

A Long-Lasting Leap Of Faith

MARCEL RAEDTS BUCKED TRADITION WHEN HE CREATED PROXCYS B.V. DOWNSTREAM BIOSYSTEMS IN 2003, BUT IT HAS PAID OFF HANDSOMELY WITH THE ASSISTANCE OF QUATTROFLOW™ QUATERNARY DIAPHRAGM PUMPS

By Dr. Andreas Frerix



Marcel Raedts went against accepted tradition when he went out on his own and formed PROXCYS B.V. Downstream Biosystems, but his decision has paid off, as did his choice to feature Quattroflow™ Quaternary Diaphragm Pumps in his company's Radial Flow Chromatography systems.

About 15 years ago, Marcel Raedts was one of those fortunate people who had found a profession that met his dreams. He was working for a company in The Netherlands that was involved in the manufacturing of systems designed for the handling of biologics that were applied in “downstream processes” to purify biopharmaceutical products.

In biopharmaceutical production, downstream processing follows the “upstream process,” which is where medicine-producing cells are cultivated until the proper amount of cells are produced. In the “downstream process”, the desired Active Pharmaceutical Ingredient (API) with potential pharmaceutical use is separated from the cell fragments and other culture media that is present in the upstream process. Chromatography offers one of the more popular and effective ways to perform this process. A chromatography-column system accomplishes purification

by selectively adsorbing target molecules (API) onto the chromatography media that is packed in a column. To perform this task, the chromatography column is carefully packed with a media (or resin) that can cost as much as \$10,000 per liter. This process requires a high, constant flow rate and is operated at moderate pressure.

Typical chromatography-column design is “axial.” In this setup, the chromatographic media are packed in a rather flat, broad, pancake-like cylinder, with the liquid stream passing through it vertically, from top to bottom, or vice versa. The result is a system that has a short, wide bed that is highly inefficient in terms of the space required, as well as its overall weight. Therefore, in axial chromatography, packed beds are typically taller than necessary in order to reduce the diameter of the axial columns, with an accepted tradeoff: reduced throughput and increased operating pressure.



Marcel Raedts, founder of PROXCYS, from the left, Hans May, Account Manager, and Dr. Andreas Frerix of Quattroflow show how a Quattroflow pump can fit into the setup of a PROXCYS Radial Flow Chromatography skid.

Over time, Raedts became familiar with an alternative to traditional axial-flow systems: Radial Flow Chromatography (RFC) columns. RFC columns offer increased throughput and reduced pressure drop, while the system’s weight and footprint can be one-quarter of the axial-flow columns. Existing RFC-column technology was only performing moderately well and Raedts determined that the columns should be able to perform much better if they were properly designed.

A Radical (And Radial) Idea

“The difficulty with my former employer was that they didn’t see the necessity, nor the possibility, to innovate the radial columns,” said Raedts, Founder, President and CEO of PROXCYS. With a potentially better solution—which involved changing the design of the RFC columns—he approached his former bosses with his idea, but was rebuffed, which led to his decision to start his own company.

Founded in 2003, Raedts called his new company PROXCYS B.V. Downstream Biosystems, with headquarters in the town of Nieuw Amsterdam, which is located in the northeast corner of The Netherlands, a short distance from the German border.

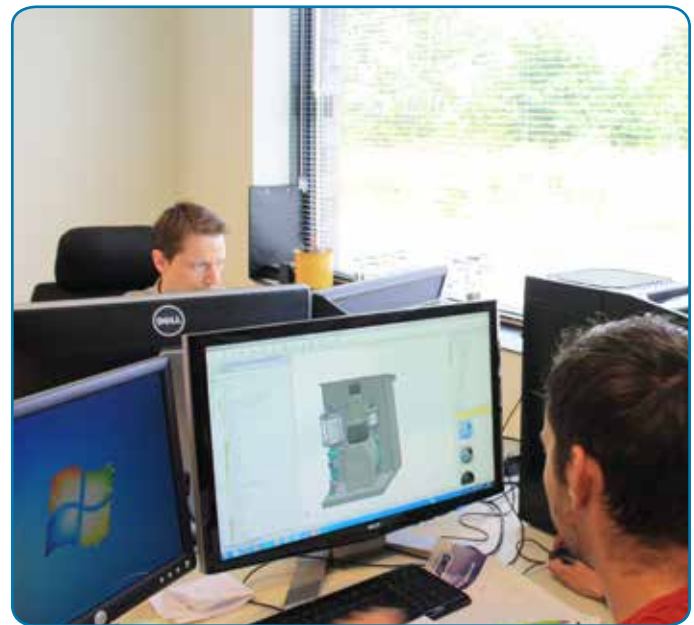
“PROXCYS was started from our garage, which is not untypical for American companies, but is quite untypical for this kind of company in Holland,” explained Raedts.

RFC itself was actually invented in the 1950s. It can be an efficient, low-pressure technology that is ideal for bio-molecule fractionation and purification. Unlike axial-flow systems where the liquid stream passes through the chromatography media vertically, RFC sees the media wrapped around a central cylinder, with the liquid stream passing through it horizontally. RFC essentially folds the horizontal bed of the axial system into a vertical cylinder and changes the flow direction from vertical to horizontal. While the purification and fractionation capabilities remain the same, the system’s footprint and weight are radically reduced.

“The performance of PROXCYS’ RFC compares well to the best axial columns on the market and they could be interchanged, but in practice that’s more difficult,” explained Raedts. “The manufacturing of pharmaceutical products is highly regulated, so if you change the way you do things, there are a lot of hurdles to overcome, like new clinical trials, etc.”

Still, there is an increasing acceptance of and more frequent changeovers to RFC from axial columns because the RFC performance is proven to be equal to or better than axial columns. In addition, there are operational benefits from the RFC’s small footprint, short bed height, ease of packing, low pressure drop and high productivity rates.

“In new processes where operators can freely choose their own systems, the benefits of our RFC columns are highly appreciated,” said Raedts. “Innovation of RFC columns began in 2002 and the development of the current patented Annular Port packing system in 2006 was key to dramatically improving RFC performance. That was when we could launch our first innovative RFC column,



PROXCYS B.V. Downstream Biosystems features a complete engineering department that is tasked with meeting the design needs of its end-user customers and knowing how Quattroflow pumps can optimize their operations.



A complete Radial Flow Chromatography system from PROXCYS, featuring a Quattroflow Quaternary Diaphragm Pump.

a five-liter high-performance RFC column that today has been scaled up to many sizes and options.”

The Proper Pump For The Process

A critical step in optimizing the performance of an RFC column is the packing of the chromatography media, typically a resin, into the column.

In the search for the proper pumping solutions, Raedts was introduced to quaternary diaphragm pumps from Quattroflow™ Fluid Systems GmbH & Co., Kamp-Lintfort, Germany. Much like Raedts, who went out on his own to found PROXCYS, Quattroflow came into being in 2000 when engineers Frank Glabiszewski and Josef Zitron realized there had to be a better pump for critical product-handling applications in the pharmaceutical and biotech industries. They developed a positive displacement quaternary pump that features four pistons and four smooth-operating diaphragms, a design that is similar in construction to that of the human heart. In 2012, Quattroflow was acquired by the Dover Corporation and became a member of Dover’s Pump Solutions Group (PSG®), Oakbrook Terrace, IL, USA.

“When we first got the Quattroflow pump, we were using it for the typical downstream operation for RFC columns,” said Raedts. “There, we discovered the attributes that make the Quattroflow an excellent pump: low pulsation, gentle product handling, large turndown ratio, high accuracy, low noise, compact design and low-shear operation. During a trial run with a packing pump, we decided to include the Quattroflow pump to see how it compared to the other types of pumps that are typically used in column

packing, usually compressed-air dual-action membrane pumps and peristaltic hose pumps.

“The Quattroflow pump performed much better than we expected and showed highly reduced resin damage. Since it has four diaphragms and five valves we expected some additional shear, but there was none at all, even at elevated flow rates! There was truly a strong similarity to the human heart in its operation and that provided proof of its suitability for demanding applications like human blood plasma fractionation. Additionally, we found an excellent clearance of any undesired residues from the pump head.”

Since most air-driven pumps are noisy, have a limited turndown ratio, pulsate and are much less accurate they are not suitable for downstream column operation. The operation of the Quattroflow pump does not have any of those characteristics and actually enabled PROXCYS to develop a new product: the Pack & Run system, which, with thanks to the compact Quattroflow pump, features a very small footprint.

The Pack & Run system allows for the completion of two critical operations within the biopharmaceutical-production process:

- High flow rate packing of the chromatography media in an RFC column via gentle yet fast handling without pulsation or shear
- Low flow rate Height Equivalent to Theoretical Plate (HETP) testing to verify that the column has been packed correctly

The Pack & Run system can also be used for the handling of biologics through a third critical operation:

- Medium flow rate for downstream processing of plasma proteins that are very shear- and pressure-sensitive

“It is very uncommon for a system to be able to perform both column-packing and an HETP test, but the Quattroflow pump is able to do so—and do it well!” said Raedts. “The key to this versatility is the large turndown ratio, low shear and excellent head clearance.”

This last attribute is most important in allowing the completion of the third critical area of operation, the processing of plasma proteins.

“Our Pack & Run systems are currently used in Phase I and II clinical manufacture of plasma protein: one tiny, floor-space demanding system that can do it all,” said Raedts. “This is not typical, especially since the processing of the clotting factors and other plasma protein is a very delicate matter. The Quattroflow pumps have also been shown to perform capably at very slow to very fast speeds, but without any noticeable increase in shear.”



Quattroflow offers four sizes of quaternary diaphragm pumps to meet the needs of a wide range of biopharmaceutical manufacturing applications.

Since the early days when PROXCYS was offering its first five-liter column, the company has grown to design and construct RFC columns with up to 350 liters (92 gallons) of column volume. Quattroflow is able to satisfy PROXCYS' growing needs because it offers four sizes of pumps with increasing flow rates:

- QF150 can supply 150 L/hr (40 gph) and is installed in PROXCYS' PAT3 systems
- QF1200 reaches up to 1,200 L/hr (317 gph) and is installed in the PAT20 and PAT40 systems
- QF4400 can deliver 4,400 L/hr (1,057 gph) for the PAT70 system
- QF20K has a flow rate up to 20,000 L/hr (5,283)

Quattroflow has also been a leader in developing single-use pumps for biopharmaceutical applications. These pumps feature replaceable heads, which eliminates the need for time-consuming cleaning 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.

With Quattroflow pumps by his side, Raedts anticipates the day in the next year when PROXCYS will begin producing a 1,200-liter column, which would be the largest in the world. For that he anticipates using two Quattroflow QF20K pumps in tandem.

Conclusion

Marcel Raedts took an undeniable leap of faith when he went against accepted practice and formed his own company. Now, what began as a dream in his garage 10 years ago, has grown into a company with an increasingly international reach. In 2009, a sales and support office was opened near Munich, Germany, to create a base in the growing German biotechnology market. To meet increased demand, in 2010 PROXCYS relocated its operations to a new 1,000-square-meter (11,000-square-foot) facility in Nieuw Amsterdam. The company is also expanding within the walls of Raedts' house, with wife, Els, and son, Patrick, also becoming involved in the day-to-day operations.

In September 2012, PROXCYS was proud to become the official distributor of Quattroflow pumps in the Benelux (Belgium, The Netherlands and Luxembourg) countries. Including the full line of Quattroflow Quaternary Diaphragm Pumps has been an important addition to the PROXCYS product family, with Raedts anticipating that the relationship will only continue to grow in the coming years.

"Quattroflow is definitely helping our clients," said Raedts. "Until two years ago, we were not applying the Quattroflow pumps into any of our systems because at the time we only had simple packing skids using air-membrane pumps like everyone else. But a simple test to compare the performance of the Quattroflow pump for column packing radically changed the landscape, knowing what was possible, we were very lucky to find a client who understood our vision and after presenting the first design with a Quattroflow pump, they were thrilled to go with that. Now, Quattroflow is a product that really helps our sales, maybe as much as 30%. We are very happy to have Quattroflow pumps as part of our RFC systems."

About the Author:

Dr. Andreas Frerix is the Applications Manager Biotech/ Biopharma for Quattroflow, part of Pump Solutions Group (PSG®). He can be reached at Andreas.Frerix@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. Headquartered in Oakbrook Terrace, IL, USA, PSG is comprised of several leading pump brands, including Abaque®, Almatec®, Blackmer®, Ebsray, Griswold™, Maag, Mouvex®, Neptune™, Quattroflow™ and Wilden®. You can find more information on PSG at www.psgdover.com.



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