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Facility of the Future: Next Generation Biomanufacturing Forum

Part I: "Why We Cannot Stay Here" – The Challenges, Risks, and Business Drivers for Changing the Paradigm

by Mark Witcher, PhD, Ruben Carbonell, PhD, Jeff Odum, CPIP, Peter Bigelow, Patricia Lewis, and Michael Zivitz

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

Introduction

This article is the first of a three-part series focused on defining the Facility of the Future (FoF) required for manufacturing biopharmaceuticals in the 21st Century. These articles are the result of discussions and presentations made by experienced industry and academic leaders from companies partially listed below at the "NextGen Facility Forum" held at North Carolina State University's Biomanufacturing Training and Education Center (BTEC) on 31 January 2012, sponsored by BTEC and IPS. The goal of the forum was to identify and clearly state all the challenges that biopharmaceutical manufacturing will face, and to begin to identify solutions to the biopharmaceutical industry's outdated manufacturing facilities that have difficulty adapting to the changing manufacturing requirements. Some of these changes include efficiently running smaller scale processes utilizing single use, disposable systems among others. The three articles will cover the topics discussed at the forum to make the Facility of Future capable of addressing all the issues that biopharmaceutical manufacturing will face in the next century.

The forum was designed around three breakout sessions covering the following questions:

1. What are the major process and design needs that are not being met by existing technologies?
2. What are the key process technologies that are important in transitioning the industry to these smaller, greener, more flexible facilities?
3. What are the regulatory and validation policies that will help cut costs and reduce time to market for products made in the new biopharmaceutical facilities of the future?

Between the breakout sessions, the following four presentations were made:

- "The Facility of the Future's Importance to Industry" by Peter Bigelow – Former President, North American Operations, Patheon, Inc.
- "The Role of Innovation in Future Facility Development" by Michael Kowolenko, PhD. – Industrial Fellow, CIMS, NC State University
- "The Role of Enabling Technologies" by Rubin Carbonell, PhD – Director, BTEC Programs, BTEC
- "Next Generation Manufacturing" by Mark F. Witcher, PhD – Principal Consultant, IPS

The forum's presentations, breakout discussions, and large

group conversations focused on the current issues facing the biopharmaceutical industry as companies move into the decision-making process for implementation of new technologies and facility design approaches. General agreement was reached that facility design concepts and technology used in current biopharmaceutical manufacturing facilities need to change considerably if they are to meet the manufacturing challenges of the future. This concern was manifested in a large number of discussion points raised in the various sessions, including, but not limited to the following themes:

- **Business Drivers** – impact of property, plant, and equipment on the bottom line; reduced depreciation targets across asset base.
- **Capital Drivers** – limited future capital availability, need to improve cash flow objectives to achieve lower overall cost of new assets.
- **Asset Utilization** – provide higher utilization of manufacturing assets.
- **Timelines** – reduce construction timelines to defer capital spending and enable emerging market development of new assets.

General consensus was reached that the facilities currently being constructed are too expensive and do not have the flexibility to respond to challenges created by future biopharmaceutical products, processes, and markets.

Manufacturing capability is a critical function for the development, launching, and supply of the biopharmaceutical market with high quality therapeutics. The first step to reaching an understanding of the FoF is to understand the challenges presented by biopharmaceutical manufacturing. For the sake of discussion, the challenges are divided into business drivers and uncertainty. After the challenges are discussed, the resulting business risks associated with manufacturing will be defined.

Challenge #1: Managing the Manufacturing Business Drivers

Like all manufacturing enterprises, biopharmaceutical manufacturing has basic business drivers that define the success of the enterprise as an efficient, cost effective contributor to the overall business. From the discussions, the basic drivers for any biopharmaceutical manufacturing facilities are shown in Figure 1.

As seen in Figure 1, the drivers can be divided into two categories. The first is patient safety and efficacy and are imperative for a successful product. The second category is basic business drivers. All the drivers rarely stand alone, and as such, must be balanced against each other to maximize the effectiveness of the manufacturing operation in meeting overall business goals. The critical-to-success factors associated with the unique drivers of each venture will result in different drivers being prioritized over others.

Product Quality

Product Quality is a given and as such, manufacturing operations must be designed and operated to reliably provide the patient population with a high quality product. In the context of this discussion, product quality is defined as the overall value to the patient in terms of the product's attributes of safety, potency, purity, and efficacy combined with other patient requirements, such as availability and cost. When all these patient-driven needs are met, product demand is typically high and the business enterprise is successful.

Excellence and Compliance

A critical driver to achieving the first driver is to maintain a facility that uses operational excellence to remain in compliance with appropriate regulatory guidelines. The regulatory guidelines provide the basis for current Good Manufacturing Practices (cGMPs) and process validation which define standards for regulatory inspections and product submissions for approval. In biopharmaceutical manufacturing in particular, meeting all the other business drivers requires manufacturing excellence which is a superset of requirements necessary to be compliant with regulatory guidelines. However, a complete knowledge, understanding, and implementation of all the applicable guidelines are required to assure compliance at all times.

Operating Cost

In terms of biopharmaceutical manufacturing facilities, the overall cost of manufacturing a product can be viewed as a combination of operating and capital costs. With the current cost pressures on the industry as a whole, understanding and controlling both of these costs is critical.

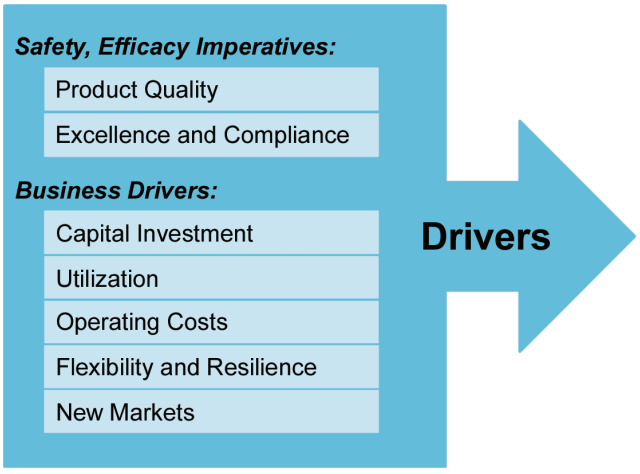

Figure 1. The business drivers can be divided into patient safety and efficacy imperatives, and business drivers associated with building and operating the manufacturing enterprise.

Manufacturing operations always look to control operating costs associated with raw materials, personnel, etc., by incorporating new technologies and optimizing the value provided by each cost component. Significant effort is being placed in advancing process technologies to increase productivity and product quality from both upstream and downstream processes that decrease operating costs and improve process performance. Single Use (SU) equipment and components is a notable example of a technology which can be used to significantly reduce start-up and operating costs in some applications.

Facility Utilization

High utilization rates almost always translate into cost effective facilities which provide high value to the enterprise. The goal is to build manufacturing facilities that are sized properly and have the characteristics and capabilities that allow them to run at a high production rate to achieve the business' objectives. Facilities that run at high utilization rates without being overloaded also tend to produce high quality products and thus are more likely to achieve the first business driver of satisfying the patient's needs.

Capital Investment

Another business cost driver is to minimize the resource investment required to develop and supply the market. Capital investment is a major component of the business resources required to bring a product from research through to the market, and to reliably supply the market with product. Deploying and operating new assets not only requires the commitment of capital, it also requires significant investment in resources that are often a rate limiting step in asset realization. As such, capital is a major contributor to the total resources the business must provide to bring a product from research to commercial supply. Assets with faster implementation schedules allow for deferral of resources, spending, and an improved cash flow.

Flexibility/Resilience

In the biopharmaceutical industry, flexibility can be a key enabler to improved facility utilization. If a manufacturing facility is flexible, with the capability to quickly and efficiently supply different multiproduct manufacturing requirements, it is far more likely to have a high utilization rate because it can handle a wide variety of the enterprise's manufacturing requirements. Of equal importance is that a flexible facility can support an emerging product pipeline where individual products may have various probabilities of success. Designing facilities with this level of flexibility protects companies from owning capital assets that require significant capital to reconfigure in order to support new products. Thus, a facility that can handle multiple phases of manufacturing for multiple products employing a variety of different processes is more likely to have a high utilization rate. Resilience is a variant of flexibility. In biopharmaceuticals, the facility must be capable of quickly and efficiently adapting to different multiproduct manufacturing requirements despite process problems and changing product demand.

New Markets

Enabling new markets is a key business driver as the pharmaceutical industry looks to meet significant, unmet medical needs while generating new sources of revenue. Many countries require local manufacturing for market access. The result is the need to configure future facilities to be rapidly and efficiently deployable to the emerging markets by a focus on optimizing the combination of capital costs, timelines, regulatory considerations, operational drivers, and the design of the process. The emergence of biosimilars will present a wide variety of opportunities and challenges.

A common theme for all of these drivers is the influence of new technology. New technology can influence cost by allowing lower cost capital solutions through smaller facilities and lower cost equipment, while also lowering operating costs with improved process performance and better utilization of raw materials, personnel, etc. New technology also can enable flexibility and higher utilization facilities. Significant effort is being placed in advancing process technologies to increase productivity and product quality from both upstream and downstream process.

Challenge #2: Dealing with Uncertainty

With the business drivers defined, the issue becomes one of managing these drivers in the context of the uncertainty intrinsic to the biopharmaceutical industry. These uncertainties translate into significant risks to the business drivers. The discussion continues by defining the uncertainty inherent in the biopharmaceutical industry and the impact of that uncertainty on the manufacturing facilities. This uncertainty can be grouped into six categories (product, process, timeline, capacity, regulatory, and location) - *Figure 2*.

These six uncertainty elements were identified as the sources of risk of either having expensive excess or unused capacity; or failing to provide the necessary high quality material in a timely manner to support product approval, or to support commercial sales. These risks ultimately result in high Cost of Goods (COG) and/or a significant loss of sales revenue.

Product

Product uncertainty comes from two possible negative clinical testing outcomes. If the product is shown to be ineffective, or is associated with significant adverse reactions, the product fails and the established manufacturing capacity is not needed. In addition, there is always a possibility that an adverse product profile may be identified after commercialization, which leaves the manufacturing facility no longer

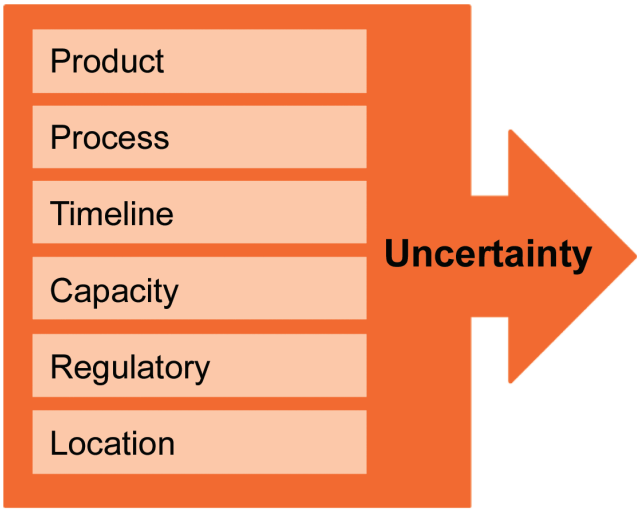

Figure 2. Business uncertainties associated with developing the product and the manufacturing enterprise.

required or severely underutilized. Clinical outcomes also can result in upside opportunities requiring additional capacity to serve the market.

Process

Another source of uncertainty is associated with the biopharmaceutical processes required to manufacture a complex, and sometimes very difficult to define and characterize protein product. The complex nature of the cell manufacturing systems and inherent complexity of the protein products provide the uncertainty of whether an efficient, cost effective process can be developed in a timely fashion to reliably provide sufficient amounts of product from a commercially viable large scale manufacturing process. Complex processes also introduce the possibility of operator errors and equipment failures that increase costs and delay production. Increased levels of training, automation, and sophisticated equipment validation and maintenance aid in decreasing the possibility of production problems.

Timeline

All of the uncertainties listed impact the timeline of building manufacturing capacity for all phases of the product development effort. The timeline element is broken out to reflect its significant overall contribution to managing the product development and commercialization effort.

Capacity

There is uncertainty in the ability to provide sufficient capacity to support product development and to supply preclinical, clinical, and commercial material. This includes uncertainty in the timing of establishing the required manufacturing capacity. Manufacturing capacity, even on the clinical scale, can be costly and time consuming to create. Critical milestone decisions and resource commitments must be made despite all the other uncertainties that provide the capacity to support the approval and launch timelines. Keeping manufacturing off of the critical path to product launch and market expansion requires significant and timely investments in development and manufacturing assets. New technologies and FoF concepts can help deliver accelerated schedules with simpler facilities and shorter lead time process systems that can provide plug-in installation and defer the need to make these capital investments.

Regulatory

Uncertainty also surrounds the regulatory approval process. Some regulatory uncertainty is associated with the product and how it is tested in the clinical setting. These issues are related and interactive with the other uncertainties described above. Regulatory uncertainty exists with establishing a manufacturing facility and operation which are compliant with regulatory guidelines. Differences in interpretation of GMP guidelines can lead to confusion and remains a distraction for many companies. In addition, some companies continue to struggle with on-going regulatory initiatives, such as PAT, QbD, design space, and process validation, particularly as defined in FDA's 2011 Process Validation Guidance. This uncertainty often results in overly conservative approaches with excessive costs and delays in development and manufacturing capacity creation.

Location

Future facility locations in emerging markets will be a key area of future uncertainty. Enabling the rapid global deployment of biopharmaceutical processes will be severely limited by today's facility and process designs. For example, high capacity, large volume stainless steel-based process trains are not ideally suited for deployment to emerging markets. The technology transfer of these existing technologies is very capital intensive and time consuming, and requires high risk upfront investments in both process and infrastructure. In addition, many emerging markets opportunities require lower capacities than traditional heavy stainless processes were envisioned to deliver.

While the individual risks associated with these uncertainties can be mitigated, the cumulative impact of these six areas of uncertainty results in significant overall risks with respect to establishing and operating the required biopharmaceutical manufacturing capacity.

Resulting Manufacturing Business Risks

Given the number of key business drivers and the large amount of uncertainty from many sources, the business risks associated with manufacturing are complex, interactive, and overlapping depending on the product and the patient

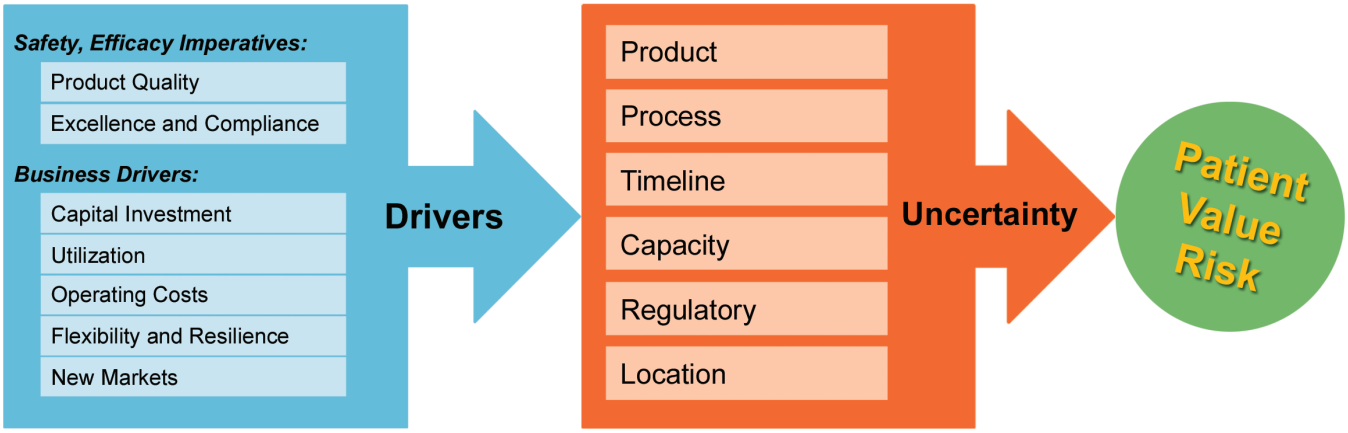

Figure 3. Patient value risks are primarily driven by patient safety, efficacy imperatives through the uncertainties; however, overall patient value risk in terms of cost and availability is also impacted by the business drivers and uncertainties shown.

indications being treated. For understanding, the risks can be lumped into risks associated with the value of the therapy to the patient (patient value risk) and the overall cost of delivering the therapy to the patients by the manufacturing enterprise (cost risk).

Patient value risks are associated with developing and supplying the therapeutic to the patient. The patient needs a timely, cost effective, reliable source of high quality product that is quickly and efficiently developed and delivered to the patient community. Figure 3 shows the qualitative relationship between the business drivers, uncertainty elements, and the overall risk to the value of the therapy to the patient. Failure of any of these relationships decreases the overall value of the therapy to the patients and thus decreases the opportunity revenue available to the business enterprise.

Cost risks are associated with the cost of supplying the therapy to the patients or Cost of Goods (COG). These costs are required to develop and launch the product as well as to provide long term supply of the product to the market place. The relative relationship between the same business drivers and uncertainties are shown in Figure 4. The capital investment required to build the facilities is a contributor to the COG throughout the product lifecycle from development through commercial supply. Anywhere along this lifecycle, a facility that is underutilized greatly increases costs while an undersized facility causes significant losses in potential revenue from failing to supply the patient population. Likewise, the manufacturing capacity needs to be available when the development and product launch timelines require it or the patient is underserved due to delayed availability of the product. In addition, inefficient or unreliable operation of the facility increases COGs through increased operating costs. Facilities of the future that look to new technology solutions also may enable a key industry transition from fixed to variable cost structures that can flex with demand.

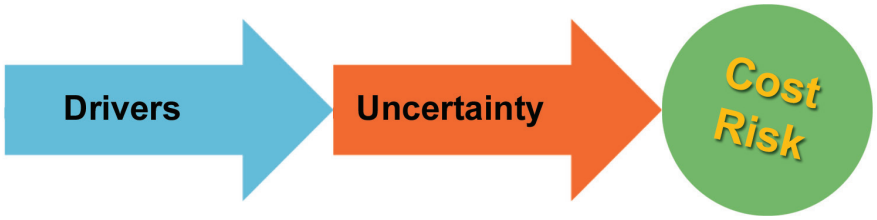

Figure 4. Product cost risks are driven through the uncertainties by the various business drivers shown. The cost risks are also impacted by the safety, efficacy imperatives of delivering a safe and effective product.

Summary

Defining and understanding the business drivers, uncertainties, and risks associated with building and operating biomanufacturing facilities is a key first step in the development of future generation facilities. The biopharmaceutical industry of today is very different and more complex than the industry that was birthed around the batch process, stainless steel asset facility model four decades ago.

Success of future facility design must be measured in terms of utilization, flexibility, and efficiency while providing a platform that supports and facilitates the operational excellence required for reliably producing high quality product while meeting an ever-evolving set of regulatory compliance guidance. As the industry looks to make this transition from current state to the future model, new enabling technologies can provide manufacturing platforms that meet the goals of being flexible with low capital unit operations changeovers, efficient movement to new markets, and a scale-out approach with smaller increments of capacity from highly productive processes to meet lower demand markets.

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The next article in this series, "Tools for Change – Enabling Technologies and Regulatory Approaches," discusses methods and approaches for achieving the business driver goals in light of the uncertainties and risks.

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