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CMO Provides Speed, Flexibility and Safety in Biopharma Manufacture

RENTSCHLER BIOTECHNOLOGIE GMBH HAS BUILT A REPUTATION AS ONE OF THE BIOPHARMACEUTICAL INDUSTRY'S TOP CONTRACT MANUFACTURING ORGANIZATIONS WITH THE HELP OF QUATTROFLOW™ QUATERNARY DIAPHRAGM PUMPS

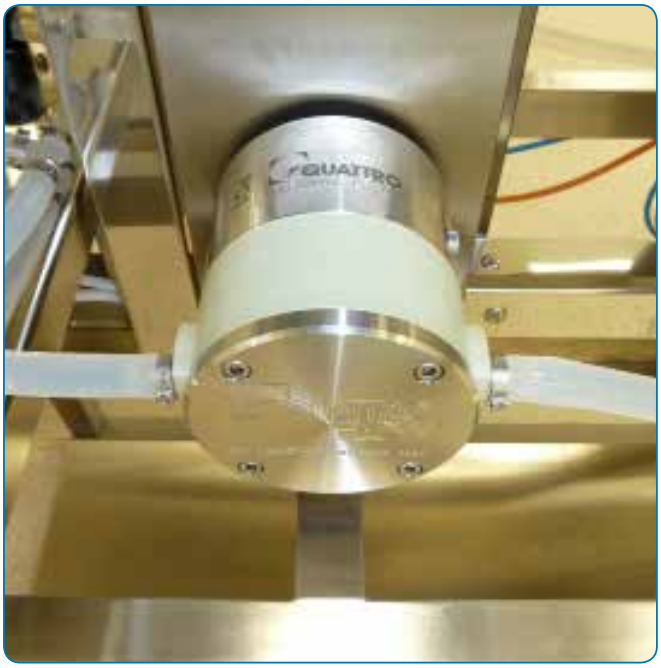
By Dr. Andreas Frerix

Rentschler Biotechnologie GmbH has built a reputation in the biopharmaceutical-manufacturing industry by becoming what is known as a contract manufacturing organization, or one that specializes in creating products for large conglomerates that need to be manufactured on a smaller scale or within a very short time frame.

In the ultra-competitive world of biopharmaceutical manufacturing, where billions of dollars in sales are constantly at stake, the best friend of large, world-renowned companies like Pfizer, GlaxoSmithKline, Bayer and Roche can often be the contract manufacturing organization (CMO) they choose to do business with. CMOs are frequently called into action when the large conglomerates have a product that needs to be manufactured on a smaller scale or within a very short time frame. In these cases, they may contract with a CMO because partnering with them can be a more cost-effective and faster alternative to producing these smaller-scale pharmaceuticals than using their own production facilities.

For nearly 35 years, one of the leading CMOs in the pharmaceutical industrial - and a company that is on the speed dial of many of the world's leading pharmaceutical manufacturers - has been Rentschler Biotechnologie GmbH, which is headquartered in Laupheim, Germany, a city located in the country's southwest corner between Stuttgart and Augsburg. Rentschler was actually founded in 1927 as a pharmaceutical manufacturer itself, but since 1979 it has been an independent contract manufacturer without its own products, and a specialist in the development and production of active biopharmaceutical ingredients.

"Rentschler is a classical CMO," explained Dr. Markus Laukel, the company's Associate Director DSP production. "We have production expertise from low-dose cytokines up to higher-dose antibodies, including biosimilars. Even though we are not specialized in any type of production, we produce everything to meet the needs of our customers. In addition to the large manufacturers, we have smaller customers all over the world - the United States, Europe, Asia - that might have no production processes, so they transfer the responsibilities for production to us. We are really focused on each project and contributing our know-how to each and every customer."



Rentschler Biotechnologie utilizes production systems that offer a wide range of liquid-handling capacities and has found that those that operate most effectively are outfitted with Quattroflow™ 1200 Single-Use Series Quaternary Diaphragm Pumps.

To help meet the specific, demanding needs of its wide range of customers, Rentschler's production facilities feature various sizes of systems to address precise production quotas. For example, its stainless-steel production systems have capacities ranging from 30 liters to 2,500 liters (8 gallons to 660 gallons), while single-use production has a scale of up to 1,000 liters (264 gallons). This gives Rentschler the versatility and flexibility that its customers - and the biopharmaceutical-manufacturing market as a whole - demand. In addition to the production of biopharmaceuticals that entail cell cultivation and purification of the target products, Rentschler also has expertise and capabilities for the formulation and filling of the final products.

Precisely What Is Needed

Recently, Rentschler has invested several million euros into a complete disposable manufacturing line with single-use process equipment that is used for the cultivation of cells (upstream process) and the following purification of the target molecules (downstream process). During this project, fully automated single-use filtration systems were acquired from PALL Life Sciences, Port Washington, NY, USA, and installed at Rentschler's production facility.

These systems are complex pieces of machinery that must be ultra-sensitive to the needs of the manufacturer and able to deliver precise processes that will not compromise the final produced biopharmaceuticals.

Further complicating matters the systems need to be extremely flexible so that a wide range of products can be manufactured, ranging from monoclonal antibodies to cytotoxins. All of these systems feature pieces of purification equipment that must be very meticulous in their ability to separate the desired end-product from any impurities that it might contain.

An example is a virus-filtration process used in the downstream production of antibodies. The pore size of the filtration media must be so small that only the antibodies can penetrate it, while still possessing the ability to effectively retain virus particles. As if this wasn't difficult enough, the antibodies must be transferred through the filter under conditions it was validated at. This means that the pressure and/or flow during the virus-filtration process need to be maintained very precisely so that the process runs under the same condition the filters have been validated at. Facilitating this incredibly precise process are transfer pumps.

"Most pumps that have been used in these applications are tube pumps," said Dr. Laukel. "These pumps are good if you have to transfer small quantities like 10 or 100 liters (2.6 to 26 gallons) at a time, but as the pumping application gets more complex and more demanding they are not the best choice for me."

That's because the pumping of very sensitive pharmaceutical components, especially in virus-filtration applications, demands that the pump produce very low levels of pulsation while still maintaining and controlling discharge pressures and flow rates.

"With tube pumps when you perform filtration and you have tight specification the pulsation is maybe a problem," said Dr. Laukel. "Also, with tube pumps you can have mechanical stress created when pumping that can be a problem for the product."

Finding The Proper Pump For The Operation

About 10 years ago, when he was working for another company, Dr. Laukel came into contact with a pump technology that did not have any of the operational shortcomings that tube pumps featured in some applications. It was called the quaternary (four-piston) diaphragm style of pump operation, and it was being produced by Quattroflow™ Fluid Systems GmbH & Co., which was founded in 2000 and in 2012 became a member of the Dover Corporation's Pump Solutions Group (PSG®), Oakbrook Terrace, IL, USA.

When Dr. Laukel became introduced to the Quattroflow technology, he admired the features of the four smooth-operating diaphragms and the design that is based on the operation of the human heart. These features and the good performance were reasons for Dr. Laukel to incorporate Quattroflow pumps into the new disposable downstream process system constructed in 2011.

"When you use other pumps you probably have strong pulsation, but the Quattroflow pumps have low pulsation, which is really good, especially for filtration applications where process parameters like pressure levels are critical and need to be controlled accurately," said Dr. Laukel. "This is the best thing about Quattroflow pumps; if you have a few liters to transfer to other vessels, you can use other pumps, but for special and demanding filtration processes, the Quattroflow pumps provide the best advantages."

Specifically, most of the systems used in Dr. Laukel´s department feature Quattroflow QF1200 single-use pumps, which can deliver flow rates as high as 1,200 L/hr (317 gph). Within Rentschler, some QF150 models with lower 150 L/hr (40 gph) flow rates are also used. The QF1200 single-use pump chambers are also autoclavable and can produce discharge pressures up to 4 bar (58 psi).

That's Not All

An added benefit of the QF1200 pumps, and one that savvy pharmaceutical manufacturers are increasingly taking advantage of, is their ability to be utilized in single-use configurations. Single-use pumps feature replaceable pump chambers, which eliminate the need for time-consuming cleaning of the pumps between batches. This increases the product's speed-to-market capabilities, which is a crucial consideration when attempting to maximize the product's market availability within its patent window. Another big advantage for a CMO like Rentschler, which has a large client base, is that single-use pumps can completely eliminate the risk of cross-contamination, which is always a concern for a contract manufacturer.

That's why Rentschler has set up a multi-product disposable facility for the manufacture of biopharmaceuticals, from upstream to downstream, from the cultivation of cells to purification of end-products.

"We have a single-use tangential-flow filtration (TFF) system from PALL and in this system we have a QF1200 pump with a disposable head," said Dr. Laukel. "Single-use systems are very important for the first clinical phases of pharmaceutical production. We have many applications where we have a lot of filtration steps and you don't want to have to take the time to clean the pumps. Single-use pumps are easier to replace than to clean. With this technology we are much faster. In most cases, we use them only once, but we can also have a dedicated disposable pump head for one product."

The single-use pumps also give Rentschler the operational flexibility to meet the needs of a large and varied client base. Depending on the application, Quattroflow QF1200 single-use pump chambers are used pre-gamma-irradiated in TFF or virus-filtration manifold sets from PALL. The flexibility of the pump allows Rentschler to also configure its own manifold sets (e.g. for bioburden-reduction filtration) and to autoclave this setup before initiating the filtration process.

"The problem for us is we must be really flexible for the customer," said Dr. Laukel. "One day we may be working with Customer A, then the next day Customer B, so you have to be really flexible; there is no standard process for us. That's another reason why the single-use Quattroflow pumps are a good choice for our operations."

Single-use versions of Quattroflow QF1200 pumps help Rentschler Biotechnologie maximize the speed-to-market capabilities of the biopharmaceuticals that it produces. This is a critical consideration when determining a product's ultimate market value within its patent window.

Quattroflow™ QF1200 Single-Use Series Quaternary Diaphragm Pump

The high level of production success that Rentschler has amassed - and the role that Quattroflow pumps have played in it - was acknowledged in 2012 when its 1,000-liter multi-product single-use facility was presented the prestigious Facility of the Year Award in the "Equipment Innovation" category by the International Society for Pharmaceutical Engineering (ISPE), INTERPHEX and *Pharmaceutical Processing* magazine. The 1,000-liter facility, which features four independent, yet connectable, all-purpose clean rooms, was honored for its ability to minimize manufacturing costs and product cycle times.

"Winning the Facility of the Year Award is really a big accomplishment in the biotech industry," Dr. Laukel said proudly. "In this system, we have QF1200 pumps with disposable pump chambers."

Conclusion

The process of developing and manufacturing pharmaceuticals is a precise, demanding and trying one. Quattroflow pumps offer features that help Rentschler Biotechnologie GmbH achieve demanding targets in several downstream processing steps.

"We do not have problems with Quattroflow pumps," stated Dr. Laukel. "They simply run and have no problems, and if we have really demanding pumping requirements, the choice is the Quattroflow pump. I see no reason not to use them. In the future, we will always want to use Quattroflow pumps."

About the Author:

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