



## Commercial Biomanufacturing with Single-Use Technologies

Modular systems allow to establish flexible facilities  
even at the 2,000 L bioreactor-scale



### Success Story

One of our multinational customers has adopted a single-use platform concept for development and GMP manufacturing across its global locations

The global biopharmaceutical market continues to grow and has been dominated by high volume products such as monoclonal antibodies. Within the next decade, however, biomanufacturers anticipate that their pipelines will become more diverse. Low volume-, highly potent products will enter the market and may require novel processes and smaller manufacturing scales. There has been an industry-wide increase in the adoption of single-use technologies for the commercial production of these biopharmaceuticals needed in low volumes. One of our multinational customers has adopted a single-use platform concept that will allow it to use the same process configurations for development and GMP manufacturing across its global locations.

## Transitioning towards Single-Use Technologies

Our customers' platform concept uses 100 L, 500 L and 2 kL single-use bioreactors for the production of clinical phases and commercial supplies. It incorporates the latest single-use technologies available on the market and a new approach for aseptic and closed processing that minimizes bioburden and improves safety.

Single-use technology is becoming ubiquitous within the biomanufacturing industry. Companies regard it as complementary and, in some cases, an alternative to traditional stainless steel equipment for the commercial manufacturing of smaller volume products. Until recently, facilities for the commercial production of biologics contained large stainless steel bioreactors, often with working volumes of 15,000 L or greater. They were typically designed to accommodate processes with cell culture titers below 4 g/L. However, the cost of constructing facilities such as these can exceed \$500 million and take up to five years. A significant component of the cost and the facility footprint was dedicated to utilities for the production of WFI, HVAC, clean steam and CIP solutions.

» Having a standardized consumable toolbox is supporting our customer's global demand planning activities.

Advances in bioprocess development are leading to higher titers and greater productivity. Titrers of CHO-based production systems have increased in recent years and nowadays average in the range 6-8 g/L. These developments together with an increased diversifi-

cation of molecule formats produced in cell culture will change the biomanufacturing landscape. New requirements may be met with smaller, more flexible bioreactors established in single-use facilities. In such facilities, different bioreactor sizes can be interchanged and allow managers to modulate production capacity to match fluctuations in product demand. In addition to improved flexibility, single-use facilities are less complex to design and have lower upfront investment costs. They are faster to construct, to commission and to launch. The time needed for change-overs between products is significantly reduced, allowing more batches to be run each year in multi-product facilities.

## Considerations for Commercial Manufacturing with Single-Use Technology

Our multinational customer completed the installation of its 2,000 L single-use manufacturing facility in Asia in the first half of 2017. Adopting the platform approach is allowing the company to seamlessly transfer processes from its other locations to this facility. The prototyping of upstream and downstream technology and the design of consumables were completed in early 2016. Facility Acceptance Testing (FAT) and Site Acceptance Testing (SAT) were performed during the second half of 2016 allowing the process qualification runs to start in early 2017. In the first instance a single 2 kL production line has been installed with the option for further expansions.

To facilitate process transfers across the company's global manufacturing network, our customer has worked with Sartorius Stedim Biotech (SSB) to standardize the many consumable



designs that were previously in use. This allows consumables to be transferred between facilities or between unit operations as the need arises. Having a standardized consumable toolbox is supporting our customer's global demand planning activities. Furthermore, using these pre-designed solutions improves the robustness and assurance of supply while reducing lead times.

- » This one piece of equipment can perform depth filtration, nano-filtration, ultrafiltration and solution adjustment steps within the downstream process.

## Innovative Single-Use Solutions

SSB was able to support our customer further by designing innovative solutions to processing challenges. Sartorius configured a FlexAct® system to perform automated harvests of the commercial-scale single-use bioreactor. This configuration incorporates new single-use pressure and flow sensors, a two-stage depth filter train and a final filter skid comprised of 0.2 and 0.1 micron membrane filters that can be readily integrity tested.

The FlexAct® system and associated consumables were designed by SSB to fit the customer's platform. This one piece of equipment can perform depth filtration, nano-filtration, ultrafiltration and solution adjustment steps within the downstream process.



MaxiCaps® MR: an extremely flexible system in a single piece with one inlet and one outlet.

SSB is also working closely together with this customer to develop large-scale, single-use sterile filtration solutions. The technology developed could be gamma-irradiated and integrity tested before and after use. The system is extremely flexible and allows users to install nine different filter capsules of different sizes and yet is a single piece of equipment with one inlet and outlet. SSB supplies the filter manifold with the necessary valves pre-installed and filters for integrity testing pre-attached MaxiCaps® MR.

- » Applying 'system marriage' techniques, well established in the automotive industry, will help reduce risks and accelerate single-use project execution.

## New Competencies for Executing Single-Use Projects

This project and others we have performed have proven that conventional project management and execution protocols developed for the construction of stainless steel facilities are not appropriate for single-use engineering projects. These traditional execution methods do not allow engineers to take full advantage of the flexibility and speed of implementation that single-use technologies permit.

Project teams in the biomanufacturing industry need to develop new competencies that allow the bringing together of hardware, software and wetware simultaneously. This is in contrast to the more traditional, sequential approach that they have used in the past. Applying 'system marriage' techniques, well established in the automotive industry, will help reduce risks and accelerate single-use project execution.

## Conclusion

In summary, we see that today's production technologies with high volume stainless steel fermenters are complemented and will co-exist with the use of disposable production platforms for research & clinical manufacturing and for commercial manufacturing of high potent and small volume molecules. The use of modular systems allows the industry to establish flexible facilities even at the 2,000 L bioreactor-scale. A robust concept for closed system processing is necessary for commercial manufacturing using disposable. Single-use technologies require new competencies from engineering teams for the design and execution of bioprocess engineering projects. It makes sense to develop such competencies together in a partnership approach between supplier and customer.

Sartorius Stedim Biotech GmbH  
August-Spindler-Strasse 11  
37079 Goettingen, Germany  
Phone +49.551.308.0  
[www.sartorius-stedim.com](http://www.sartorius-stedim.com)