8 Questions

to ask before planning your next single-use biomanufacturing facility

Xcellerex

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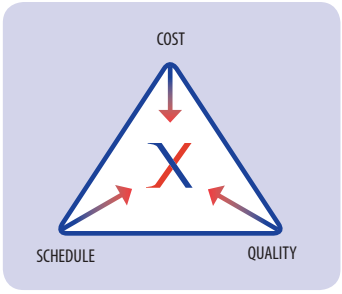
Deployment of new GMP biomanufacturing capacity is a battle of tradeoffs. Push to accelerate your timetable? Cost or quality considerations must be compromised. Need to drive down total investment? Build-out time or quality must be sacrificed. As single-use technology establishes wider acceptance, certain tradeoffs may be lessened, but serious challenges remain.

Overcoming the limitations intrinsic to conventional biomanufacturing strategies requires a fundamental rethinking of bioproduction architecture. With its FlexFactory® biomanufacturing platform and a deeply experienced team to support its effective implementation, Xcellerex offers a new level of freedom from historical limitations.



Conventional biomanufacturing strategies involve difficult tradeoffs between cost, timing and quality. FlexFactory delivers a new level of freedom from compromise.

In this paper, we examine eight critical considerations facing the biopharmaceutical and vaccine production landscape, and how each is addressed with this new, proven approach to biomanufacturing.

QUESTION 1

Can you achieve a level of process productivity suitable for commercial success?

As the biopharmaceutical and vaccine industries race to embrace single-use technologies, questions remain as to whether process productivity and scalability issues will slow the technology's adoption for commercial production. Increasingly, single-use performance limitations are being overcome, but with certain process areas still being converted.

FlexFactory is an open, technology-neutral platform, which means that operators can select the best combination of upstream and downstream technologies for their particular process, and Xcellerex will integrate those choices into a FlexFactory facility. Xcellerex searches out and tests nearly every emerging single-use technology to ensure the platform can accommodate the best possible configurations for client productivity. This testing and its internal use also enable Xcellerex to provide deep process support for a wide variety of technologies. The company's PDMax™ process development team also works with clients to apply the best available technologies and other tools to ensure a commercially viable process is secured.

Xcellerex has successfully manufactured nearly 20 biotherapeutics and vaccines for use in clinical trials over the past several years. The company's biomanufacturing and process development teams have accumulated an extensive body of data demonstrating that FlexFactory delivers comparable productivity and scalability across a range of cell lines, even in complex processes. Externally, Xcellerex is delivering FlexFactory technology for clinical manufacturing to leading biotherapeutics and vaccine manufacturers. Likewise, multiple 2000L XDR single-use bioreactors are being employed in a commercial plant currently under construction.

Note: Extensive productivity and scalability data on FlexFactory and XDR is available by contacting Xcellerex.

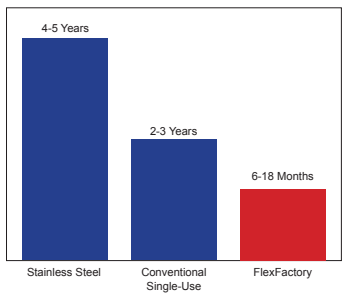
QUESTION 2

How long will it take to get the GMP facility built, validated and operational?

Construction, build-out and start-up of conventional stainless steel plants could take 4-5 years or more, including many months of painful validation. Through the elimination of CIP/SIP infrastructure, conventionally designed single-use facilities promise to cut that time by as much as half. The FlexFactory architecture is nearly 100% single use, thus eliminating the need for sterilization and CIP equipment.

In addition, FlexFactory takes facility simplification several steps further by utilizing Controlled Environmental Modules (CEMs) to effectively shrink the clean room around each unit operation, eliminating the need for clean room construction, complex HVAC design, and validation. The entire upstream/downstream operation can be co-located in a simplified single-suite facility with basic HVAC and utilities requirements.

Further, Xcellerex's turnkey process automation and electronic batch control package reduces development time and expense for the client.



New FlexFactory capacity can be put in place in as little as 6 months, dramatically improving the agility of drugmakers to meet market demand.

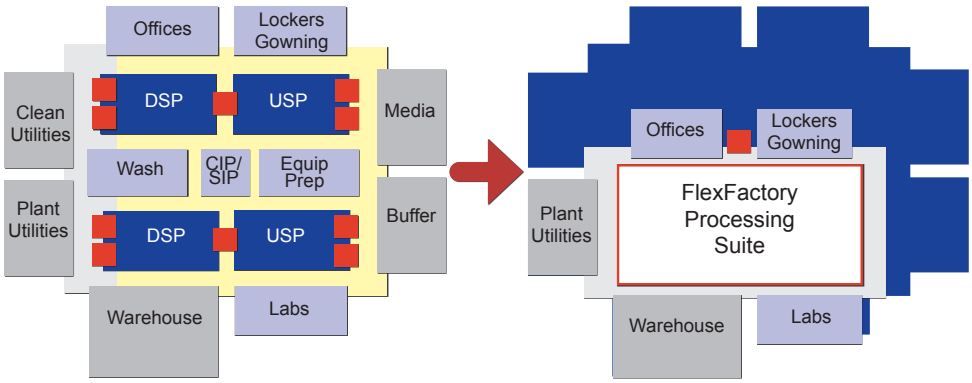
Additionally, through its TransPlant service, Xcellerex assembles the FlexFactory line, develops SOPs, performs system IOQ, and operator training before the equipment is shipped to the customer facility. Once installed at the customer, the first GMP run is typically just 3-4 weeks away.

The result is **FlexFactory deployment times of 6-18 months**. As an example, a current project will deliver a validated FlexFactory for clinical trials to a client in Europe in seven months, which includes a GMP run performed by a newly trained customer team at the Xcellerex facility.

QUESTION 3

What will it really cost?

The move to single-use manufacturing saves considerable capital expense through the elimination of CIP/SIP infrastructure. However, single-use technology that is deployed in a traditional biomanufacturing architecture still requires the construction of multiple clean-room suites, as well as expensive HVAC systems for each. FlexFactory lines are housed in a single Class 300,000 suite, with a single HVAC system. In total, the plant footprint is reduced by 40% or more (see illustration). These factors result in a capital cost for FlexFactory that is as much as 65% less than a comparable fixed-pipe stainless steel facility.



Stainless Steel Layout

Equivalent FlexFactory Layout

Similarly, FlexFactory enjoys all the operating cost advantages delivered by single-use technology, including reduction in CIP/SIP cycles, validation and turnaround time. FlexFactory furthers these gains by drastically simplifying the validation process for the clean room suites and HVAC systems. FlexFactory adds another layer of efficiency by allowing a single team of operators to work together in a single upstream/downstream suite. This reduces labors costs, and improves communication and other efficiencies. Maintenance staff can even work within the suite, as all FlexFactory mechanicals are external to the controlled environment modules. In addition, because FlexFactory can accommodate simultaneous multi-drug production, utilization rates are improved, reducing cost of goods sold by 30% to 40%

QUESTION 4

What will it take to make your single-use process GMP compliant?

An important attraction of single-use technology is the reduced risk of cross-contamination by using disposable containers, which translates to improved manufacturing quality. However, multiple clean rooms still require time-consuming validation. In addition, each piece of equipment and the overall process need to be validated.

With FlexFactory, Xcellerex delivers a complete system in "pre-validated" or validatable form. Because FlexFactory does not require large conventional clean rooms with multiple HVAC systems, validation is simplified and accelerated.

FlexFactory also includes the eFactory process automation platform, which integrates documentation, process verification, data collection and overall control of the plant. Xcellerex trains operators to ensure they are in compliance, and eFactory ensures that each operator is qualified to execute each process step.

QUESTION 5

How will you integrate robust process control architecture?

A commercial process requires the integration of complex upstream and downstream unit operations to work efficiently, but it also demands robust process automation architecture to ensure operational integrity and GMP compliance. When assembling a production line comprised of equipment from multiple vendors, this complex task falls on the shoulders of the client's process automation team (if one exists) or it is outsourced to an engineering firm, and can add months of work and significant additional cost to a new deployment.

Process automation is greatly simplified because a FlexFactory plant itself is greatly simplified compared to a large, complex traditional plant. In addition, Xcellerex designs each FlexFactory with eFactory™ Process Automation. This architecture delivers true fault-tolerant redundancy across every aspect of the communications, process automation controllers (PAC), data historian and batch execution servers.

The platform also includes automatically generated electronic batch records with an electronic "watchdog." The watchdog reduces the chance for human error by identifying and communicating deviations in real-time, often soon enough to salvage a batch. Batches can be released by exception, eliminating lengthy paper-based QA reviews and speeding up overall batch release time by weeks or months.

QUESTION 6

Where will you get in-depth process support and training?

As noted previously, integrating a process with several emerging technologies can be a daunting challenge. Many equipment manufacturers offer very limited process expertise to support the adoption of their products, leaving the drugmaker to his own devices. This can lengthen the deployment timeline and introduce unnecessary risks and costs.

Rather than simply offering FlexFactory hardware to clients, Xcellerex offers a comprehensive, fully-integrated hardware/software/compliance/process support package. The Xcellerex team includes decades of experience in biomanufacturing, process development, systems engineering and process automation. These resources work hand-in-hand with customers throughout the planning and deployment of a FlexFactory system. In addition, Xcellerex is able to operate the FlexFactory line at its biomanufacturing operation prior to final deployment at the client's facility. This provides opportunity for SOP development, system validation, and operator training. When the FlexFactory is installed at the customer location, it can be quickly site-validated and started-up by pre-trained operators.

QUESTION 7

How easy will it be to change the process or adapt it for multi-drug production in the future?

FlexFactory is perfectly tailored for simultaneous multi-drug production in a single open suite. Because each unit operation is contained in its own clean room environment, each FlexFactory module is capable of processing a different drug, at the same time. Single-use plants in a conventional manufacturing architecture are limited to producing one drug at a time in separated cleanrooms. While changeovers in a conventional single-use plant may be an improvement over traditional stainless steel systems, they remain much more involved than what can be accomplished with FlexFactory.

QUESTION 8

What will the FDA and other regulators think about your disposables-based process?

Generally speaking, regulators favor single-use manufacturing because of the reduced likelihood of contamination and cross-contamination. FlexFactory offers two additional levels of safety which regulators find very appealing. First, the CEM modules place the operator outside of the clean room, eliminating the largest single source of potential contamination. Second, FlexFactory's real-time electronic quality assurance monitoring of the facility provides a significantly enhanced level of compliance.

Over the course of several review meetings with FDA, EMEA and other bodies, FlexFactory has received positive reviews, especially around its "quality-by-design" engineering.

CONCLUSION

The shift to single-use technology brings exciting advantages to biopharmaceutical and vaccine manufacturers. However, the shift to disposables is only a partial step forward. Additional gains in speed, control, quality, flexibility and overall cost are available by employing single-use operations within the FlexFactory platform from Xcellerex.

From its unique vantage point as both practitioner and platform designer, Xcellerex has challenged the foundations of bioproduction architecture. Rather than accept tradeoffs as unavoidable, Xcellerex sought new routes that eliminate barriers altogether. In addition to innovative hardware and software design, every FlexFactory system includes the know-how of experienced Xcellerex CMC, process development, regulatory and process automation teams... all focused on helping clients get where they need to go — faster.

Xcellerex believes that biomanufacturing strategy is a cornerstone of its clients' long-term prosperity and is dedicated to providing systems, tools and resources to bypass the tradeoffs that wait on the road to success.

APPENDIX: What is FlexFactory?

FlexFactory features the novel application of **three technologies** to advance the way biopharmaceuticals and vaccines are manufactured. Together with Xcellerex's in-depth process development, biomanufacturing operations, system design and process automation expertise, FlexFactory delivers unprecedented speed, flexibility and control for bioproduction.

1. FlexFactory production lines utilize **single-use technology** for all process steps, eliminating the need for costly CIP/SIP infrastructure and the related processing slowdowns for cleaning and validation. Operating expenses and carbon footprint are also dramatically cut as water use for cleaning is eliminated. FlexFactory can utilize nearly any combination of single-use downstream technologies and brands, so users are assured the best possible design for their process needs.

2. Each FlexFactory process step is isolated in its own **Controlled Environment Module (CEM),** effectively shrinking the clean room around each unit operation. Upstream and downstream modules can occupy the same shared space with greatly simplified HVAC requirements. And operators can move freely from operation to operation, without the burden of gowning and degowning. The CEM architecture also enables the FlexFactory train to be 100% modular, allowing the owner to adjust and swap-out modules to easily accommodate simultaneous multi-product production.

3. FlexFactory also features user-friendly eFactory™ **process automation with electronic batch records f**or robust process control and to remove inefficiencies associated with conventional paper-based QA/QC reporting. The chance for human error is minimized, and deviations are caught in real-time, often soon enough to salvage a batch. Batches can be released by exception, eliminating lengthy QA reviews and speeding up overall batch release time by weeks or months. Robust system architecture provides true fault-tolerant redundancy in the communications, PACs, data historian and batch execution servers.

For additional information

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