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Facility of the Future: Next Generation Biomanufacturing Forum

Part II: Tools for Change – Enabling Technologies and Business and Regulatory Approaches

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This article is the second of a three-part series focused on defining the facility of the future required for manufacturing biopharmaceuticals in the 21st Century.

Introduction

This is the second of a three part series to define the Facility of the Future (FoF) required for manufacturing biopharmaceuticals in the 21st Century. The articles are the result of discussions and presentations made at the "Next-Gen Facility Forum" held at the North Carolina State University in the Biomanufacturing Training and Education Center (BTEC) on January 31, 2012. The three articles cover the topics discussed at the Forum.

In the first article, Part I: "Why We Cannot Stay Here" – The Challenges, Risks, and Business Drivers for Changing the Paradigm," we elucidate why the biopharmaceutical manufacturing paradigm and the basis of designing and operating manufacturing facilities must change if the industry is to move forward.[1] We reviewed the imperatives, drivers, uncertainty, and risks faced by the industry - *Figure 1*. The patient value and cost risks are impacted by the drivers through various elements of uncertainty.

In this second article, we will review and discuss recent advances in various technologies, and the regulatory and business approaches that provide enabling methods for addressing the drivers and uncertainties identified in the first article.

As shown in Figure 2, drivers and uncertainties are impacted by a number of enablers. These enablers are created or improved by advances in a variety of technologies and the business strategies used to build and operate manufacturing enterprises. In Figure 3, the factors that create or modify the enablers are placed into the following three categories:

- Advances in medical and protein technologies
- Advances in process, facility, and computer technologies
- Advances in approaches and regulatory initiatives

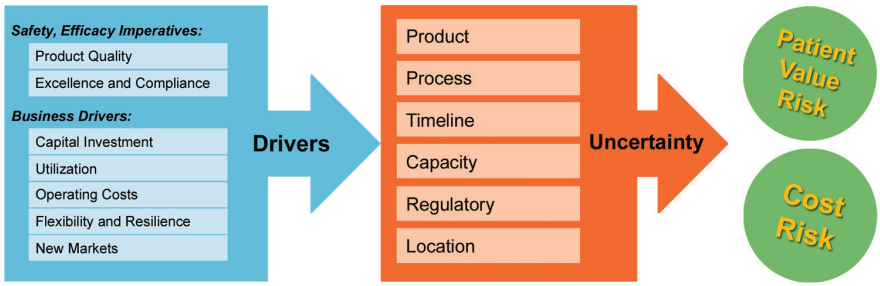

Figure 1. Business drivers, imperatives, and uncertainties.

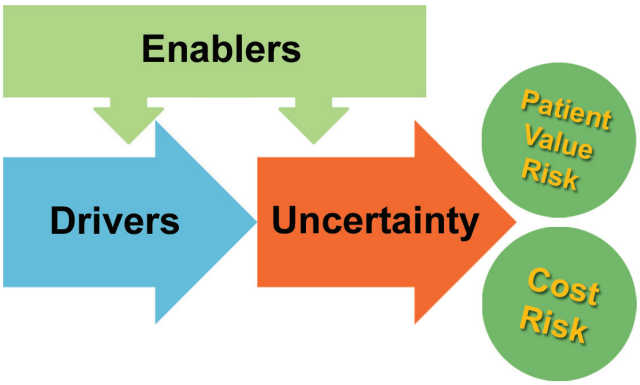

Figure 2. Both the drivers and uncertainties are impacted by enabling technologies and approaches, which in turn impact patient value and cost risks.

Advances in Medical and Protein Technologies

Advances in medical technology are providing a better understanding of both the patient's therapeutic needs and the impact of the therapies they take to satisfy those needs. Significant advances are also being made in protein science and biochemistry related to characterizing the product's Critical Quality Attribute's (CQA's) impact on a diverse patient population. To a large extent, these advances are outside the scope of this article, but they do impact the drivers and uncertainty shown in Figure 1. These advances will result in safer, more effective therapeutic drug products along with improving the industry's ability to develop the required manufacturing processes and production facilities.

Advances in clinical testing methods also fall in this category. Improvements in how biopharmaceuticals are tested and monitored in the patient population are an important set of enablers. All these advances create many opportunities and place more pressure on manufacturing enterprises to be faster and more effectively.

Advances in Process, Facility, and Computer Technology

During the Forum's breakout sessions, a wide variety of advances in processes, facility, and computer technologies were discussed. For organizational purposes, these advances are grouped as shown in Figure 4.

These seven groups are placed in the same broad technology category because they all interact and are used in concert to define, design, and build a biopharmaceutical manufacturing facility.

The following is a summary of these technology advances.

- **Upstream Performance** – significant advances have been made in cell culture yields over the last two decades. Typical yields have increased from fractions of to upward of 10 grams per liter.[2] These increases have come through media optimization and improvements in cell lines. Improvements are expected to continue as systems biology and specialized artificial cell lines with metabolisms modified to achieve specific performance goals are developed. Better harvest and recovery technologies will further improve the performance of upstream processes. In addition, various bioreactor options, such as perfusion, attached, suspension, and micro carrier technologies also are likely to improve upstream performance and efficiency.

- **Downstream Performance** – while improvements in downstream processing lag behind advances in upstream processing, significant improvements in downstream processes are being observed. More selective capture steps using affinity chromatograph are possible along with the use of selective membranes and monolithic structured for Tangential Flow Filtration (TFF) processes. Advances also may be seen in non-chromatographic methods,

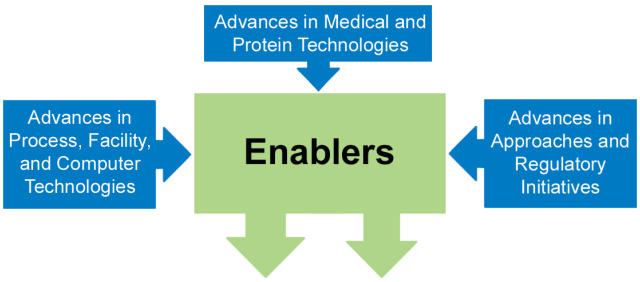

Figure 3. Enablers come from advances in the three categories shown.

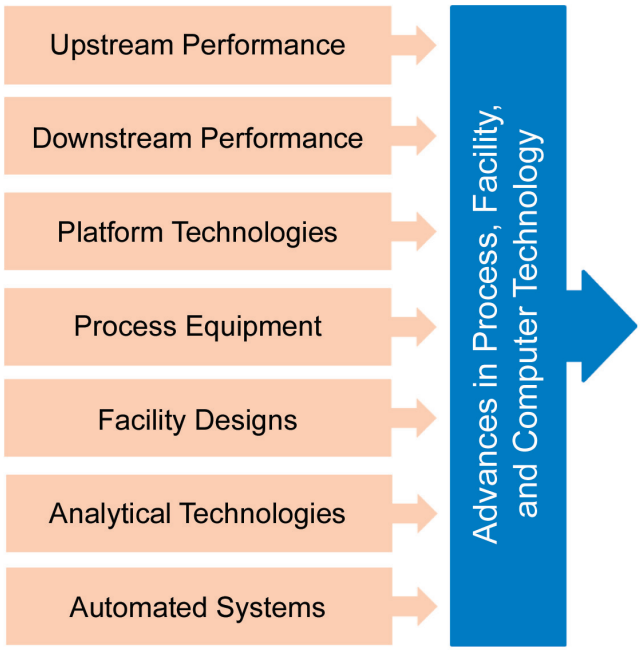

Figure 4. Advances in technology come from a variety of sources.

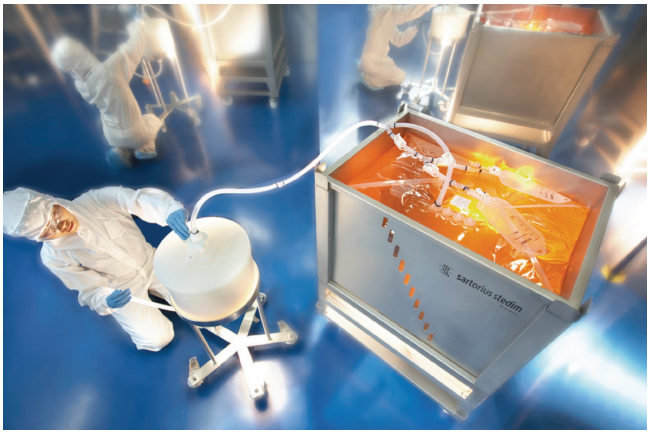

Figure 5. Single Use buffer storage systems provide flexibility for preparing and distributing buffers to a wide variety of unit operations (*photo courtesy of Sartorius).*

Figure 6. Portable Single Use System (SUS) based unit operations can be configured to perform a variety of processing steps (*photo courtesy of Sartorius).*

such as highly selective precipitation of target proteins. Advances also will be seen in automated, multi-batch processes using smaller disposable columns.

- **Platform Technologies** – as the industry's experience with manufacturing processes increases, platform technologies for a number of unit operations are being developed and marketed. These platform technologies, some based on well developed proprietary technology, will provide significant enablers for future improvements. Notable platform technologies are being seen in bioreactor and purification systems.

- **Process Equipment** – advancements are being seen in equipment and equipment components unlike any time in the past decade. In particular, the increase in Single Use Systems (SUS) or disposable components are being developed and implemented in a much broader range than ever before. SUS provide a significant advantage in reducing cleaning, sanitization, and sterilization development and validation requirements. SUS also provides significant opportunities to isolate the process from the surrounding environment enabling a wide variety of process implementations and facility designs. In addition, advances in bioreactor configurations, centrifuges, and TFF units are enabling a variety of process and facility modifications that enhance flexibility and improve utilization.

- **Facility Designs** – a number of facility design options are being discussed in different global industry forums. Facility design and layout options are now possible that improve adaptability and flexibility. These include facility design strategies that range from shared common space in large general operating areas (ballrooms) to highly segregated process steps in many small rooms (matrices).

  In addition, modular construction techniques have been developed for building facility components at contractor factories for assembly at the construction site in "ready to go" modules. These modules contain integrated HVAC systems facilitating a variety of possible combina-

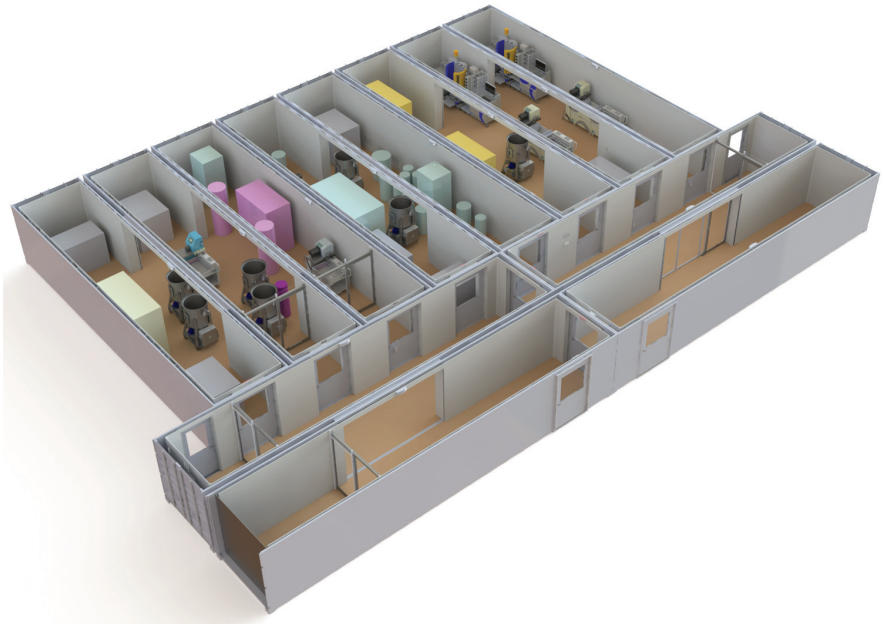

Figure 7. Conceptual layout of one of Biologics Modular's modular manufacturing facilities (*image courtesy of Biologics Modular).*

Figure 8. Manufacturing Execution Systems (MES) support a wide variety of critical information management activities.

tions. Preassembled panels and components can be used to provide easily configurable and reconfigurable cleanrooms to address different process requirements. These different approaches provide opportunities for reducing costs while improving flexibility.

- **Analytical Technologies** – major advances in sensor technologies for measuring specific Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs) are being developed as part of the Process Analytical Technology (PAT) initiative.[5] PAT enables better process performance through improved on-line and off-line process monitoring and control.

- **Automated Systems** – a wide variety of software and support hardware systems are becoming available to implement improvements in infrastructure systems. These include Manufacturing Executions Systems (MES), Electronic Batch Records (EBR), and Laboratory Information Management Systems (LIMS) to name a few. These computer technologies enable many significant improvements to the drivers and uncertainty.

Collectively, these scientific and technical advances provide significant enablers that create many opportunities to build better manufacturing facilities.

Advances in Approaches and Regulatory Initiatives

The third category of advances shown in Figure 9, come from: 1. Evolving regulatory initiatives issued by various global regulatory agencies; 2. Improvement in business practices; and 3. Operational approaches that result in significant manufacturing infrastructure improvements.

- **Regulatory Initiatives** – three regulatory initiatives have provided considerable guidance that enable better strategies for developing manufacturing processes. The primary enabler is the structure for working with the complex technologies and the assistance they provide in aligning the communications between industry and the regulatory agencies during the approval process. These initiatives are:

  - 2011 FDA Process Validation Guidance[3]
  - ICH Q8(R2) Pharmaceutical Development Guidance[4]
  - Process Analytical Technology (PAT)[5]

  The Q8 document defines the key terms: design space, Quality Target Product Profile (QTPP), Quality by Design (QbD), and Real Time Release Testing (RTRT). The design space concept provides a mechanism by which companies can compile process knowledge and understanding into a standard format for review and understanding the product and process information by regulatory agencies. Some suggested examples of design space representations are provided in ICH Q8 (R2). The QTPP provides a comprehensive definition of the product and becomes part of the design space. The use of Quality by Design (QbD) concepts also provides future opportunities if a workable definition of QbD can be identified and put into common practice by industry and the regulatory agencies. RTRT places a higher burden on monitoring and controlling process performance rather than relying on end product testing results for releasing product.

  The 2011 Process Validation Guidance provides a framework for structuring the process development effort from early process definition to operation of the

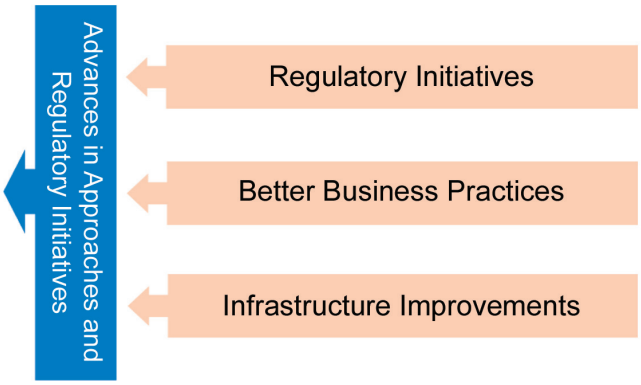

Figure 9. Summary of advances in business practices, approaches, and regulatory initiatives.

commercial manufacturing facility. The PAT initiative stimulates and focuses the pharmaceutical industry's efforts to improve process monitoring and control. These initiatives and guidance when embraced and aggressively used provide significant opportunities to improve the development and licensing of new products.

- **Better Business Practices** – using the regulatory initiatives, companies can apply good engineering and development practices to more efficiently and rapidly build the process's design space using sophisticated experimental tools such as Design of Experiments (DOE) and platform process technologies to develop better performing processes. A more sophisticated approach to current Good Manufacturing Practices (cGMPs) also provides a number of opportunities to run not only multiproduct, but multiphase manufacturing operations within a single facility. If appropriate cGMPs are used to control the facility's operation during production to maintain control of the facility along with the integrity of other ongoing manufacturing operations, the facility will be capable of manufacturing a wider variety of products.

- **Infrastructure Improvements** – advances in computer technology provide a wide variety of opportunities for improving operational infrastructure systems such as Electronic Batch Records (EBR), Manufacturing Execution Systems (MES), Laboratory Information Management (LIMs), Direct Digital Control Systems (DDC), and material and resources planning tools.

All the above advances provide enabling technologies for improving the business drivers and reducing the uncertainties shown in Figure 1. The next challenge is to organize the enabler into groups to better understand how they can be used to create a facility of the future.

Enablers

Taking all of the advances in medical technology, process, facility, and computer related technology along with advances in regulatory initiatives and business methods, the following enablers are defined in Figure 10 along with their relationship to the drivers and uncertainties.

The following discussion briefly summarizes the enablers:

- **Better product characterization** – improvements in characterizing the product come from advances in protein chemistry along with improvements in analytical technologies (PAT). Better understanding the product attributes (CQAs) assists with product characterization and understanding the impact of impurities, contaminants, variant product species, and degradation products on patients.

- **Faster product and process development** – many of the advancements identified contribute opportunities to streamline elements of the product's development timeline. Scientific and engineering experience with platform technologies when combined with improved business practices and a structured regulatory framework provide enablers to rapidly develop better process technology. More rapid process development provides opportunities for reducing facility design and construction timeline pressures.

- **Smaller, portable, flexible processes** – the improvements in the upstream and downstream processes along with the SUS technologies enables a wide variety of facility options. These processes require less facility resources and can be moved and managed within smaller and theoretically, less expensive facilities.

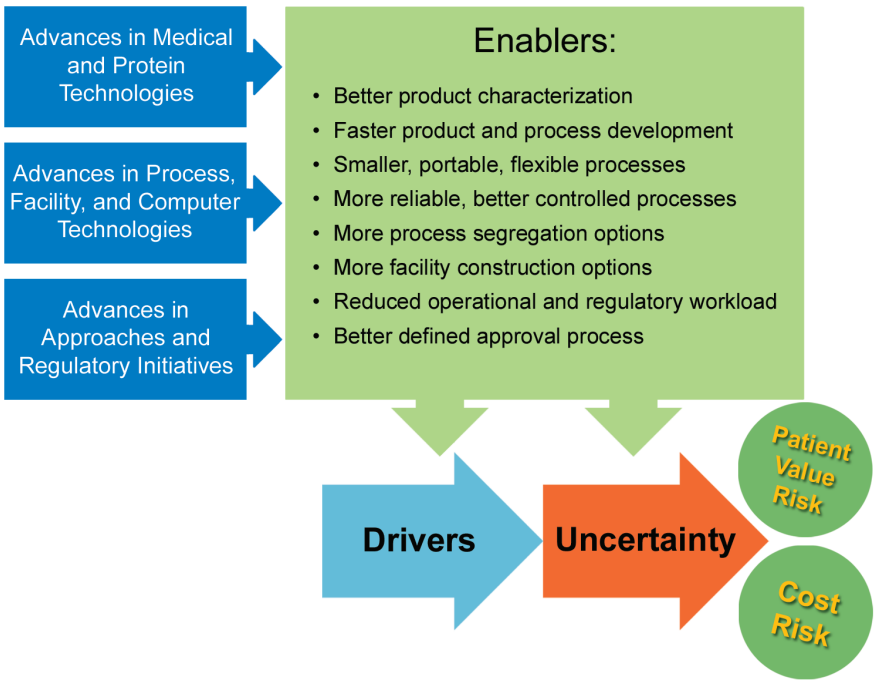

Figure 10. From the advances in medical, protein, process, facility, and computer technology as well as Approaches, and Regulatory Initiatives, the Enablers can be assembled in the groups shown.

- **More reliable, better controlled process** – advancements in using sophisticated development tools described in the regulatory guidance enable significant improvements in the quality of the processes that will be used in the manufacturing facilities. Platform technologies modified and evolved through advanced experimental methods (DOE) to build sophisticated design spaces provide more opportunities.

- **More process segregation options** – the use of skid mounted, portable SU systems provides for a wide variety of options and thus enables solutions to facility design problems that can positively affect the business drivers and uncertainties. Depending on manufacturing and enterprise requirements, process segregation strategies range from a few large common areas to many small highly segregated area layout scenarios.

- **More facility construction options** – design, engineering, and construction options ranging from stick-built to modular approaches become available.

- **Reduced operational and regulatory workload** – several advances provide opportunities to reduce operational and regulatory workloads. SUS technology significantly reduces the cleaning validation required to get a manufacturing operation up and running. Other process and computer advances provide opportunities to automate support processes thus reducing personnel workloads which improving business drivers and reducing uncertainty.

- **Better defined approval process** – regulatory approval for complex biopharmaceuticals is driven by the level of product and process understanding. Many of the advances cited above provide opportunities to enhance understanding and thus enable improvements in the regulatory approval process. With the effective communication tools describe in the guidance, the transmittal of that understanding from industry to regulatory agencies should be enhanced.

Summary

This article identifies a number of technological advances that impact the industry's ability to design and build more flexible and capable manufacturing facilities. In addition, advances in regulatory and business methods enable more efficient approaches to develop and license new products. These advances impact the patient value and cost risks by changing the drivers and uncertainties discussed in the first article. The final article in this series will discuss how these enablers can be used to manage the business drivers and reduce uncertainties for the facility of the future.

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