

SINGLE-USE PUMPS *Taking Center Stage*

Single-use pumps meet the challenges of biopharmaceutical manufacturing

■ **By Wallace Wittkoff**

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 intracellular 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.



Quattroflow 1200 Quaternary Diaphragm Pumps showing the plastic single-use pump-head option.

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



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

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)

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.

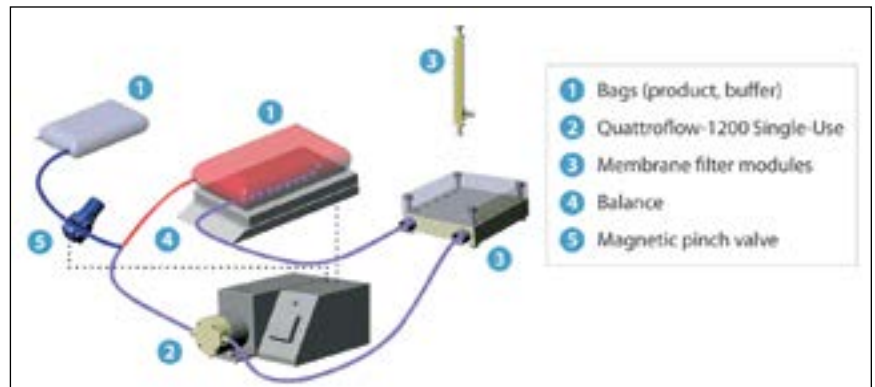
The critical issue in these target-component extraction techniques is that biologics are extremely sensitive to change or damage from outside influences, such as shear, temperature changes and light. That means the extraction process that these target components are subjected to require a type of pump 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 extractable
- 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

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.
- **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



Automated concentration and diafiltration process using only five components.

feeding of the resin extremely important

- **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, and 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.

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.

“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

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. This 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.



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 flowrates as low as 1 L/hr (0.0047 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.

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. Single-use positive displacement quaternary diaphragm pumps— can dependably meet these challenges and allows biopharmaceutical manufacturers to confidently meet many of their most crucial biologic-handling and manufacturing needs.

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