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Q & A

Interest Grows in Single-Use Pumps

Speeding up development can pay off
at the bottom line for drug companies



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The traditional pharmaceutical and biopharmaceutical industries are distinct entities. The commonality is they both produce drug products for human and animal health. The two industries use different feed stocks, different production techniques and, not surprisingly, different technologies and equipment.

One of the key differences: the pharmaceutical industry relies largely on synthetic chemical processes while biopharma relies largely on cellular processes. That difference has led to the development of new lines of processing equipment optimized for biologic processes. The latest development is single-use pumps. Wallace Wittkoff, Hygienic Market Director for Pump Solutions Group (PSG®), discusses the need for single-use technology.

Pharmaceutical Technology: Why does the biopharmaceutical industry use single-use technology?

Wallace Wittkoff: New drugs are coming from the biopharmaceutical industry, which is producing these substances from biologic processes. Speed to market in introducing these drugs mean billions of dollars for drug companies. Single-use technology permits the development process to occur much faster and at a lower cost.

The need for speed is not only to begin commercialization of drugs quicker. There is also a very important 20-year patent window that has to be considered. The patent submission needs to occur during the drug development process. After the request for a patent has been filed, the developer has to wait for Food & Drug Administration (FDA) approval. When that approval comes, the developer has to be ready to introduce the product to market. If the drug's development takes additional time after patent approval, the patent may run through a good portion of its protection before the drug has a chance to get commercialized.

On average, there are only about seven years left on the patent for the typical product when it goes to market. Every year a drug is covered by its patent is worth billions of dollars in sales, so every year, every month, every day that the development process can be accelerated means a lot to the bottom line. Single-use technology, whether in pumps, transfer tubing, single-use bags or vessels, accelerates the process of doing multiple trials and eliminating time spent in cleaning and validation, thus accelerating the development process.

What are some of the challenges in the production and handling of biologics?

Wittkoff: Biologics start with very delicate cell structures. These cell structures are grown in an environment that needs to be very strictly controlled so that these bacteria, viruses, or other cells grow properly. Once the biologic material is extracted, drug manufacturers are looking for target proteins.

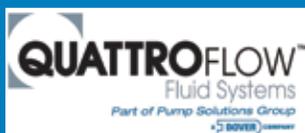
In order to purify these proteins, many processes are used, some chemical but also filtration processes like tangential or cross flow filters, chromatography columns or centrifuges. These processes have to be done in a very controlled manner to obtain the highest yields. The target protein cannot be damaged through heat or shear, for example.

What benefits do single-use pumps bring to biologic manufacturers?

Wittkoff: In the typical biologic development process, a target protein is first identified. Then toxicity in animals and humans is evaluated. Then the drug goes through the clinical phase trials, and at some point during that process, a patent is filed to protect this know-how. Subsequently, a filing is made with the FDA.

This multi-year process is occurring while no revenue is being generated. The key goal of biopharmaceutical companies today is to bring the product to market faster. Technology for single-use bags, transfer lines are all well-advanced for this purpose. The missing element has been a single-use, non-pulsing pump technology to go along. With Quattroflow, the complete system is finally single-use. As these target proteins are analyzed and variations are developed, they can be run. Whether they produce results or not, subsequent runs can

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be done very quickly because the factory can be rebuilt using single-use technology.

If a protein run is not appropriate or has to be adjusted, the entire line gets quickly disposed of and a new single-use line is set up and run. That can be done a lot quicker than a permanent line.

With a permanent line, the process must be thoroughly cleaned and validated after each run. The process of validating a cleaning process is extremely expensive and also very time-consuming, sometimes taking weeks or months. Single-use technology really hits that speed objective because you can very quickly dispose of the first run and set up the next run. There is no cost, which runs in the 10s of thousand dollars, with treating the contaminated cleaning fluid of permanent equipment.

How important is low shear, low slip, controlled temperature and low pulsation operation when handling biologics?

Wittkoff: These all are extremely important. Take a common filtration process in the biopharmaceutical industry, the tangential flow filter. Fluid flows across the filter and not through it, unlike normal-flow filters. The velocity of the media that is being filtered must be very precisely controlled to achieve the proper filtration. If the flow is too low, the filter might foul. If the flow is too high, the filter could be damaged by excessive friction.

That means you need to have controlled low-pulsation flow. Pulsation also will cause a disturbance in the filter media and in filtering, so no pulsation is a very desirable characteristic. Since these products are biologically derived, temperature is usually a consideration as well.

What are the shortcomings of current pump technologies that are commonly used in biologic handling applications?

Wittkoff: Prior to the Quattroflow pump, there has not been a solid candidate for disposable, low-pulsation, constant, controlled, low-shear pumping. The typical pumps that have been used, peristaltic for example, are single-use pumps, but peristaltic pumping is pulsating, so it is not adequate for some filtration systems.

In addition, there are limitations on discharge pressure. Some filters need more than 30 – 50+ PSI, and the peristaltic pump, by the fact that the pumping element is a hose, cannot withstand higher pressures. The other issue with peristaltic pumps is that spalling occurs over long-duration use. Spalling is the process in which the hose gives off particulates that can go into the product stream, which may not be desirable. There have been developments to reduce spalling, but it remains an issue.

Lobe pumps have historically been the low-pulsation choice. However, it is not a single-use design. In addition, the lobe pump is not truly positive when working with low-viscosity solutions. When there is low viscosity, slip is considerable in lobe pumps, from 20% to 100%, depending on conditions.

Centrifugal pumps are not positive displacement and their operation causes a lot of shear. Centrifugal pumps turn at high RPMs and much of the energy that is produced by the motor gets converted into heat. Experimentation with recirculating fluid shows the temperature creep that occurs with centrifugal pumps. Plus, centrifugal

The Quattroflow Family of Single-Use Pumps



pumps do not have a constant displacement per revolution, so controlling flow through tangential flow filters can be an issue.

Why are the Quattroflow pumps the best choice for use with sophisticated filtering systems?

Wittkoff: The reason is the four-head, gentle diaphragm actuation of the Quattroflow. The multiple diaphragms work in conjunction to produce an essentially constant flow with no slip. Quattroflow is able to maintain a constant, controlled flow displacement per revolution that can be linked to a control system. That ensures that the Quattroflow is pumping the correct flow rate and proper velocities to optimize the filtration process, the chromatography column and properly feed the centrifuges without pulsation, which could cause imbalances that are harmful to the centrifuge and the product being separated.

Can you describe the operating principle of Quattroflow's positive displacement diaphragm pump?

Wittkoff: The pump has four diaphragms and they are driven one after another by a connecting plate that is moved back and forth out of its central position by an eccentric shaft. This means there is no mechanical seal or slip areas in the pump. Essentially, an inner chamber produces a negative suction capability that transfers the product to an outer chamber via the four diaphragms that are working in unison to generate the discharge pressure that maintains a constant flow.

How do single-use pumps enhance a drug manufacturer's speed-to-market product capabilities?

Wittkoff: Speed to market and cost are critical. One way to achieve speed is working with contract research organizations and contract manufacturing organizations. You can purchase start-up companies that are able to utilize the flexibility of single-use technology to develop new drugs more quickly. Faster development draws the interest of the larger pharmaceutical companies to take these to market. Time is of the essence. The time that drugs are protected by patents is a significant driver to the top and bottom line of these companies and their values in the marketplace. Removing the high cost of cleaning is a bonus.