Automation in Single-Use

Unlocking the True Potential of Single-Use Technology

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Single-Use Automation: Unlocking the True Potential of Single-Use Technology

As single-use technology has become more established in biopharmaceutical manufacturing it has been applied to more complex unit operations involving higher value products.

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Guy has worked in the biopharm industry for the last 20 years starting his career as a scientist at a well-known CMO in the UK before moving to more commercial roles. During this time, he has been involved in many projects implementing single-use technology in both upstream and downstream bioprocessing.

Guy now works as division marketing manager at Parker Bioscience Filtration where he is focused on bringing Parker's expertise in motion and control to bioprocessing to create robust solutions in single-use technology that enable customers to improve the quality and accessibility of biopharmaceuticals.

This has driven the need for greater process control and, as a result the use of single-use automation has grown. But why has automation not been more widely adopted in single-use processes and what benefits can be realized?

History of Automation in Single-Use

When single-use technology first arrived on the scene in the late nineties, the processes that it was applied to were relatively simple and low risk.

These included simple filtration and storage applications of buffers and cleaning solutions. With these filtration steps typically involving lower value, non-blocking solutions of easy to dissolve salts, automation would have been seen as an unnecessary over-complication. It was thought sufficient to have an operator watch the process to make sure nothing became disconnected, a bag did not overfill or a tubing set burst as a result of a blocked filter.

The first hint of what was possible came with the integration of pressure sensors into single-use assemblies to monitor the pressure across the filter membrane, delta P (dP).

As the benefits of single-use became clear and the technology became established, there was a drive to utilize it in more process steps. Single-use was no longer being applied to simple buffer preparation but to process steps where the output would form part of the batch record and the value of the product passing through the assemblies increased dramatically.

These process steps included, for example, clarification, tangential flow filtration (TFF) and virus filtration. These unit operations required relatively complex monitoring and control as well as data acquisition. Only by automating the equipment could these systems operate, protect the process and collect and store the data in a way that was compliant to cGMP.

So, if automation of single-use steps is key, what is stopping its implementation?

Implementing Automation

In a recent survey conducted during a Parker webinar the audience was asked: *What would restrict you from implementing automation in your single-use process?* The results shown in Figure 1 were observed.

Almost 20 percent of the respondents stated that their process does not require automation. Given that automation enhances safety, can improve the efficiency of a process and, if nothing else, frees up operators from passively watching a process to be able to carry out

more value-added activities, it could be argued that all processes could benefit from some level of automation.

Accuracy of sensors was called out by 15 percent of respondents. Looking into this we see sensor accuracy of +/- 0.02 bar being vailable for single-use in-line pressure sensors. Calibration to fully traceable NIST (National Institute of Standards and Technology) standard should further raise confidence in the device being used.

Cost was reported by nearly 50 percent of respondents as the reason why they would not implement automation. It should be acknowledged that putting an automated system in place does incur cost, but this should be seen as an investment.

The reward for this investment has been seen in the form of time saving, complexity reduction, improved process security and standardized training.

This all adds up to a rapid return on investment. In fact, in one study completed by Parker, the time to demonstrate a return on investment was less than 12 months[1].

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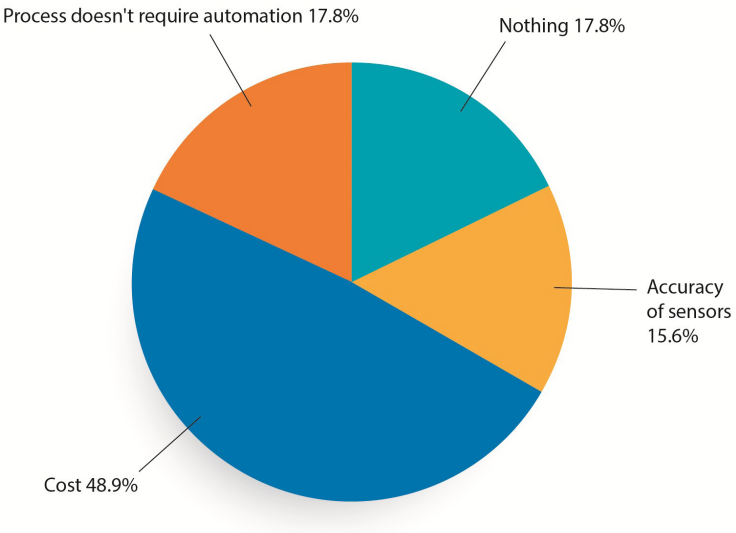

Figure 1: Responses from a Parker webinar audience to the question: What would restrict you from implementing automation in your single-use process?

Benefits of Automation

Having discussed some of the barriers to automation in single-use, we need to look at some of the reasons in favour.

To illustrate why you would implement automation in single-use, we should look at the key drivers in the biopharmaceutical industry and how they are addressed by single-use automation.

These answers could equally be applied to the question: *Why implement single-use technology?* Since both are closely linked, single-use system implementation and single-use automation should be viewed jointly with automation taking the advantage gained from single-use technology to a higher level.

Key Market Drivers

Speed to market: Automation can address speed to market in a number of ways.

If the same technology on the same automation platform has been used across the development process as will be used at scale, the scale-up will be easier to complete and more predictable when compared to a process that uses multiple automation platforms.

Having access to the same equipment and product contact materials can greatly ease technical transfers by eliminating a number of variables from the process, not to mention simplified validation, notably extractables & leachables data.

An automated single-use system can be ordered, shipped and validated in far less time than its stainless steel equivalent.

Investment decisions: These can be delayed.

If it takes five years to build and validate a multi-use (CIP/SIP) facility but only two years for the equivalent single-use facility, you can have three years' worth of extra data before pushing the button on what would be a multimillion dollar investment.

Multi-product facilities: Facilities of the future need to be capable of making more than one product.

Single-use has clear advantages in a multi-product facility, namely not having to validate CIP/SIP cycles and maintain costly utilities.

Automation takes this to the next level as it allows operators to run multiple recipe driven processes even when the have limited experience of the process being run. All TFF processes follow a certain high level routine but products will have differences in the recipe. Being able to call up and run an automated process helps to eliminate process errors.

Regulatory: Products need to be safe and effective, and processes need to be robust and repeatable.

The more automated a process is, the more repeatable that unit of operation should be, subject to a constant feed stream. Automation will also contribute to simplified training and to a reduction in operator driven deviations. Additionally, an automated system allows for the creation of a batch record along with the compliant storage of data and the audit trail for the data set, easing the lot review process.

Economic: With biosimilars coming on line, more and more focus is placed on cost of goods sold (COGS).

How does spending money on putting in an automated platform aid the lowering of COGS? Simply put: by making the process more repeatable, standardized and robust, you increase the predictability of the process.

Through automation, you can decrease the number of people involved in a unit operation and simplify the supply chain around the process. In effect, you can do more with less.

Continuous processing: Single-use technology and continuous bioprocessing are two of the biggest trends in bioprocessing. Continuous bioprocessing will be, or in some cases is, the next big thing to hit the bioprocessing world. Sinlge-use is an enabling technology.

The benefits of single-use are so great that it would be difficult to see why you would switch back to a fixed platform. So, to allow continuous processing of single-use processes, the automation of valves, feedback from sensors and control logic will need to be in place. Or, to put it another way, single-use continuous manufacturing processes will need an automated approach if they are going to work.

Automation in Action - Normal Flow Filtration

When discussing normal flow filtration (NFF) on a single-use platform, an experienced operator may remember making a manual intervention of turning down a pump speed when a line started to balloon because of a pressure build up.

The first step in process automation came with a pressure sensor linked to a display so the pressure could be read from a monitor. Next was linking this to an alarm to alert the operator and the next level of automation applied would monitor the dP and switch off the pump once a trigger point had been reached.

Finally, we are able to see the full benefit of automation for this step by using the R/P Stat method.

R/P Stat Method

R/P Stat is an automated method for controlling NFF that can improve filter capacity by up to 30 percent.

It works by controlling the pump speed based on the measurement of dP. The process starts running at a set speed and pressure is monitored.

As the pressure builds up over time, instead of reaching a trigger point for pressure and switching the pump off, the pump speed is reduced to prevent the dP building to a point that would trigger a process stop.

By running in this fashion, the process can run for longer (see Figure 2).

Such an application offers two key advantages:

- **A smaller filter can potentially be used as the safety margin on the surface area need not be as great.**
- **It is easier to handle unpredictable feed streams, for example, harvesting cell cultures in process development laboratories where the cell density, cell viability and productivity can vary widely from batch to batch.**

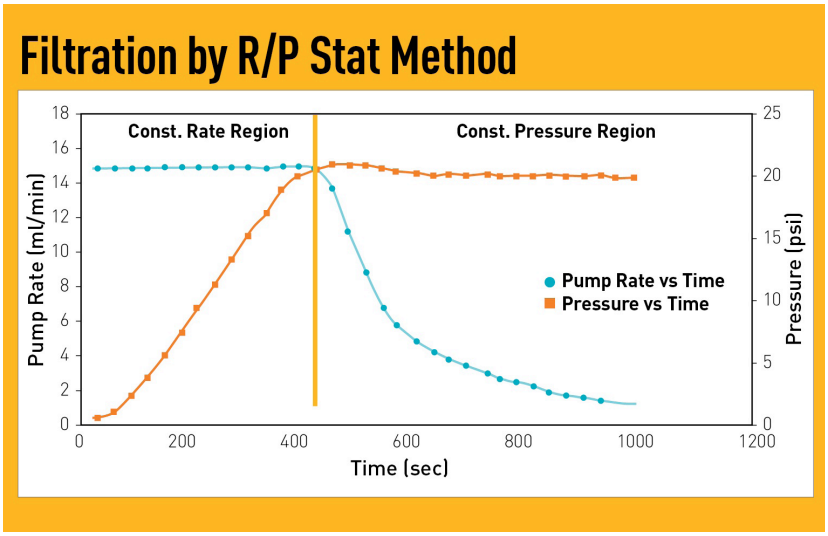

Figure 2: The R/P Stat method can increase normal flow filtration capacity by up to 30 percent

Automation in Action - Tangential Flow Filtration

If we were to look at a more complex operation like tangential flow filtration (TFF), there are a number of inputs to be monitored and controlled and a range of outputs that could trigger the end point.

Monitored Functions

Cross flow rate: Pump rate measured against a set point

dP: Pressure drop across filter

Transmembrane pressure (TMP): Driving force across membrane

Retentate volume: Measure of flux

Outputs for End Points

dP: Excessive dP could trigger a process stop

TMP: Excessive TMP could trigger a process stop

Retentate volume: Reduction to a specific volume or failure to maintain a volume would trigger a process stop

Feed / transfer tank: Reaching a measured volume would trigger a process stop

Volume or mass related process end points are relatively easy to control based on measurements from a load cell. Through monitoring a change in the volume, by measuring weight, process decisions can be made.

Obtaining a particular mass in the retentate tank during a concentration step would indicate that a certain concentration factor has been reached. Alternatively, during a diafiltration step, reaching a set point on the permeate side would indicate that the required number of diavolumes have been processed.

Process decisions involving pressure are more complex as pressure is a function of the pump speed and pressure control valves. However, through automation, this balance can be achieved, for example, to maintain a set dP or TMP in the process

The system will open and close valves and increase or decrease pump speed based on the programming logic to maintain the required set points, but also the required process conditions, such as cross flow rates, to maintain a shear rate in a hollow fibre.

Figure 3: A Parker SciLog® automated tangential flow filtration system

Data Acquisition
It would be impossible to manually take a reading from three pressure sensors, two pumps and a couple of balances every second over a four-hour period while at the same time calculating dP and/or TMP then adjusting the system to maintain a set point. Through automation, however, this level of data capture and process control is possible.

The other major advantage of an automated process is the generation of a data set that is unambiguous, has the capacity to be copied without error, can be stored in multiple places, has an audit trail of changes and can be downloaded easily for analysis without error.

Conclusion

Single use technology is a key enabling technology allowing quick turnaround times between batches and facilities to be multi-product, while driving down the cost of goods.

This, in turn, enables more people to access lifesaving biopharmaceuticals.

Without automation, these single-use systems would have limited application, but through automation it is possible to achieve data acquisition, process monitoring and control and batch record generation, so allowing more complex unit operations to be run in cGMP compliant production environments.

As a result, the true value of single-use technology can be realized.

References
1. Proctor G, Single-use technology: The next 5 challenges to conquer, 2016

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