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Embracing Innovation in Biomanufacturing

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Innovations in bioproduction of therapeutics over the past 20 years have led to impressive improvements in product yield, process controls, and manufacturing safety. Industry 4.0 concepts have been embraced across the bioprocess industry and are leading to better bioprocess control through process automation, "big data" and data analysis, process simulations, the industrial internet of things (IIoT), cybersecurity, the cloud, blockchain/serialization, and additive manufacturing. Such advances help to ensure that a process results in the same outcome every time. As Sean Werner (president of Sexton Biotechnologies) commented in a video interview from last summer, "We can't control the inherent variability in biology, but we do understand a few of the components of the process that we can control" (**1**).

In the highly regulated field of biotherapeutics manufacturing, even process changes that lead to improvements can require process revalidation and therefore be perceived as generating risk. However, the bigger risk is the loss of opportunity.

Regulatory hurdles are cited by risk-averse parties as a reason to delay process innovation, but regulation is not what has impeded innovation in biomanufacturing. The current innovation model for manufacturing of biotherapeutics is inefficient and systematically leaves some needs unaddressed. The rewards of fast, well-controlled, easy-to-deploy, and mobile technologies — which could lead to more accessible (and less-expensive) biotherapeutics — often are not seen to outweigh perceived risks. Many innovations have struggled for adoption by the industry, and many simply have been abandoned by their inventors, who ran out of money and time to bring them to broader use.

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Innovators find it hard to make compelling business cases in an environment characterized by long product development times and resistance to change and regulatory risk. A better understanding of the risk frameworks created by improvements and radical solutions to current process bottlenecks could inspire and inform regulatory assessments. With a clearer path for taking and managing risk, fresh interest from investors may come to meet innovators.

Innovation Examples

Over the past two decades, and despite the above challenges, significant innovations have been introduced in biomanufacturing.

Single-Use Bioreactors: The introduction of single-use (SU) bioreactors was a disruptive step in response to an industry call for greater flexibility in manufacturing tools, improved contamination-risk profiles, and designs for use in multiproduct facilities. The Wave bioreactor was the first such SU system designed for bioprocess manufacturing. Introduced in 1996 by Wave Biotech, the design introduced a wave-motion system incorporating a plastic bag on a rocking platform to provide agitation and gas transfer, with no need for stirring. In 2007, Wave Biotech was acquired by Xcellerex (which was itself acquired in 2012 by GE Healthcare Life Sciences, now

Cytiva). In response to Thermo Fisher Scientific's introduction of a stirred-tank bioreactor in 2006, Xcellerex launched its own model in 2012, followed by the company's introduction of the FlexFactory platform as an end-to-end process and automation solution for single-use monoclonal antibody (MAb) manufacturing.

Although downstream processing (DSP) has been slower to adopt innovations, significant changes have occurred there as well, such as introduction of SU depth filters to replace centrifugation for cell debris separation and application of membrane chromatography to replace expensive chromatography columns and bypass their limitations.

"Ready-to-use manufacturing rooms" such as the KUBio modules and FlexFactory equipment by Cytiva and GCon's prefabricated POD cleanrooms offer more flexible configurations than do brick-and-mortar constructions. Some systems can be prequalified before they enter a site to expedite their delivery. Other advantages include ease of repurposing, moving, and even reselling as needed.

By listening and responding to user concerns, innovators have addressed significant obstacles to broad introduction of SU equipment. One example is that SU connectors and tubing are evolving to increase interchangeability across different unit operations and compatibility of equipment across manufacturers. SU manufacturers also are providing designs that minimize concerns over extractables and leachables, and some producers of SU technology are finding innovative ways to reduce the environmental impact of the large amounts of plastics generated as waste (**2**).

Process Analytics and Automation: The US Food and Drug Administration (FDA) defines *process analytical technologies* (PAT) as systems "for designing and controlling manufacturing through timely measurements (during processing) of critical quality and performance attributes for raw and in-process materials and also processes with the goal of ensuring final product quality" (**3**).

Automation of PAT can answer automation challenges in biomanufacturing. SU systems also are being adopted for PAT, with use of disposable sensors becoming more widespread. Novel SU probe and flow-cell pH sensors eliminate previous constraints associated with preintegration of glass pH sensors into consumables — for example, during presterilization calibration, which help to ensure sensor measurement accuracy.

With applications across upstream and downstream unit operations, sensors now are integrated into a number of commercially available SU bioprocessing platforms. SU valves for fluid-flow control with compact, durable SU designs for simple installation and maintenance also are being integrated with SU bioprocessing platforms. Process automation provides technical and strategic advantages because it enables better process control.

Automation systems need to be adapted to specific processes. Early implementation is likely to lead to improved product quality. "A well-controlled process may be the differentiator when looking for investment in competitive areas" (**1**).

Continuous Manufacturing: The trend toward improving process efficiency and control has advanced continuous manufacturing (CM) processes with introduction of perfusion systems in upstream processing/production, representing yet another important innovation. CM potentially provides significant improvements in development and production of biopharmaceuticals.

However, the drug industry has been slow to adopt CM largely because of costs and regulatory concerns. The FDA presumes that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, more flexible, and more efficient CM capabilities. The agency appears to be committed to dedicating resources and adapting regulatory discretion to ease the fears of the pharmaceutical industry and support its transition to CM (**4**).

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The Urgency of Innovation

The COVID-19 pandemic brought to the forefront the consequences of accepting inflexible manufacturing systems that do not incorporate cutting-edge technologies. Although the industry reacted and adapted during 2020, it has not been accustomed to practicing rapid innovation. But now it has been compelled to move quickly in earnest, causing much debate about speed and safety of innovation during this current global crisis.

Urgency to develop a vaccine has propelled investment in novel product platforms. Manufacturing pandemic vaccines at the scale and speed needed was identified early on as a major challenge. Biomanufacturing can provide requisite capacity, but are current biological manufacturing platforms the most capable for current needs? Innovation in manufacturing platforms has been fast in terms of implementing improvements but slow in introducing and updating novel systems and technologies.

Seeking Innovation in Expression Systems: The BioPlan Associates 17th Annual Report and Survey of Biopharmaceutical Manufacturing Capacity and Production (**5**) reports innovations that reflect the growth of the industry and intensification that may lead to new developments. Use of >1,000-L SU bioreactors increased by a remarkable 20% from 2019 to 2020. Manufacturers of cell and gene therapies increased in numbers. Facilities equipped for mammalian-cell operations remain expensive to establish, including long timelines for development of production cell lines.

The industry has devoted considerable

biomanufacturing capacity to platforms based on Chinese hamster ovary (CHO) cells. A concerning trend, as noted in the report, is that mammalian cell culture domination of the biomanufacturing landscape leads many bioprocess professionals to gain experience with such platforms only. Thus, facilities are concentrating on mammalian production lines, even when producing biotherapeutics that could be made less expensively using microbial expression systems. Additionally, the focus on CHO-based production and the market opportunities it represents leads to prioritizing development of process tools for CHO cell culture. But what if CHO is not the best system, but simply the one that got the most investment "because it works" and because its regulatory path is well established?

Innovation in expression hosts nevertheless has continued despite a general preference for CHO. Biogen announced a few years ago that it is seeking out production systems that are alternatives to CHO cells. Pfenex, an independent company (acquired by Ligand on 1 October 2020), was spun out of Dow Chemical in 2009 and carved out a niche for itself using an industrial *Pseudomonas fluorescens* system for biosimilar production. Following an initial public offering on the New York Stock Exchange, which brought the company US$50 million in 2014–2015, Pfenex's first product was approved in 2019. Another company, Dyadic International, has been expanding use of its C1 strain of *Myceliophthora thermophila*. Dyadic hopes to use that workhorse of other industries for pharmaceutical applications, and the company has been progressing research collaborations with large pharmaceutical partners.

Plant-based expression systems long have been studied as potential biotherapeutics platforms. Eukaryotic organisms can produce specialized proteins and chemicals, and plants present the advantage of harboring no human or animal viruses. More than 20 companies are active in this field globally, with 19 products in clinical development (three of which are in phase 3 trials). The number of companies filing for clinical trials is growing, with preclinical candidates in development representing the largest proportion of the plant-based pharmaceuticals pipeline. Some plant-made products — e.g., recombinant human collagen (rhCollagen)-based products from companies such as CollPlant, chemotherapies such as paclitaxel, veterinary vaccines, and products used in cosmetics — already have received market approval. The current rapid progression of SARS-CoV-2 vaccine candidates by Medicago, Kentucky Bioprocessing, and iBio Inc. further indicate vast opportunities brought about by these scalable and affordable platforms.

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Embracing Innovative Models

Which business model will equip the next generation of radical innovators in bioproduction? The model chosen needs to fit the type of innovation. Two aspects seem clear though: Regulation is a friend, not a foe of innovation in bioproduction processes; and bioproduction needs to become faster, more portable, more affordable, and more accessible while remaining safe. Incremental innovation will not deliver on such needs. These indeed are interesting times for innovation in bioproduction.

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