrane. As it passes across the membrane, the portion of the feed stream that is smaller than the membrane's pore size passes through the membrane. This is different from what is known as normal-flow (NFF), or "dead-end," filtration, in which the feed flows entirely through the filter membrane with the size of the pores determining which portion of the feed is allowed to pass through and which will remain trapped in the

filter membrane. TFF is different from NFF in biologics applications because the tangential motion of the fluid across the membrane causes any trapped particles to be "rubbed" off, similar to passing your hand across a piece of sandpaper. This mode of operation means that a TFF process can operate continuously with relatively high solids loads without fouling of the filter, which is also known as filter blinding. The quaternary diaphragm Quattroflow pump provides the good constant flow control that is essential for optimal filtrate (desired product) yields for TFF filters.

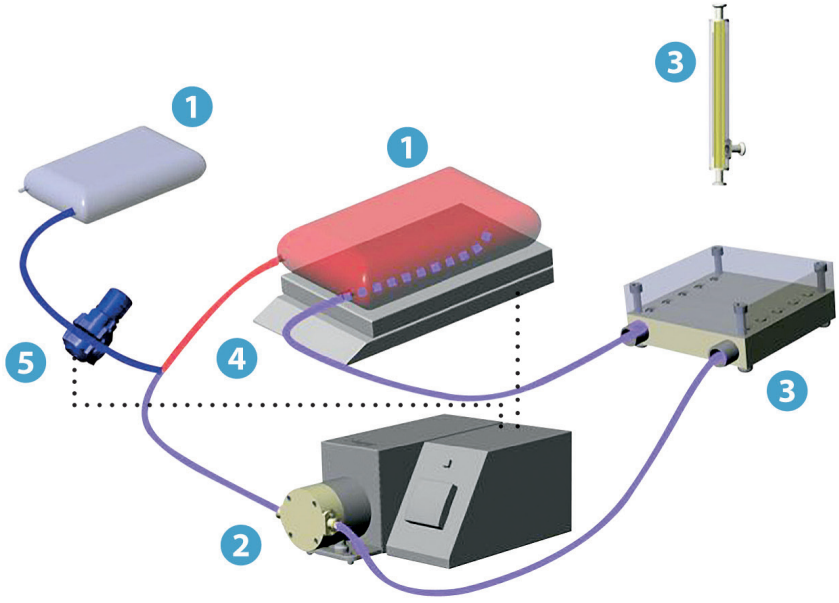
- **Chromatography Columns**—A typical chromatography column is a glass, steel or plastic tube that is filled with resins that are compressed in a certain format through which a feed stream product flows to either capture or purify this feed stream. These chromatography columns contain filter media that need careful handling. A resin, for example, can cost as much as $10,000 an ounce, making proper feeding of the resin extremely important. In this application, a quaternary diaphragm Quattroflow pump can be used to pack the resin into the chromatography column and then pump the biologic material through the column. Both are critical operations that require a high, constant flow rate and pressure.

- **Centrifuges**—A centrifuge, really a separator and not a filter, consists of an elaborate vessel that can be fed with a biologic substance and spun around a central axis in order to separate the materials according to their different specific gravities/weights, or to separate particles that are suspended in the liquid. The biologic's target product can be the high, intermediate or low specific-gravity substance that is spun out of the centrifuge. As centrifuges spin at high speeds, a proper, constant feed rate is essential in order to minimize potentially severe vibration that could cause equipment damage.

In all three processes that are used for target feed stream purification, the requirements of the pump are precise: constant, low-slip, low-shear, low-pulsing flow. Any deviation from these requirements can result in deleterious effects for the substance being handled, as well as damage to the media that are used in the filter (membranes for TFF and resins for chromatography columns), which are costly. Improper flow and transfer rates can also produce the unbalanced operation that results in a damaged centrifuge.

Over the years, several different types of pump technologies have been used/tested for these processes, and while there are applications that they are best suited for, they have been found to be deficient in the purification processes described above:

- **Peristaltic (Hose) Pumps**—These pumps produce pulsation, have limited flow and limited pressure-handling ability. For example, they cannot reliably produce the higher discharge pressures (such as 60 psi) that are required in some biologic-handling applications. They are also known to release some small quantity of hose material—in a process known as "spalling"—into the pumped product, which can compromise its purity. If the shed hose material is captured by the filter, it can blind the filter, making its operation not as efficient as it should be and lead to contamination.



AUTOMATED CONCENTRATION AND DIAFILTRATION PROCESS USING ONLY 5 COMPONENTS.

1. Bags (product, buffer)
2. Quattroflow-1200 Single-Use
3. Membrane filter modules
4. Balance
5. Magnetic pinch valve

- **Lobe Pumps**— First, there are no established single-use lobe pump options. In addition, since biologic fluids are contained in a low-viscosity aqueous solution lobe pumps are not a good match as excessive slip occurs during their operation. The slip can vary between 10% to 100%, depending on the system's back pressure. This slip will also result in increased shear damage and energy consumption, and if used in a long-duration recirculation loop, such as a TFF filtration system, there can be noticeable heat addition to the product. Lobe pumps also have mechanical seals, which produce a controlled leak that does not provide full product containment unless special seals and seal barriers are used. The sterility required in biologic fluid handling means that no outside contaminants can 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 acquire, validate and maintain.

Quattroflow 1200 Quaternary Diaphragm Pumps with plastic single-use (left) and stainless-steel multi-use pump-head options.

- **Centrifugal Pumps**—These pumps are not positive-displacement, resulting in poor flow control when discharge conditions change. Also, high-shear and heat buildup can occur because of relative inefficiencies compared to positive displacement pumps. Another concern is that some are magnetically driven, meaning that instead of mechanical seals, the pumps are coupled and driven by a motor and magnet combination. For single-use applications, disposing the magnets imbedded in the other materials can prove an issue.
- **Piston Pumps**—Like lobe pumps, there are no mainstream single-use options. While certain piston pumps can meter with no feedback needed, these pumps are generally complex, leading to higher cost and adverse pulsation and suction conditions that must be managed.

Single-Use Pumps Needed

One key manufacturing trend that can reduce development cost and increase speed-to-market is the adoption of single-use technologies. In certain cases, permanent stainless-steel process lines are very costly to set up, lack the production flexibility in biologic development, and have complex and time-consuming cleaning and validation requirements. Therefore, much expense and time can be saved by simply starting each trial process with a fresh, sterile set of single-use process-equipment components. These components can consist of bags instead of stainless-steel vessels, special agitators instead of stainless-steel shaft agitators, single-use tubing, coupling and valves instead of their stainless-steel equivalents, and filter systems, many of which are single-use by their very nature. Prior to Quattroflow, single-use low-pulsation positive displacement pump options were not suitable for many needed biologics production processes.

"Many of the leading filtration and purification system designers worldwide prefer Quattroflow pumps; there's a reason for that," said Jeff Blease, President of Triangle Process Equipment, Wilson, NC, USA, a pioneering company behind the use of quaternary diaphragm pump technology in the Americas. "The Quattroflow pump gives you the low shear of a peristaltic pump along with the low pulsation and high-pressure capabilities of rotary lobes without the inherent dangers and drawbacks of either technology, such as burst tubing, excessive temperature rise, or rubber and metal shavings contaminating the process from upset conditions."

The Solution

For a growing number, the solution to the strict single-use pumping requirements that are demanded in the biologics-filtering process can be found in the positive displacement quaternary diaphragm technology that has been developed by the German company, Quattroflow™, which also introduced to the market the single-use configuration for use in critical product-handling applications in the pharmaceutical and biotech industries. In January 2012, Quattroflow was acquired by the Pump

Solutions Group (PSG®), which is a conglomeration of several of the world's leading pump manufacturers that operates within the Dover Corporation's Dover Energy™ business platform. PSG has integrated the manufacture of Quattroflow pumps into the operations of its Almatec® subsidiary, which is headquartered in Kamp-Lintfort, Germany.

The main advantage of Quattroflow pumps used in biologics-handling applications is its unique form of operation: The quaternary diaphragms are driven one after another by a connector plate, which moves back and forth out of its central position in a stroke that is generated by an eccentric shaft, with the length of the stroke determined by the angle of the eccentricity. In other words, the Quattroflow technology has been modeled on the operation of the human heart—which is eminently capable of pumping whole human blood, one of the most shear-sensitive products around—with its four pumping chambers and check valves keeping product flow constantly moving forward.

The Quattroflow's pump chambers contain no rotating parts that can be subject to friction, meaning that there is no operational heat buildup that can compromise the product. This mode of operation also means that the pumps can run dry, are self-priming, and produce little or no shear because of low slip. In addition, they offer low-pulsation, leak-free operation while having great dry/wet suction-lift capabilities. These pumps can provide constant flows from 1 L/hr (0.0047 gpm) to 20,000 L/hr (88 gpm) with some of the highest turn up/down capabilities in the industry.

This turn-down capability and range for the Quattroflow pump is unique in the biopharmaceutical industry. As biologics go from development to clinical trials and then to commercialization, proper scale up is essential. The same pump technology in a lab needs to handle flow rates as low as 1 L/hr (o.0047 gpm), as well as commercial production flow rates of 20,000 L/hr (88 gpm) or more. This scale-up capability assures that the pump's operation does not adversely affect repeatability and production rates.

Quattroflow pumps also possess the versatility to be fitted with explosion-proof motors, DCA motors or air motors; essentially you can drive Quattroflow pumps in any way you can drive other pumps. Because of the controlled low-slip aspect of this pump technology and high turn-down capability, this pump also benefits from new generations of vector drives for precision applications.

The essential element that Quattroflow pumps help to contribute to speed to market is the commonality of single-use configurations. Basically, a single-use pump enables biopharmaceutical manufacturers to optimize the cost of cleaning and validating their pumps. The result is not only a quicker production process, but one that delivers preferred levels of product purity and sterility with no chance for cross-batch or cross-product contamination.

Here are some of the other advantages that can be realized when Quattroflow single-use pumps are used:

- Can be used for one product, or in one production campaign, which can last anywhere from one or two days to several months and possibly comprise a number of batches.
- At the conclusion of the production campaign, the pump is removed and the pump chamber that has come in contact with the fluids is disposed of.
- Can also be used for a set amount of time before the wetted parts are replaced, which eliminates elevated maintenance costs
- The pump has a removable and disposable plastic chamber that contains the diaphragms.

- If the operator needs to use a stainless-steel pump, the plastic pumping chamber can be replaced with a stainless-steel one.
- If there's a pump failure, the old chamber can be taken out and replaced with a new one in five minutes, eliminating excessive downtime
- Lower hardware, cleaning and validation costs

- Used when cleaning in place (CIP) or steam sterilization is not practical or possible. This represents a significant simplification and cost reduction to the overall process as there are no contaminated cleaning chemical and water solutions that need to be treated and disposed of. The costs to properly treat and dispose the cleaning fluids can alone be the driver to require use of single-use alternatives.

Single-use pumps that are made from FDA/USP class VI conforming/approved materials also have a lower cost compared to their stainless-steel counterparts. Further, for example, with a 500-liter batch of biologics, which has a market value of $5 million-plus and the need to offer it to the buying public as quickly as possible, an additional $500 or more for a replaceable pump head essentially becomes an attractive cost of doing business. The total cost of using a single-use pump is less because the cost to replace the head may pale in comparison to the cost of validating the cleaning (which can run in the tens of thousands/millions of dollars), plus the entire cost to install a permanent stainless-steel process line. A common notion in this industry is that the cost of the paper backing up the equipment used is higher than the equipment itself. The Quattroflow, by using a standardized and documented single-use variation, reduces that paper and cost.

For cases where the total cost of a permanent stainless-steel process line is more attractive, the Quattroflow pump head can be converted to a stainless-steel head with the same controlled flow, low-shear, low-slip and high-purity operation, with the addition of desirable high-cleanability attributes.

Conclusion

Advances in the ability to produce and use biologically derived drugs has created an exciting opportunity for manufacturers in the biopharmaceutical market. However, while this continuing trend is packed with possibilities, they can only be realized if the development and manufacturing processes for these products are optimized, both in regards to speed-to-market considerations and contaminant-free production requirements. Quattroflow has identified the challenges in this process and has responded with a pump style—single-use positive displacement quaternary diaphragm pumps—that dependably meets challenges and allows biopharmaceutical manufacturers to confidently meet many of their most crucial biologic-handling and manufacturing needs.

About the Author:

Wallace Wittkoff is the Hygienic Market Director-Americas for Pump Solutions Group (PSG®), Oakbrook Terrace, IL, USA. He can be reached at +1 (502) 905-9169 or Wallace.Wittkoff@psgdover.com. For more information on Quattroflow's full line of positive displacement quaternary diaphragm pumps, please visit www.quattroflow.com or call +49 2842 961 0. PSG is comprised of several leading pump brands such as Abaque™, Almatec®, Blackmer®, EnviroGear®, Griswold™, Maag®, Mouvex®, Neptune™, Quattroflow™, RedScrew™ and Wilden®. You can find more information on PSG at www.psgdover.com.

QUATTROFLOW™ Fluid Systems
Part of Pump Solutions Group
A DOVER COMPANY

World Headquarters
Almatec Maschinenbau GmbH
Carl-Friedrich-Gauß-Straße 5
47456 Kamp-Lintfort Germany
T: +49 (0) 2842/961-0
F: +49 (0) 2842/961-40
www.quattroflow.com

PSG® PUMP SOLUTIONS GROUP
A DOVER COMPANY