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# Facility of the Future: Next Generation Biomanufacturing Forum

## *Part III: Identifying Facility Requirements Based on Specific Business Drivers and Uncertainties Using the Enabling Technologies*

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This article is the third 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 third in 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 "NextGen Facility Forum" held at North Carolina State University in the Biomanufacturing Training and Education Center (BTEC) on 31 January 2012. The three articles summarize the topics discussed during the Forum.

The first article, "Part I: Why We Cannot Stay Here – The Challenges, Risks, and Business Drivers for Changing the Paradigm," elucidated why the biopharmaceutical manufacturing paradigm and the current generation of manufacturing facilities must change.[1] It summarizes the broad, industry-wide imperatives, challenges, business drivers, uncertainties, and risks discussed at the Forum.

The second article, "Part II: Tools for Change – Enabling Technologies and Business and Regulatory Approaches," summarized advances in biopharmaceutical technologies discussed at the Forum that impact most of the biopharmaceutical industry.[2] The advances provide important enablers that can be used to modify and, to some extent, control the drivers and uncertainties described in the first article.

In this third article, we will discuss this interaction between enabling technologies, drivers, and uncertainties shown in Figure 1. Although enablers, drivers, and uncertainties represent common challenges to the biomanufacturing industry, the resulting process and facility design will be the result of the application of these enabling technologies.

## Planning New Facilities for the Future

Deciding what type of facility to build and when to build it is a challenging responsibility. The key to success in designing and building the Facility of the Future (FoF) is to deploy the right mix of enabling and traditional technologies. The discussion here will focus on selecting from the diverse mix of enabling technologies to mitigate the risks stemming from the project drivers and uncertainties shown in Figure 1.

To begin the process of developing FoF concepts, companies must be able to define and prioritize the business drivers, and make appropriate assumptions regarding uncertainties to reflect the most significant business issues to be solved, while characterizing the drivers in light of the environmental uncertainties. Another way to think about this is to ensure that there is clear alignment of the expected business outcomes for the program.

When the project is initiated, it is critical to have a clear consensus on the key assumptions that influence the success of the program. The following are examples of critical aspects (drivers and uncertainties) of the business decisions that must be established by making the appropriate assumptions before starting the capital project:

- **Location** – a critical look at the location where the project will be delivered will influence aspects of the engineering solutions, including Environment, Health, and Safety (EHS) requirements and infrastructure demands.
- **New Markets** – the markets the product will supply guide the quality requirements that, in turn, impact the project scope, cost, and schedule.
- **Capacity** – the team must establish a common understanding of the products and doses to be supplied in conjunction with the required flexibility of the facility and process.
- **Cost Structure** – the pricing structure and the capital impact on Cost of Goods Sold (COGS) must be established.
- **Regulatory (Quality, EHS, and Engineering)** – before initiation of FoF, engineering, clear quality and compliance expectations must be defined and aligned between all parties involved in the project.

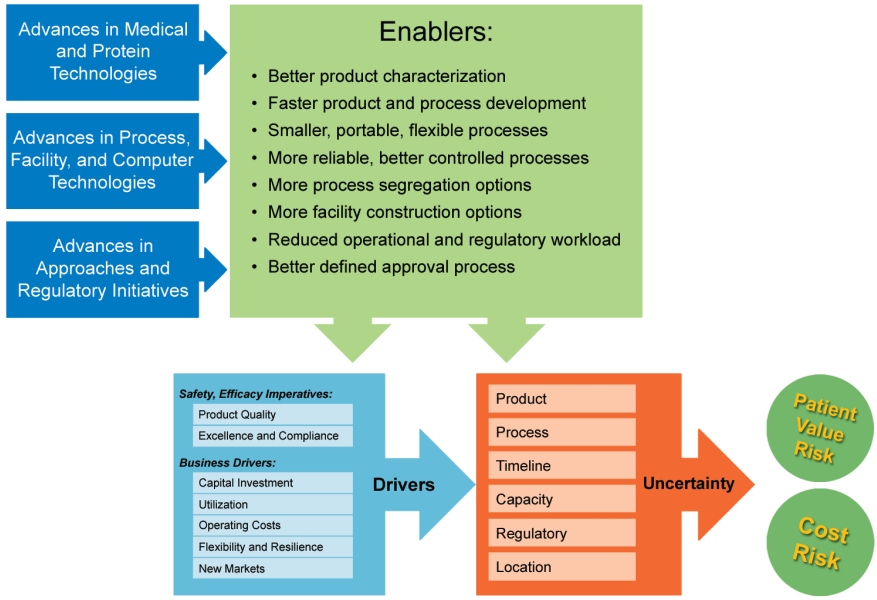


Figure 1. Drivers, uncertainties, and enablers.

The imperative driver remains ensuring that the product that ultimately reaches the patient is safe and effective and that the safety of the employees and the environment (EHS) is not compromised. The path to meet this imperative may, however, be different than the traditional norms, e.g., in the case of new markets where EHS requirements are driven largely by local regulatory requirements and GMP requirements must be aligned to meet the regulatory requirements of the countries in which the product will be registered.

Finally, the operational philosophy to implement the enablers for the facility must be established. The likelihood is that the unique circumstances of the FoF will drive operational differences from the facilities and processes that have been traditionally developed for the biopharmaceutical industry. These differences may be seen through examples such as less (rather than more) automated facilities or more manual setups rather than the large and complex piping networks that were seen in traditional stainless steel facilities. Misalignment on the operational needs and expectations can result in companies building the wrong processes and facilities required for sustainability.

In order to develop and document a clear set of requirements for the expected business outcome, the regulatory basis, operational requirements, collaboration between

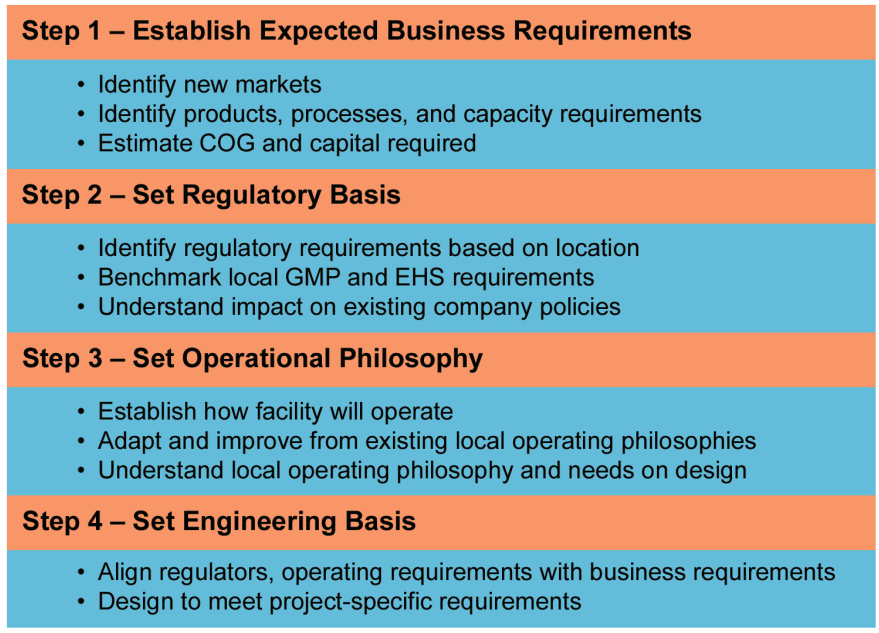


Figure 2. Facility of the future design process.

enterprise management, the engineering team, and the local operating management must be established. With this done, the engineering should begin with an innovative concept design effort.

This design process is shown in Figure 2. While this process is not unique to FoF projects, the assumptions for each of these steps may vary greatly from the assumptions that have traditionally been used by the biopharmaceutical industry.

Making appropriate assumptions which balance the risk and reward proposition with implementation will be a key differentiator in the future. Many companies struggle with these decisions and get caught in an indecision loop trying to balance the drivers against each other. The essence of failing to establish, align, and agree on a primary, or dominant driver, is an "indecision loop" shown in Figure 3.

These loops can have any number of driver elements. The enterprise gets caught, unable to decide which priority is dominant and which drivers need to be identified as subordinated assumptions in order to deal effectively with what is truly critical to success. Defining which driver is dominant establishes a clear set of priorities making the resulting decisions viable. The old clichés apply: "If everything is important, then nothing is important," and its first corollary, "If you deal with everything, then you wind up not dealing with anything." The failure to make timely decisions becomes a primary failure mode for some companies.

Indecision loops can be made more complex when elements of uncertainty are added. For example, the loop's complexity in Figure 3 can be increased by adding timeline and capacity uncertainties. The primary tool for minimizing the impact of uncertainties is to develop and reach a consensus on a carefully thought out and clearly stated set of business assumptions.

The balance of this paper will explore two sets of drivers. The first driver is the product safety and efficacy imperatives, including EHS considerations, shown in Figure 1. Basically, you have to make a safe and effective product; and you have to receive the required regulatory approvals to sell it. The second primary driver/uncertainty that will be discussed is the deployment of processes and facilities to new markets.

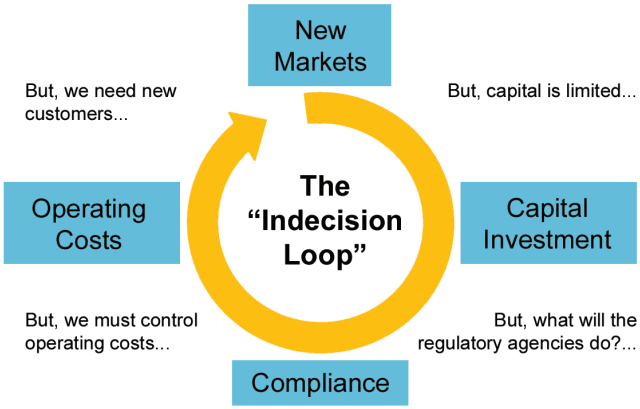


Figure 3. Indecision loop created by not establishing priorities among the various business drivers.

## Enabler Impact on Product Safety and Efficacy Imperatives

Medical technology is rapidly advancing toward a better understanding of the Critical Quality Attributes (CQAs) required for safety and efficacy. Identifying and establishing appropriate product CQA requirements remains an area of very high uncertainty. Many product failures result from an incomplete understanding of the required CQAs for safety and efficacy. The CQAs are collectively combined into the product's Quality Target Product Profile (QTPP).

The first enabler, better product characterization, allows the product to be more clearly defined based on the medical needs of the patient population. This clearer definition provides the enterprise with more precise product and process development goals. The uncertainty with respect to the product's performance in clinical tests during clinical trials and the patient population after commercialization is reduced. In addition, the sensitivity of the CQAs on safety and efficacy can be better defined.

The second enabler, more reliable, better controlled processes, allows processes to better meet the QTPP requirements defined by the medical technology. With better targets and development methods, processes can be developed which reduce the uncertainty of the processes' ability to manufacture a safe and effective product.

The final enabler, better defined approval process, improves compliance by better aligning industry's understanding of regulators' expectations for achieving operational excellence. Operational excellence is the fundamental driver for both producing high quality product and efficiently meeting all necessary regulatory requirements.

With respect to specific application of the enablers to the imperatives shown in Figure 4, the following questions could be a starting point for identifying the best facility options to satisfy the imperatives:

- Does the facility provide an optimum environment (not too small or too large) to execute the process steps?
- Based on the manufacturing requirements, does the facility incorporate and support optimal segregation strategies for separating the products and processes manufactured in the facility?
- Does the facility design facilitate the use of existing and future advanced process control technologies?
- Is the process train designed for reliable operation given the operational design basis?
- Does the facility design meet current as well as likely future technology enablers and thus will be able to meet future regulatory expectations?

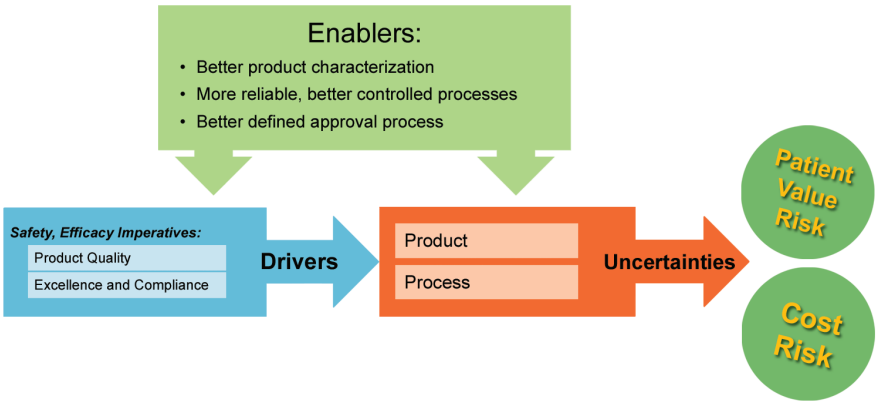


Figure 4. Relationship between enablers and safety and efficacy Imperatives and uncertainty.

- How can secondary business drivers be best satisfied while meeting the imperatives?
- How can the impact of the uncertainties be minimized?

Biopharmaceutical manufacturing runs the gamut from development facilities and pilot plants to commercial facilities producing product for sale. These companies vary widely from small biotech startups to large, integrated biopharmaceutical companies and Contract Manufacturing Organizations (CMOs). As mentioned, the unique circumstances of each company will help drive the critical-to-success factors for the program and, ultimately, the resulting engineering solutions.

With alignment on the imperative that the product must reach the patient and must be safe and effective and that the safety of the employees and the environment must not be compromised, the discussion will explore how this is done in the case of entering new markets. This case study will look at the unique challenges of a CMO; however, this example can also be applied to other business models in the industry.

The example is for illustration purposes and provides insights into several important primary drivers and how they interact with other possible secondary drivers. Priorities and approaches are management driven and can, and should, vary depending on the leadership team of each company. The example is based on a set of priorities set by a hypothetical leadership team and may be significantly different than what other leadership teams would do in the same situation.

## Case Study: New Market Development

Identifying, creating, and developing new products and markets is an important driver for most companies as they look to meet unmet medical needs and generate new sources of revenue. For many, it is the reason they exist. New products can be found in both advances in medical technologies that identify new therapeutic targets, and in biosimilars and biobetters evolved from existing therapeutics. Expanding to new markets has traditionally been synonymous with emerging markets, but can also include competing and delivering existing products to traditional markets not yet tapped by the company. In the case of emerging markets, future facilities may need to be localized in order to allow market access. As mentioned in the first article in the series, many emerging market opportunities require smaller capacities and more flexibility to keep the facility fully utilized.

In this example, the enterprise is a large CMO needing to attract new customers with new products. As shown in Figure 5, the company sets new markets (new customers) as its priority business driver. Reaching new markets will require a competitive product pricing structure. As a result, the leadership ranks utilization/operating cost as its second most important driver because of its impact on Cost of Goods Sold (COGS). Because utilization has the single largest impact on operating costs, utilization is matched with operating cost. Underutilized facilities that are either not needed or not designed to do what they need to do are the root cause of many of the industry's manufacturing cost problems today.

The needs of the future remain the number one uncertainty for the industry and influence the considerations for our future facilities. As a result, a third associated driver, flexibility, is used to deal with new processes and to enable simpler future process improvements. In past facilities, flexibility came with a huge price tag and introduced significant complexity to the process train and facility design. New enabling technologies, such as single use systems, in conjunction with smaller batch sizes allow the use of movable equipment such that future facilities can be more flexible.

Designing the FoF to enable a higher utilization and flexibility will drive the following considerations:

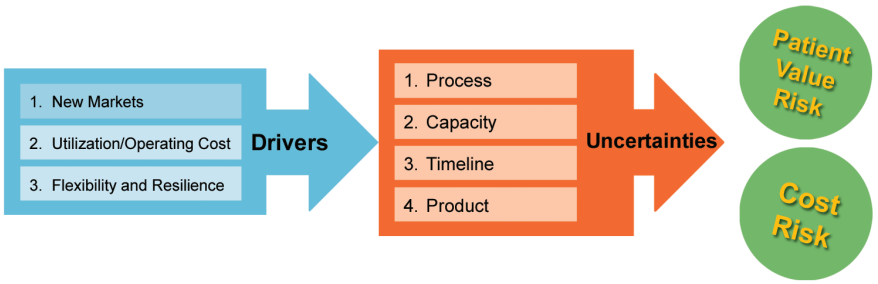


Figure 5. Business drivers and uncertainties for the example large CMO Enterprise.

- Development of a manufacturing platform that is adaptable and allows low capital unit operations changeovers either between product campaigns or even in the case of future introductions of new technology.
- Allows "scale-out" versus "scale-up" for unpredictable market requirements.
- Utilizes closed processing that allows flexible open plan layouts with the possibility for multiple products to be running in parallel.
- Provides a simpler and more reliable process.

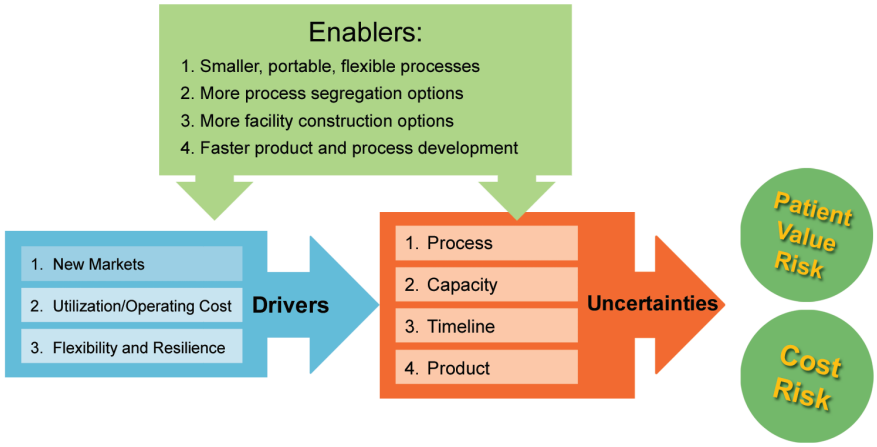


Figure 6. Impact of enablers on the business drivers and uncertainties for a large CMO enterprise example.

The drivers coupled with the uncertainties are shown in Figure 5. The remaining drivers are subordinated and defined as assumptions.

The uncertainties are evaluated and ranked as shown in Figure 5. The process is the first uncertainty because the CMO has decided it wants to handle a broad range of customers with a broad range of processes. Capacity is viewed as the second primary uncertainty because the leadership team wants the enterprise to be able to run preclinical, clinical, and commercial manufacturing to attract and keep customers. Multiphase manufacturing, which minimizes tech transfer issues, is viewed as a critical CMO business development objective. Customer timelines are always an uncertainty. Dealing effectively with customer timelines is also viewed as a significant business development opportunity. Product uncertainty is viewed as an issue because the customer's durability as a client depends on the long term viability of the product. Thus, identifying and attracting customers with good products is important. The uncertainty of location and regulatory, although important, are regarded as secondary issues to be dealt with on case-by-case bases rather than considered in the facility design.

Evaluating the drivers with respect to the specific business model must be done by looking at the customer base. Because many diseases are being more precisely defined and subdivided into therapeutic families based on differences in patient populations, new products are likely to have smaller material requirements. As an example, breast cancer has been shown to have a number of subpopulations requiring different chemotherapy regimens for treatment.[3] Thus, one monoclonal antibody (mAb) may become many different mAbs depending on how the patient population is characterized and subdivided for treatment. In addition, biosimilars may require smaller processes as new generation manufacturing processes are developed and small niches are created and attacked in the market place. Thus, capacity flexibility as a driver may become very important to take advantage of new market opportunities.

With respect to addressing new market uncertainties, timeline pressures are likely to increase because of an increasing emphasis to get to the market quickly. Product development timelines are generally acknowledged to be too long and the pressure to speed up development to commercialization timelines is growing. Although the critical path timelines generally go through clinical trials and regulatory approvals, improvements in medical technology, adaptive clinical trial designs, and faster product and process development tools may place greater pressures on manufacturing timelines.

The relationship between the primary applicable enablers, new market business drivers, and uncertainties are shown in Figure 6. Four enabling technologies were identified by the leadership team as having a significant impact on

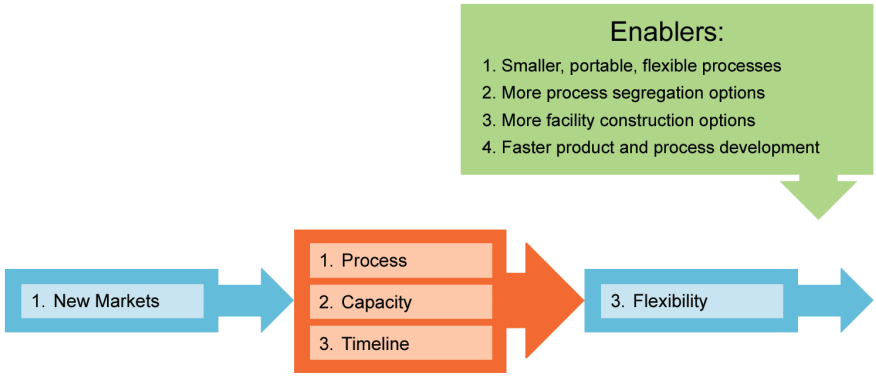


Figure 7. Enabler impact on facility flexibility.

the business model described in Figure 5. The enablers are ranked by the leadership team in the order of their perceived business impact.

Based on the previous discussion, the key to new markets appears to rely on the enterprise's ability to quickly run a broad portfolio of processes at a wide range of capacities. This is not true for all enterprises, but for the example being discussed, flexibility appears to be the real primary driver. Conceptually rearranging Figure 6, we get Figure 7 as being the real focus of the facility design issues.

How will the enterprise use the four enablers to design the best, most flexible facility to attract new customers? Enabler 1 (smaller, portable, flexible process) allows the operating process to be decoupled from the facility. Designing the process as an integral part of the facility is no longer necessary. The process uncertainty can be managed easily by configuring and moving the skid mounted unit operations into the facility without having to make facility changes. Upside capacity uncertainty becomes more manageable using the scale-out method of replicating the process to double the capacity. Downside capacity uncertainty is controlled by removing the process and installing another process from the customer scheduling queue. Timeline uncertainty is managed by being able to move processes in and out depending on balancing the various schedule requirements for the customer base. Simple facilities running portable processes also reduce capital cost requirements.

Enabler 2 (more process segregation options) provides a variety of facility design options. When combined with Enabler 1, closed Single Use System (SUS) processes can be installed in either large operating spaces (ballroom concepts) or small segregated spaces depending on the enterprise's facility control and process operating methods. Large operating spaces potentially reduce operating workload, while highly segregated spaces may increase the flexibility to rapidly add and remove processes from the facility. Each enterprise can use Enabler 2 to their advantage depending on anticipated business requirements.

Enabler 3 (more facility construction options) and the fact that SUS processes are decoupled from the facility by Enabler 1, make a wide variety of options for building manufacturing facilities available. When combined with the large single operating area option provided by Enabler 2, a very simple facility can be quickly constructed. Modular, design/build methods can be used to expand the facility very quickly if facility capacity becomes a problem. Using rapid design-build methods to scale-out processes provide for very rapid expansion of capacity. These simpler facility design, accelerated schedules, shorter lead time process systems, with plug-in installation can dramatically improve facility deployment schedules allowing companies more flexibility in executing business decisions about product and market needs.

Enabler 4 (faster product and process development) increases the emphasis on timeline uncertainties. If the same manufacturing facility can be used for preclinical through commercial manufacturing, then the development time to market can be decreased because tech transfer is no longer required. A seamless transition can be achieved as the process is scaled up and manufacturing requirements satisfied. An SUS, skid mounted process implementation facilitates moving the process to a second manufacturing facility constructed using Enabler 3 in any location simply by moving the skids, or their clones, with minimal revalidation requirements.

While the above example discusses one approach for a CMO business model, the following might be relevant questions for identifying the FoF for other enterprises seeking to address new markets as a primary driver.

- What will be the capacity requirements of the new products?
- What is the length of production commitments for new products?
- What is the scale of the new products?
- Which manufacturing requirements can be carried out in a single facility?
- Should multiphase manufacturing be considered or should the facility specialize in one type of manufacturing?
- Should the facility focus on one particular type of process (e.g., mAb) or should the facility be configured to handle

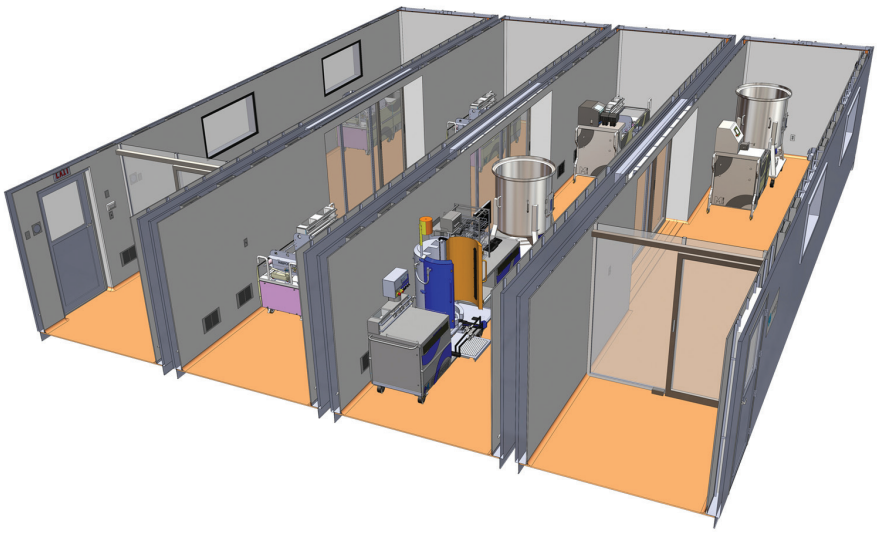

Figure 8. 200L Flexible mAb development facility concept *(image courtesy of Biologics Modular)*.

a wide variety of process formats?
- What is the projected utilization of existing capacity?
- How important is the timeline?
- Should existing capacity be maintained and new capacity constructed?
- Should existing capacity be removed to make way for new process formats?
- How can SUS be best used to deal with the primary drivers?
- Will a scale-out or scale-up approach be the most appropriate for dealing with capacity related uncertainties?

## Summary

The application of the identified enabling technologies to the business drivers in light of the uncertainties is very much dependent on the individual enterprises. An enterprise's manufacturing requirements can range from making a single product for early clinical testing to manufacturing a wide variety of different products over their entire development/commercialization lifecycle.

As the biopharmaceutical industry grows and the product mix becomes more complex, dealing with the business drivers and related uncertainties for defining, designing, and building new manufacturing facilities will be very difficult. Fortunately, the tools in the form of the enablers discussed are available to meet these challenges and continue to be enhanced by advances in technology and better business practices. This article provides a start in creating a framework that can be used to apply the enablers to solve industry's complex manufacturing business driver/uncertainty combinations.

## References

1. Witcher, M.F., Carbonell, R., Odum, J., Bigelow, P., Lewis, P., and Zivitz, M., "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," *Pharmaceutical Engineering,* January/February 2013, Vol. 33, No. 1, www.PharmaceuticalEngineering.org.
2. Witcher, M.F., Carbonell, R., Odum, J., Bigelow, P., Lewis, P., and Zivitz, M., "Facility of the Future: Next Generation Biomanufacturing Forum, Part II: Tools for Change – Enabling Technologies, and Business and Regulatory Approaches," *Pharmaceutical Engineering,* March/April, 2013, Vol. 33, No. 2, www.PharmaceuticalEngineering.org.
3. Sims, A.H., Howell, A., Howell, S.J., Clarke, R.B., "Origins of Breast Cancer Subtypes and Therapeutic Implications," *Nat. Clin. Pract. Oncol.,* 2007, Sept, 4(9): 516-25.

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