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Current Opinion in Chemical Engineering

Transformation of biomanufacturing by single-use systems and technology

Gregory T Frank

Biomanufacturing has been and continues to be transformed by the rapid innovation and adoption of single use technology (SUT). SUT has changed how bioprocesses are designed, scaled, operated, controlled, and the speed at which new technology can be incorporated into biomanufacturing. We are continually seeing advances in single use bioreactors, mixing vessels, harvest technology, and downstream bioprocess equipment. This transformation has not been limited to bioprocess equipment. In this contribution, a summary of how SUT is rapidly transforming bioprocesses and the facilities they operate in will be discussed, including SUT enabled bioprocess intensification through high cell density perfusion and continuous biomanufacturing processes. Examples of how SUT has opened up new approaches to achieving regulatory and bioprocess requirements resulting in simplified, less costly facilities to build and to operate will be presented.

Address
Amgen, Inc., 1 Amgen Center Drive, MS B30W-2-A, Thousand Oaks, CA 91320, United States

Corresponding author: Frank, Gregory T (gfrank@amgen.com)

Current Opinion in Chemical Engineering 2018, **22**:62–70

This review comes from a themed issue on **Biotechnology and bioprocess engineering: biomanufacturing**

Edited by **Michael Betenbaugh** and **Nigel Titchener-Hooker**

https://doi.org/10.1016/j.coche.2018.09.006

Introduction

The early success of the biopharmaceutical industry depended on engineering cell line genomes to produce therapeutic proteins and antibodies [1,2] and the development of process equipment and facilities to produce biotherapeutics in a controlled environment subject to regulatory requirements. Mammalian cell bioreactors producing biotherapeutics often had 15 000 L working volumes (WV) to meet demand due to low cell concentrations and cellular productivity resulting in low product titers. The result was large facilities to house multiple large-scale stainless steel (SS) bioreactors, low-productivity purification trains, large medium and buffer handling equipment, and complex utilities. Building such a facility can take five years and cost $450 million dollars [1,3]. Once built modifications to accommodate new processes, therapeutic modalities, or demands are costly and disruptive.

Zhang [4•] commented that new innovations such as metabolic engineering, systems, or synthetic biology could revolutionize biomanufacturing in terms of product titer, yield, volumetric productivity, scale-up feasibility, and sustainability. We should add that Single-Use Technology (SUT) combined with advances in bioprocesses, medium, and cell line productivity are already transforming biopharmaceutical manufacturing.

Biomanufacturing trends

Macro trends reshaping the biopharmaceutical industry include new therapeutic modalities, increased competition in most therapeutic areas, loss of patent exclusivity, biosimilars, and shrinking market size as blockbusters are replaced by lower demand therapeutics, orphan drugs, and personalized medicine such as immunotherapies and regenerative medicines in company portfolios. These trends drive biomanufacturing towards increasing flexibility, reducing time to market, deferring capital investment, and lowering operating costs as companies adopt a more strategic view of biomanufacturing to gain cost efficiencies in processes and facilities [5].

Adaptable multi-product biomanufacturing is needed to accommodate variable product demand, wide range of process scales, and the increasing diversity of biotherapeutic modalities with new process requirements. Biosimilars require low cost, fast to build, flexible biomanufacturing technology to manage investment risks, market share uncertainties, regulatory approvals, and patent litigation, all balanced against the reward of attaining major market share that comes with being first to market with capacity to meet product demand. The biopharmaceutical industry is responding by investing in innovative technologies, including SUT to implement process intensification, continuous manufacturing (CM), and closed processing to increase operational efficiency and lower facility costs [5,6•,7–9].

Single-use technology

Two notable advances led to widespread application of single-use bioreactors (SUB) assembled from engineered polymer films and components forming a fully closed, presterilized, ready-for-use mammalian cell culture bioreactor.

Introduced in1996 the Wave™ was the first SUB to gain wide acceptance [10]. It consists of a 2-dimensional polymer bag containing the cell culture supported on a platform that rocks back and forth to mix and generate gas mass transfer. In 2004 Hyclone launched a 250 L WV stirred-tank SUB consisting of a self-contained 3-dimensional cell culture bag supported by an open top jacketed stainless-steel (SS) shell. Larger SUBs quickly followed, 1000 L (2006), 2000 L (2009), enabling upstream SUT from spin tubes to commercial scale [11–14]. Rapid adoption of SUBs for biomanufacturing has been driven by speed, simplicity, flexibility, and cost.

Advances in material science and engineering allowed larger, more complex SUBs and single-use systems (SUS) to be fabricated. The maximum SUB scale is mainly limited by polymer material properties, fabrication techniques, and operational challenges to install large bags without damage. It was commonly thought that the largest economical scale SUB was 2000 L, but 4000 L SUBs have recently been fabricated by ABEC as they have overcome those limitations. SUT now includes mixers and storage vessels for medium, buffers, harvest and downstream process pools of up to 5000 L.

Incorporating SUT into downstream biomanufacturing has lagged due to limited availability, or the available options are unable to satisfy process requirements. Compared to upstream, downstream SUT requires additional development. Suppliers recognize this and are developing SU centrifuges, single-pass in-line concentrators [15], chromatography, TFF, viral inactivation, viral filtration, and final fill-finish solutions [16]. Even with downstream SUT limitations some biomanufacturers have proposed end-to-end SU processes for mAbs, antibody-drug conjugates, and vaccine production (Figure 1) [17,18].

Engineering SUT

SU systems are highly technical assemblies that are challenging to design, construct, and verify suitability for its intended service. To construct large 3-D mix vessels and bioreactors, multi-layered engineered polymer film sections (Table 1) are cut and welded together to form a fully closed, SU vessel onto which functional components such as probe ports, agitators, filters, and tubing are welded. This assembly is carefully packaged to eliminate transportation damage and sterilized using a validated gamma-irradiation cycle. To meet regulatory and end-user requirements fabrication materials and methods must be fully documented to demonstrate material traceability, fully qualified fabrication, validated sterilization procedures, and adequate leak testing to demonstrate robust fabrication and qualified transportation.

Environmental life cycle studies have concluded that replacing traditional SS bioprocessing equipment with SUT can reduce overall environmental impacts, suggesting better sustainability. Although most SU plastics are incinerated, a substantial portion are disposed of in landfills. To minimize the release of plastics into the environment both end users and suppliers should implement continuous improvements to post-use SUT management practices [19•].

Regulatory implications

A closed process is completely isolated from its surroundings. During normal operations the outside environment cannot contaminate the process, and the process cannot contaminate the surrounding environment. A closed SUT process can be achieved using components, equipment, and instruments that arrive pre-sterilized using gamma-irradiation and assembling them using aseptic tube welding or aseptic connectors. This contrasts with traditional biomanufacturing that depends on subjecting process equipment to complex, labor intensive steam sterilization, or chemical sanitization using hazardous chemicals. An early demonstration of a closed bioprocess spanned the cell culture seed train through production bioreactor (A Lahille, *AIChE Annual Meeting* 2013, Presentation:548a**)**, but more recently has been extended through final fill-finish operations [16].

Regulatory agencies and biomanufacturers now recognize that closed SUT processing leads to less costly, more efficient biopharmaceutical production that can be performed in controlled not classified (CNC) environments. FDA pre-pivotal guidance states that SUT facilitates conformance with cGMP requirements and streamlines product development since using disposable SUT reduces cleaning requirements, contamination risk, and closed processing alleviates the need for stricter room air quality classification, allowing the use of CNC biomanufacturing facilities.

These same concepts are being extended to clinical and commercial biomanufacturing reducing environmental monitoring and controls, requirement for cleanrooms, expensive air handling systems, and segregated pre-viral and post-viral process suites [20•]. The result is less complex biomanufacturing facilities with reduced capital and operating costs.

Transforming biomanufacturing

Biomanufacturing has been slow implementing upstream process intensification using perfusion due to shortcomings in cell retention technology [21•]. SU tangential flow filtration (TFF) and alternating tangential flow (ATF) membrane filtration systems have advanced and are now being integrated with SUBs to achieve high cell density, high productivity perfusion processes. By initially retaining both cells and product in a bioreactor their concentrations increase until the product is recovered after a few weeks by switching to a more open membrane. Operated