Editorial

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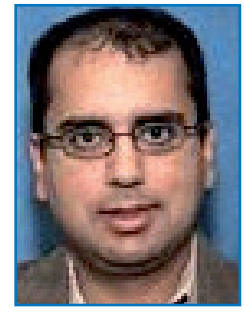
Driving value through biopharmaceutical manufacturing

There is much to learn from other process industries, both in terms of process technology (e.g., continuous processing), as well as in terms of automation and process control.

Over the last 30 years the biopharmaceutical industry has had remarkable successes and has delivered tremendous value to our society through the development of innovative medicines. This success has been primarily based on innovation in R&D, from advances in recombinant DNA technology to utilization of 'big data' in order to better match medicines to patients. The role of operations in general, and of manufacturing in particular, was restricted to that of an enabler. Consequently, innovative approaches in biologics manufacturing were, for the most part, focused on delivering sufficient quantities of product to the clinic or the market. Efficiency gains were not believed to contribute enough to the value-chain to warrant taking a risk, neither from a regulatory filing standpoint nor with regard to program timelines.

Like biological organisms, industries also go through life cycle stages of embryonic, growth, maturity and decline. It could be argued where the biopharmaceutical industry currently is in its life cycle, or how long a particular stage will last; however, most people will agree that our industry will follow a similar life cycle and as we progress through this life cycle, operations will become a more important part of the equation. The economics of developing a drug pipeline are more challenging than ever. The cost of testing new molecules in the clinic is becoming increasingly expensive, forcing companies to maintain a high number of programs providing 'shots on goal', while finding better mechanisms of failing targets and molecules early and cheaply. Finding the right mix between internal R&D and sourcing new molecules from the outside is important, with a large emphasis on creative use of partnerships. At the same time, the reimbursement environment is changing, with an increasing focus on the cost of healthcare. Biosimilars are presenting a real threat to the exclusivity of biologics. Globalization with complex and differentiated local rules adds to the challenges. Finally, our industry has experienced substantial consolidation, requiring the remaining competitors to find additional means to differentiate themselves in an increasingly narrowing field. The transformation going on in our industry requires operations to become a bigger part of the value-chain and biologics manufacturing to turn itself from an enabler to a competitive value-driver.

In the broadest sense, a value-driven activity must impact either cost or revenue in order to increase bottom line profits and drive value for shareholders. In the last 10–15 years our collective focus has been on lowering cost by using two instruments: improving cell culture process productivity (commonly referred to as 'high-titer processes') and increasing the scale of production. We submit, that while our industry has been extremely successful with both of those instruments, associated cost savings expected to logically follow have not materialized. One reason may be that overall utilization of the installed capacity remains low. New drug approvals have been slow and, in the name of control and flexibility, companies



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continue to build dedicated sites, resulting in significantly underutilized facilities.

If addressed correctly, the current overcapacity opens up a tremendous opportunity. Traditionally, the biopharmaceutical industry has been reluctant to share manufacturing capacity and most companies have built their own in-house facilities or formed long-term relationships with a few select contract manufacturers. Over recent decades, we have seen manufacturing platforms consolidate to quite an extent and modern plants share many design elements and are quite comparable in their capabilities. We might state that biopharmaceutical manufacturing has become a lot more industrialized; we have grown up from manufacturing being an art, to manufacturing being a predictable, efficient and reliable element of the overall biologics supply chain. Coupled with the great increase in productivity and robust methods of product changeover, we are now in the position to share installed capacity between manufacturers. This increases capacity utilization of existing facilities, reducing overall cost of goods. It also allows companies with new products, where the overall market potential might be not as predictable, to delay decisions to build new capacity until the market need is stabilized. Building commercial biologics manufacturing capacity not only requires significant capital, but the effort it takes to build an effective and compliant manufacturing organization should also not be underestimated.

Partnerships, where an established manufacturer commits some of their capacity to another company, may sound like a risky proposition. The capacity provider might worry that such a partnership binds capacity for future successful programs of their own, thus limiting progress of promising programs. The capacity taker might worry that their product might not receive the commitment and dedication of the provider, when resource conflicts with in-house products arise. This is where the second important piece of innovation in our industry comes into play. Over the past decade, we have seen great progress in the use of disposable equipment across all unit operations of a biologics drug substance process. By now, it is possible to manufacture a drug substance in an entirely single-use flow path, starting with a high cell density bank through drug substance fill into a single-use storage bag. There are even systems allowing sterile fills into vials using disposables. Using single-use equipment as a fully closed system allows breaking with the traditional design of biopharmaceutical manufacturing plants. A validated closed flow path from front to end allows manufacturing in ballroom-type facilities, reducing the need for costly segregation approaches between upstream, downstream and supporting activities. The flexibility of disposable bioreactors allows matching the size of the equipment to the amount of product needed, leading to a flexible volume manufacturing paradigm, which reduces overproduction and allows a more precise management of the supply chain. Finally, a validated closed flow path may allow for adapting the room classification strategy, opening a path to manufacturing in general pharmaceutical manufacturing space. These possibilities allow much shorter timelines and capital requirements when establishing new manufacturing capacity. An established manufacturer could install additional capacity much faster, thus alleviating concerns regarding conflicts between in-house and partnered capacity. In addition, the reduced effort in setting up this capacity will make decisions regarding manufacturing locations easier, opening up an avenue to establishing local manufacturing in new markets with reduced capital risk.

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Does this mean that the traditional large volume stainless steel plants are outdated and no longer needed? By no means; biological products are highly complex entities that, at times, are quite complex to express, despite recent advances in cell culture productivity. It is quite likely that low productivity processes will continue to exist. In addition, large disease areas, such as Alzheimer's disease, may present the challenge of manufacturing for much larger patient populations than traditionally served by biologic drugs. Traditional large plants will be needed in the foreseeable future. To realize the possibilities offered by the innovation discussed above, we need to consider a new design paradigm for biopharmaceutical manufacturing plants: a hybrid design that efficiently mixes traditional fixed designs with variable volume designs in single-use equipment. This will provide a manufacturer with capacity that can be turned on and off quickly without the typical risk of a large volume traditional plant. These flexible facilities can be used to provide quick access to clinical grade material and also

be valuable extensions to fixed capacity. Finally, they allow experimentation with innovative manufacturing approaches in an environment of lower capital risk. With these novel designs, capacity sharing partnerships can become a very effective tool to move biomanufacturing from a potential rate-limiting nuisance to a value driver that is worthy of investment.

Before we conclude our discussion, we would like to come back to the initial discussion of changing the role of operations from enabler to value driver. We argued that the role of manufacturing was to enable innovation in novel medicines, while innovation in manufacturing was initiated on an 'as needed' basis to avoid supply shortfalls. Process innovation has been dramatic over the last 10–15 years, with over 1000-fold increase in productivity on average. The increase in process productivity has not appeared on the bottom line due to significant capacity underutilization. The fastest way utilization can be improved is through sharing capacity, participating companies will see an immediate benefit on their bottom line. Furthermore, we need more attention to the overall efficiency of manufacturing and openness to breaking with the traditionally very conservative design of our processes.

There is much to learn from other process industries, both in terms of process technology (e.g., continuous processing), as well as in terms of automation and process control. There is much efficiency to be gained from moving towards more automated processes and allowing in-process analytics and control a bigger role in assuring the quality of our products. The next frontier for biopharmaceutical manufacturing is right ahead of us, with innovation being the key to allow manufacturing to advance from enabling to driving value.

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