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Continuous processing optimization with smarter tools

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Due to a paradigm shift in the pharmaceutical industry, there is rising pressure to come up with faster, more cost-effective ways to produce drugs for the patients who need them. As orphan drugs and personalized medicine begin to replace traditional blockbuster products, pharmaceutical companies are looking at new and innovative ways to quickly and efficiently deliver drugs to target populations in the thousands rather than the millions. In addition, the need for lower drug prices has been pushed into the spotlight not just by regulators, but also by the advent of biosimilars. As a result of these changes, industry experts must find a way to produce drugs that address the issues around both drug pricing and time to market while also maintaining quality and profits.

Based on production volume, most of today's blockbuster drugs are still manufactured in stainless steel facilities. Yet, these facilities take at least five years to launch and offer little to no flexibility in the face of changing demands. In addition, traditional and fed batch production models used in these facilities require huge development costs and are fairly substantial in terms of ongoing manufacturing. If a drug is more successful than expected, many companies are not prepared to scale up to meet the new demand. At the same time, a drug that doesn't meet its original demand expectations while a large stainless steel facility is being built for it, results in a significant loss of non-recoverable capital expenditures. Conversely, for orphan or precision medicine drugs, rapid product turnover in manufacturing is far more important than capacity (volume).

Single-use technology (SUT) has long been viewed as a viable solution to this growing problem. It offers the flexibility to change a production configuration to meet demand while also offering a number of other cost benefits, such as savings related to the elimination of clean-in-place (CIP) and sterilization-in-place (SIP) processes. However, traditional and fed batch models fail when trying to adapt to single-use flexibility due to the required rewriting of code and revalidation.

The best way to utilize the flexibility of single-use is to pair it with a modular automation system in a continuous processing configuration. This setup eliminates the limitations and burdens of manual control while optimizing the throughput from upstream to downstream. Despite the many benefits this paradigm provides, the industry still has many concerns about continuous processing. Through the application of technology available today, manufacturers can reap the significant cost savings provided by a continuous processing strategy while also applying the controls necessary to successfully monitor and control it.

Efficiency and flexibility through end-to-end processing

When it comes to facility utilization, the cost per gram of an antibody is directly correlated to the usage of the facility. A large facility operating only three months of the year leaves nine months during which the capital invested in the facility simply lays fallow. Smart factories that use continuous processing and automation enable a high degree of utilization due to process flexibility and multi-product production. The adoption of these modern facilities, while an intimidating change for some, is the next logical step in a history of process evolution.

Dating back to the 1980s, production was achieved through very simple batch processes with little involvement by personnel, limited monitoring, and minimal to zero process control. As the demand for higher titer increased, drug processes became more sophisticated and the industry moved toward a fed batch model. A process in this type of model took between 7 and 20 days to complete, depending on the complexity of the fed batch and what was being done to the cells.

As the realization that parameters played a critical role in reproducibility grew, experts began adding pH, dissolved oxygen, and temperature monitoring to the bioreactor to increase success. To coax out either the protein or the monoclonal antibodies desired, a substrate was introduced or the temperature was shifted. In addition, more refined process control was implemented, including various strategies for how to feed and ship the cells.

Over time, this manipulation of production platforms resulted in much higher titers, but also resulted in questions around how to appropriately adjust downstream operations. In the past, when titers were low, batch time for upstream was about two to three weeks with downstream processing taking about two to five days. As titers improved, upstream could run for around two weeks, and the downstream became a bit more intense. This reduced the capacity mismatch but did not eliminate it. With continuous processing, the upstream and downstream are unified. Upstream no longer runs constantly with downstream skids being activated and utilized for only small increments in time. Matching the upstream and downstream capacities drives down the production costs to the raw materials and leaves a process that can be used over and over.

Higher titers and batch concerns fuel continuous processing fears

The pharmaceutical industry does not have a reputation for being open to change, and for good reason. Not only are human lives at risk, but also millions of dollars can be lost should a problem occur with just one batch. However, while fears about change are valid, concerns regarding continuous processing may just be the result of a lack of knowledge about a platform that is still so new to, and sparsely used by, the industry.

One concern is related to the handling of higher titers. Some feel that despite the added efficiency a continuous processing strategy offers, it is going to be more costly to implement. Thankfully, companies like Thermo Fisher Scientific, GE, and Sigma-Aldrich offer sophisticated media support for cell cultures with higher titers. In addition, cell lines are now more robust. As continuous processing becomes the well-trodden path as opposed to the novelty, the timeline for development will be reduced, ultimately resulting in cost savings.

Higher efficiency and production can also be achieved through the smaller footprint of continuous processing if capacity is utilized properly. For example, when running perfusion, which retains the cells while fresh media flows into the bioreactor, the cell population may take five days to reach its peak. Once the cell population reaches, and is maintained at its peak, the downstream can run for up to 60 days at this maximum cell population. This is especially beneficial with slow-growing cells because once they have finally grown and built up their population, a large quantity of product can be produced and purified. Thus, both the media and chromatography column will be fully utilized with little or no waste; in a fed batch process, harvest after two weeks limits the use of the downstream columns and effectively restarts the long waiting period to reach peak population and product production after each batch. Therefore, in fed batch mode, upstream and downstream efficiency and material utilization are reduced as cell productivity is in a start-and-stop mode, thereby reducing overall productivity of the facility. In a multi-product facility running continuous processing, the output and productivity of the facility can grow as more lines are added.

Another concern about continuous processing is related to the continuous flow of product from a production skid and what effect this will have from a regulatory perspective. With traditional methods, a batch is easily defined as the final product or material from a sequence of processes. In a fed batch environment, there is an exact point when a process begins and ends and a well-defined plan of how to manage it. When something goes wrong, it is much easier to determine how much product has been affected. If materials are constantly flowing through a continuous processing platform, where does a batch begin and end? This is where automation can play a key and enabling role. Constant monitoring of materials notifies operators when a problem occurs, and any material collected before that error is usable. There is also the concept of micro-batching, where a batch is defined in time periods. By defining a batch with specific time frames, a batch can be deemed “good” or “bad” based on when it was produced.

How automation can be used to overcome objections to continuous processing

With continuous processing, there are many moving parts operating at the same time as well as data and batch records that need to be managed. To do this successfully, this type of platform must be:

» *Scalable* – Enable rapid process transfer into higher production volumes in order avoid repeating optimization at each scale-up step.

» *Flexible* – Allow for multiple products to be run through the platform while also easily validating them.

» *Universally controlled* – Ensure multiple bioreactors from any vendor can be controlled at a commercial scale; allowing for rapid changeover using preset configurations.

Because of the implementation of SUT in a continuous processing platform, the design can be adjusted based on client needs. However, the principle of feeding in fresh media and nutrients while constantly producing products remains the same. With a perfusion setup, this step can require up to 12 pumps (compared to only a few in a fed batch operation). An offline analyzer with an integrated auto sampler allows for monitoring and control of viable cell density during this process by pumping the sample into various analytical instruments and sending data back for analysis.

Cell separation can be done in a variety of ways. However, because the method of perfusion is more suitable for unstable active pharmaceutical ingredients (APIs), it has become the most widely used in a continuous processing platform. Perfusion can be done using one of the four different cell retention methods below. These methods require pressure monitoring to ensure optimal filter performance, which is critical with single-use bioreactors and required for feedback control and alarming.

» *Tangential flow filtration (TFF)* – Flows media through a filter while holding cells back. The filter is then flushed to put the cells back into the bioreactor.

» *Alternating TFF* – Retains the cells and puts new media back in, and then the cells can be flushed back through the filter. Pressure monitoring is required for both forms of TFF.

» *Floating filter filtration* – Retains cells inside the bioreactor while removing spent media from the vessel and backfilling it with fresh media. This method is popular for rocking (wave) bioreactors.

» *Acoustic separation* – Separation is performed in a resonator chamber with an acoustic field generated by a transducer. Ultrasonic forces produced in the standing wave field aggregate and hold the suspended cells against flow. These cells are then flushed back into the bioreactor. This method is popular with glass vessels up to 20 liters.

» *Centrifugation* – For cell culture where the product is excreted by the cell, a fixed volume is removed from the bioreactor and backfilled with fresh media; the supernatant is separated from the cells in the centrifuge and harvested while the cells are flushed and returned to the bioreactor. This method has been scaled up to 1000L in volume.

Like every other part of a continuous processing platform, perfusion requires automation and monitoring of key process parameters. A considerable amount of data will be generated for regulatory compliance and to prove the process is running the same every single time.

Smart systems, which are a valuable way to capture this data, also mitigate the need to train and retain highly skilled operators. In terms of process control, these systems offer unique advantages. These include weight management of several feeds with only one scale, pre-calibrated sensors with long-term drift resistances, cascade control, preconfigured settings, and custom software. They are also specifically designed to address the challenges of process intensification.

Summary

While continuous processing is perceived as adding complexity to biopharma operations, this complexity is not only manageable with automation, but it is also a way to improve the industry's aging business models. While skepticism exists, the automation solutions available offer unique and innovative ways to overcome the platform's biggest challenges, much as cruise control and auto parking have enabled for drivers of cars. Doing so requires not just knowledge but also the willingness to push the boundaries of modern technology to improve patient care. Innovative bio-pharmaceutical companies are already leading the way in this arena, as significant advances in bio-production efficiency are expected over the next three to five years.

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