BioPhorum

IMPROVING THE BIOMANUFACTURING FACILITY LIFECYCLE USING A STANDARDIZED, MODULAR DESIGN AND CONSTRUCTION APPROACH

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Authors

Abbvie
Kevin A Dalby
John Derkach
Derek Sawyer

Chugai
Shingo Goto

CRB
David Estape
Charles Heffernan

Exyte
Stefan Kappeler

G-CON
Maik Jornitz
Dennis Powers

GEHC
Steve Gravallese
Joe Makowiecki

PM Group
Austin Lock

Roche Genentech
Doug DeVeny

Thermo Fisher Scientific
Mark Thomas Smith

BioPhorum
Clare Simpson
Danièle Wiseman

About BioPhorum

The BioPhorum Operations Group's (BioPhorum's) mission is to create environments where the global biopharmaceutical industry can collaborate and accelerate its rate of progress, for the benefit of all. Since its inception in 2004, BioPhorum has become the open and trusted environment where senior leaders of the biopharmaceutical industry come together to openly share and discuss the emerging trends and challenges facing their industry.

Growing from an end-user group in 2008, BioPhorum now comprises 53 manufacturers and suppliers deploying their top 2,800 leaders and subject matter experts to work in seven focused Phorums, articulating the industry's technology roadmap, defining the supply partner practices of the future, and developing and adopting best practices in drug substance, fill finish, process development and manufacturing IT. In each of these Phorums, BioPhorum facilitators bring leaders together to create future visions, mobilize teams of experts on the opportunities, create partnerships that enable change and provide the quickest route to implementation, so that the industry shares, learns and builds the best solutions together.

BioPhorum Technology Roadmapping

BioPhorum Technology Roadmapping establishes a dynamic and evolving collaborative technology management process to accelerate innovation by engaging and aligning industry stakeholders to define future needs, difficult challenges and potential solutions. The Phorum involves biomanufacturers, supply partners, academia, regional innovation hubs and agencies, serving to communicate the roadmap broadly while monitoring industry progress.

The project through which this paper has been developed is part of a broad portfolio of collaborative technology implementation projects, mobilized to impact the most critical challenges identified by the first edition BioManufacturing Technology Roadmap. This paper is an example of how the Phorum is continuing to deliver tangible results on its mission to accelerate industry innovation.

For more information on the Technology Roadmapping mission and membership, go to https://biophorum.com/phorum/technology-roadmapping/

1.0

Executive summary

Traditionally, biopharmaceutical facilities can take up to three to five years from design through qualification before they are ready for full operation. Such facilities are often product dedicated, requiring significant and costly modification to accommodate additional products, once the original product lifecycle has ended. This inherent inflexibility, including the inability to scale production capacity easily, has become a major concern for the biopharmaceutical industry, especially given the increasing pressure to reduce costs and quicken the speed to market for drug products.

To address these concerns, the BioPhorum Modular & Mobile Technology Roadmap working group has composed this white paper. It proposes a standardized design approach along with an example facility concept for a 2 x 2,000L monoclonal antibody (mAb) drug substance manufacturing facility, primarily utilizing a single-use technology (SUT) platform. Although realizing that such a platform does not suit all situations, the authoring team selected the mAb process with SUT due to its current prevalence in the industry compared to other, more unique processing platforms. The example facility solution can be used as a template for similar 2,000L-scale mAb projects or as a catalyst from which to develop standardized facility templates for other manufacturing applications. In addition, the example facility focuses on demonstrating how a modular design approach may be realized using various construction methods – including traditional stick-built, prefabricated and skid assemblies, as well as modular cleanrooms or complete modular building units – without requiring major reconfiguration. At the core of this investigation is the intent to align the biopharmaceutical industry around a common understanding and approach to the design and construction of manufacturing facilities that makes the capital project process more predictable by:

- reducing schedule durations
- improving project cost certainty
- increasing facility design repeatability
- ensuring greater regulatory compliance.

The paper begins by articulating a business case that describes the drivers for and benefits of a standardized modular approach. This section evaluates the economic and timeline advantages of modular design and construction in comparison to traditional methods by focusing on the current needs of the industry, for example reducing time to market. It also reviews the different modular construction solutions available and the business impact of increased standardization as well as off-site prefabrication, including the effects on project schedule timelines.

Section 4 (Key concepts) discusses the modular design approach and illustrates a multi-level, multi-scale structure with which to develop and organize modular solutions. It allows for the end-user to make decisions regarding the depth of detail to include in modular standards and what type of options might be integrated. Employing the idea of modularity as a plug-and-play tactic for design as well as operations, appears to offer the highest level of flexibility in all aspects of the facility's lifecycle. Modular construction methods and applications are also categorized to align the industry further around some common terminology and definitions.

Section 5 sets out a standard facility example layout. This is the first instance of an example layout provided by the BioPhorum team, but the intention is for the working group to create additional examples for other processing platforms and modalities as part of subsequent publications. The facility scope, assumptions, areas and process layout are described in detail to create an adequate overview of the basis for the example layout.

The example facility is designed for a high level of flexibility but also challenges current cleanroom classifications, segregations and regulatory flows, aiming not only to solve the current industry needs, but also advance facility design to meet future needs as well.

The closing sections of the paper review the challenges and opportunities associated with modular, standardized designs and address some of the quality and regulatory aspects of a standardized facility model in greater depth. Challenges and opportunities are described in detail across multiple areas of design, construction and operations, including high-level potential regulatory reactions and adoption hurdles. The final section continues the discussion around the distinct advantages for regulatory agencies to which standardized facility design contributes, as well as the benefits it offers the end-user.

In summary, this white paper creates a vision of how a future biopharmaceutical manufacturing facility might look when rooted in the future needs of the industry. The example layout proposes a tangible solution based on a modular, standardized approach that can be used as it is, or as a catalyst to change the generally conservative mindset of the industry. The industry must continue to venture outside existing legacy methods of facility design and construction to optimize our manufacturing platforms and better serve patient needs in the future.

2.0

Introduction

In July 2017, BioPhorum published the Biomanufacturing Technology Roadmap first edition. The intent was to initiate a dialogue between key industry players, including biopharmaceutical manufacturers, the supplier community, academia, and government regulators in the pre-competitive space and to work towards achieving a more efficient industry in which important therapeutics would be delivered with greater certainty, speed, and quality to patients, in a more cost-effective manner. Based on a comprehensive assessment of the market trends affecting the biopharmaceutical industry and its key business drivers, the focus of the Biomanufacturing Technology Roadmap was to present areas of opportunity for potential solutions for the industry, and to encourage continual innovation, research and development in the biopharmaceutical community to serve future patient populations successfully.

The Biomanufacturing Technology Roadmap is based on a number of technology domains centered on process, construction and manufacturing technologies. It comprises the following sections:

- Process technologies
- Automated facility
- Modular and mobile
- In-line monitoring and real-time release
- Knowledge management
- Supplier partnership management

Each section was managed and written by specialists from a cross-sectional group of companies associated with the industry.

The Standard Facility Design project team recognized that modular and mobile concepts offer an opportunity to transform traditional design and construction approaches away from delivering typically custom-designed, fixed assets with limited flexibility and adaptability to more standardized, modular manufacturing facilities that can be designed and constructed in significantly less time, providing cost, operational and speed to market advantages. After publication of the Biomanufacturing Technology Roadmap, the Standard Facility Design project team focused on the immediate task of delivering a white paper on the delivery of a standardized facility using modular design and construction approaches. This paper is the outcome of that task.

3.0

Business case

3.1 Background

Industry needs and strategies require new approaches and facility solutions

In the biopharmaceutical industry, the business case and value proposition for a standardized, modular approach to facility design has never been stronger. Manufacturing and logistics strategies are evolving to adapt to the changing industry landscape which includes new, innovative, personalized medicines and increasing global demand, coupled with a requirement to produce drugs locally. These strategies require manufacturing capacity to be deployed more rapidly than previously expected within the industry – in many cases within months rather than years. The traditional approach to designing and constructing unique purpose-built facilities for manufacturing biopharmaceuticals is not fully effective for executing these strategies. However, a standardized and modular approach can be.

Designing, constructing and qualifying a traditional stick-built biopharmaceutical manufacturing facility can take three to five years, depending on the size, location, and complexity of the project. To self-produce a drug commercially that is still in clinical trials, a manufacturer will have to invest significant capital in a new facility prior to clinical results and regulatory approval. If the drug fails in the clinical trials, such capital investment is often not recoverable. If the drug gains regulatory approval, the capacity requirements at facility start up often change significantly from initial calculations. The result is an oversized and under-utilized facility or one which does not have the capacity to meet current demand. Due to the 'fixed' nature of its design and construction, the facility is not sufficiently flexible to adapt for increased capacity or major process changes. The one exception being contract manufacturing organizations (CMOs) who, due to the multi-product nature of their business, have had to design and evolve their process and facility operations continually to be flexible enough to adapt to the changing needs of their clients.

3.2 Traditional approach

The associated risks of extended project timelines and delays

The risk of delays with traditional construction projects is high due to a number of factors, which can drive a project schedule well beyond its original intended completion date. This will have adverse financial implications for the manufacturer as well as potentially contribute to drug shortages or unavailability of drug products. The implications include additional, unplanned project costs and capital investment, deferred start-up and revenue generation, as well as unexpected caveats from inspectors regarding design, material or construction details. For a new product entering the market, a delay in the start-up of the facility can shorten the window of patent exclusivity and reduce the ability of the manufacturer to maximize its revenue and profit prior to patent expiration.

Factors impacting facility project timelines vary from project to project in nature and magnitude, depending on the size and scope of the project. Delays can occur at every phase of a project including design, construction, commissioning, and qualification. For a unique facility, the engineering design phase alone can take six to 12 months and go through significant revision from initial concept design through final approved detail design. If all stakeholders (e.g. Quality, EHS) are not included in the design process from the start, the timeline for design approval can be pushed out beyond the original schedule to gain consensus from all parties. Additionally, there will be timeline risks during the engineering design phase, regardless of the facility construction type (e.g. stick-built, modular) if there is no pre-existing, standardized design being leveraged.

The construction phase of the project often holds the highest risk for delays and timeline extension. A facility construction project is a highly complex operation with hundreds of contractors from multiple organizations having to coordinate and perform their work together at the project site. The logistical challenges of stick-built facility construction often do not allow for efficient project execution. Factors such as weather, construction material

delivery delays, labor availability and disputes can adversely impact a project schedule. In an effort to maintain the original project schedule, additional costs can be incurred by paying a labor premium or overtime, however, due to on-site labor limitations, often the schedule is not recoverable. This is most likely due to factors such as headcount density restrictions, labor laws, and unavailability of qualified labor depending on the project location. What unfortunately can occur at this point is the need to expedite in order to accelerate completion, adversely impacting the quality of the constructed facility. These quality issues are then identified during the commissioning and/or qualification phase and need to be addressed to satisfy the quality and regulatory requirements. This necessitates contractor rework, causing further delays. Typically, the number of quality issues and deviations identified during commissioning and qualification directly impacts the time to facility start-up.

3.3 Standardized, modular approach

The terminology of the approach defined

The terms 'standardized' and 'modular' can take on different meanings to different individuals in the biopharmaceutical industry depending on background, expertise and perspective. For the purpose of this paper, which focuses on facility design, we use the term 'standardized' to mean 'pre-engineered' or 'pre-designed'. This approach suggests that a new facility design need not be unique, but rather utilize and leverage a pre-engineered facility design. Many of the biopharmaceutical processes for products such as monoclonal antibodies do not vary significantly between manufacturers and lend themselves to this approach. This approach is analogous to purchasing a standard process equipment skid (e.g. for UF/DF) from a supplier rather than designing and fabricating a customized system.

The term 'modular' is often used to describe various methods of facility construction inside and outside the biopharmaceutical industry. For the purpose of this discussion, modular is used to describe the design approach and the method of construction. A modular design approach considers each process unit operation as an independent module, including process equipment, utilities, and personnel, and then defines what the process envelope should be from a dimensional and environmental perspective. These modules are then combined to form a complete manufacturing process with the appropriate adjacencies, segregation, and connectivity for material, personnel, product, and waste flows.

Modular construction takes on various forms based on the technologies and products that are available from the different suppliers. Examples of modular construction are:

- cleanroom wall/ceiling panel systems (e.g. AES, Plascore, Daldrop)
- prefabricated cleanroom units (e.g. G-CON, IPM Technologies, GermFree)
- pre-engineered shell buildings (e.g. Butler)
- facility solutions (e.g. GE KUBio™, Pharmadule Morimatsu, KeyPlants).

The first two examples follow what is often referred to as the 'box-in-box' approach where the modular cleanroom box is installed within the shell building box (third example). The facility solutions approach is one which constructs a complete facility, internal and external, using multiple modular sections. The commonality between all of these modular construction solutions is that a portion of the facility is fabricated off site in a controlled environment location and then delivered and assembled at the construction site. The complexity and time required for installation and assembly varies between the different modular solutions based on their inherent design and construction attributes.

3.4 Benefits of a standardized modular approach

The case for shorter, more predictable project schedules

The value in the standardized modular approach to facility design and construction lies within its ability to execute a project faster, more efficiently, and with less risk than a traditional construction approach. The overall project schedule can be well controlled and is more predictable, providing the manufacturer with the ability to utilize their capital more effectively and have a high level of confidence that the facility will be operational on time. A shorter and more predictable project schedule potentially allows the manufacturer to delay capital investment in a new facility until later in the product's clinical trial phase, minimizing their risk. Additionally, having the facility and manufacturing capability available when required for production allows the manufacturer to initiate revenue generation, maximize profit opportunity within the patent window (if applicable), and provide drugs to the respective patient base.

Timelines are reduced at all stages of a facility project when taking a standardized, modular approach. By starting with a standard pre-engineered design, the design phase for the project might be reduced to under 12 weeks, based on client acceptance of the pre-existing conceptual/basic design and the detailed design activities focused on the requirements specific to the geography and adherence to local code requirements. This standard design can be immediately reviewed by all stakeholders on the manufacturer's project team at the start of the design phase and get the appropriate feedback. If the standard design does not meet all of the manufacturer's requirements, it will likely be at least 80% appropriate with design modifications required to achieve 100% acceptance. Even in these cases, the time saved during this phase can be up to six months as compared to the traditional design approach.

Efficiency of project execution and control of schedule is realized during the construction phase when the modular facility is fabricated off-site in a controlled environment. Concurrent or parallel construction of both the cleanrooms and shell building structure helps reduce the schedule as compared to a stick-built facility which requires the majority of construction activities to be performed sequentially, with the shell building being constructed before the cleanroom infrastructure can be installed. When fabrication takes place within a fabrication shop, the entire process is well controlled and coordinated by a manufacturing team with knowledge and experience in modular construction and working within the manufacturer's quality system. It is feasible to start on procurement and fabrication activities prior to final approval of the complete detailed design package using a phased risk-based approach. If there are delays in delivery of materials and equipment, schedule recovery is also more effective in a fabrication shop.

The on-site complexity, risk, and probability of project delays caused by factors such as weather and labor contract or scope disputes are significantly reduced in the fabrication shop environment. The less activity and manpower that is needed on a facility project worksite, the lower the risk and likelihood of issues, which minimizes costs and risks of schedule overruns. It also reduces health and safety risks during construction and installation, since a large percentage of the facility is prefabricated in a controlled environment where external risk factors are mitigated through qualified and trained staff, optimized processes, and quality and safety standards. While some site work and construction activities are required, up to 80% of a facility can be fabricated off-site. This helps reduce the complexity and time required for overseeing the on-site activities and allows the end-user team to focus on their primary responsibilities.

The time required for on-site installation and assembly can vary depending on the modular construction approach selected. For example, installation and assembly of prefabricated cleanroom units within a building can be completed in days because of the level of prefabrication in the factory, versus a modular cleanroom wall/ceiling panel system which typically can take weeks to months to construct on-site and integrate with facility utility systems, depending on the size and complexity of the facility. Some of the modular construction solutions available also provide factory acceptance testing of the critical cleanrooms prior to shipping to the project site. This allows for identification and correction of most installation or operational issues before delivery, minimizing the probability of schedule delays that may occur at the project site during commissioning.

If the modular solution supplier can provide comprehensive standardized protocols for site acceptance testing or installation and operational qualification for the critical cleanroom areas, the time and effort required by the end-user's team to validate the facility can be reduced. Following a risk-based approach, such as the one defined in the ASTM E2500 standard, the supplier's protocols and/or testing execution results can be leveraged as part of the end-user verification. This reduces the time and cost associated with generating and executing customized validation protocols, typically performed by a third-party consultant, and also eliminates unnecessary repeat testing.

3.5 Business impact

The value proposition for a standard modular solution

The value of a standard modular approach can be realized in many ways depending on a drug manufacturer's current situation, strategic approach, and future needs including, but not limited to, the following:

- Improved speed to market or clinic for a new drug product
- Deferring of capital investment in the new facility
- Flexibility to adapt to changing market or network needs more rapidly
- Providing a viable path for small or resource limited companies
- Enabling repurposing of facility assets.

The phrase 'time is money' rings true in many businesses, but in today's changing world it is even more critical in the biopharmaceutical industry. Historically, this industry has not kept up with other manufacturing industries that have evolved continuously by adopting new and innovative approaches and technologies to improve their processes for expanding production capability and capacity. In the past decade, there has been a growing trend in the industry among manufacturers, suppliers, and regulators to invest in innovation and change to improve quality of products, efficiencies of operations, and responsiveness to patient and market needs. The advancement and adoption of disposable single-use process technologies and systems is arguably the best example of this and has helped reduce the time required for implementing manufacturing capability for new drugs and for increasing manufacturing capacity for existing products.

As described in the section above, by following a standardized modular approach with a well-controlled and predictable project schedule and minimized risk of delays, biopharmaceutical companies can both reduce the time required for designing, building and validating a new manufacturing facility, as well as have a high level of confidence that their facility will start up on time. Using a standardized pre-engineered facility design can reduce the engineering design phase by up to six months, and in some cases even longer as compared to engineering a unique design. The time reduction realized with standard design will usually be consistent, regardless of the modular solution utilized. However, the time required for the construction phase of the project and the on-site manpower required will vary depending upon the modular solution selected. As an example, Figure 11 in the Appendix illustrates the comparison of project execution timelines for building a new facility following a traditional stick-built approach versus a prefabricated modular approach. The key driver for the difference observed is the level of interior cleanroom fabrication that is performed off-site in the factory in parallel to the shell building. The higher the level of off-site prefabrication, the less time is required to execute and complete the facility project.

3.5.1 Speed to market

The financial implications and value that this brings to each company can vary depending upon factors such as whether it is a new drug or therapy, market demand and price, competitive landscape, etc. Today, a modular construction approach will typically require a higher upfront capital investment (5–10%) as compared to stick-built construction; however, the timeline reduction and faster facility start-up will typically result in earlier revenue generation. The financial benefit of being able to manufacture drug products sooner than later, will usually far outweigh the additional capital investment required. For a company that is launching a 'first-to-market drug' the timing is critical, especially if there are competitive products not far behind. Being late to launch, even by months, can have tremendous impact on the drug's market share if a competing product launches first.

Table 1 summarizes the business case for reducing the timeline for the start-up of a new manufacturing facility launching a typical mAb product. The case is based on assumptions that can be typical for this type of product/manufacturing process and is shown as an example for this discussion. The intent is to reinforce the argument that the schedule and timing for starting a new production facility can have significant financial implications for a drug manufacturer, with the potential for generating hundreds of millions of dollars in additional revenue and profit. In this case, the additional profit generated would easily provide the return on the premium invested by following a standardized modular approach. As an example, if a drug manufacturer invested $110m in a new standardized modular mAb facility, which cost 10% more than a traditional stick-built facility ($100m), the additional $10m investment could potentially be recouped, within the first two to three months after start-up.

3.5.2 Deferring of capital

Because of the duration of project schedules and the unpredictability of traditional on-site construction, drug manufacturers have had to make large capital investments in new facilities long before they require the capacity for their drug products. This has posed significant financial risk to the companies in the following scenarios:

- a facility built for a drug product that failed in clinical trials and/or did not get regulatory approval
- a facility which was oversized and under-utilized for a drug product that did not achieve the expected market acceptance
- a facility which was undersized and not capable of meeting the market demand for a drug product.

A standardized, modular solution with a shorter and more predictable project timeline is needed to ensure drug manufacturers have the required capacity when they need it to produce their drugs. This also helps to mitigate their financial risks by allowing the delay of capital investment to a timepoint much closer to when capacity is required or to when a new product is developed further in clinical trials, having a higher probability for regulatory approval. This approach can help companies prevent wasting millions of dollars in capital building a facility that cannot be used as intended or prevent the loss of millions of dollars in revenue.

3.5.3 Flexibility to adapt

Determining manufacturing capability and capacity requirements is typically the first step when designing and planning for a new facility. This relies on sales forecasting, which is often challenging, especially when it comes to estimating the increase in demand for a new drug product over time. Most companies have a good handle on the requirements for the first two to three years, but beyond that can be difficult. It becomes even more challenging if the new facility will be producing a drug for multiple countries, with regulatory approvals coming at different times.

As the industry looks to the future, with the changing global landscape and the advancement of new personalized medicines, drug manufacturers need to plan for the unexpected and be capable of responding more rapidly to changes in market needs and manufacturing demand when they occur. This may be the need to scale out an existing operation, bring in a new product or process, or establish manufacturing capability for the same product in a new geography. And with each of these scenarios come the associated technology transfer risks, quality requirements, and regulatory challenges that are all impacted by a drug manufacturer's process and facility response and deployment strategies.

Most of the facilities built over the past 50 years within our industry, have been purpose-built and inflexible in that they have required significant facility modification, requalification, and impact on manufacturing operations to adapt to changes in capability and capacity needs. With the advent of single-use technologies, drug manufacturers today have more flexible process solutions that can provide a more agile operation as compared to traditional ridged stainless steel-based process systems. When single-use processes are coupled with a modular facility solution that allows for the incremental addition of a manufacturing footprint, scaling up capacity or bringing new product capability online can be done more rapidly than a traditional facility, with less impact on the existing operation.

When a standard, modular facility platform approach is adopted, new facilities can be replicated, eliminating the need to design and build from a blank sheet. Once the first facility is built, qualified and operational, the lessons learned from the experience as well as the leveraging of protocols, procedures, training, etc., can contribute to further reducing the time and costs associated with the implementation of subsequent facilities. This approach can benefit the small start-up companies with their first commercial product, the large global pharmaceutical players that are investing in new personalized therapies, or CMOs that need to more rapidly provide capacity for their growing client base.

3.6 Conclusion

Reduced timelines and predictable project schedules for designing and constructing new facilities are becoming more important in the biopharmaceutical industry today in order for drug manufacturers to meet the growing demand for their products in a changing global landscape. By implementing a standardized modular approach for these new facilities, manufacturers can reduce the time, risk, and complexity typically experienced when taking a traditional unique stick-built approach to their facility design and construction. The reduction in schedule can be realized at all phases of a project including design, construction, start-up and qualification (depending on the modular approach that is taken), and the percentage of off-site prefabrication that can take place. Although a modular construction approach may require a slightly higher up-front capital cost than a stick-built facility, the return on investment can be achieved if the manufacturer can reduce the time it takes to get their facility operational and their product(s) to market without delay. It is important for all drug manufacturers today to evaluate the benefits of a standardized modular approach for their new facilities and assess these against their manufacturing and logistic strategies from a timing, cost and agility perspective. The ability for the biopharmaceutical industry to respond more rapidly to changing market needs to provide drugs to the patients, when they need them and where they need them, is more important than ever.

Facility costs can no longer be determined by only simply considering the cost per square foot of capital investment, but must be carefully assessed, taking into consideration all factors that influence the total cost of ownership, including but not limited to the following:

- Reduced design costs (conceptual, basic, detailed), by following a standardized facility design approach
- Speed of facility deployment and manufacturing start-up
- Deferment of capital investment
- Reduction of on-site construction activities, personnel, risk, and liability by following a prefabricated, modular approach
- Ability to scale up or scale out capacity with minimal interruption to existing operations
- Repurposing or redeploying of manufacturing capability
- Reduced burden of qualification by replication of standard facility design.

In order to accurately assess and compare the standardized and prefabricated modular approach to traditional non-standardized facilities, all of the factors listed above should be considered and used to determine the net present value and return on investment for the different options being considered.

Table 1: Revenue and profit potential based on project timeline reduction

	Timeline reduction in months			
	1	3	6	12
Value per batch	$7,000,000	$7,000,000	$7,000,000	$7,000,000
Batches per week	0.67	0.67	0.67	0.67
Weeks per month	4	4	4	4
Revenue per month	$18,760,000	$18,760,000	$18,760,000	$18,760,000
Profit per month	$7,504,000	$7,504,000	$7,504,000	$7,504,000
Total revenue	$18,760,000	$56,280,000	$112,560,000	$225,120,000
Total profit	$7,504,000	$22,512,000	$45,024,000	$90,048,000

Business case assumptions:

Drug product type: mAb
Production facility capacity: 2 x 2000L bioreactors
Overall process yield: 70%
Overall cycle time per production reactor: 21 days
Titer: 5 g/L
Revenue value per gram mAb: $1,000
Net profit: 40%

Final grams/batch	7.000
Dose	0.1 g/dose
# doses/g	10
Price/dose($ USD)	100

4.0

Key concepts

4.1 Introduction

While traditional design and construction methods have served the biopharmaceutical industry well over the last four decades, recent advances and trends in manufacturing processing and product types, as well as increased economic pressures have created the need for greater and accelerated application of more innovative approaches to facility realization. The move toward higher levels of standardization and modularization for biopharmaceutical facilities is intended to address this need, but requires a fundamental mindset shift among manufacturers, engineering consultants, suppliers, and constructors regarding the ways in which these facilities are designed and constructed. This change in approach is focused on enabling:

- Faster facility deployment and/or deferred capital expenditure
- Rapid product launch and technology transfer
- Better adaptability of production capacity with demand
- Easier facility repurposing for increased asset lifecycle
- Reduced cost of goods sold (COGs)
- Localization of manufacturing for smaller-volume manufacturing or rapid response.

With increased alignment across all principal stakeholder teams, the resulting future state is targeted to achieve an almost 'off-the-shelf', 80%-or-greater reuse of design and construction elements from project to project, including consistent, repeatable:

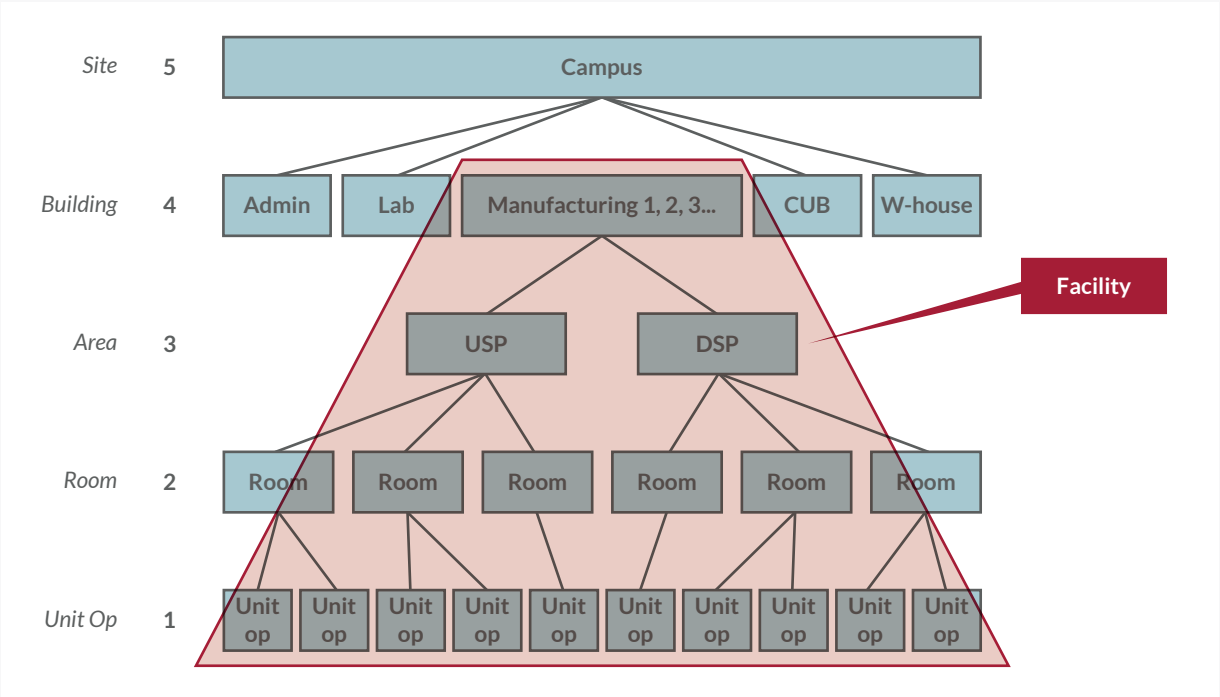
- Layout and equipment modules
- Process/utility/automation interconnections, regulatory flows and area classifications
- Facility qualification practices in collaboration with regulators
- Robust supply chains for all components.

4.2 Modular design approach

A modular design approach requires the development of catalogues to document and manage these design elements as part of sustainable frameworks that can evolve over time as processes and technologies change. These collections, while in some ways specific to individual pharmaceutical companies, can share many common attributes that fulfill the requirements across the industry as a whole, naturally contributing to an ongoing and increasing level of standardization for facilities, as well as the equipment they accommodate. The responsibility for their creation can therefore be shared according to the expertise, capacity and capabilities of all participating organizations. In order to be effectively integrated on a project however, all of the elements must adhere to a basic set of design principles that allow a level of interchangeability and adaptation to specific project and manufacturer requirements without causing wholly customized solutions.

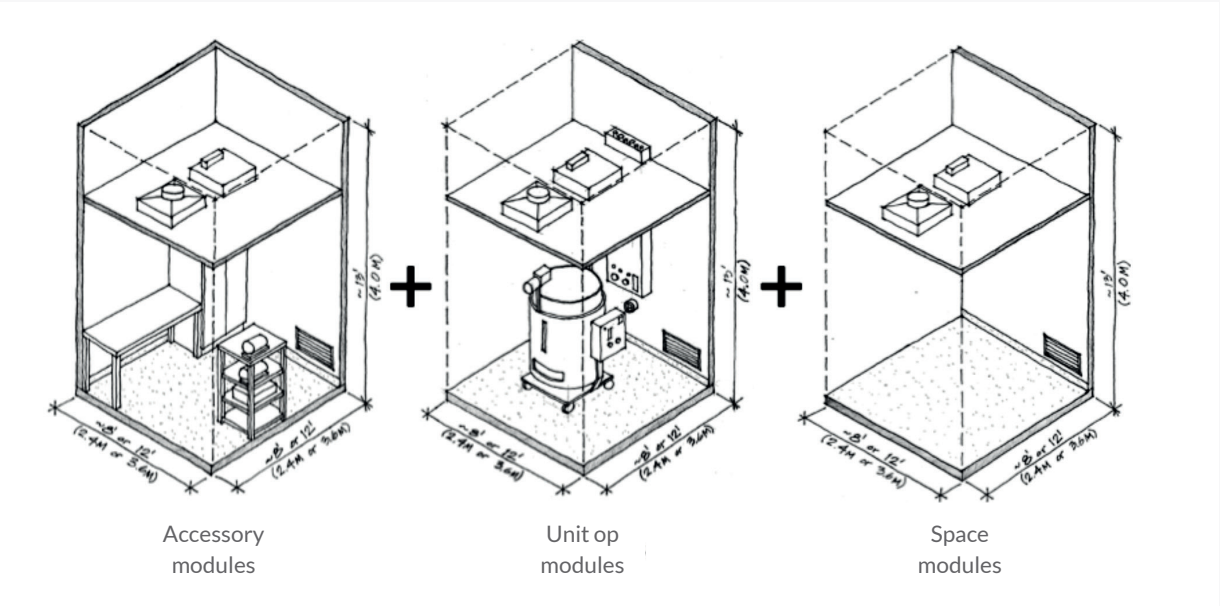
As illustrated in the diagram, manufacturing facility design becomes a process of aggregating predefined modules of unit operations and support spaces to create larger and larger modular elements across five levels of scale or standardization. Level 4 (Building) represents the limit of scope and extent of this paper.

Figure 1: Scope of facility modularization



Further articulation of this idea includes creating design modules that encompass predefined solutions for equipment operations, accessory support areas, as well as space modules for circulation, access and component staging. Depending on the sophistication of the digital platform in which these modules are composed, additional facility information can be attached to each module through a database to account for attributes like area classification, utility requirements, power loads, data connections, lighting levels, and even architectural finishes. All of the most probable, preferred adjacencies for module-to-module connections must also be conceptually solved as part of the development process, allowing for the quick arrangement of these 'building blocks' in various combinations to create conceptual design solutions that are as 'plug-and-play' as their physical realizations are ultimately intended to accommodate. Standard designs, with defined ranges or limits of operation, can be conceptually established at all levels of standardization, from unit op to campus, to maximize the impact of this approach on the speed of execution in addition to improving cost certainty.

Figure 2: Proposed module attributes



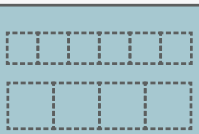
Key to ensuring the applicability of this approach to multiple technologies, vendors, and construction methodologies, among other critical requirements, is a strict adherence to common dimensional units. Suggested design module increments of approximately 2.4m x 2.4m x 4.0m and 3.6m x 3.6m x 4.0m appear to fit well with typical over-the-road transport limits in most countries, as well as with some industry-standard construction module sizes already being fabricated. Further breakdown of these planning units to 1.2m or even to 0.6m increments is possible and yields additional flexibility to meet specific design requirements. The ultimate intended result is to allow a facility design to be quickly converted for realization at any time in a variety of methodologies without necessitating complete reconfiguration.

Figure 3: Recommended construction module sizes based on over-the-road transport limits

Multiple design modules can be combined to form physical construction modules

- *Over-the-road transport w/ no permit required: ~ 8' w x 48' l x 13' h (2.4m x 14.4m x 4.0m)*
- *Over-the-road transport w/ permit: ~ 12' w x 48' l x 13' h (3.6m x 14.4m x 4.0m)*

Note: Larger modules possible utilizing barge shipment or over-the-road transport with pilot vehicle escorts



4.3 Modular construction options

The various methods of modular construction currently available can also enhance the schedule, lower cost and improve quality performance of pharmaceutical facility projects. When integrated with a modular design approach, these benefits can be extended even further.

It is important to establish common definitions for the different methods that can be utilized exclusively or in a variety of combinations. Two major categories exist for modular construction:

1) Hybrid modules, which require an existing or stick-built building shell in which to construct or place them. These range from typical equipment skids to complete prefabricated cleanroom units that are simply plugged into the shell building utility services.

2) Full facility modules, which include all the required building super- and infrastructure in addition to interior walls, ceilings, equipment systems, etc., and even exterior cladding and roofing if desired.

Figure 4: Construction module definitions/options

longest

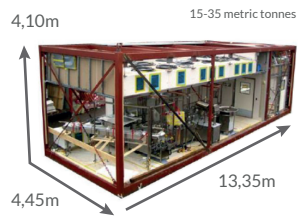
Time required from design freeze through OQ

shortest

most

Flexibility for design, operations, modifications and expansion

least

Option		Typical elements
Hybrid modules *Stick-built building shell with* Process units Technical units Room units (Box-in-Box)		**Process/utilities** Package units Skids and superskids
		**Interstitial zones** Piperacks HVAC
		**Prefabricated wall/ceiling components**
		**Prefabricated cleanroom units**
Facility modules Complete structural building units		**Standard bay** **Large bay**

As always, there are performance trade-offs in these options. While modular design is generally transparent in a facility layout, increased modular construction has more tangible impacts. Greater modularization in construction typically reduces the time from firm project scope definition through operational qualification (OQ) (see Section 3). It also, however, results in reduced flexibility to accommodate late changes in design or modifications for future operations, due to an increase in systems density as well as the amount of supplemental building structure required at the boundaries of each construction module.

Project teams must carefully consider the level of modular construction to integrate relative to specific project goals, objectives and requirements, in addition to particular inherent aspects of the site location. Schedule priorities, first-cost limits and total-lifecycle cost targets all contribute to such evaluations from a project execution perspective, while future flexibility, adaptability and/or mobility needs inform the decision-making from a project requirements point of view. Site condition criteria, moreover, might include material availability, craft labor skills, transportation access and import duties. By concurrently mapping all project priorities and existing conditions, the most appropriate selection can be derived and then more quickly applied to the design, given the complementary relationship of the modular design standards with modular construction options.

4.4 Conclusion

Aligning the biopharmaceutical industry around a standardized, modular facility design and construction framework will facilitate the quick, agile response to a dynamic technology and regulatory context by accommodating modest adaptation versus major redesign and retrofit. Promoting the creation, maintenance and use of catalogues for modular designs at all scales and levels of standardization by all project stakeholders enables significant reuse of facility elements from one project to the next and ensures greater cost certainty along with more rapid execution timelines, all for the ultimate benefit of patients.

5.0

Standard facility example

5.1 Introduction

In this section, the methodology of modular facility design described above is applied to the design of a 2 x 2kL mAbs facility. This is to demonstrate, by way of example, how a standard facility design can be developed using design modules. The facility layout depicted in this standard facility design is a worked example and is not necessarily a recommended design.

5.2 Basis of design

The standard facility example comprises both production and support rooms and is served by a single-circulation corridor. Additionally, the main production rooms are also served by a waste corridor. This waste corridor also serves as a visitor viewing corridor.

The standard facility example contains the following production rooms:

- Seed lab (ISO 8/Grade C)
- Cell culture/harvest/pre-viral purification (ISO 9/Grade D)
- Post-viral purification including bulk filling (ISO 8/Grade C)

Note: All ISO class designations are 'in operation'.

The standard facility example contains the following primary support areas:

- Locker rooms
- Solution prep with distinct areas for both media and buffer prep and hold
- Glass wash, autoclave and clean parts storage
- Column pack
- Control/operator work room
- General logistics areas for incoming components, raw materials, waste, etc.

5.3 Related auxiliary functions

The following elements will most likely be required for the facility to function but are not part of the standard facility example:

- Facility building shell
- Warehouse (including cold storage, freeze/thaw)
- Powder dispensing
- QC labs
- Administrative offices
- Plant utilities
- Clean utilities
- Chemical and solvent handling
- Process waste treatment
- HVAC and building services
- Electricity, servers, plant control center (e.g. BMS, PCS, MES)

The design and construction methodology for these elements, however, must be carefully coordinated to ensure that their delivery schedule is aligned with the rest of the facility.

The following are not part of the standard facility example:

- Equipment design
- Definition of single-use equipment and components and other consumables

5.4 Standard facility example process design basis

The standard facility example will support a 2 x 2kL fed-batch submerged mammalian cell culture based mAb with a 5g/L titer. It will be adaptable to other similar fed-batch processes.

The facility is designed for concurrent multi-product operation, subject to open/closure risk assessment. This is because the process will primarily be considered 'closed' or 'functionally closed'. Open processing will only occur within the seed lab.

The facility is intended to accommodate a nominal biosafety rating of BSL 1.

5.5 Standard core room sizing basis

The process rooms have been sized to accommodate a mAbs fed-batch process comprised of the following unit operations and equipment items:

Table 2: Proposed modularization for production area

Production area	Production room	# of module bays	Unit operation	# of equipment
Upstream process	Seed lab	1	Working cell bank	1
			Incubator and refrigerator	1
			Bio-safety cabinet and lab bench area	1
	Cell culture	5	N-3 single-use bioreactor: 20L	2
			N-2 single-use bioreactor: 100L	1
			N-1 single-use bioreactor: 500L	1
			Production single-use bioreactor 2kL	2
	Harvest	1	Centrifugation	1
			Product break tank mixer	1
			Depth filtration/microfiltration	1
Downstream process	Pre-viral purification	4	Product break tank mixer: 3kL	1
			Purification unit operation bays	4
	Post-viral purification	3	Purification operation bays	2
			Sterile filtration and bulk filling	1

The solution prep room will be sized to accommodate media and buffer preparation and hold. It will be comprised of the following unit operations and equipment:

Table 3: Proposed modularization for support area

Production area	Production room	# of module bays	Unit operation	# of equipment
Solution prep	Solution prep	3	Media prep SUM: 100L	1
			Media prep SUM: 500L	1
			Media prep: 2kL	1
	Solution prep check with assumed titer (5g/L)	3	Buffer prep SUM: 1kL	1
			Buffer prep SUM: 2.5kL	1
			Buffer prep SUM: 200L	1
	Solution prep	4	Buffer prep hold bags	11+

5.6 Assumptions

The following assumptions relate to this approach:

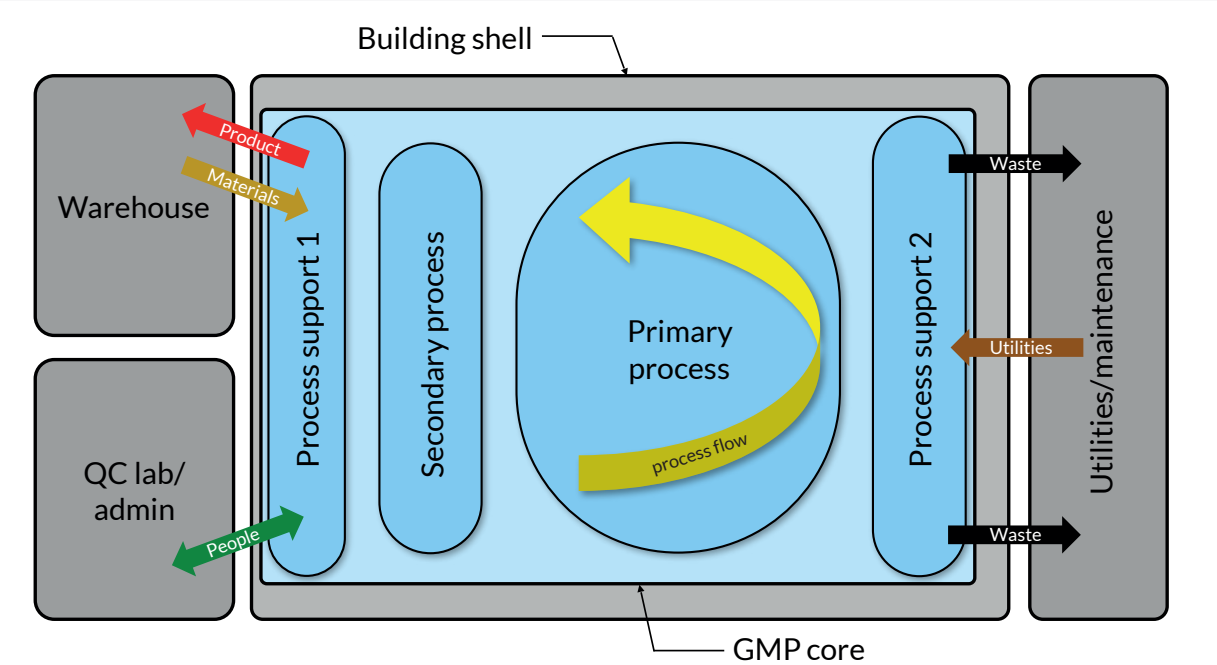
- The process train is comprised of single-use equipment with the exception of a small number of unit operations:
  - harvest centrifuge
  - chromatography columns (it is anticipated that more manufacturers will move to single-use chromatography columns or space-saving membrane absorbers.
- The only equipment subject to CIP from a CIP skid will be the harvest centrifuge. Other equipment such as chromatography columns and UF/DF membranes will be cleaned using buffers prepared within buffer prep.
- The facility provides for traditional column packing.
- Whilst it is anticipated that bulk drug-substance filling will be a closed operation into single-use containers, provision has been made for open-filling into legacy containers.
- Viral segregation is provided with nano-filtration at the boundary between pre-viral purification and post-viral purification rooms.
- Media and buffers will be prepared within the same room.
- Media and buffers will be prepared using single-use technology. Powders will be charged to the single-use mixers using closed single-use bags for preparation and hold.

5.7 Standard facility example layout

Based upon the process requirements already described and interpreted according to the modular design approach described above, the standardized facility team has developed an example conceptual layout to demonstrate how such a design methodology might be manifest in a facility layout.

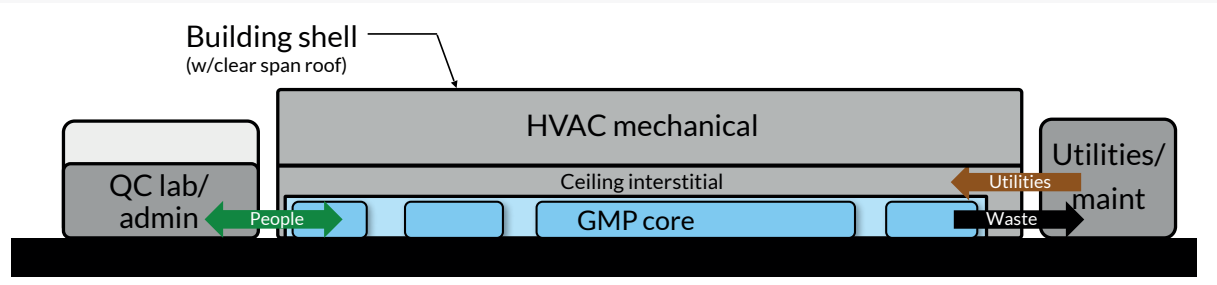
At a macro level, the proposed organization is a simple collection of functional blocks that can be added, taken away or resized as specific project requirements dictate. While the overall configuration can be modified to suit a variety of site sizes and shapes, the basic relationships between blocks should be maintained to optimize the flow of people, materials, utilities, product, and waste. Process flow within the primary process areas should always be counterclockwise to facilitate SUT equipment connections, which are typically left-to-right.

Figure 5: Functional block diagram of mAb drug substance manufacturing - plan view



The GMP core of the example facility utilizes a 'box-in-box' scheme in section as well as plan. Although the supporting functions of QC lab/admin, warehouse and utilities/maintenance are out of scope for the detailed discussion of this paper, it is envisioned that they flank the GMP core, appropriately adjacent to where their interfaces are most direct, either at the ground-floor level, or ceiling interstitial space and second-level HVAC floor above.

Figure 6: Functional block diagram of mAb drug substance manufacturing - section view

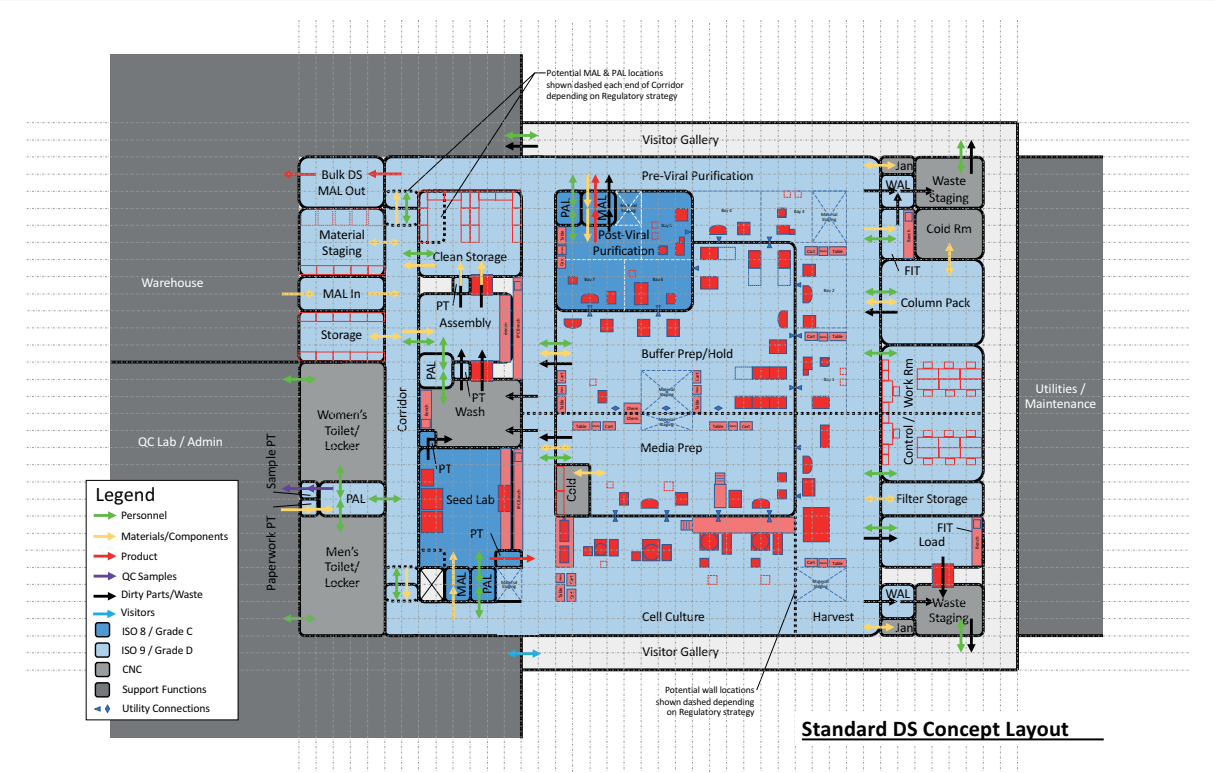


At a more detailed level, the example layout embodies several other planning principles intended to push the boundaries of traditional facility design and advance further the approach to pharmaceutical manufacturing buildings, as well as establish the basis for an industry-wide standard. Key aspects include:

- an open ballroom layout to the maximum extent possible
- media/buffer solutions – adjacent to unit operations with through-wall feeds limiting transport to ≤ 200L
- materials/consumables staging – minimum one batch distributed throughout process areas
- regulatory flows – bidirectional personnel with unidirectional waste
- visitor accommodation outside the GMP boundary with considerable view of process technology

Figure 7 illustrates the example layout. Flows for personnel, materials, components, product, samples, waste, and visitors are indicated by different colored arrows. The location of the arrows indicates probable door locations. Proposed area classifications are depicted by color shading within the room areas.

Figure 7: Standard drug substance concept layout



Regardless of how aligned the industry becomes in its level of standardization for the design and construction of pharmaceutical manufacturing buildings, there will always be a need for facility designs to respond to subtle variations in quality and regulatory requirements. These differences might be driven by authorities specific to location and jurisdiction, special product or process requirements, and/or a particular manufacturer's internal quality policies. While it is impossible to anticipate all possible permutations around these issues, the example layout does attempt to address some of the more common variables that are seen throughout facilities and provide optional adaptations that do not require significant reconfiguration of the layout.

- Media prep can be segregated from buffer prep/hold with the addition of an internal wall.
- Harvest operations can be segregated from cell culture and pre-viral purification for wet, changeover operations by integrating a wall and door at either end of the area. Utilizing sliding doors that stay open allows the free flow of personnel and materials during normal operations.
- Upstream process (USP) areas can be segregated from downstream process (DSP) areas by adding material and personnel airlocks at each end of the entry access corridor, as well as a contiguous internal wall separating cell culture and harvest from pre-viral purification, and the wall separating media prep from buffer prep/hold discussed above. An additional internal wall separating the control/work room in two halves, allows for a GMP technician work area for each major process zone.

Other critical aspects of the example layout that must be maintained in order to enable this flexibility include, two waste staging areas, two janitor cleaning storage rooms and a wash area that provides access from both the USP and DSP areas if needed. Standard HVAC systems and controls should also be designed to permit separate zoning according to the various wall configuration options.

Figure 8 shows the example layout overlaid with the specific unit operation design modules. Modules for accessory areas and open-space zones have been omitted to highlight those modules related to process equipment and operations.

Figure 9 shows the example layout overlaid with a possible arrangement of construction modules. Additional columns are required in some of the open ballroom process spaces to adequately support the intersection of separate modules.

Figure 8: Standard drug substance concept layout – level 1 design modules: unit ops

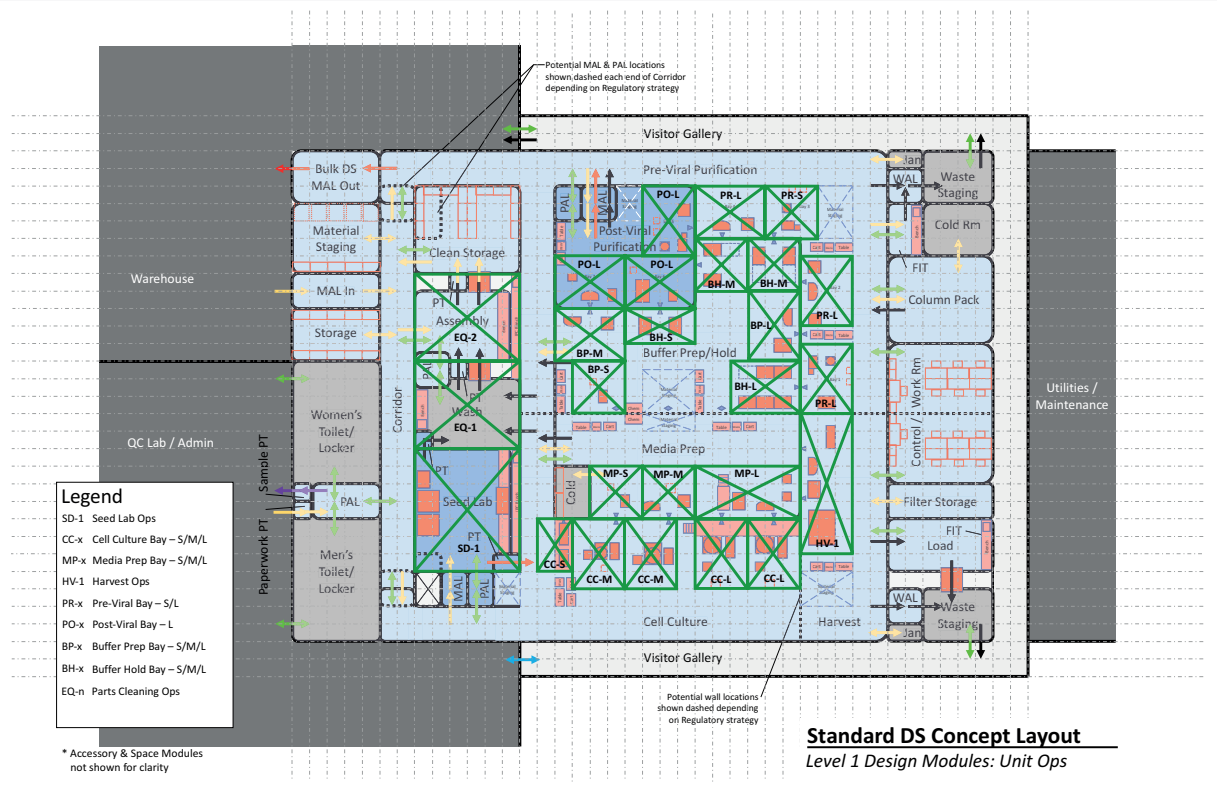
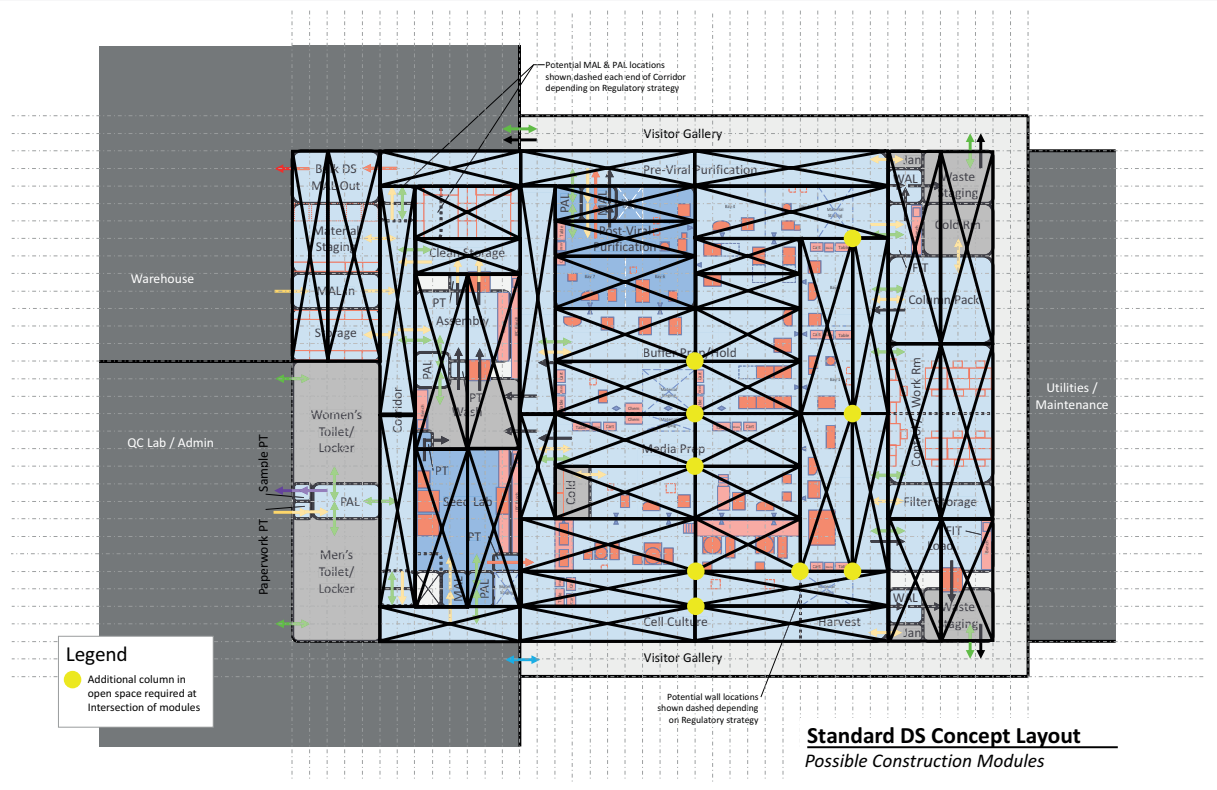


Figure 9: Standard drug substance concept layout – possible construction modules



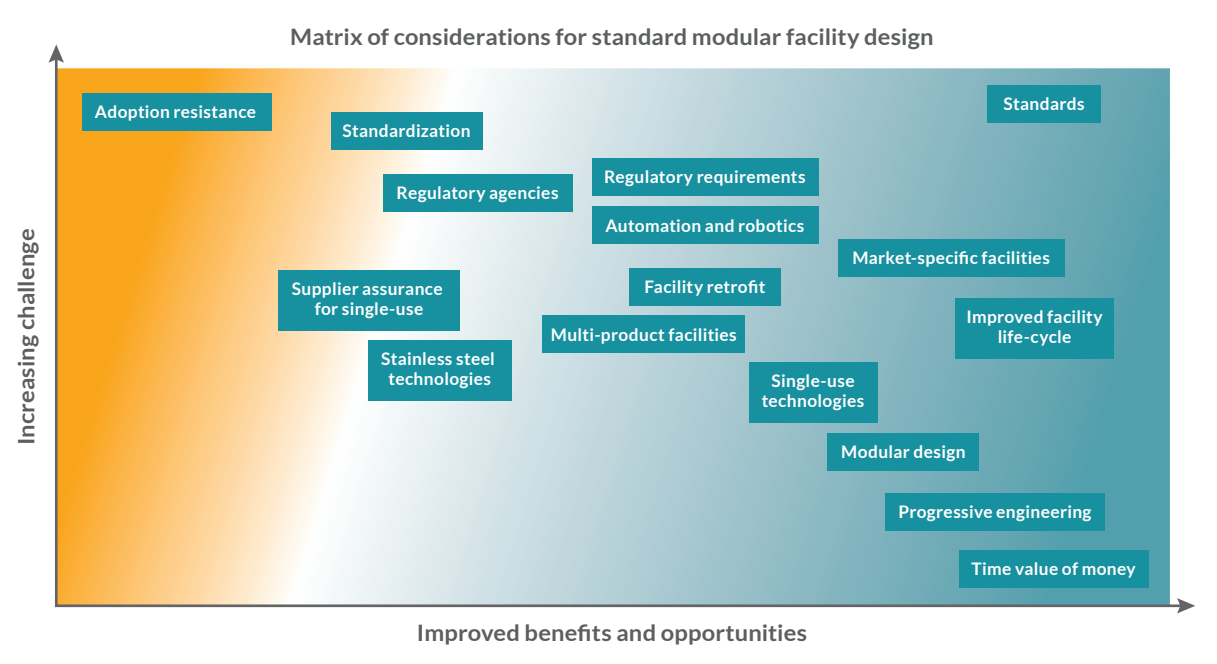
Although not graphically illustrated, the modular design approach (see section 4.2), also allows for the straightforward integration of modular construction techniques for ductwork and piping distribution in the ceiling interstitial spaces, as well as HVAC units in the upper-story mechanical areas. In addition to rapid repeatability, the adaptability provided by a standardized modular facility design maximizes opportunities most effectively to fulfill the cost, schedule, quality and operational requirements of project after project for biopharmaceutical manufacturers.

6.0

Challenges and opportunities

Due to the complex, scenario-specific nature of bioprocessing facilities, it is difficult to capture all the potential nuances, benefits, and challenges of working towards standardized, modular and flexible facility design in a single, brief article, such as this paper. Figure 10 and Table 4 below highlight some topics for consideration and possible impacts that are beyond the scope of discussion for this paper. Each may need to be considered more completely for a given facility situation. Each topic for consideration may present opportunities, pose challenges, or both, depending on the scenario in which they are applied.

Figure 10: Matrix of key topics that influence, or are influenced by, standardized modular facility approaches.
The placement of the topics in the matrix is relative and the relations may shift depending on shifts in industry and regulatory environments.



In the table below, there are points of discussion for the architect, engineer, or others who are applying the key concepts of a modular approach. The column headed 'Mitigation, example facility', highlights concepts and technologies that will mitigate some of the challenges of each consideration, as well as how the example facility in this paper addresses certain challenges.

6.1 Challenges and opportunities detail

Table 4: Challenges and opportunities with suggested mitigations

Consideration	Opportunities and benefits	Challenges	Mitigation, example facility
6.11 Adoption resistance due to pre-existing traditional facilities and/or technology transfer concerns	An underlying principle of standardizing facility design is to start with existing designs instead of taking a blank-slate approach. It may be possible to leverage an existing design of a given customer to alleviate adoption resistance concerns.	The economic inertia of and user-familiarity with the more established ground-up, stainless-steel, customized facility has led to resistance from a variety of interested parties to adopting standardized facilities. For example, parties with existing SS-capabilities have a considerable sunk-cost bias to maintain and may continue to fit the majority of their production into these facilities, driving down cost-per-use. Resistance may also arise from quality groups, who must shoulder the burden of qualifying new and additional technologies or designs. This burden can include writing documentation, designing test plans, and experimentation time. Qualification burden is even greater for existing licensed products and processes. See also **6.21 Progressive engineering**	Standardizing facilities and the approach to facility design across companies, or within a single company can reduce the burden on manufacturing science and technology (MSAT) quality groups by allowing documentation to be transferred with little or no modification from previous facilities. For example, the facility proposed in this paper should enable simplified documentation if the facility is reproduced in multiple locations, or even within the same campus site.
6.12 Regulatory agencies in a global marketplace with diverse experience and exposure to technologies	There is potential for standardized facility designs to reduce regulatory burdens (e.g. qualification testing and documentation) on users by presenting the agencies a more unified approach, improving user experience and increasing understanding of such facilities; and potentially decreasing and streamlining acceptance barriers by regulatory agencies repeatedly exposed to similar standardized design concepts. See also **6.13 Regulatory requirements**	Regulatory agencies often offer a barrier to newer technologies, in understandable efforts to keep patients safe. In addition, regulatory requirements become continually more stringent, further elevating and complicating this barrier.	As the industry standardizes through industrial consensus, data, and education, regulatory agencies will likely follow suit.
6.13 Regulatory requirements due to pre-existing traditional facilities and/or technology transfer concerns	Consistent design of facilities will lead to more consistent expectation of regulatory agencies, who may streamline regulatory requirements, as well as inspection and approval processes and timelines. See also **6.12 Regulatory agencies**	See also **6.12 Regulatory agencies**	
6.14 Standardization of technologies	Standardization of technologies (i.e. making all technologies uniform), such as SUTs, has the potential to streamline facility design and reduce risks associated with supply assurance. Standardization benefits users through commoditization, as seen in the example of shake flask labware for lab scale and seed train. This has yet to be fully realized in other technologies such as single-use bioreactors.	While users are driven to want a commodity-like standardized product to increase competition and reduce cost, vendors are generally incentivized to pursue the opposite strategy to maximize product exclusivity and profit. This economic model is very difficult to overcome without lifted IP restrictions enabling secondary-vendor competition.	As technologies (e.g. SUTs) age, the restrictive patents will expire and may eventually lead to commoditization of key SUTs.

Table 4: Challenges and opportunities with suggested mitigations (continued)

Consideration	Opportunities and benefits	Challenges	Mitigation, example facility
6.15 Standards developed to characterize designs and technologies	Differing from standardization of technologies, the development of standards does not rigidly define technologies to be virtually identical, but rather seeks to create standards that define key product attributes and performance criteria. Application of such standards might more readily enable users to switch between qualified vendor technologies without re-qualification burden. Standards may also be more appealing to vendors than technology standardization, as meeting standards enables comparability without relinquishing IP and exclusivity of performance.	There is an inherent challenge in obtaining consensus on standards, as each user may have different end-use cases. Also, vendors are poorly incentivized to meet any given set of standards unless a clear consensus has been defined by the industry, or the vendors attempt to meet every custom 'standard' set by individual customers and users.	Education and industrial consensus will be required. Industrial forums will be indispensable in connecting users and user requirements.
6.16 Geo-market specific facilities	The ability to replicate facilities more easily through standardized, modular designs may enable market-specific facilities to be readily 'cloned' into new and emerging geographical markets.	The nuance of regulations and logistical challenges in each geographical market may impede the acceptance and implementation of market-specific facilities.	The proposed example facility is designed to meet the diverse regulatory demands that may be seen in geo-market specific facilities. For example, specific geo-market regulators may not currently accept combined media and buffer preparations. The example facility addresses such a concern by including segregation walls to be included as needed by regulations or requirements.
6.17 Single-use technologies (SUTs) in the bioprocess	SUTs are perhaps the key enablers for standardized facilities to be flexible, modular, and mobile. SUTs have the potential to enable completely closed processes, which can have many benefits, such as reduced regulatory burden, reduced environmental monitoring and process segregation, rapid technology transfers and product changeovers, and increased flexibility of facilities for multi-product operations. Leveraging SUTs for in-facility design generally leads to simplified facility utility requirements by largely removing the need for CIP/SIP utility and related piping.	There are potential risks associated with SUTs, perhaps the largest of which is SUT failures leading to loss of sterility and thus product. While SUTs have continually improved in robustness over the last decade or more, failure frequency remains a potential risk. To alleviate this risk, SUT vendors have produced integrity testing technologies, enabling in situ QC of devices. A secondary risk is the leachables and extractables associated with SUTs, which are difficult to identify and more difficult to characterize their potential effects. See also **6.18 Supplier assurance.**	To address the risk associated with L&E, Biophorum has established a set of L&E testing standards, to which SUT vendors are complying, dramatically increasing the available L&E database with the hopes of improved L&E understanding.
6.18 Supplier assurance of single-use to deliver key enabling single-use technologies in a timely, competitive, and cost-effective manner	See also **6.14 Standardization** and **6.15 Standards**	SUTs, and other consumables, pose a logistical challenge in that shipments must be frequently received and stored by a facility, potentially increasing warehouse size. These items must be brought into and out of the operating space, increasing the necessity of good facility design for material flow. SUTs are often incompatible by design, restricting users to a single or only a few vendors. Furthermore, technology qualification can lead to regulatory lock-in with a single product. This can pose a considerable risk of a single source of supply. See also **6.17 Single-use technologies.**	Standardization efforts will reduce the cross-technology qualification burden for regulatory groups. Reducing qualification burden will open the possibility to more suppliers, reducing concerns of supplier assurance. Modular design principles, such as equipment modules proposed in this paper, could also streamline the interchange of equipment types within a facility.

Table 4: Challenges and opportunities with suggested mitigations (continued)

Consideration	Opportunities and benefits	Challenges	Mitigation, example facility
6.19 Stainless steel technologies in the bioprocess	While SUTs potentially enable streamlined standard facility design and increase mobility and modularity of facilities, standardizing facility design still presents an opportunity for permanent or semi-permanent stainless steel (SS) installations. Specifically, SS unit operations (e.g. bioreactors) could be made into 'product catalogue offerings' similar to how SUT-skids have been. Indeed, facilities could also benefit from becoming 'product catalogue offerings'.	Traditionalists who insist on stainless steel, permanently integrated solutions may prevent the full value of standardized designs – such as flexibility, speed, and mobility – from coming to fruition. Furthermore, traditional blank-slate approaches will disallow the potential benefits gained from applying previous designs to future facilities.	Single use Product Development of legacy SS processes.
6.20 Modular design	Modularity in design through the characterization of standard 'parts' streamlines and simplifies architectural and engineering (A&E) workflow. This may enable A&E work to be done more quickly and allow focus to be applied in more detailed, bespoke areas of the design. See also **6.111 Progressive engineering**	See also **6.14 Standardization** and **6.15 Standards**	A key element of the proposed example facility is that fundamental spaces and adjacencies rarely, if ever, change. For example, fundamentally, cell culture will always require adjacencies to media prep, regardless of process or approach. These fundamental adjacencies can be a preexisting aspect of modular design streamlining design for any facility.
6.21 Progressive engineering enabling focused introduction of new techniques and technologies or focus on key challenges of a given facility design	Standardized design principles may never meet the bespoke nature inherent to bioprocess facilities due to many factors (process requirements, local regulation, etc.). However, standardized designs may enable movement towards a Pareto principle in design, where a large portion of the design is rapidly and confidently addressed through standard existing modules, enabling A&E groups to devote considerably more focus and resources towards progressive engineering or facility-specific challenges.	Traditional thinking of facility consumers and A&E design groups that facilities must be from scratch will stymie potential gains from standard design and past efforts. See also **6.11 Adoption resistance**	Time, education, and economic analysis may all be required to move towards a progressive modular design approach. As the benefits of progressive engineering crystallize over time, there will likely be a realization of user requirement alignment, i.e. an understanding that a large portion of user requirements are uniform across most facilities.
6.22 Time value of money increased through faster ROI or lowered **Net Present Cost (NPC)**	Standardized modular facility design can increase the time value of money in one of two ways: 1) through faster return on investment (ROI) by rapid deployment and/or 2) reduced NPCs and associated risks by deferring capital investment until needed. Furthermore, standardization and modularity of design can streamline construction and validation time of secondary facilities.	See also **6.11 Adoption resistance**	

Table 4: Challenges and opportunities with suggested mitigations (continued)

Consideration	Opportunities and benefits	Challenges	Mitigation, example facility
6.23 Multi-product facilities	While traditional facilities would experience high regulatory qualification burden to run multiple products in a given space, modular flexible facilities can reduce that burden through leveraging intelligent design, operation experience, and SUTs. For example, open floor plans or 'ballrooms', enable a facility to be easily configured for current and future operations. This reduces capital risks associated with single-product markets.	Multi-product segregation requirements are still debated and vary between regulatory agencies or inspectors. There is a need to define what a 'functionally-closed' process entails. Occasionally, bioprocesses become open post-process (e.g. depth filtration). This complicates the requirements of potential segregation. See also **6.12 Regulatory agencies** and **6.13 Regulatory requirements**	The proposed facility example suggests good design can incorporate temporary segregation of 'dirty' or open processes, when required. As the target markets for biotherapeutics move to smaller markets, the commercial manufacturing volumes and post-clinical ramp-up will be smaller. This makes smaller, modular, multi-product facilities, such as the proposed example, increasingly valuable. See also **6.16 Geo-market specific facilities**
6.24 Brownfield retrofit	Greenfield design is less restricted in design space than brownfield design. Utilizing the modular approach may not fit precisely in a brownfield facility. However, the design principles, such as adjacencies and fundamental segregation needs can readily inform the design and end user of clear expectations of facility capacity.	Brownfield may be constrained due to utilities, physical limitations and adjacencies available.	A standard for understanding fundamental user requirements enables rapid suitability evaluation of brownfield sites.
6.25 Flexible facility lifecycle	The reality of facility lifecycle is occasionally overlooked when confronted with the immediate needs of a facility. However, new processes and technologies continue to be deployed, such as continuous processing, personalized medicines, and high-intensity cell culture. Standardized, modular design should enable many aspects of future technologies with minimal reconstruction required.	New technologies may pose challenges that exceed the ability of the modular facility to meet product requirements, which might include physical constraints and utilities available. This is generally a low risk, particularly as bioprocess technologies get intensified and miniaturized, leading towards more uniform and simplified utility and space requirements. See also, **6.24 Brownfield retrofit**	Improved ease of access is provided by good modular facility design. Such access, and generalization of needs (e.g. unit operation modules) work to future-proof facilities against new processes and technologies. Engage key component/system suppliers early in the design process to establish aligned modular approaches and continue expanding global network capabilities.
6.26 Modular building material	By building with modular materials or in a modular construction format, much of the construction can be performed off site, decreasing timeline risks associated with non-modular approaches.	Modular materials can impose physical limitations on the final design, which may arise from material properties, commercial availability, or transport constraints. Prefabricated parts must be reasonably shippable.	There are an increasing number of suppliers globally who can furnish components/systems in a modular setting. Many of these suppliers also have on-shore representation. Working with key suppliers to expand their global network is critical.
6.27 Automation and robotics	Facility standardization and modularization will streamline the integration of automation and robotics into facilities, potentially accelerating automation integration, improving facility efficiency, and reducing operational errors. Automation is also key for the successful implementation of many of the technologies proposed in this paper.	Automation is often thoroughly customized and therefore very costly. This time and money cost is due to reduced efficiency in implementing the automation.	Work through industrial forums, such as BioPhorum's Automation workstream, will improve the modularity and standards of automation, which dovetails with aspects of the standard modular facility to improve.

7.0

Quality and regulatory requirements

7.1 Quality

Standardization should not be limited to design and construction but should be extended throughout facility qualification. Standardized facility platforms allow structuring the qualification effort in standardized modules, where all documents and activities are predefined and scheduled. These qualification efforts will run smoother with each consecutive site following the same standardized principle, as any learnings of the previous qualification efforts can be transferred. Even if this approach is already a common practice for system units (e.g. water system) it is now possible to extend it fully to the entire facility and benefits in terms of cost and time will follow. Parallel, modular training programs for operators can be put in place or even completed in advance of the facility being finalized. Once construction is complete, trained personnel can immediately progress with the qualification and operations.

7.2 Regulatory

For many years, some regulatory authorities have voiced their support for agile and flexible facilities. The standardized facility platform design is based on these principles. As the site is process intensified, it can be built faster, in different locations and with a high degree of flexibility utilizing adaptable process technologies.

It is important that global regulatory authorities see the benefits of the standardized facility platform to gain efficiency effects such as abbreviated review processes, pre-approval inspection or market approval inspections.

The benefit of standardization of facility layouts is the familiarity for the regulators. The standardized facility design will act as a template. Regulators, reviewers and inspectors know the processes, the facility layout and its specifications. The facility and its quality system have been inspected previously, becoming a familiar entity for the regulators. Reviews may be abbreviated, since there is a preexisting knowledge base of the formerly inspected standardized facilities.

The effects of a standardized facility are not only beneficial for new facility entities, but also for any technology improvements and the resulting post-approval change. For example, when a technology improvement is implemented into a standardized process, the subsequent approval within the duplicated process entity may be abbreviated.

8.0

Conclusions

Employing a standardized modular approach to biopharmaceutical facility design provides benefits throughout the entire lifecycle of such facilities. These benefits may be further enhanced when also applied to commissioning and qualification requirements, as well as construction methods if clearly aligned with the business drivers and context of specific projects. As demonstrated in the business case comparisons and articulated through the example facility case, a standardized modular approach can reduce project schedule durations, increase project cost certainty, facilitate rapid design reuse, expedite regulatory review, and improve overall compliance. In addition, standardized modular facilities are inherently more flexible and adaptable to new bioprocess technologies and changing market demands, allowing them to meet patient needs productively over longer periods of time with lower costs required to continually retrofit or replace.

While a traditional fed-batch cell culture process is used as the basis for the example facility, the concepts and methods of standardized modular facility design can be beneficial to a variety of other applications. Other process platforms might include intensified fed-batch, perfusion/continuous processing, and cell/gene therapy facilities. In coming work, we will examine the impacts of a standardized modular approach on other applications to evaluate its appropriateness and highlight the benefits specific to these different use cases.

9.0

Definitions/glossary

9.1 Definitions

Term	Definition
Ballroom	facility design in which all process operations take place in an open common area without physical wall or room separation
Bidirectional	facility design where personnel and materials flow in out of areas through common doors and passageways
Box-in-box	a facility construction approach incorporating a modular cleanroom structure (box) which is independent of the main shell building structure (box)
Closed process	a process system that is designed and operated so that the product is never exposed to the surrounding environment See ISPE Baseline Guide Vol 6: Biopharmaceutical Manufacturing Facilities
Module	a set of standardized parts or independent units that can be used to construct a more complex structure, such as an equipment skid, pipe rack, room or building
Modular	a method or basis of design or construction which involves standardized units for easy construction and flexible arrangement of separate parts, that when assembled form a complete whole
Multi-product	manufacturing of different drug substances or drug products on the same fixed or flexible process lines; manufacturing of different materials needs segregation with a planned and defined campaign changeover, including cleaning, according to a validated procedure
On-site construction	the planning, design, and construction of a building at the final installed location, also known as traditional construction
Off-site construction	the planning, design, fabrication, and assembly of building elements at a location other than their final installed location, also known as prefabricated and modular construction
Primary process	manufacturing of drug substance – cell culture through bulk filling including solution/buffer prep and hold areas
Process support	lockers, material staging and storage, waste handling, column packing and technician work areas
Qualified	the state in which all installation and operational qualification tests of plant systems and critical environments have successfully been completed and the plant is ready for handover to the owner
Secondary process	seed lab and parts washing areas
Standardize	the process of creating and/or using consistent, repeatable solutions or standards
Stick-built	a common method of building, in which raw materials are shipped to the site which they are intended to occupy on building completion; materials are cut to size and assembled on site rather than in a factory or similar facility
Standard	an established and industry-accepted element, component, or configuration of multiple elements or components that can be readily reproduced and repeatably utilized
Unidirectional	facility design where personnel and materials flow in out of areas through dedicated and separate entry and exit doors and passageways
Shell	the exterior building structure of a facility

9.2 Acronyms

Term	Definition
A&E	Architectural and Engineering
ASTM E-2500	American Society of Testing and Materials
BSL	Biosafety level
CAPEX	Capital expenditure
cGMP	Current good manufacturing practice
CIP	Clean in place
CMO	Contract manufacturing organization
COGS	Cost of goods sold
CUB	Central Utilities Building
DSP	Downstream processing
EHS	Environmental health and safety
FAT	Factory acceptance test
HVAC	Heating, ventilation, air conditioning
IP	Intellectual property
IQ	Installation qualification
ISO	International standards organisation
L&E	Leachables and extractables
mAb	Monoclonal antibody
MAL	Material Air Lock
MES	Manufacturing execution system
MSAT	Manufacturing science and technology
NAMUR	Interessengemeinschaft Automatisierungstechnik der Prozessindustrie User Association of Automation Technology in Process Industries
OQ	Operational qualification
PAL	Personal Air Lock
PAT	Process analytical technologies
PT	Materials Pass-Through
QC	Quality control
SAT	Site acceptance
SIP	Steam in place
SS	Stainless steel
SUT	Single-use technology
UF/DF	Ultrafiltration/diafiltration
USP	Upstream processing
WCB	Working cell bank
WAL	Waste Air Lock

Appendix

Business case supporting data

Figure 11: Construction methods timeline comparison