

# Mix And Match

QUATTROMIX™ SINGLE-USE MIXING SYSTEM COMBINES QUATTROFLOW™ QUATERNARY DIAPHRAGM PUMPS WITH THE BIOPHARMACEUTICAL EXPERTISE OF SINGLE-USE SYSTEMS PROVIDER JM SEPARATIONS

By Dr. Andreas Frerix



When engineering and design firm JM Separations identified single-use pumps as a technology they could offer their customers as a better manufacturing solution for the biopharmaceutical industry, the company helped develop the QuattroMix™ Mixing System, which features Quattroflow™ Single-Use Quaternary (Four-Piston) Diaphragm Pumps.

## Introduction

The manufacturers of biopharmaceuticals must be cognizant of and be prepared to overcome a significant number of operational challenges—from both a micro and macro perspective—as they shepherd their products from production line to, ultimately, the hands of the consumer.

The day-to-day (micro) challenges must all be consistently met, otherwise the production run will be a failure. Since many biopharmaceuticals are extremely sensitive to change or damage from outside influences, the main challenges for manufacturers typically include:

- Maintaining a high level of purity and sterility
- Achieving low levels of leachables and extractables
- Minimizing impact of particle shedding from contact materials contaminating the product stream

- Utilizing shear-sensitive product handling
- Producing a controlled, constant product flow with low pulsation
- Minimizing addition of heat to the production process
- Achieving a high level of volumetric consistency

## QUICK FACTS

**Company:** JM Separations BV

**Location:** Tilburg, The Netherlands

**Market:** Biopharmaceuticals

**Challenge:** Incorporate single-use pumping technology that would efficiently perform and enhance batch-mixing operations

**Solution:** Quattroflow™ QF1200SU Quaternary (Four-Piston) Diaphragm Pumps

The JM Separations team – John van der Veeken, left, Tom van der Veeken, middle, and Mark van Trier, right – are filling a niche in the batch-mixing world with the QuattroMix™ Single-Use Mixing System.



Every QuattroMix™ Single-Use Mixing System features a Quattroflow™ Single-Use Quaternary Diaphragm Pump to circulate the liquids and solids in a mixing bag in order to achieve the necessary mix and dilution rates, all within an optimized time frame.



From the big-picture (macro) perspective, biopharmaceutical manufacturers are most commonly confronted with the following concerns:

- Optimizing equipment and maintenance costs
- Increasing speed-to-market capabilities
- Maximizing the earning potential of the biopharmaceutical's patent window

The only way to achieve success in meeting these challenges, both small and large, is by incorporating production equipment and systems that reliably perform efficiently and effectively. Finding and utilizing the proper pump technology will help the biopharmaceutical manufacturer defeat the many challenges inherent in the production process, while providing peace-of-mind knowledge that the needs of the consumer will be met satisfactorily.

## In The Mix

A critical link in the biopharmaceutical-production chain is batch mixing, whether it's a liquid/liquid solution or a liquid/solid solution. The demands in batch mixing are similar to those of overall biopharmaceutical manufacturing: utilize a process that maintains the hygienic integrity of the product during manufacture, while delivering the capability to perform the mixing process in a time-sensitive and cost-effective manner.

Two decades ago, friends and colleagues, Mark van Trier and John van der Veeken, set out to form their own biophar-

maceutical trade company, the result of which was JM Separations BV, which they headquartered in Tilburg, The Netherlands. Over the years, the company's mission has evolved and JM Separations has become an engineering and design firm for the biopharmaceutical industry.

"Over time we had more and more of a passion to have our own manufacturing, our own products, our own engineering team and supply the customer with process solutions," said van Trier.

"We really want to help customers with their solutions," added van der Veeken. "Mark is better in some areas and I'm better in others, but together we make a great team."

In recent years, the duo observed the industry-wide growth of single-use equipment and especially pumps in biopharmaceutical processes and identified that as an enabling technology that they could offer their customers. They believed these pumps were a better manufacturing solution because of the low cost compared to permanent stainless-steel pumping systems and the simultaneous ability to ensure the necessary level of high-purity production that is required. Specifically, they felt they could fill a niche where batch-mixing operations could be performed and enhanced through the use of single-use pumping equipment.

For a solution, they reached to the past, in this case, to former colleague Frank Glabiszewski, who had worked with van Trier and van der Veeken in the early 1990s. Since then, however, Glabiszewski had, with partner Josef Zitron, invented the positive displacement quaternary (four-piston) diaphragm pumping principle and founded Quattroflow™ Fluid System GmbH & Co in Germany. In 2012, Quattroflow was acquired by the Dover Corporation's PSG®, Oakbrook Terrace, IL, USA, which is comprised of several of the world's leading pump product brands. PSG has subsequently integrated the manufacture of Quattroflow pumps into the operations of its Almatec® subsidiary, which is headquartered in Kamp-Lintfort, Germany.

"In 2010, we started working with Frank Glabiszewski of Quattroflow to build a mixing system," said van Trier. "In 2013, he said, 'I think I have the solution for you.'"

That solution, which would come to be called the QuattroMix™ Single-Use Mixing System, and also prompted JM Separations to create a new division named JM Bioconnect®, features a Quattroflow Quaternary (Four-Piston) Diaphragm Pump used to circulate the liquids and solids in a mixing bag in order to achieve the necessary mix and dilution rates, all within an optimized time frame.

The main benefit of using Quattroflow pumps in biopharmaceutical-mixing applications is its form of operation: the four-piston 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



The QuattroMix™ system has a very basic, easy-to-understand operating principle and includes a single-use mixing bag, a Quattroflow™ pump and a 16-hole mixing plate that is built into the bag.

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 and leak-free operation. Quattroflow pumps also have some of the highest turndown capabilities in the industry, which ensures that the pump’s operation does not adversely affect repeatability and production rates.

## All That, And So Much More

“What makes this unit so nice is that we can work directly with the pumps from Quattroflow,” said van Trier of the QuattroMix. “We like them because the pumpheads minimize particle shedding, which is very important for biopharmaceutical companies.”

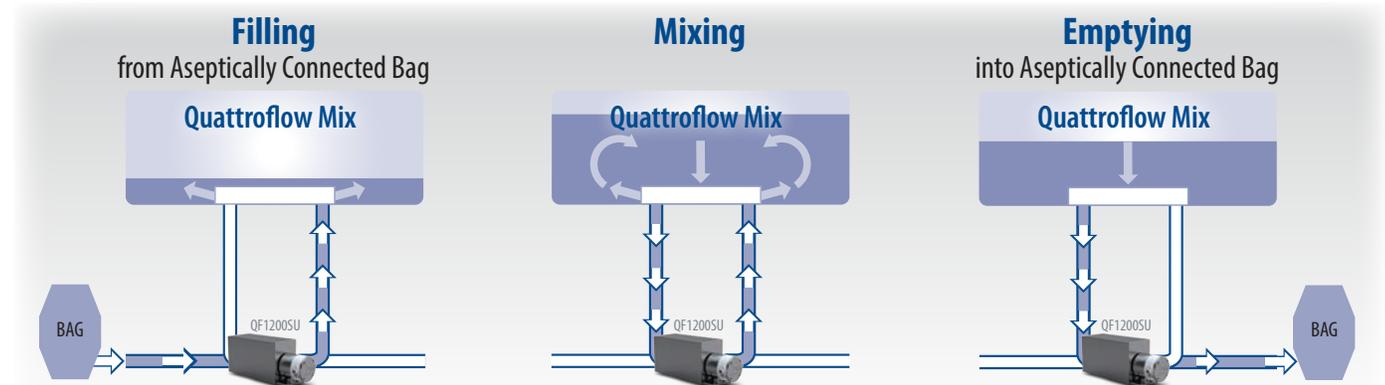
The QuattroMix system has a very basic, easy-to-understand operating principle. A single-use mixing bag is filled via a Quattroflow pump through a 16-hole mixing plate that is built into the bag. After the proper amount of mixing agent is injected into the mixing bag, the Quattroflow’s pumping action through the mixing plate forces the liquid

from the bottom of the bag, up around the outer walls and back down through the mixing plate in the center, where it is recirculated through the pump.

“Together with PSG we have invented a very nice mixing system that’s based on the technology of the Quattroflow pump with the mixing plate inside, and the technology from JM Bioconnect that has all of the parts together to make a nice single-use piece of process equipment,” said van Trier. “Since the Quattroflow pumps have a nice capacity, they can run up to 1,200 liters an hour (317 gph), we can mix very well. We can mix liquid/liquid solutions and we can also mix liquid/powder solutions.”

The unique, impeller-free operation of Quattroflow pumps also gives them distinct operational advantages over competitive types of mixing systems.

“The challenge for other suppliers of mixing technologies is that most of the mixing systems have a magnetic part on them or they have an impeller,” said van Trier. “Some mixing solutions have magnetic beads so a magnetic part will not work with that application. If you have a mixer inside the bag, that creates the chance for contamination on the impeller since the impeller has to go through the bag. This is something that you don’t have with this type of installation. You have a pre-packed complete unit with the pumphead next to it. You install it as a complete unit, install the disposable pumphead to the motor and start



Another benefit of the QuattroMix™ system is that filling, mixing, emptying and post-mixing filtration steps can all be accomplished by utilizing the same Quattroflow™ pump.



Since the QuattroMix™ system has come on the scene, the JM Bioconnect® customer base has rapidly grown to include such global pharmaceutical giants as Johnson & Johnson, Pfizer and Novartis

filling with water; basically it's a plug-and-play unit."

The Quattroflow pump is also versatile enough that it can be used to transfer the newly mixed solution from the mixing bag to a storage unit without the need to utilize another pump. This decreases the chance that product contamination will occur.

Of course, the fact that the Quattroflow pump utilizes a single-use pumphead brings with it a whole host of operational benefits, namely:

- Lower initial cost than permanent stainless-steel systems
- No expense of time or cost for equipment cleaning and validation
- Quicker production processes that optimize speed-to-market capabilities
- Easy removal and disposal of pump chamber once production run is completed
- Ideal when clean-in-place or steam sterilization is not practical or possible

"In the biopharm industry, single-use has become more and more popular because we want the product to come to market as quickly as possible," said van Trier. "They don't want to spend time cleaning because cleaning and validation take a lot of time and also a lot of labor goes into the cleaning cycle. With single-use you don't have to clean anymore, your operators can just make the product, get a new bag, put it in place and go forward. It's also cheaper when compared to stainless steel, and after 30 minutes the customer has his liquid perfectly prepared; that's the aim of the system."

On top of all that, JM Bioconnect has turned to another Dover company, CPC, St. Paul, MN, USA, for the connectors that link the mixing systems to the mixing bag and pump. Specifically, the AseptiQuik® line of connectors help the QuattroMix become a completely sterile system with no additional sterilization procedures required.

Currently, JM Bioconnect is offering the QuattroMix system with mixing-bag capacities of 50, 200, 500, 1,000 and 1,500 liters (13 to 396 gallons). The JM Bioconnect name is now registered in the United States and several countries in Europe and Asia, and its customer base has rapidly grown to include such global pharmaceutical giants as Johnson & Johnson, Pfizer and Novartis, as well as smaller companies that require customized mixing systems.

## Conclusion

The challenges are many in the production of biopharmaceuticals, but if they can be properly identified and managed correctly, the benefits are immense for both consumers and the manufacturer. The only way that critical mixing applications can be completed successfully is if the proper equipment, from pumps to bags to hoses to connectors, is utilized. JM Bioconnect has struck gold in this area with the QuattroMix Single-Use Mixing System, the success of which rests notably on the incorporation of Quattroflow Quaternary (Four-Piston) Diaphragm Pumps.

"With this integrated system featuring Quattroflow pumps we eliminate a lot of problems other suppliers have," van Trier summarized. "Minimal particle generation, elimination of the chance of contamination, elimination of a magnetic field inside the bag, elimination of an extra pump to transfer the fluid to another place. All these things are built into the design of the system."

## About the Author:

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