Implementing a Single-Use Biomanufacturing Strategy

Important Considerations

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Implementation of a Single-Use Biomanufacturing Strategy

Recent trends in biomanufacturing technology and the biopharmaceutical market are supporting the increased adoption of single-use (SU) manufacturing systems. On the demand-side, the biopharma industry is focusing on niche and rare diseases with smaller patient populations, resulting in the need for smaller, more agile biomanufacturing capacity. Increasing developments of biosimilars are also leading to fragmentation and dispersion of manufacturing capacity. Changes on the supply-side through technological advances have resulted in higher titers, enhanced specificity and better down-stream yields, reducing the need for large, expensive, dedicated, and inflexible stainless steel based facilities. These technological developments have brought the culture volume needs into the realm of single-use systems for a large number of biopharmaceuticals.

Biomanufacturers are increasingly recognizing the advantages of single-use systems, which include: improved quality, safety from cross-contamination, flexibility, productivity, and time savings. For Gallus these advantages have allowed single-use systems to deliver improved cost efficiency along with:

- 50% reduction in capital cost
- 50% faster build-out of new manufacturing suites
- 80-90% reduction in clean water and steam use
- Reduced operating labor per unit of output

It should be noted that SU systems do have a higher raw material and disposal costs; however, they do bring a high degree of flexibility to the manufacturing process. This flexibility allows rapid product change-over with minimal risk to product integrity. It is also possible to readily change total manufacturing volume by simply increasing or decreasing in the number or size of SU reactors used in a campaign.

This paper provides an overview of the process used at Gallus BioPharmaceuticals, a cGMP contract manufacturer of mammalian cell biologics, to select and implement a SU biomanufacturing strategy and why the GE FlexFactory platform was chosen as the best solution.

As an experienced contract manufacturing organization (CMO) Gallus needs to be able to deliver the right amount of manufacturing capacity to its clients, either via a "pay per batch" approach or via virtual ownership of capacity (SuiteSPACE™ Model), as well as being able to operate a clinical services suite (CSS) according to cGMP standards, and accommodate all types of early-phase mammalian cell culture processes and products. The need for such flexibility made the decision to use a SU manufacturing system the obvious choice, the challenge was in selecting the right system.

Selecting the Right SU System

As part of Gallus' selection process, the following criteria were evaluated:

- Ease of scalability
- Commercial production scale offering (i.e. up to 2000 L)
- Large bioreactor working volume range with capability to operate at 20% of maximum working volume
- Flexibility of operation (e.g. perfusion or batch fed, various cell types)
- Complete SU manufacturing solution (i.e. upstream and downstream)
- Bioreactor and bag technology leadership
- Quality reputation
- Prior use in commercial processes to facilitate regulatory path forward

Gallus determined that the FlexFactory™ platform offering most closely met the requirements and offered the best fit to the selection criteria over other commercially available alternatives because of the following factors:

- Portable turn-key system, including hardware, automation, connectivity and software
- Process service and start-up support
- Requires less than 9 months from completion of design to build and equip a GMP-ready suite
- Reduces capital expense by 50% compared to conventional investments
- Maintains the same or better manufacturing quality as stainless bioreactors
- Allows for a portable, rapidly deployable, and easily replicated manufacturing facility
- Eliminates the risk associated with bespoke bioprocessing equipment integration

The availability of a continuous range of bioreactors from 10 L through 2000 L designed for seamless transition from one scale to the next was a key factor. For commercial scale operations, the ability to use multiple 2000 L reactors means a saving of the time and money associated with implementing process changes or improvements.

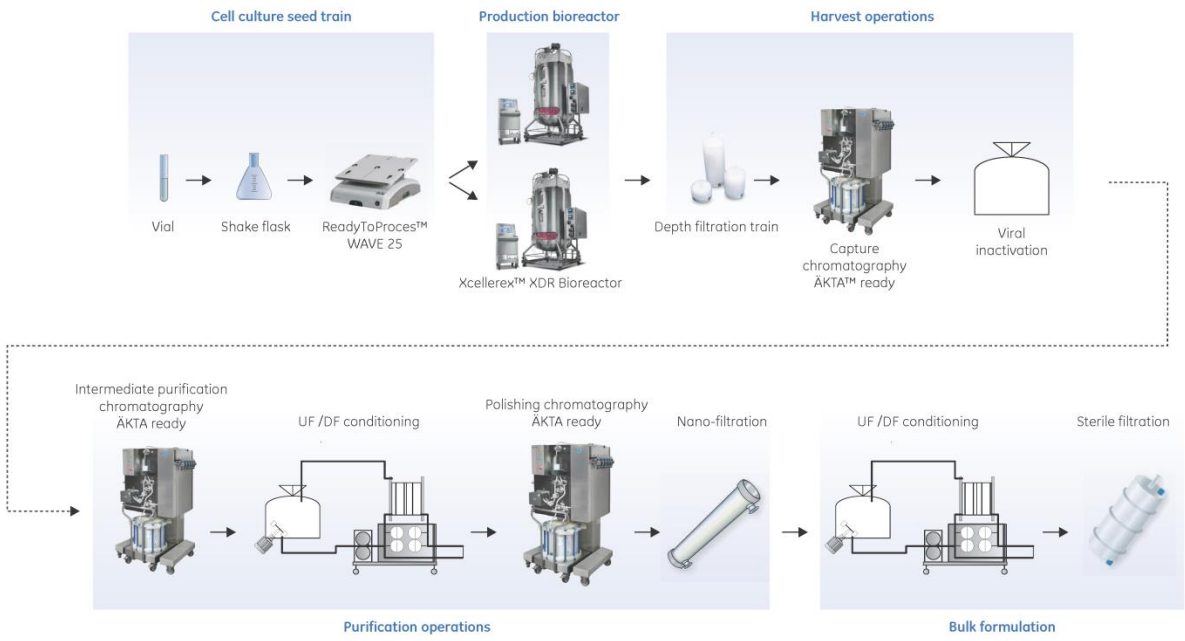
The fact that the XDR bioreactors in FlexFactory platform are routinely used in perfusion, batch and fed-batch modes with mammalian, microbial and insect cells was also important. These bioreactors employ a novel design that locates the sparging area below and adjacent to the bottom mounted impeller to closely approximate conventional stainless steel stirred-tank bioreactors. This design, combined with the configurability of the sparging scheme, enables good control of dissolved oxygen and pH, resulting in enhanced process productivity.

The choice of film in the two-film construction of the bioprocess bags creates a physically robust process environment. Options in bag configuration for numbers and types of probes, sampling manifolds, multiple exhaust lines, exhaust condenser bags, and baffles all work together to support specific applications and modes of operation.

In addition, the system control software automation platform provides the operator with a highly flexible interface for assigning field devices, including pumps and flow controllers, to control loops and allows the ability to change setpoints over time.

The FlexFactory platform provides a complete up-stream and down-stream biomanufacturing solution. The Controlled Environmental Module (CEM) component provides a separate ISO 7 environment for each purification step. The entire manufacturing process can be contained within a single ISO8 hall reducing time and cost for build out. Segregating products and cell lines with single-use down-stream processes minimizes change-over and cleaning requirements, thereby, decreasing the risk of contamination.

Overall SU system quality was fundamental to the Gallus selection process and the fact that each element of the FlexFactory platform had been developed with a strong focus on quality, robustness and real-life performance was vital. As the center of the bioprocess manufacturing train, bioreactor quality and robustness are essential and the XDR reactors had been extensively tested with real-life cell lines under production conditions to confirm performance and robustness. Crucially, the bioprocess bags used by the system were also designed to deliver the required quality and robustness using a validated and reproducible manufacturing process.



Example Process Flow Diagram (provided by GE Healthcare)

Conclusion:

In order to meet the ever evolving needs of its clients, Gallus chose to implement the FlexFactory SU platform to support its biomanufacturing strategy. The system delivered the flexibility, cost effectiveness, and technical benefits to enable Gallus to meet the needs of its clients today and readily in the future.

The GE FlexFactory at Gallus BioPharmaceuticals Clinical Services Suite in St. Louis, Missouri

This is the first in a series of 3 papers. Subsequent white papers will address qualification of the FlexFactory platform and the implementation for GMP clinical and commercial production runs.