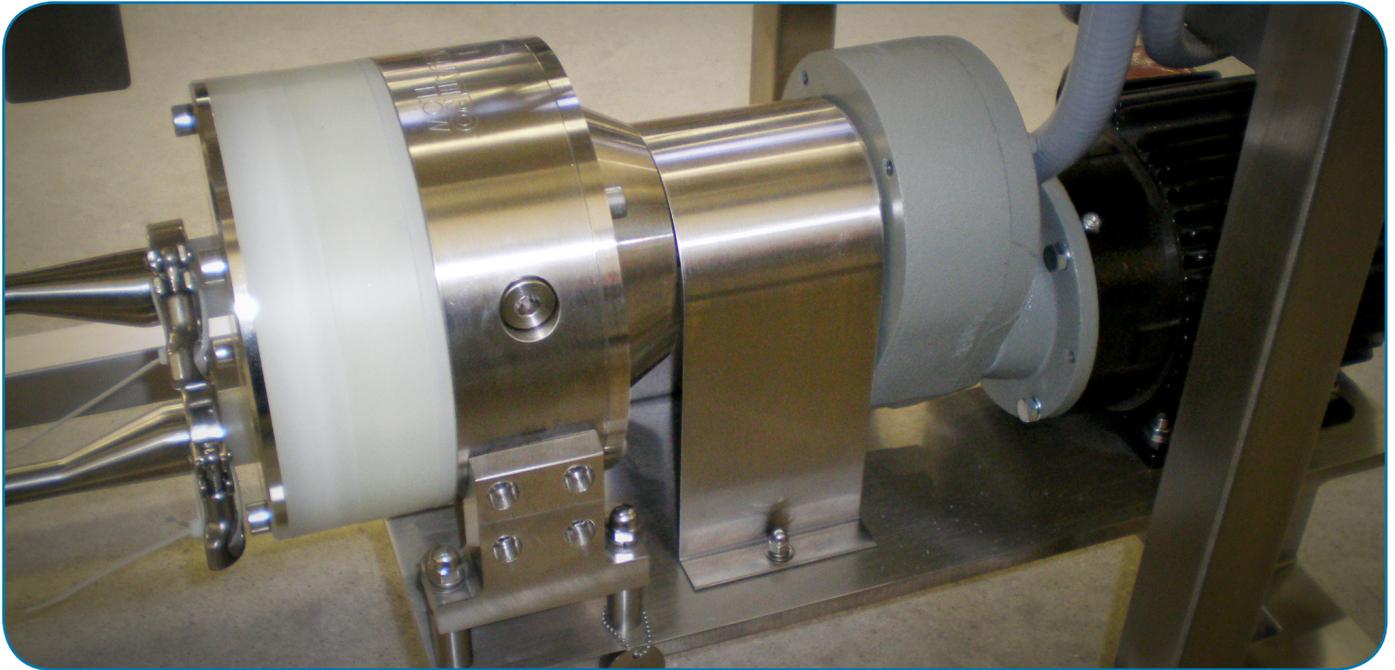


A New Member Of The Family

FAMILY-OWNED AND -OPERATED COTTER BROTHERS FINDS THE ANSWER TO THE CHALLENGES INHERENT IN FABRICATING BIOPHARM PROCESS SKID SYSTEMS IN THE FORM OF QUATTROFLOW™ QUATERNARY DIAPHRAGM PUMPS

By Wallace Wittkoff



The pump chambers in the Quattroflow quaternary diaphragm pump, such as the one in this Cotter Brothers biopharm process skid, contain no rotating parts that can be subject to friction, meaning that there is no operational heat buildup that can compromise the biologic product.

From a young age, we've all been taught to "forgive and forget." While that's an admirable idiom to live by, in the world of biopharmaceutical manufacturing, where biologics are being used as a feedstock more and more often, that's just not possible.

"This industry is the only industry I know that is non-forgiving," said Randy Cotter, Sr., who is Engineering Manager for Danvers, MA, USA-based Cotter Brothers Corporation, a leading global biopharm process skid system designer and fabricator. "If you make a mistake in this industry, it doesn't go away—and you don't get a second chance. So, you have to know what you're doing and have high confidence going in."

Cotter knows of which he speaks. As a pioneer in the biopharm process skid system industry in the late 1970s, he founded Cotter Corporation, first as a welding company then as one that specialized in building process skid systems for the biotechnology and semiconductor industries. In 2001, Cotter sold his company. In 2005 he

returned to his roots as a consultant for Cotter Brothers Corporation, a company founded in 2003 by his sons, Randy, Jr. (President) and Tim (Vice President).

From the start, Cotter was at the forefront of the growth of the biopharm industry and is actually the author of many of the industry's operating standards that are still in place today. As opposed to the much more refined and unforgiving industry that biopharm manufacturing has become today, those early years were filled with trial and error, but the successful operators were those that were able to most effectively learn from their errors.

"When we started there was limited documentation of how to do things. We have learned through our experience and from our mistakes," said Cotter. "It's hard to say that those who make the most mistakes are the smartest, but with common sense, learning from your mistakes, having a good background, they all help you realize the best way to do things."

Finding the best, most efficient and cost-effective way to do things is imperative in the biopharm manufacturing industry. The biopharm industry has grown into a multi-billion dollar global behemoth, with biologically derived



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drugs (or biologics) playing an increasingly major role in the development of blockbuster drugs that can provide treatment or cures for any number of diseases and illnesses. These products must be produced in pristine hygienic and sanitary conditions, and in a way that allows them to make their way to the consumer marketplace as quickly as possible so that the value of patent windows can be optimized.

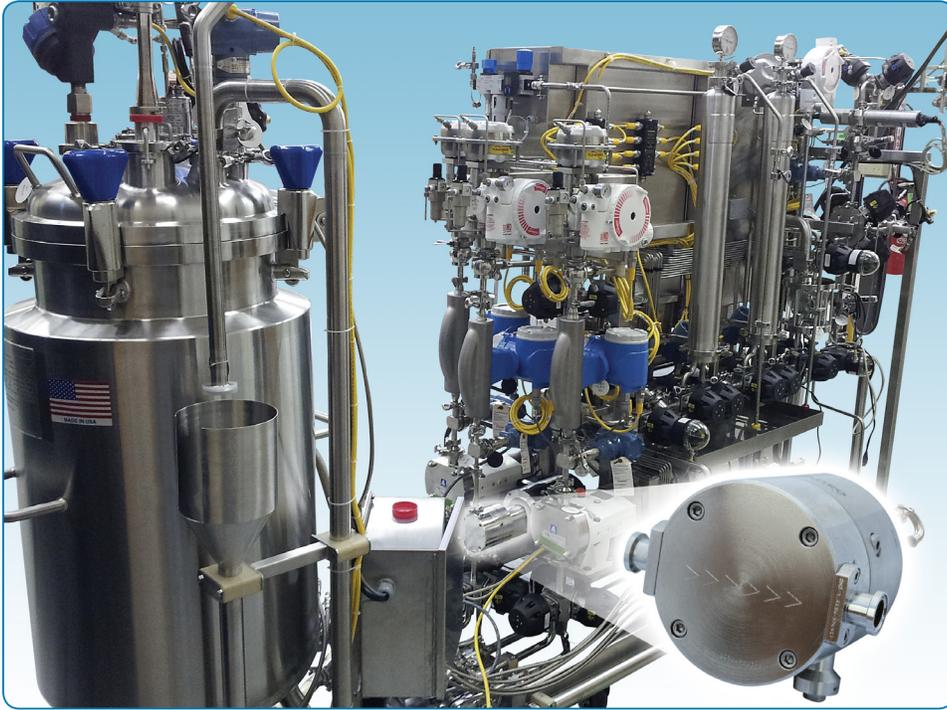
Going With The Flow

The harvesting and purification of biologic material is a precise, exacting process. In what is termed the “upstream” portion of the process, cells are fermented in a bioreactor until they have reached the end of their life cycle and expressed an anticipated amount of therapeutic proteins. The cells and the protein solutions are then separated by filtration and/or centrifugation before moving on to the “downstream” phase in which the target therapeutic protein is isolated and purified. Downstream processing will often utilize both of the following unit operations:

- **Tangential Flow Filtration (TFF)**, which is also known as cross-flow filtration, is a process in which 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 the filter, which is also known as filter blinding.
- **Chromatography Columns** typically feature 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 adsorptive media, which selectively can bind product molecules. This resin needs careful handling, for example, one ounce can cost as much as \$10,000, making proper feeding of the resin extremely important.

“Early on in this biopharmaceutical industry, people didn't have a lot of expertise in process systems; they'd just buy a chromatography system or a filtration system,” explained Cotter. “However, our client base and the people in our industry have matured, and the majority of the people now create their own systems, they have internal specs and all of them have requirements and an understanding of what they're doing and how to do it. Early on, the only pump for chromatography or filtration was a rotary lobe or peristaltic pump, and it was always a challenge to get the right pump for the application.”

In the search for additional pump options to meet some of the diverse requirements of its clients, Cotter Brothers looked to one of its vendors, High Purity New England (HPNE), Smithfield, RI, USA, for solutions. HPNE specializes in supplying products and services to the biotech, biopharm, pharmaceutical, microelectronics and



Cotter Brothers designs and builds some of the most sophisticated biopharm process skid systems in the world. This skid features a Quattroflow quaternary diaphragm pump, among other pumps, for a critical application in this process.

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 biologic product. This mode of operation also means that the

food industries in the Northeast United States. At the time of Cotter Brothers' search, HPNE had recently learned of a new positive displacement quaternary diaphragm pump technology for the downstream biopharm industry that was being produced by the German company Quattroflow™ Fluid Systems GmbH & Co.

"Our relationship with Cotter Brothers started when HPNE took on the Quattroflow line here in New England," said Dave Bianchi, Technical Sales Manager for HPNE. "Cotter Brothers knows the biopharm industry well and they recognize that the Quattroflow pump is one of the best products for a growing need with their customers. Our two companies just work well together."

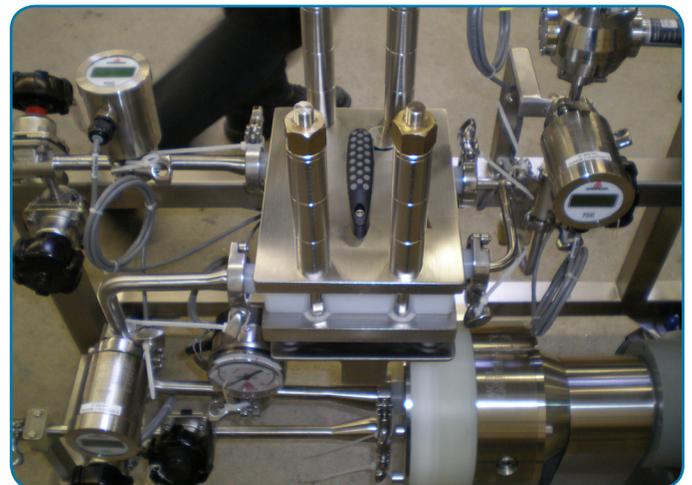
Meeting A Need

Quattroflow, which was acquired by the Dover Corporation's Pump Solutions Group (PSG®), Oakbrook Terrace, IL, USA, in January 2012, has designed its pumps to be ideal for critical TFF and chromatography applications in biologics production and handling.

The main advantage of a Quattroflow pump in these applications is its unique form of operation: The quaternary diaphragms are driven one after another by a nutating connector plate, which moves back and forth out

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 16 mL/min (0.54 oz/min) to 360 L/min (95 gpm) with some of the highest turndown capabilities in the industry.

"Many of the systems produced by Cotter Brothers are for either TFF or chromatography. The low pulsation and low shear generated by a Quattroflow pump makes it



Quattroflow quaternary diaphragm pumps can run dry, are self-priming and produce little or no shear because of low slip.



Quattroflow™ QF1200

ideal for those operations,” said Bianchi. “They had been using rotary lobe pumps, which are the old workhorse in the bioprocess industry, but a lot of lobe pumps take a great deal of maintenance and when they go down, they go down spectacularly. Cotter is finding that an increasing number of its clients are looking at the option of diaphragm pumps for certain applications.”

When Cotter and his sons were made aware of the Quattroflow pump technology and the benefits it could offer the process skid systems they fabricate for the biopharm industry, they had one reaction: These pumps are going to help address a lot of our clients' concerns with regards to their process.

“All of a sudden, the Quattroflow shows up and you have a pump that is attractively priced with an exceptional turndown ratio, a high level of accuracy and flow rates that are perfect for chromatography and filtration. Quattroflow pumps are a perfect fit for us,” said Cotter.

“They also reduced the issue of galling; it’s gone away. A couple issues we had early on were steamability and drainability; they’ve been fixed now. The perception in the industry was that you couldn’t use a pump with check valves, but that’s been addressed. So, the Quattroflow pump is steamable, cleanable, drainable, accurate and has a high turndown ratio, along with the ability to do low flows with accuracy that we can’t achieve with other pump types.”

Conclusion

In an industry as demanding and exacting as biopharm manufacturing, you need channel partners and equipment that you can rely on every time. Cotter Brothers has found both in High Purity New England and the Quattroflow pump.

“Without Dave Bianchi’s knowledge, we would not be where we are today. Dave has bent over backwards for us, I can’t say enough about him and High Purity New England,” said Cotter. “They really brought us a winner in the Quattroflow pumps. We were one of the first ones to use them and over the last three years we have recommended them to our clients when appropriate for their application. Our clients have liked the Quattroflow pumps and we are finding that more are starting to request them.”

About the Author:

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