BIOMANUFACTURING TECHNOLOGY ROADMAP

MODULAR AND MOBILE

Acknowledgments

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1.0 Summary

Biopharmaceutical products, and cell and gene therapies, are currently produced in fixed facilities that require a significant upfront, at-risk capital investment. Often, these traditional facilities are also product-dedicated, meaning that the facility lifecycle correlates to the product lifecycle and can require significant investment to retrofit for new applications.

Modular and mobile concepts offer an opportunity to shift from these large, fixed assets to networks of smaller, standardized manufacturing facilities. These can be built in less than half the time and in a way that defers costs until there is greater certainty about market demand and the probability of clinical and market success.

New modalities are emerging within the biopharmaceutical field, such as viral vectors and gene technologies, where smaller processes require higher segregation and containment. These present a challenge to traditional facilities. Modular and mobile concepts could provide a ready solution for these product types and enable a quicker changeover between them.

Challenges include the following:

1. industry consensus to define and achieve standardization of equipment format and consumable items
2. simple design that is fit for purpose[1] and/or repurposable, enabling easy scale up and scale out, and easy relocation
3. treating the facility as equipment for qualification, simplifying verification and validation, and eliminating repetition
4. standardization of regulatory validation requirements and the global harmonization of other relevant regulations, such as building and safety requirements
5. operational robustness, including efficient capital funding management, maintenance processes and training provisions
6. distinct environmental challenges related to the increased use of single-use systems (SUS).

Standardization of the manufacturing platform provides the opportunity to accelerate the delivery of therapies to the market and to improve product quality and patient safety. The responsiveness of supply chains can be improved and the regulatory review for new products and for adding additional capacity can be simplified. Unique applications are possible for high-containment processes as well as pandemic responses. Ultimately, the approach can further the miniaturization of processes and facilities to enable the delivery of personalized medicine at the bedside of a patient.

2.0 Introduction

In the history of the biopharmaceutical industry, there has been a cyclical demand for manufacturing capacity. This can lead to concerns that there is not enough capacity for the products that the industry has in the pipeline. This cyclical nature leads to some potential hurdles that need to be addressed for our industry to be successful. These include:

1. high capital cost – biopharmaceutical manufacturing facilities tend to be more expensive than small molecule plants as they are more complex, have intricate equipment, are more highly automated and they require more maintenance to be kept in a validated state at all times. This higher capital cost leads to a greater depreciation, which then will reflect negatively on the cost of goods
2. capital investment well before demand – to meet regulatory requirements, biopharmaceutical products must be produced at scale and preferably in the facility where they will be manufactured. This cycle forces the industry to make decisions and commitments to spend large amounts of capital before it can accurately predict product success or accuracy of sales forecast
3. high inventory and long cycle time – a cell culture process could take around 60 days to complete with further time required for quality acceptance, filling and shipment. This long cycle time forces companies to have a buffer of inventory to eliminate the risk of a stock-out situation
4. lack of flexibility – traditionally, manufacturing suites are built around a platform process or specific product. The suites are also designed with a 'best guess' forecast in mind. Because of these drivers, factories are not always the most flexible in terms of scale and potential capacity fluctuations
5. cost of goods – due to a number of points already raised, the cost of goods for products may be an issue. Generally, depreciation, labor costs and materials drive the cost of goods. Being able to tackle any of these issues will help to drive the costs of goods down
6. difficulty of change for new technologies – the regulated state and possible non-flexibility of manufacturing operations make it very difficult to introduce new technologies. A new technology may require shutdowns, revalidation, further regulatory approval and significant capital, which all need to be evaluated before trying to incorporate a change.

[1] "Fit for purpose" in this report is intended as a design concept and not in the sense of contractual specification.

2.1 Vision

Biopharmaceutical therapy development has always been a costly and risky endeavor. However, recent changes in the market (such as increased payer cost pressure, increased competition and demand for in-region manufacture) when coupled with inaccurate market forecasts and uncertainty in the success of Phase III clinical trials has made it necessary for manufacturers to reduce costs and improve efficiencies. Traditionally, biopharmaceutical manufacturing has been centered on monoclonal antibody (mAb) and primarily based on stainless steel facilities that require a significant amount of upfront capital investment and take a number of years to build and qualify. To ensure sufficient capacity is available for new products, companies have had to invest in facilities or reserve contract manufacturing organization capacity well in advance of clinical trial results, based on early market forecasts that are usually inaccurate. This traditional environment has resulted in significant increases in the cost of goods due to underutilization of facilities or the need to quickly secure contract manufacturing organization capacity or, alternatively, an even more significant impact on lost profits due to an inability to supply market demand. This situation also limits patient access to medicines and reduces the amount of capital that companies have to invest in developing new products. Compounding this situation is a recent trend towards smaller-volume products for smaller patient populations and the potential for curative treatments through gene therapy. Both of these require lower volume, segregated higher containment and, in some cases, localized production facilities.

Modular and mobile concepts offer a potential solution to these problems, as well as opportunities to enable new types of therapies. By using standardized, modular designs for manufacturing facilities and by treating the facility as equipment, companies have the potential to accelerate drug development and launch; defer decision-making on adding capacity until later in a product lifecycle when there is more certainty about clinical trial success and market projections; and enable the rapid addition of capacity by 'scaling out' to respond to changes in market demand without disrupting existing operations. Treating the facility as equipment accelerates the procurement and licensure of new manufacturing capacity. By reducing the size of manufacturing operations to make them mobile, companies can more effectively deliver lower-volume therapies (including gene therapy and personalized medicine), enable pandemic disaster response and may have the potential to produce and deliver treatments at a patient's bedside.

2.2 Scope

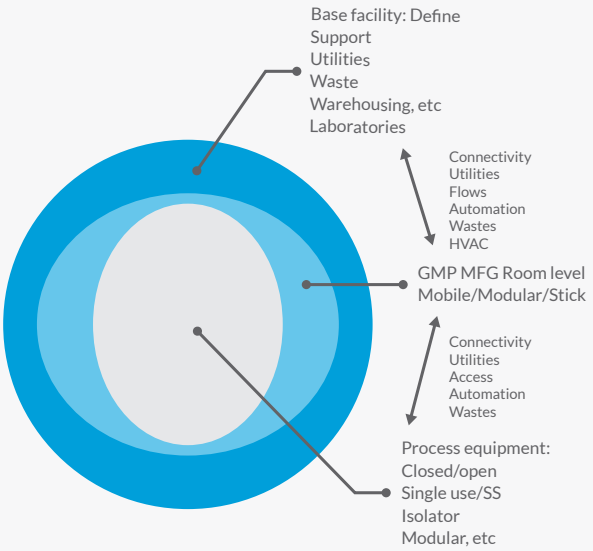
To understand the scope of the Modular and Mobile roadmap, it is helpful to first understand some definitions:

Modular – employing a set of parts as independent units that can be used to construct a more complex structure

Mobile – able to be moved freely and easily.

These are complementary concepts that can be applied to varying extents across the design space. A 'Russian doll' model (see Figure 1) illustrates nested layers of design functionality in a biomanufacturing facility. Modular and mobile design concepts can be applied within and across the design layers of facility, room and equipment with connectivity as a key enabler.

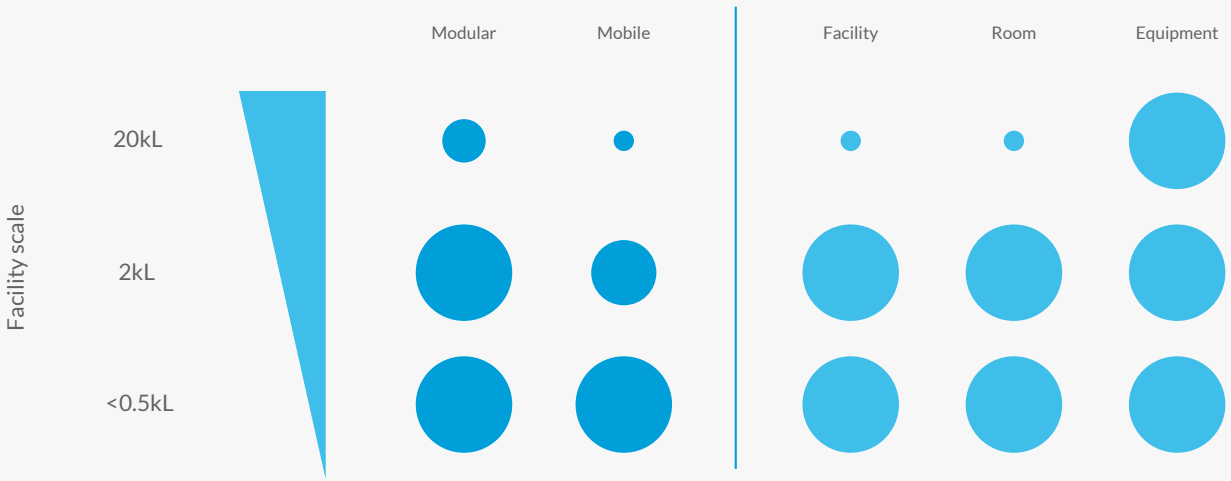
Figure 1: Modular and mobile 'Russian doll' – Layers of design functionality



MFG – maufacturing, GMP – Good manufacturing practice, SS – stainless steel

The degree to which each of the concepts can be applied partly depends on the facility scale, as indicated by the production bioreactor volume in Figure 2. Modular concepts can be applied across all scales with benefit since they can be applied to the equipment at larger scales, while mobile concepts are not very applicable above the 2kL scale due to modular mobile cleanroom unit (MMCU) transport limitations. Additionally, 2kL is the largest scale of single-use bioreactor currently available. Single-use process equipment supports the modular and mobile approach since it reduces capital expenses and build times, transferring costs to operational expenses that can be covered once an asset is returning revenue.

Figure 2: Applicability of modular and mobile concepts



Source: Charles Heffernan, GSK

There are different factors that motivate the adoption of a modular and mobile approach, and the extent to which they are used:

1. scale of the process (modular and mobile concepts are more easily employed for a smaller footprint processes)
2. scale of the market (a smaller market makes modular and mobile concepts more advantageous)
3. product maturity (new product introduction favors modular and mobile concepts due to lower capital costs and faster build times)
4. speed to market (modular and mobile concepts offer potential to reach the market sooner)
5. centralized vs localized manufacturing (distributed and in-country manufacturing drives modular and mobile concepts)
6. containment (the need for high-containment biosafety levels drives modular and mobile concepts)
7. uncertainty in demand (a modular and mobile SUS new product introduction launch facility defers the need to make decisions and enables rapid capacity additions)
8. flexibility in process platform and scale (modular and mobile concepts allow for the use of the facility for multiple processes)
9. cost (modular and mobile concepts have lower capital costs and move some costs to operational expenses, which can be covered when a product is returning revenue).

The scope of this document includes end-to-end manufacturing from drug substance (DS) to drug product (DP) and packaging across the full range of capacity scenarios. While it is recognized that design solutions may vary with scale, the concepts of connectivity and standardization required to enable speed and flexibility are the same. To illustrate modular and mobile technology needs, this roadmap will focus mostly on modular cleanrooms and process equipment for smaller-scale processes or process intensification. In practice, similar concepts can be applied to larger-scale and 'open ballroom' designs to enable speed and flexibility across the range of capacity scenarios.

Moving forward, modular and mobile must be implemented as a holistic concept to be effective in generating the truly innovative manufacturing capability of the future. Therefore, this document outlines the important linkages to other roadmaps that enable all of the components required for modular and mobile design, i.e. process technology, component connectivity, configurable automation platforms, integrated process analytical technology (PAT), real-time release (RTR) and supplier management. These topics will be discussed further in Section 5: Linkages to other roadmap teams.

A key enabler of modular and mobile approaches is the development of standards for room, utilities, equipment, single-use components and automation design. With standard design solutions and seamless connectivity, modular and mobile manufacturing will become flexible and cost effective while decreasing on-site validation requirements and improving speed to market.

2.3 Benefits

Some modular and mobile concepts are already embraced throughout the biomanufacturing industry, from disposable formats and mobile unit operations within facilities to the assembly and deployment of entire facilities to the location of manufacture. Different product classes, manufacturing and business scenarios will benefit from different aspects of mobility and modularity in biomanufacturing. Some of the main benefits are listed below.

Flexibility aligned with emerging product classes and smaller patient populations

The increasing sophistication of companion diagnostics and stratification of medical indications is likely to bring about an unprecedented number of biologics that make it into and past Phase I and target small patient scales, the smallest being N=1 patient (truly personalized medicine). To manufacture such a wide portfolio of drugs, the only viable solution would be a small-scale, modular and mobile approach.

Payer pressure to reduce cost

It is too early to predict the impact on the cost of goods/cost of supply of the smaller scales (bioreactor volumes of 100L down to <1L) compared to that achieved with the larger assets. In a fully utilized large-scale plant, the cost of goods is expected to be much lower due to economies of scale. However, in an under-utilized facility these costs surge and therefore small plants could offer economical gains in addition to flexibility. Even if the $/gram cost for any single drug is not reduced in comparison to that of large-scale facilities, it will collectively de-risk the financial commitment to larger assets when a biopharmaceutical manufacturer needs to develop a portfolio of drugs, where only a few may reach the mass market.

Reducing manufacturing costs alone is not sufficient to reduce the cost of treatment. It is not in the remit of this report to discuss the innovation needed across the entire process of bringing drugs to the market. In certain cases, e.g. biosimilars in developing countries, the cost of biomanufacturing is still very important for patient access to drugs.

For new classes of biotherapeutics, such as cell therapy and certain types of gene therapy targeted at the individual patient or small patient populations (1–100

patients), the manufacturing costs are prohibitive for wide patient access or have been operated at a financial loss by biopharmaceutical companies (e.g. as part of social mission programs). For such therapies to be a value proposition for biopharmaceutical companies and to become accessible to the mass market, they must first be operated at significantly reduced costs (75% reduction in the cost of manufacturing being an initial estimate). Application of mobile and modular concepts in streamlining and managing these costs is going to be crucial, as traditional ways of manufacturing and economies of scale in the cost of goods per product do not apply in supplying small dosages.

Regional manufacturing

Modular and mobile concepts enable flexible manufacturing, whether used to secure regional market access, scale out of identical processes (thus avoiding the complexities of scale up transfers) or satisfying the need for urgent manufacture (e.g. pandemics or managing unexpected inventory shortages). Modular and mobile concepts may assist with regional access by enabling the rapid, cost-effective delivery of standard, modular facilities to local regions.

Speed to clinic and fast to market

It is expected that platform approaches will be adopted in manufacturing plants. Moving from bespoke to standardized, off-the-shelf solutions will reduce both the cost and completion time of ready to use biologics facilities. The time to assemble and reach a validated status for a modular and mobile plant will depend on pre-validation of the individual parts and of the assembly process. Assuming the technology needs for standardization, economies of scale of producing the required standard for good manufacturing practice (GMP) use and supply chain, it would be possible to further reduce speed to clinic.

Repurposability

Modular and mobile cleanroom systems are not designed and constructed as product-dedicated systems, but can be utilized for multiple product lifecycles or processes. Modular and mobile containment units need to be flexible and robust to be re-used when the existing production process is not required any longer. In instances where modular and mobile cleanroom space is not required any longer, such as for media preparation when concentrated media feeds replace the traditional unit operation, the modular and mobile unit can be repurposed for other processing steps. Modular and mobile systems can also be relocated if demands change.

3.0 Scenario needs

This section provides an overview of the ways that modular and mobile concepts can be employed to five drug substance biomanufacturing scenarios as well as the two drug product biomanufacturing scenarios described in this roadmap. The concepts can be applied to the facility, room and equipment. This section starts with the description of a scale-out strategy that can be applied to both intermediate scale drug substance scenarios, followed by application to the large-scale scenario, and concludes with application to the small-scale scenarios. Table 1 presents the biomanufacturing scenarios and a summary of needs.

Starting with the challenge of supplying new products, companies can significantly accelerate speed to market, reduce capital and defer decisions to add capacity. They achieve these benefits by standardizing their product development efforts to deliver processes that fit with pre-established guardrails, for example, of a 2kL mostly single-use manufacturing platform that can be quickly replicated or 'scaled out' to respond to changes in market demand. Technology transfer is accelerated, and the need for comparability studies during technology transfer is removed, by developing processes within a standard framework that include materials, disposables, equipment, automation, procedures and recipes. Capital expenditures are deferred and reduced since facilities that strategically utilize single-use can be built in less time and at a lower cost. When a more accurate estimate of sales volume is established, products can then be transferred to a larger-scale facility if a reduction in the cost of goods and increased volumes are required. Using this approach, cost and risk can be allocated to each asset and discharged through development and launch. This approach can be applied to both of the disposable 2kL biomanufacturing scenarios that use a fed-batch or perfusion-based upstream process as well as the low-volume/high-value drug product scenario. In terms of design, the equipment and automation could be modularized and installed in a large 'open ballroom' facility. Alternatively, the room itself could also be modularized using MMCUs that allow for processes to be swapped in and out of a facility and offers increased containment for heightened biosafety requirements. MMCUs are portable, which makes them particularly relevant for vaccine manufacture and pandemic responses. Additionally, they offer the potential for economies of scale if a sufficient number of companies are buying a standardized design. Regardless of the approach chosen, both present the opportunity to co-locate drug product filling lines with drug substance facilities, therefore improving the responsiveness of supply and increasing efficiencies in inventory, headcount and quality control (QC).

In the large-scale biomanufacturing scenario (i.e. 20kL), modular concepts can be applied to the facility build as well as to the equipment and automation. Facility build times can be decreased due to parallel design and construction by fabricating equipment as interconnecting modules that are connected once the facility shell is complete. Future expansions can be accelerated by building a central core of utility systems that are sized to support such expansions or that have the capability of adding additional utility supply modules at a later date. Additional space and bays can also be created in the building design to add additional manufacturing trains in a modular fashion. Once a standardized design is accepted or developed, future build times can be reduced and economies of scale could be realized if multiple companies use the same design.

Scenario 4 (less than 500L) allows the full application of modular and mobile principles along with an integrated DS–DP approach. This approach can create significant efficiencies from having a shared infrastructure and personnel as well as eliminating significant amounts of unfinished inventory typically held at an active pharmaceutical ingredient site. One can envision facilities ranging from those with a 500L continuous bioreactor to a facility that fits into a cargo container, a backpack or on a chip. Continuous bioprocess facilities on the larger end of this spectrum could offer a cost of goods that are comparable to traditional large-scale stainless steel facilities, with a much smaller footprint that makes them amenable to scaling out or being used to meet demands for in-region manufacture. Facilities on the smaller end of the spectrum can enable new treatments, such as gene therapy and personalized medicine at a patient's bedside, as well as localized responses to pandemics or biological attacks. Standardization at this scale fully bridges the gap between process development and commercial supply.

Table 1: Bioprocessing scenarios, key technologies and capabilities

		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Description	BXR volume	SS >10kL BXRs	Disposable 2kL BXRs	Disposable 2kL BXRs	Disposable <500L BXRs	Disposable <50L BXRs
	BXR mode	Batch	Continuous	Batch	Continuous	Batch/continuous
	DSP mode	Batch/continuous	Semi-continuous/ continuous	Batch/semi-continuous	Continuous	Batch/continuous
	Facility design	Segregated suites/ large footprint	Moderate footprint/ ballroom or MMCUs	Moderate footprint/ ballroom or MMCUs	Small footprint/ballroom or MMCUs	Small footprint/ballroom or MMCUs
	Processing	Low bioburden	Closed	Closed	Closed	Closed
	Product	mAb and other CHO TPs	mAb and other CHO TPs	mAb and other CHO TPs	mAb and other CHO TPs	Cell/gene therapy
	Business drivers that influence a modular and mobile approach	• Capital cost • Speed of build/add capacity • Quality control for in-region manufacture	• Capital cost • Speed of build/add capacity • Quality control for in-region manufacture • Development cost • Response time to changes in demand • Access to CMOs		• Capital cost • Speed of build/add capacity • Quality control for in-region manufacture • Development cost • Response time to changes in demand • Cost to build • Inventory cost (co-location of DS/DP) • Containment and segregation • Decentralized manufacturing	
Modular and Mobile foundations	Facility	• Traditional build • Central utility modules • Modular suite design • Supply that can turn up/down or expand	• Modular wall panels can be utilized for support, laboratory and office areas. Alternatively, these can be modular • Process and utilities can be packaged within a module • Multiple interconnected modules are likely • Utilities module(s) connects to multiple processes		• Everything fits within a module (e.g. utility, support and laborato ry). Modular wall panels can be utilized for support areas if more cost effective • Size may lead to multiple modules that are connected • Utilities module(s) connects to multiple processes	
	Room	• Modular design principles • Downstream modular-type concepts • Pre-engineered rooms	• Open ballroom with heating, ventilation and air conditioning (HVAC) above, or each unit operation has own local HVAC • Isolators around certain unit operations • Alternative for MMCUs for high-containment operations		• A variety of scales can be provided, such as suitcase, benchtop and/or 500L ballroom or MMCU scales • Fully integrated and contained, delivered easily in this format • Minimal on-site start-up qualification and/or pre-qualification	
	Equipment	• Modular process skids	• Modular process skids • Cost-effective process contact components for fully single-use product path • Media delivery for continuous equipment • Continuous chromatography requirements • Plug and play, common interfaces for equipment and automation • Infrastructure to physically move what may be large equipment		• Modular process skids • Cost-effective process contact components for fully single-use product path • Media delivery for continuous equipment • Continuous chromatography requirements • Plug and play, common interfaces for equipment and automation	

BXR – bioreactor, CHO TP – Chinese hamster ovary cells therapeutic protein, CMO – contract manufacturing organization, DP – drug product, DS – drug substance, mAb – monoclonal antibody, MMCU – modular mobile cleanroom unit, SS – stainless steel, SUS – single-use system

Table 1: Bioprocessing scenarios, key technologies and capabilities (continued)

		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Technology/capability needs	Standardization	• Automation interconnectivity	• Facility and process design standards • SUS compatibility/interconnectivity • SUS standards • Multiple SUS sources of supply • Facility and SUS vendor certification • Sensor integration • Technology transfer methodology • Harmonization of regulatory and building codes • Automation interconnectivity			
	Fit for purpose, simple design	• Platform capability instead of product-specific approach • Ease of changeover	• Modular off-site build of prefabrication plug-and-play modules • Platform capability instead of product-specific approach • Standard spacing unit operations and utility panels • Ease of changeover • Family validation and pre-qualification approach • Space to add additional capacity or unit operations and to perform maintenance • Repurposability • Ability to add capacity without service interruption • Robust disposables • Compatible SUS connectors • DP/DS co-location – small, flexible fillers			
	Facility as equipment		• Facility and room treated as equipment for purposes of qualification • Family validation approach, prefabrication and pre-qualification • Standard facility designs that are replicated • Design that complies with majority of regulatory and building codes			
	Operational robustness		• Robust SUS performance and supply • Standard and effective training • Cycle of continuous improvement			
	Drug product		• No technology transfer from clinical to commercial • Standard, modular and portable filler design that can fill multiple formats.			

BXR – bioreactor, CHO TP – Chinese hamster ovary cells therapeutic protein, CMO – contract manufacturing organization, DP – drug product, DS – drug substance, mAb – monoclonal antibody, MMCU – modular mobile cleanroom unit, SS – stainless steel, SUS – single-use system

4.0 Future needs, challenges and potential solutions

4.1 Industry standardization

4.1.1 Needs

The current state of the industry allows for any manufacturing facilities and processes to be assembled from its discreet parts. However, the final assembly requires a lengthy and detailed consultation with vendors to provide a multitude of bespoke solutions. These solutions vary with the interpretation of a modular build, personal experience, bias and business models by both vendors and biopharmaceutical clients alike. The construction of a manufacturing plant (even small- to mid-scale) using these custom solutions would be expensive, time-consuming and possibly difficult to scale out, especially where certain activities (e.g. welding and customized connections) carry operator variability that increases contamination risks.

While it is understood that no two biologics will be made using the same process, it is reasonable to claim that most biologics can be made using a combination of units of operation, while allowing for special cases where additional units of operation may be required. Each unit of operation can be considered a module, with standardized manufacturing specifications set and approved by industry-wide experts and regulators. Assembling a final process from its modular parts can also be standardized, controlled and regulated so that the end result is, by quality and design, a pre-validated or easily validated system. Speed of setup, production and teardown (if appropriate) is then minimized.

To enable the rapid fabrication and assembly of cost-effective manufacturing plants that can consistently produce a quality product, standardization is required at a multitude of levels including facility, room, equipment, automation and consumables. To error-proof the assembly process and operation of the resulting biomanufacturing plant, standardization needs to apply when training operators for the assembly, installation and qualification of the modular plants (containing all required bioprocess equipment), following GMP principles and with the use of easy to follow visual guides. The training aspect is crucial in the scenario of a multitude of biomanufacturing plants being installed, in an industry with high rates of employee turnover.

We envisage that in the medium-term the manufacturing of small- to mid-size manufacturing plants will be widely adopted and streamlined with the help of the elements outlined in Table 2, Section 4.1.2. To achieve this, biopharmaceutical companies will need to adopt processes to the plant range of capabilities. In the current state, standardized manufacturing is technically possible but the end users tend to add bespoke alterations.

We propose that biopharmaceutical companies, vendors and contractors catering to the biopharmaceutical sector and regulators come together to set such requirements and agree on standards for SUS interconnectivity and design, facility design and fabrication, automation, and associated testing and validation procedures. Such collaboration will then enable the benefits of modular and mobile manufacturing to be realized across the industry.

4.1.2
The needs, challenges and potential solutions table

Table 2: Industry standardization – needs, challenges and potential solutions

		Current	2019	2022	2026	Scenario(s)
(Metric 1)	Profit/return on investment					1-5
(Metric 2)	Operating expenditure	$100/g	$50/g		$10/g	1-5
(Metric 3)	Capital expenditure (CAPEX)	$100m	$50m		$25m	1 (including utilities and support)
Need	Facility and process design standards: standard facility designs for manufacturing of small- to mid-scale facilities. Includes 'room as equipment' (where a room can be as small as a table-top container or large enough to house up to a 2kL bioreactor and associated unit operations) and all true needs for a facility, e.g. cleanroom classification, wall surfaces, sanitization, air changes or modus, automation and fire suppression needs, mobility					
Challenge	Industry mindset, design elements considered trade secrets, knowledge will reduce barrier to entry by smaller bioprocessing players					
Potential solution	Industry-wide collaboration to develop and publish standard designs, including educational forums, close collaboration with vendors and contractors, to define and promote quality and design standards with the prospect that standardization will increase demand and reduce prices for modular and mobile facilities. Establish a 'bare minimum' platform that ensures safety and reliability, and that is accepted by the biopharmaceutical industry and the Food and Drug Administration					

SUS – single use system

Potential solutions manufacturing readiness level

Research | Development | Production

Table 2: Industry standardization – needs, challenges and potential solutions (continued)

		Current	2019	2022	2026	Scenario(s)
Need	SUS compatibility/interconnectivity: commercially available bags/tubing/connectors/vessels that are compatible, interchangeable and of fit for purpose quality					
Challenge	Vendors are largely developing proprietary lines of products with compatibility and connectivity to encourage purchase of the entire train, including connectors, tubing, sensors and software from the specific vendor. Significant R&D investment has been made to drive exclusivity of their products and intellectual property has been generated in the form of patents and trade secrets that each business will seek to capitalize on					
Potential solution	A cross-licensing model, like the ones used in the semi-conductor industry, that provides for pre-agreed royalties and reduces barriers to standardization An independent industry body that drives standardization without alienating vendors of equipment, consumables and raw materials					
Need	SUS standards: needed for component manufacture, performance, testing and closed system validation					
Challenge	There needs to be a strong incentive for the industry to rally around common standards. There may be pushback from suppliers from risk of price reduction. Some suppliers may choose to not invest in standard biopharmaceutical applications if their profit margins fall and the lock-in of customers to their own product lines is threatened					
Potential solution	A business model will need to be adopted to allow suppliers and manufacturers to be profitable. If a sufficient number of industry SUS users are requesting products that align with the standards, SUS vendors may find increased volume and improved efficiencies in the delivery of supply. The expected increase in demand from biopharmaceutical/Biopharmaceutical customers should be a powerful incentive					
Need	Multiple SUS sources of supply: multiple approved vendors are required for parts and consumables					
Challenge	Currently, many, if not most, SUS systems are proprietary or custom, lack interconnectivity and are only available from a single source of supply. To enhance the security of supply, improve operations and reduce costs, a catalog of standard SUS designs that are available from multiple vendors is required					
Potential solution	An industry collaboration with vendors to create a catalog of standard SUS designs and standards so that they can be supplied by multiple vendors					
Need	Facility fabrication contractor certification: approved contractors and vendors who can assemble modular facilities					
Challenge	Vendors and contractors are employed to create similar facilities for the industry, but they have differing standards					
Potential solution	Industry body to offer vendor and contractor certification for alignment with facility fabrication standards					

SUS – single use system

Potential solutions manufacturing readiness level

Research | Development | Production

Table 2: Industry standardization – needs, challenges and potential solutions (continued)

		Current	2019	2022	2026	Scenario(s)
Need	SUS vendor certification: approved vendors for the supply of these parts and consumables					
Challenge	Many different vendors and a lack of standardization					
Potential solution	Industry body to offer vendor and contractor certification for alignment with SUS standards Easy to find information for vendor and product standards					
Need	Reduced cost and time to market for delivering new capacity or expansions					
Challenge	Currently, fixed stainless steel facilities require significant upfront investment of capital and take a long time to build					
Potential solution	Use standard technology transfer methodology (i.e. 2kL platform with scale out, with follow-on transfer to larger scale, if required)					
Need	Sensor integration: sensors (connection to process analytical technology) to be easily integrated at specified points in the manufacturing plant					
Challenge	All sensors are implemented in the bioprocess after a stage of internal development that can be time-consuming and discourage changes to newer, better options					
Potential solution	Guide of suitability of sensors and clear guidelines to apply to bioprocess trains easily and safely with minimal testing					
Need	Harmonization of regulatory and building codes					
Challenge	Currently, there are differing regulatory and building code requirements that affect facility and process design. This can be problematic when trying to use a standard modular design in multiple geographic areas					
Potential solution	Ensure that standard, modular designs for biomanufacturing facilities and processes comply with a majority of world markets. Utilize existing regulatory harmonization groups to develop and gain support around standard requirements. Use this as a model for doing the same with building code requirements					
Need	Disposal strategies for single-use materials					
Challenge	The industry has not considered the long-term effects of disposing single-use components used in bioprocessing					
Potential solution	Explore solutions for recycling, energy reuse or greener manufacturing and disposal strategies. This activity would have to be funded as an industry-wide initiative High-temperature incineration with carbon capture					
Need	Common interface for software controlling various equipment or other outputs (e.g. measurements: to be addressed in the Automated Facility report)[1]					
Challenge	[1]					
Potential solution	[1]					

SUS – single use system

Potential solutions manufacturing readiness level

Research | Development | Production

Table notes: [1] See Automated Facility report for the definition of needs, challenges and potential solutions.

4.2 Fit for purpose, simple design

4.2.1 Needs

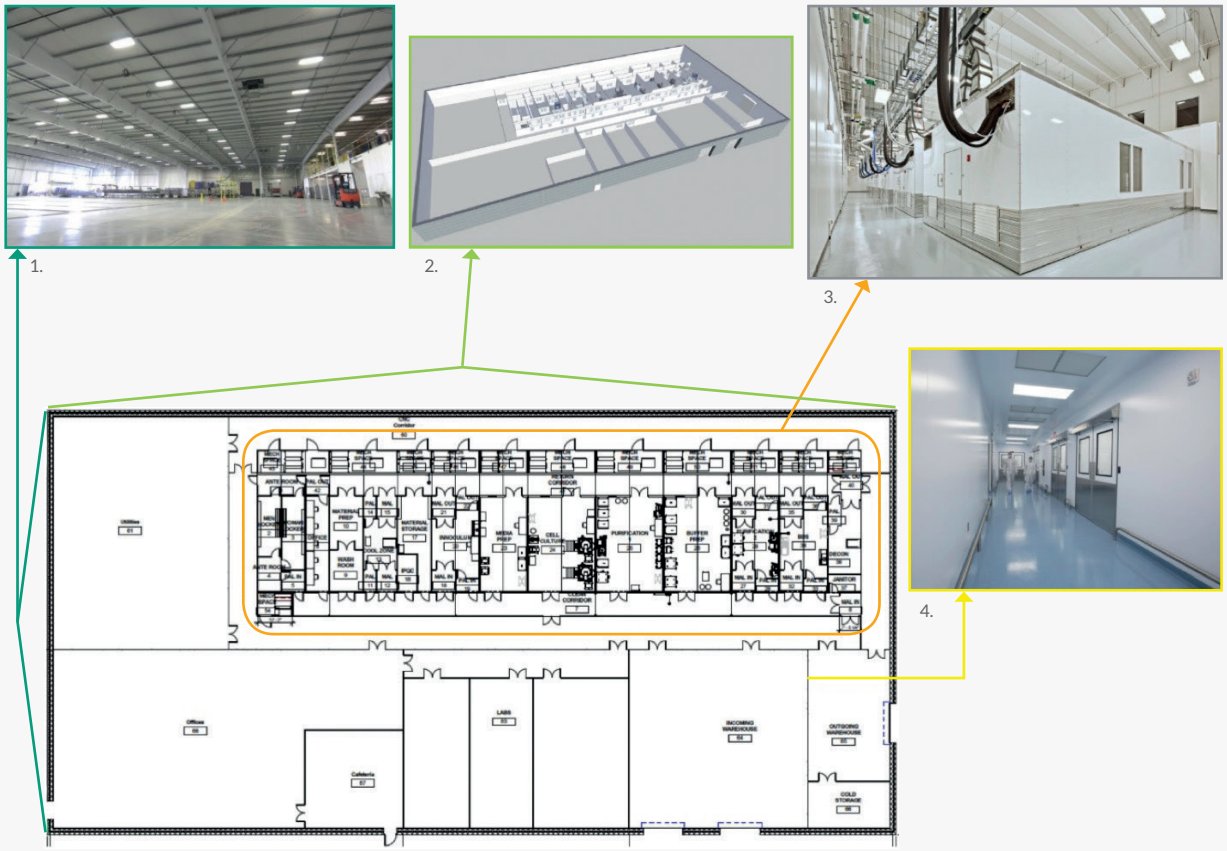
Modular and mobile design must be simple and fit for purpose[2] to be effective at shifting the paradigm away from a custom facility design. Challenges include enabling fast changeover between products, flexibility to support different process platforms and scalability to meet demand. There is a delicate balance that must be struck to address current needs while maintaining flexibility for future requirements. To be successful, biomanufacturers must embrace standardization of facility layouts and support functionality, while fighting the urge to cut costs by customizing designs to address only current production needs. The result may be larger facilities with spare unit operations bays and extra utility drops that may not be used in the near term, but standardization will result in speed and cost advantages while enabling true plug-and-play configurations to support a variety of process platforms and scales.

Additionally, these designs are more flexible and repurposable for future products, which extends the facility lifecycle and can be designed to allow for capacity additions without interrupting current operations. Figures 3 and 4 show examples of what these facilities could look like. Figure 3 shows a facility where a quick to fabricate, cost-effective shell contains office, laboratory, utility and support areas made from prefabricated wall panels and process modules fabricated as MMCUs. Figures 4–8 show an example of a facility completely assembled from prefabricated modules. Both approaches can offer the benefits of modular and mobile manufacturing. Although initially more expensive, once standardized designs are used by a number of companies, economies of scale overcome the cost of additional flexibility. Table 3 presents the needs for fit for purpose, simple design.

The benefits of pre-designed modular and mobile cleanroom units could be pre-defined installation qualification/operational qualification documentation packages, which may be modified slightly to suit different purposes, but otherwise can be used by the end-user. Pre-qualified systems offer the advantage of being able to rapidly bring a new facility or capacity expansion on-line, hopefully with accelerated regulatory approval as discussed in Section 4.3. These document packages can only be made available when the cleanroom unit is greatly standardized and materials, parts, design details and functionality are known.

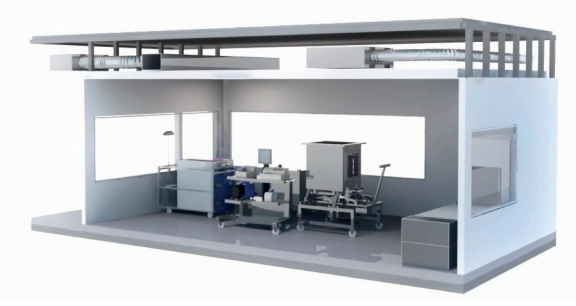
[2] "Fit for purpose" in this report is intended as a design concept and not in the sense of contractual specification.

Figure 3: Potential configuration of a scalable, modular facility using a shell building, wall panels and MMCUs for the process[3]



[3] 1. Shell building (courtesy of Butler Manufacturing)
2. 3D facility layout (courtesy of G-CON Manufacturing Inc.)
3. Modular/mobile cleanroom units (courtesy of G-CON Manufacturing Inc.)
4. Modular cleanroom panel structure (courtesy of AES Clean Technology Inc.)

Figure 4: Graphic simulation of a single module containing pre-installed, fixed installations (HVAC) and mobile process equipment, and 62 modules to build up a mAb facility comprising process, clean utilities and cleanroom/HVAC[4]



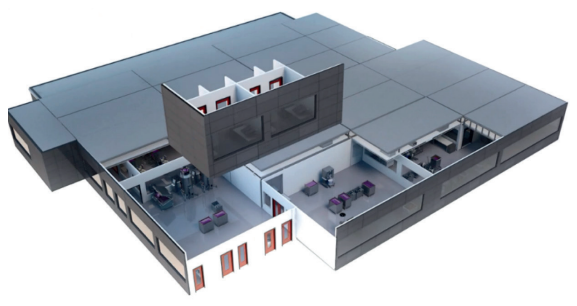


Figure 5: Case study – assembly onsite in Wuhan, China

Figure 6: 62 modules in place after eight days

Figure 7: Bird's-eye view of modular facility after completion

Figure 8: Interior cleanroom fit out with mobile process equipment during operation

[4] Figure 4 with kind permission of GE Healthcare Bio-Sciences AB and Figures 5-8 with kind permission of JHL

4.2.2
The needs, challenges and potential solutions

Table 3: Fit for purpose, simple design – needs, challenges and potential solutions

		Current	2019	2022	2026	Scenario(s)
(Metric 1)	**Number and types of products per facility**	1	Multiple of the same kind	Multiple of different kinds	Multiple of different kinds	All
(Metric 2)	**Ability to adapt module to future needs**	Limited with re -qualification	Possible without interruption of existing processes	Possible without interruption of existing processes	Possible without interruption of existing processes	All
(Metric 3)	**% profitable utilization of plant and kit**	80%	90%	95%	98%	All
(Metric 4)	**Ability to support in-region/localized manufacturing**	None	Yes	Yes	Yes	All
(Metric 5)	**Platform design choices**	None	Yes for mAb	Yes for mAb, recombinant protein and fill finish	Yes for all	All
Need	Ease of changeover: • vaporized hydrogen peroxide is sanitizable • ability to accommodate high segregation • unit operation bay and utilities sized to accommodate a range of unit operations					
Challenge	Culture: acceptance of non-optimized layouts, oversized utilities and oversized facilities. Segregation requires additional airlocking. Cost per square foot mindset					
Potential solution	Standardized unit operation bays, standard utility panels and spacing, expandable room modules, standardized airlocks for segregation and total cost ownership analysis					
Need	Ability to repurpose for different unit operations and scale: • standardized spacing of unit operations and utility panels • connectivity of cleanroom units • plug-and-play automation and control – open architecture • closed system designs • robust construction materials, and wall and flooring surfaces • autonomous HVAC for cleanroom unit					
Challenge	Culture: custom process fits, proprietary equipment and automation, cheap materials use and change aversion					
Potential solution	Standardized layout configurations and standard automation platform					

mAb – monoclonal antibody, HVAC – heating, ventilation and air conditioning

Potential solutions manufacturing readiness level

Research | Development | Production

Table 3: Fit for purpose, simple design – needs, challenges and potential solutions (continued)

		Current	2019	2022	2026	Scenario(s)
Need	Additional unit operations for new product – ability to add a unit operation bay					
Challenge	Culture: facilities custom designed for current processes. Hesitancy to deploy the 'unknown'					
Potential solution	Process rooms designed for expandability or standard rooms with spare bays					
Need	Existing stick-built facilities require custom engineering design and build for expansions – modular, off-site builds using standard designs. Family validation approach and pre-qualification. Harmonization of regulatory and building code requirements					
Challenge	Architecture and engineering resistance, regulatory acceptance					
Potential solution	Standard modular designs, family validation and pre-qualification					
Need	Ability to increase scale without major interruption: • pre-fabricated, plug-and-play facility modules • oversized or adaptable utility infrastructure • spare or expandable shell space • individual air handling and HVAC systems					
Challenge	Culture: custom, optimized designs focus only on current needs. Adverse to overbuilding, spare capacity and non-optimized space					
Potential solution	Standard designs with modular utilities and spare space to expand. Autonomous cleanroom units without interconnections					
Need	Sufficient space for operations and maintenance					
Challenge	Fitting design into existing limits available					
Potential solution	Standard unit operation spacing to accommodate maintenance and operations					

mAb – monoclonal antibody, HVAC – heating, ventilation and air conditioning

Potential solutions manufacturing readiness level

Research | Development | Production

4.3 Facility as equipment

4.3.1 Needs

Since prefabricated cleanroom modules are self-containing units, and are often pre-qualified off-site, the onus of qualification work may be lower than for traditional cleanroom infrastructures. Given the quality of materials used, and the containment of the modular and mobile system, it may be argued that risk is lower than for traditional stick-built infrastructures. Such infrastructures tend to have a high complexity due to the interconnected heating, ventilation and air conditioning ductwork and may utilize epoxy coated hygroscopic materials, such as gypsum walls. The more interesting discussion is around following the implications of 'cleanroom as equipment'.

Using modular and mobile cleanroom systems, it is possible to think of the room or cleanroom box, as equipment. By considering the types of benefits that have accrued to the industry from standardized, single-use process equipment, one may project that similar gains may be had by standardizing the cleanroom/facility. Once the standards are affirmed and the equipment is manufactured on a production line, most risk has been driven out of the facility expansion process. Short production timelines coupled with pre-qualification could radically decrease capital and regulatory risk. Another financial benefit may be the shorter depreciation time for cleanroom systems when treated as equipment: instead of 20–30-year depreciation spans, one depreciates the piece of equipment in 5–7 years.

The other regulatory risk accrues from the disparate nature of building code, code interpretation and code enforcement for issues such as fire, egress control, structural, etc. To take full advantage of these modular and mobile rooms/facilities these issues will need to be addressed and aligned.

Furthermore, modular and mobile cleanroom systems are commonly autonomous from each other, which means they have their own air handling systems and are not interconnected. This creates multiple advantages, such as capacity flexing (mothballing a cleanroom without disrupting the other cleanroom spaces) if the capacity is not required. The system can then be brought up and running quickly by sanitizing the system with vaporized hydrogen peroxide before running it. If an excursion happens, for example a viral contamination, one can segregate the individual unit, then contain and sanitize it. Table 4 presents the needs, challenges and potential solutions.

4.3.2
The needs, challenges and potential solutions

Table 4: Facility as equipment – needs, challenges and potential solutions

		Current	2019	2022	2026	Scenario(s)
(Metric 1)	Time to release product	2 months	1 month	1 week	1 day	1–5
(Metric 2)	Time to launch product (from transfer to greenfield 'new product introduction' site to launch)	3+ years	18 months	12 months	6 months	
(Metric 3)	Time to add capacity (new site/existing site)	3 years	12 months	6 months	4 months	
(Metric 3)	Time to add capacity (existing site)	2 years	10 months	2 months	1 month	
(Metric 4)	Time to repurpose a module (process change/product change)	18 months	9 months	4 months	2 weeks	
Need	Standard facility designs for small- to mid-scale facilities					
Challenge	Resistance by A&E firms to start creating facility and cleanroom infrastructure platforms as these could potentially threaten hourly charges revenue streams					
Potential solution	Industry adoption that shifts A&E approach					
Need	Family validation approach and pre-qualification					
Challenge	Since the performance of environmental controls is the result of a complex interplay of many factors (from materials, application methods, cleaning solution effectiveness, HVAC design, building controls, training, etc.) it requires significant investment					
Potential solution	Adapt approaches from GMP and existing family approaches, along with design qualification of parameter space with worst-case performance challenges at the factory					
Need	Family of parts that fit extremes					
Challenge	Fitting design into existing limits available					
Potential solution	Modular and mobile parts, which can be connected and disconnected to place into the shell building, as well as recesses that embrace any structure (e.g. pillar)					
Need	Design that is fit for many environments					
Challenge	Mindset of owners towards custom designs					
Potential solution	Platform examples that illustrate the benefits of standardization – faster, more predictable = lower total lifecycle cost					
Need	Room as equipment (room can be as small as a table-top container or large enough to house up to a 2kL bioreactor and associated unit operations)					
Challenge	New technical challenges on the regulatory paradigm shift to maximize benefit and timelines					
Potential solution	Summarized later in the document [1]					

Potential solutions manufacturing readiness level

Research | Development | Production

Table notes: [1] See Section 7 Regulatory considerations [2] See section 4.5 Drug product

Table 4: Facility as equipment – needs, challenges and potential solutions (continued)

		Current	2019	2022	2026	Scenario(s)
Need	Closed system validation, testing methods					
Challenge	Workstreams are under way to generate data that illustrate closure but are not mature and have only been started for unit operation closure					
Potential solution	Extended vendor qualification programs demonstrating acceptable performance under worst-case conditions. Performance specification under surrogate challenge conditions. May model as walk-in isolators.					
Need	Accelerate product release through co-location of drug substance-drug product					
Challenge	Industry resistance due to the costs associated with preparation of traditional materials favors decentralization of activity					
Potential solution	More robust filling technology with pre-prepared consumables operable at lower cadence using less experienced and sophisticated labor					
Need	Maximize on/at-line testing and decrease longer assay durations					
Challenge	Traditional filling methods have inherent risks. The known failure rates often do not justify reduction of testing duration, etc.					
Potential solution	Need to design filling operations from the ground up to quantitatively, and by many logs, reduce the risk to patient					
Need	Drug product small flexible filler					
Challenge	Large legacy of installed capability with relatively low costs					
Potential solution	The push by regulators to quantitatively reduce risk and by the emergence of the need for small, high-value, distributed-fill events will motivate companies to use small flexible fillers [2]					

Potential solutions manufacturing readiness level

Research | Development | Production

Table notes: [1] See Section 7 Regulatory considerations [2] See section 4.5 Drug product

4.4 Operational robustness

4.4.1
Needs

Moving away from highly customized fixed assets to modular and mobile facilities with simple, fit for purpose designs enables increased operational robustness including facility uptimes, reliability, operator safety and product quality. A cycle of continuous improvement is made possible through the use of multiple and identical manufacturing facilities since improvements are quickly transferred across to these facilities and best practices captured in future designs. The rapid changeover of equipment and processes, which is made possible through the design and use of SUS, supports high facility utilizations and will require efficient and nimble training and qualification approaches. Simple, fit for purpose designs provide the opportunity for improved training and simpler operations, which reduces the time to on-board new operators, reduces the need for highly skilled labor, reduces operator error and improves safety. Robust supply chains are necessary to support the heavy reliance on single-use components and the robustness of SUS must be improved to ensure productivity and product quality. Finally, a better alignment of capacity with demand will enable efficient supply chains and reduce the costs of underutilization that occurs with traditional facilities. Needs, challenges, and potential solutions for robust operation are shown in Table 5.

4.4.2
The needs, challenges and potential solutions

Table 5: Robust operation – needs, challenges and potential solutions

		Current	2019	2022	2026	Scenario(s)
(Metric 1)	Recordable injury and illness rate					
(Metric 2)	Ease of use – time to on-board operator					
(Metric 3)	Uptime, reliability and ease of maintenance					
(Metric 4)	High utilization	80%	90%	95%	98%	2-5
Need	Robust supply chain to support heavy use of SUS					
Challenge	Material shortage for critical SUS components					
Potential solution	Dual sourcing of SUS from approved vendors using same standard design					
Need	Robust performance of SUS components					
Challenge	Currently, SUS components are often made in a bespoke fashion that introduces variability and can lead to component failure. Shipping and handling can also create risk of failure					
Potential solution	Standardization of SUS across multiple vendors allows for more consistent fabrication and testing, which decreases the risk of failure					
Need	Standard, rapid and effective training: • training centers with standard design • access to a number of centers					
Challenge	Lack of standard training centers					
Potential solution	Training centers identical to facilities/modules. Visual training approaches that simplify training. Technology that allows for remote troubleshooting, training and observation (e.g. smart glasses). Simplification of operator/user experience through use of electronic batch records and standard operating procedures					

SUS – single-use systems

Potential solutions manufacturing readiness level

Research | Development | Production

Table 5: Robust operation – needs, challenges and potential solutions (continued)

		Current	2019	2022	2026	Scenario(s)
Need	Operator training in installation qualification (for equipment) or site acceptance test for construction					
Challenge	Lack of training programs					
Potential solution	Standard approach to installation qualification and site acceptance test. Standard training programs					
Need	Cycle of continuous improvement					
Challenge	Lack of process to enable continuous improvement					
Potential solution	Facility/module manufacturers work closely with owners to ensure that improvements/lessons learned are transferred across existing units and incorporated into future designs					
Need	Off-line monitoring with feedback					
Challenge	Technology					
Potential solution	Vendor market potential					

SUS – single-use systems

Potential solutions manufacturing readiness level

Research | Development | Production

4.5 Drug product

4.5.1 Needs

Flexibility and agility in future modern drug product filling facilities will be highly important. One crucial aspect of this will be the ability to develop a product on the same platform and scale that will be used in commercial production. This allows for quicker technology transfers and better comparability. Modular and mobile filling for drug product provides the platform for flexibility and agility in the future. Table 6 shows the needs, challenges, and potential solutions for drug product.

For larger-scale commercial manufacture, additional same-scale fillers could be added to increase output. This scale-out concept vs scale-up provides standardization of the filler technology and allows one to realize the benefit of modular and mobile filling. Modular and mobile also enables co-location of DS and DP facilities, which creates efficiencies from shared infrastructure including grounds, utilities, labs and resources, and eliminates the need to hold significant amounts of DS in inventory. The purpose of this section is to provide an overview of the future capabilities required by biopharmaceutical manufacturers.

1. Mobility:
   a. the goal is the capability to take a standardized filler, install it into a modular and mobile cleanroom and deploy it anywhere in the world, depending on need
   b. advances in portable cleanroom technologies and the ability to quickly set up an environment for filling
   c. the ability to integrate the filling systems into modular cleanrooms will allow for the quick deployment of an end-to-end system and enables the pre-qualification within the cleanroom.
2. Sterile filtration
3. In-line formulation:
   a. automatic dosing of filler ability, e.g. the product plus buffer dosed separately – in-line formulation
   b. the system should allow continuous drug substance and drug product flow
   c. product can be formulated such that desired final quality can be achieved during in-line formulation.

4. Filling platforms
    a. modular and mobile fillers will need to have a standardized approach to filling
    b. to be successful, a modular filler will need to be capable of filling multiple formats including vials, syringes and cartridges. The change over time between formats would need to be minimized
    c. interventions and human interaction with the filling operation would need to be minimized to ensure quick filling times and high-quality product. The goal is to have zero human interaction while filling. Automatic format part change and self-diagnostic systems (i.e. the machine has the capability to rectify some of the failures that may occur) are some of the other goals that are foreseen in the field of drug product.
5. Stoppering and capping:
    a. able to stopper and cap in one step.
6. Labeling and serialization
    a. to facilitate mobility, standardized symbols should be used in place of words for common identifiers
    b. an electronic media should be used in place of printed product information to help ensure flexibility and mobility (e.g. radio-frequency identification (RFID) and web addresses for product literature in local languages)
    c. serialization systems should be interoperable with different sensor/camera manufacturers
    d. localization of serialization and aggregation data should be avoided; a central/regional (drug product manufacturer-independent) repository should be used.
7. Lyophilization integration:
    a. able to move product for lyophilization, or to other operations, without human contact in a controlled environment.
8. In-process controls:
    a. very low line losses – current 0.5 to 2L to <100mL with the aim being zero
    b. temperature control – ability to keep product at a controlled temperature within the filler chambers in the filler rather than a larger cold room
    c. fill accuracy, i.e. weight checks, vial fill height or some other means
    d. fill potency – associated with the inclusion of in-line formulation
    e. label integrity – associated with the inclusion of labeling and serialization
    f. particle clearance
    g. ability to provide online automated testing and control to facilitate RTR.
9. Spare parts:
    a. spare and format parts inventory are another two aspects that need to be improved. The goal is to have an 80% reduction in spare and format parts.

4.5.2
The needs, challenges and potential solutions

Table 6: Drug product considerations – needs, challenges and potential solutions

		Current	2019	2022	2026	Scenario(s)
(Metric 1 – Cost)	Reduction in total cost to supply		25%		50%	1–5
	Cost of upfront investment in manufacturing	$80–100m	$70–80m		$50m[1]	
(Metric 2 – Speed)	Time to release product (end-to-end)	6–8 weeks	3 weeks		1–2 days	
	Speed to market	5 years	3 years		1 year	
	Facility build speed	3–5 years	2 years		<1 year	
(Metric 3 – Flexibility)	Technical transfer from development to commercial	6–12 months	2–3 months[2]		2–4 weeks	
(Metric 3 – Quality)	Yield	96–97%	98–99%		>99%	
	Deviation-free fill lot	80%	90%		>95%	
	Reject fill rate	1–2%	0.5–1.0%		<0.1%	
Need	No technology transfer from clinical to commercial					
Challenge	Existing networks within companies have non-standard, small- and large-scale systems in pilot and commercial sites respectively					
Potential solution	Standard filling systems defined on the basis of capability and not clinical and commercial – highly flexible system					
Need	Mobility					
Challenge	Size, cleanroom technologies and non-adaptability of one international standard to another (e.g. US and European electrical systems)					
Potential solution	Portable and modular cleanroom technologies					

Potential solutions manufacturing readiness level

Research | Development | Production

Table notes: [1] Due to cloning and saving in validation [2] Cloned filling

5.0 Linkages to other roadmap teams

From the facility perspective, modular and mobile can imply an easy assembly and delivery to a location as a complete unit (e.g. mobile cleanroom) for use in manufacturing. The facility space, however, is simply an environment in which to manufacture product. For the successful implementation of the factory of the future, modular and mobile concepts must extend beyond the facility and/or room to the manufacturing process (i.e. the equipment and operations that occupy the space). Without this synergy, the result may be a rigid and costly process that occupies a modular and mobile structure, while opportunities for rapid development of novel therapies at reduced costs could be lost.

This Modular and Mobile report links to all other roadmaps and also links to external organizations. Some of the key linkages include:

1. technology development
2. automation
3. PAT and RTR
4. supply partner management
5. drug product
6. BPOG/regulatory closed-system guidance
7. industry standards.

5.1 Process Technology

Process technologies must be developed to enable modular equipment design. This is important when considering the size of process equipment, its connectivity and its ultimate capacity to support manufacturing demand. A modular facility may have varying degrees of mobility depending on scale, but ultimately will consist of a room or rooms with utility and data connections at regular intervals to allow for the connection of various process unit operations. The term 'plug and play' is often used when referring to modular and mobile equipment. The vision is that equipment is easily connected to utilities, data and other unit operations with minimal installation effort and can be run automatically with minimal configuration setup.

Scale-out strategies can be employed when capacity or product mix limitations are challenged, but a truly modular and mobile facility will depend greatly on the technologies employed. Improvements in titer can drive down upstream processing (USP) equipment sizes. Improvements in the loading capacity of filters, resins and membranes in downstream processing can reduce equipment sizes and buffer requirements. Ready to use primary packaging material in the filling area can drastically reduce not only the footprint but also the operator resources required to run the operation. Such process technology improvements will allow for smaller, more flexible process footprints.

As single-use components have grown in popularity, challenges have arisen in connecting components designed or built by different suppliers. For true modular implementation of single-use technology, standardization of connectors is critical. Process equipment must be able to be flexibly arranged and connected to each other without added complexity of incompatible connectors.

5.2 Automated Facility

Modular automation is another key linkage. When implementing a modular solution, there is an expectation that unit operations and equipment can easily be arranged, re-arranged, swapped out or eliminated in a seamless fashion without the need for extensive automation integration or development. Automation platforms should be standardized based on configurable parameters for unit operation control and monitoring of inlet and outlet streams. With a common set of parameters and ranges, modular setup and configuration become simple and without extensive testing and validation. This enables mobile, validated automation systems that can reduce or eliminate redundant testing on site.

Three main aspects of integration are required:

- integration of physical components, i.e. parts of the sum of the manufacturing facility. This needs to be safe and easy to execute based on the pre-agreed specifications of the approved components
- integration of process control between components and in-line and online analytics. Seamless communication will be required across software controlling different components or designed by different vendors. The team appreciates this is a stretch goal considering the current state of the industry, but is a necessary goal to work towards. The aspect of integration is a major theme of Industry 4.0 and therefore this section will not go into further detail
- automation must be able to rapidly adjust the heating, ventilation and air conditioning system to enable scaling without pressure changes, i.e. when a modular and mobile cleanroom unit is docked against an existing structure, the automation needs to enable to have all units run in accordance to specification without changes.

5.3 In-line Monitoring and Real-time Release

A third major linkage to modular and mobile concepts is with process analytical technologies and RTR testing. By reducing the need for redundant QC testing, facilities will become smaller and more mobile. Advances in PAT and RTR testing should also reduce support staff requirements and the associated facility footprint, streamline end-to-end cycle times and simplify the overall process for more seamless implementations anywhere in the world.

Testing technologies must be designed to easily connect and interface with equipment and the facility for flexible set-up and configuration, such as:

- testing for critical quality attributes and critical process parameters
- minimize requirements for specialized central QC lab.

5.4 Supply Partnership Management

Modular and mobile concepts will not be successful without support from supply partners. Some key issues include enabling plug-and-play capability through equipment design, standard single-use connectors, standard interfaces, configurable standard automation platforms, quality and testing of SUS, and advances in PAT.

An agile and reliable supply chain of raw materials and consumables is also critical. The goal is to shorten lead times from order to delivery to minimize on-site inventories and ultimately reduce facility footprints. Furthermore, standard vendor-supplied testing and documentation can significantly reduce the need for redundant end-user testing and verification.

As the number of biological products on the market increases, and new process technologies such as continuous manufacturing are introduced, the complexity of biopharmaceutical supply chain will also increase. Evidence indicates that current production programs are already stretching parts of the industry, with examples of players failing to deliver to the market. This challenge will only increase as sites move from the current 'one line, one product' setup towards agile and flexible multiple-product operations and are required to manage both current and future technologies under one roof. Therefore, securing multiple sources of key manufacturing components such as chemicals, cell culture media, consumables or even specialized equipment is key. Furthermore, standardization of components and increased compatibility between different vendors will allow for easy switching between different techniques and products in bioprocessing, if required by the product, process or customer.

To support the demand for fast-to-market, customized, regional and, in some cases, personalized manufacturing, the biopharmaceutical industry and its suppliers need to work more closely to drastically shorten delivery times and create a standardization of components to prevent single sourcing for most critical components. This is also supported by the fact that regulatory authorities prefer pharmaceutical manufacturers to have a full understanding of and control over their supply chain. In addition to shortening lead times, industry and suppliers will need to work together to improve the quality of disposables through supplier quality programs, audits and agreed testing standards.

Within BPOG's modular and mobile community, several large biomanufacturing companies have identified component compatibility between different vendors as one of the biggest gaps in a flexible, modular and plug-and-play approach in their facilities to provide the agility that is currently required in biomanufacturing. This is especially true with respect to SUS, automation platforms and connector compatibility (interchangeability). Having to deal with adaptors or adding complex tubing sets creates risks of operator errors, leaks, damage and product loss. Standardization of single-use devices is also an important part of the broader implementation and integration of these devices into biomanufacturing facilities. Standards will significantly facilitate the adoption of SUS as end users will be able to directly compare 'like with like'. If these standards receive an endorsement from regulatory authorities, end users will be able to have a much higher level of confidence when widely implementing SUS into commercial manufacturing[5].

Another hot topic in the creation of an agile supply chain is around lead times of key manufacturing components. The lead times for production consumables and materials can be several weeks to months for some custom-made cell culture media or resins. Since leveraging vendor testing for internal release before use is not commonly used, significant extra time is added before materials can finally be used in manufacturing. Complex change control procedures add even more time when changes are required on the components. To improve the agility of the end-to-end s upply chain of critical manufacturing components, this should be one of the next major topics in the industry that both biomanufacturers and component suppliers should engage in.

5.5 Closed system guidance

Industry guidance is needed on the definition of closed systems and the acceptability of closed system processing in lower grades of space or non-graded space as a key enabler to simplify facility design and operating costs. This also creates greater opportunities in equipment utilization and inventory reduction through simultaneous multiproduct manufacturing.

[5] http://www.pharmtech.com/top-trends-biopharmaceutical-manufacturing-2015

5.6 Industry standards

While supplier innovation is an important driver for industry change, it also creates challenges of variability across suppliers with a lack of interconnectivity, poor supply chain robustness and higher costs. As a result, the current state of industry adoption of standards is relatively low and highly customized. Development of industry standards to define key design aspects of equipment and facilities will simplify the design and implementation of modular and mobile manufacturing. This will lead to greater industry adoption of new technologies, creating a much larger market for suppliers and enabling robust and flexible solutions at lower costs to end users.

5.7 Other industry initiatives

There are a number of industry initiatives relevant to modular and mobile:

1. Standardized Disposable Design – single-use disposables group involving industry consortia, manufacturers and disposables suppliers working to develop simple, standard designs for real-world SUS
2. Parenteral Drug Association's Manufacturing initiative, including manufacturers, suppliers and regulators
3. Advanced Mammalian Biomanufacturing Innovation Center
4. National Institute for Innovation in Manufacturing Biopharmaceuticals/National Institute of Standards and Technology
5. American Society of Mechanical Engineers, Bioprocessing Equipment Group
6. American Society for Testing and Materials, E55 working group
7. International Society for Pharmaceutical Engineering, Facility of the Future working group
8. Portable, Continuous, Miniature and Modular (Pfizer/GSK consortium with GEA and G-CON working on small footprint oral sold dose platforms)
9. Academic work including the Massachusetts Institute of Technology's partnership with Novartis and the Rutgers University partnership with Johnson & Johnson
10. International Consortium of Antivirals and other parties' work on an innovative vaccine platform. The proposals have been submitted to the World Health Organization. The Bill & Melinda Gates Foundation is involved, which also had a grand challenge for Innovations in Vaccine Manufacturing for Global Markets
11. Biomedical Advanced Research and Development Authority's pandemic preparedness and investments made, for example, in Emergent, Novartis and Texas A&M Center for Innovation in Advanced Development and Manufacturing.

6.0 Emerging and/or disruptive technologies

New medicinal drug developments and improvements in processes also create the need and opportunity for new technology innovations and strategies. For example, substantial improvements in cell expression rates and cell densities in cell culture processes allow further process intensification, meaning smaller processes and lower footprint needs. Also, single-use process equipment replaced, to a large degree, stainless steel reusable systems and increased the efficiencies of manufacturing output. Other technologies are either emerging or need to be developed to fulfill newly created demands of the industry.

In addition, macro-economic trends influence the biopharmaceutical industry, which need to be addressed by the use of new technologies. Centralized manufacturing processes need to be decentralized and established within other countries (in-country/for-country manufacturing) or precision medicine processes are required to be in position at a hospital or the cancer treatment center level. Biosimilar approvals are on the rise, which means the need to become more agile and cost efficient within the originator processes, but also for biosimilars, being produced in specific regions, to allow multiproduct manufacturing to utilize the capacities to the fullest.

Table 7 introduces some of the strategic needs and emerging technology requirements to be fulfilled or targeted.

Table 7: Emerging technology trends

Category	Subcategory	Description
Strategy	In-country/for-country manufacturing	A multitude of emerging economies is asking for drug manufacturing sites within their country. The industry reacts to it and is looking for smaller footprint, agile and flexible manufacturing sites, which may even be relocated if the capacity is no longer needed within the country.
	Multitenant/product facility area	To share administrative and financial burdens (such as QC and rent), it could be that either multiple companies share the same shell building with modular and mobile cleanroom clusters or one tenant uses these clusters to manufacture multiple products.
	Modular/mobile cleanroom distribution centers	To react rapidly to shifting demands, modular and mobile cleanroom distribution centers could be established, which sanitize, prepare and store the units and ship them when required. It could be that a leasing firm runs such distribution centers and sends the specified cleanroom unit to the end-user for a certain period.
	Facility platform catalog	Modular and mobile makes it possible to create facility platform catalogs according to applications. These catalog platforms would abbreviate design times; for example, they could bridge the conceptual layout/design phase, by using a cookie cutter layout and red-line it if necessary.
	Mobile laboratory overflow systems	Facilities that run through validation activities require a larger laboratory space, which then falls to a standard level once the process validation period is over. To satisfy the elevated laboratory space demand, mobile lab systems could be exploited, which would be distributed to a site that needs the overflow laboratory capacity.
Financials	Facility depreciated as equipment	Modular and mobile cleanroom units can be classified as equipment when these systems are autonomous systems, which will shorten the depreciation to 5–7 years instead of 20–30 years.
	Leasing facilities	Since modular and mobile cleanroom units are repurposable, these units could be leased and re-used after the lease ends. The benefit of leasing is the lack of the need of premature investment. The end-user can lease a cleanroom for 3–5 years to assure the success of the drug product being developed and could possibly buy-back the leased cleanroom infrastructure. If there is a failure, the asset is not lost.
	Repurposing cleanroom infrastructures	Traditional infrastructures are difficult to repurpose and usually have one product lifetime. Robust modular and mobile systems can be re-used or repurposed. The system can be cleaned and sanitized, as can the compact duct system within the modular and mobile cleanroom space.
	Reusing facilities by gutting them	Mothballed facility space could be gutted and re-used as shell buildings for modular and mobile cleanroom infrastructures. It may be possible to re-use the utility system within the old site.
	Delaying investment decisions	The rapid build of manufacturing infrastructure allows the delay of investment decisions.
Automation	Increasing automation needs for continuous bioprocessing	Continuous processing requires exceptional controls of all processing unit operations. New sensor technology and innovative process analytical technologies need to have a real-time process control and react when excursions occur.
	Robotics and automation use in drug substance processing	To avoid labor intensive and manual processing steps, automated or robotic designs in upstream and purification processes need to be established. For example, robotic systems for cell culture media composition and mixing could be utilized to avoid any human intervention and prevent possible contamination (mycoplasma). Similarly, automated and robotic systems could be used for column packing or running the columns, including the buffer feeds. Since single-use technology uses a large array of tubing, intelligent tubing guides and automated valving is required to avoid misconnections or elevated human error rates.
	Robotic automated systems for filling	Robotic fill systems require oversight to assure that the filling process worked in accordance with the specification. Control systems also need outstanding automation, including video footage, fill volume controls, material flows, container integrity, etc.
	Real-time or rapid release	This is much needed for some precision medicines as the product cannot be stored for a long time and must be administered as fast as possible.

[5] Beck, J.T., Williamson, B. & Tipton, B., Bioseparation (1999) 8: 201

Table 7: Emerging technology trends (continued)

Category	Subcategory	Description
Automation (continued)	Environmental monitoring	Current environmental monitoring of cleanrooms is outdated technology. If new, more agile and flexible modular and mobile cleanroom infrastructures are used, including for multi-purpose or multi-patient use, the environmental monitoring technology needs to shift to a more rapid approach. The rapid collection and analysis of the sample, in- or at-line, need to have more enhanced automation systems, which can inform and/or alert the end-user.
	Big data analysis	As more sensors are used, and real-time data is collected, big data analysis and storage systems are needed. Data collection will become better as processes require stringent controls. However, data collection requires new, more rapid data analysis systems to be able to understand and utilize the data.
Miniaturization	Process intensification	Processes will be intensified by: • continuous manufacturing • new cell expression systems • more efficient purification technologies. Process intensification will require smaller footprints, which can be placed in modular and mobile infrastructures.
	Isolator-based, robotic fill systems	Fill systems will be fed with pre-sterilized vials, syringes or cartridges. These container systems will be filled via a robotic arm moving the needle to the container. These systems do not need human intervention.
Precision medicine	Cell/gene therapy	Cell and gene therapies are small-volume processing sites, which can go down to a milliliter size . Often, the final product cannot be sterilized by typical means, such as sterile filtration. Therefore, these processes are run as the 'platinum standard' of aseptic processing and require exceptional containment options, as well as the ability to sanitize the entire cleanroom structure appropriately. Modular and mobile systems can be seen as walkable isolators, which show robust containment and the possibility to sanitize with vaporized hydrogen peroxide. Furthermore, these processing units may not be used in a centralized fashion but as decentralized, hospital-based processing units. In addition, such processing units usually need to be scaled up once the patient base rises. The scale up has to happen without interrupting existing processing units. Modular and mobile units can be docked against each other without the need for rebalancing or requalification, since the systems are interdependent.
	Cancer vaccines	These are commonly patient-by-patient processing systems utilizing isolators in which one sample at a time is modified and reconstituted. Containment and cleanliness are essential to avoid cross-contamination. These systems must also be on a local basis, since the patient sample cannot be transported long distances and require proper logistics (e.g. needle-to-needle assurance).
Pandemic response	Miniature mobile vaccine manufacturing	Vaccines in a pandemic scenario may need to be manufactured close to the point of origin. The manufacturing systems could be modular and mobile units or mini-sites that are shipped to the point of use.
	Autonomous cleanroom, multi-product manufacturing	Common vaccine manufacturing systems are large and often run in campaigns, which means that the site is shut down after the campaign is completed. It may be that modular and mobile units, being autonomous from each other, allow the use of the entire site for a campaign and use parts of the site when the campaign is over. An example could be an egg-based vaccine site, which manufactures campaigns for seasonal flu and uses parts of the site for rubella or measles when the flu campaign is over.
Training	Standard operating procedures	Instead of reading stacks of paper to run a specific or entire process, new media could be used such as videos or augmented reality. Both would enable the user to see precisely what is required to be done and reduce the risk of interpretation. Augmented reality dot matrix patches can be placed on all equipment and information accessed via mobile devices.

7.0 Regulatory considerations

Scope

The regulatory considerations for modular and mobile cover the following scenarios (see Table 8):

- scalability
  - the addition of flexible capacity to existing facilities
- products manufactured
  - existing facilities manufacturing commercial sales products
  - existing facilities introducing new products
- regulatory inspections
  - pre-approval inspection
  - routine GMP inspections.

Regulatory strategy/objective

The room is assessed as a standard design, which has been reviewed or inspected in order for the following:

- the room is specified as part of 'design space'
- standards apply for qualification and approval.

Table 8: Regulatory considerations

Regulatory issue/challenge	Regulatory opportunity/ benefit	Regulatory engagement plans	Stakeholders	Proposals

Room is assessed and inspected as a standard, previously reviewed unit	Reduced inspection demand	Build on the global drive for harmonization.
		Identify vehicles for joint discussion.
		Reviewing the 'known'
			FDA, EMA, ISPE, PDA, vendors	• plan input to FDA OBP reviewers
				• present to FDA ETT
				• form cross-industry group
				  • guidance paper(s)
				  • risk profile

Change management process/technology transfer adapts to include modular and mobile approaches	Reduced regulator submission demands	Build on the current desire for harmonization and standards	FDA OBP, FDA ETT, EMA, MHRA	
Qualification and validation adapts to include modular and mobile approaches	Reduced inspection and submission demands	Build on the current desire for harmonization and standards	FDA OBP, FDA ETT, EMA, MHRA	
Avoiding drug shortages through rapid deployment and qualification	Enhanced security of supply	Demonstrate robust capacity and supply chains	FDA, EMA	Demonstrate qualification case and timeline through modeling
Data integrity	Reduced variation in processes		FDA, MHRA, WHO, ISPE, PDA	Demonstrate through case study
Patient unmet needs: accelerated submissions	Flexible response to make new medicines available to patients		FDA (BTT), EMA (PRIME)	
Pandemic response	Flexible response to unplanned demands		FDA, BARDA	
Harmonization of regulatory and building code requirements	Reduction in variability of requirements – standardize building requirements		ASTM, IBC, vendors, ISPE	Form cross-industry group

ASTM – American Society for Testing and Materials, BARDA – Biomedical Advanced Research and Development Authority, EMA – European Medicines Agency, EMA PRIME – EMA's PRIority MEdicines, FDA – Food and Drug Administration, FDA OBP – FDA's Office of Biotechnology Products, FDA ETT – FDA's Emerging Technology Team, FDA BTT – FDA's Bridge to plant, IBC – International Building Code, ISPE – International Society for Pharmaceutical Engineering, MHRA – Medicines and Healthcare products Regulatory Agency, PDA – Parenteral Drug Association, WHO – World Health Organization

The modular and mobile parameter space covers the continuum from unit operation to the process suite to the whole facility. Regulatory risk could be segregated into lower and higher risk process phases; for example, lower-risk upstream processing to higher-risk filling processes.

Regulator risk falls into a low category when the containment and control robustness of the modular and mobile cleanroom infrastructure can be demonstrated. Regulatory risk may be reduced when the concept of facility cloning and facility standardization is fully leveraged.

A standardized modular and mobile cloned cleanroom design space, once reviewed or inspected by the regulatory authority, is no longer an unknown, but very familiar to the regulator. Once a regulator gains familiarity with a system, the regulator will at least lower their skepticism towards the robustness of the system. Familiarity also means that regulators will know and look at the weakest link of such modular and mobile systems, so the end-user and regulator know what will be scrutinized and therefore everybody is prepared. Besides, the end-user will make sure that any weakness will be effectively controlled to maintain robustness. Familiarity will not just help an inspection, but also a review of a new filing. Again, the reviewer is familiar with the systems reviewed and understands their capabilities, which will raise the confidence of the reviewer and may accelerate approval.

Regulatory authorities are very familiar with certain pieces of process equipment and understand their robustness and capabilities. This commonly means that they will not revisit the equipment, knowing that it has functioned appropriately and to specifications in multiple sites and environments.

A similar approach may be possible towards modular and mobile cleanroom systems. Regulators may come to see the design of MMCUs as pre-qualified with new installations only cloned or copied. In one scenario, as the modular and mobile cleanroom infrastructure is fully matured, it may be possible to have a pre-approved validation/qualification protocol that enables a significant reduction in pre-approval inspection lengths, possibly up to total elimination.

We conceive of a day when unit operations in modular cleanrooms could be standardized and/or pre-qualified, thus significantly reducing the procurement, installation and qualification timeline for additional capacity. Coupled with shortened/eliminated regulatory risk and timelines standardization could enable the industry to quickly and flexibly respond to market requirements, either to avoid drug shortages or the accumulation of large inventories of drug product, e.g. vaccines. This approach could significantly reduce fixed costs and capital risk and increase market access to critical therapies.

The trends in the industry are aligning and point to the possibility of these projections. These trends include the acceptance and proliferation of single-use technology, pre-packed columns, prepared buffers and media, process intensification, continuous processing and emerging unit operation standards. Another key trend is the requirement for distributed manufacturing as many governments around the world desire, and increasingly demand, in-country production. Enabling techniques include risk-based qualification, advances in GMP, family approach, bracketing, closed-system verification (where a room environment is not a critical factor) and enhanced vendor quality systems. As closed, single-use unit operations require a higher qualification involvement by suppliers, such trends will also be seen in the cleanroom infrastructure segment. Prefabricated cleanroom infrastructures have the potential to be pre-qualified, thus the vendor must have an appropriate quality system to reduce the qualification burden at the end-user site. Vendors have to submit supporting data for the end-user to shorten the regulatory review timeline.

With all of the mergers and acquisitions, break ups, repositioning, swaps, etc. in the industry many sites have now operated under numerous locations and countries and most employees have worked for multiple companies. In effect, this removes and reduces the special knowledge and know-how advantages that one company or another may have over another thus commoditizing biologics manufacturing. Control and competitive advantage between companies will be achieved through intellectual property and emerging modalities. These factors predict a drive to standards across the industry established parameter space and products (e.g. mAbs). An illustrative example of our direction is from the nuclear power industry where an operating license will be granted without the possibility of legal action if all pre-approved end points have been met for facility commissioning and qualification.

In another conformation of where segregation and containment become critical, modular and mobile concepts offer the possibility of multi-product/multi-class manufacturing within the same facility footprint. The enabling capability for this path is the demonstrated room and equipment manufacturing techniques that eliminate risk or cross-contamination. Isolator and single-use technologies are accelerating the path to follow for this modality. Autonomous cleanroom systems, which have an individual air handling and duct loops, support containment robustness and segregation. This is particularly important in personalized medicine using patient cells or individualized viral vectors. This is also important when contaminations occur within the

bioprocess industry; for example, minute mouse virus, which could be eliminated by fumigating individual cleanroom units, instead of the entire site.

Additional compliance difficulties for standardization and rapid deployment come from the multi-jurisdictional, international issues raised by regulators and local authorities. Because modular and mobile construction falls under the jurisdiction of local governments, aligning building codes and their interpretation will be key. Some of these key areas are seismic and fire control requirements that may vary broadly.

With an increasing regulatory familiarity and confidence in the robustness of the process equipment and cleanroom/facility infrastructure, the possible burdens of post-approval changes may be lowered. Currently, any new technology implementation or process improvements require 4–5 years before the change is approved by global regulatory authorities. The length of change implementation, and the financial and risk burden, delays the industry to push technology enhancement. A regulatory harmonized view on the exceptionally well working process technologies, in conjunction with robust containment by modular and mobile cleanroom infrastructures, may also support a harmonized view of post-approval changes. It will be a major advantage when global regulators recognize the approval by one or two major regulatory agencies as being sufficient. New technology implementation such as modular and mobile may raise the confidence of regulators, enabling them to subsequently see the improvements submitted by vendors and end-users as being beneficial, instead of scrutinizing such.

With the vision now broadly described, it falls to the biopharmaceutical community of vendors, manufacturers, academics, patient advocates and regulators to map out a path to realize the powerful benefits of speed, flexibility and cost.

8.0 Conclusions and recommendations

Modular and mobile manufacturing techniques have the potential to address several key issues facing the industry, e.g. the large capital expenditures required well in advance of demand, high inventory levels, long cycle times, high cost of goods and a lack of flexibility in modifying facilities or adopting new technologies. Modular and mobile addresses these issues by enabling the rapid technology transfer and launch of new products, rapid tailoring of capacity with demand, repurposing facilities to increase lifecycle, mobility of facilities to enable localized patient treatment or pandemic response, increased containment for new treatment modalities and miniaturization to enable personalized medicine.

To realize the benefits of modular and mobile, the industry will need to make progress with the following recommendations:

- develop a standard, simple, fit for purpose design of facilities and processes packaged in a modular format. These modules can then be fabricated, tested and delivered more quickly and at a lower cost than traditional facilities. They can be added or removed as needed, without interrupting operations, and can be repurposed to align capacity with demand
- industry consensus on standards will be required to define the capabilities and interconnection of the facility, room, process, equipment, automation and SUS with a key need to focus on interconnection. This will require collaboration between pharmaceutical companies and vendors
- collaboration with regulators will be required to enable a new regulatory strategy where the facility is treated as equipment for the purposes of validation and qualification – allowing for faster regulatory licensure of follow-on capacity additions or new products
- operational robustness, operator safety, product quality and, ultimately, patient safety will be improved through standardization and continuous improvement. The robust supply and performance of disposables will need to be supported through improved supply chains
- efficiencies in drug product operations and supply chain inventory of drug substance will be improved through design and co-location of drug substance and drug product facilities.

Using these strategies, drug manufacturers can successfully respond to market trends and business drivers enabling the faster introduction of new products to market, improved quality and better supply chain performance. These changes will help the industry to reduce cost, enable the development of new therapies and increase patient access to medicines.

9.0 References

A. Pralong (2013), *Single-use technologies and facility layout – a paradigm shift*, BioPharma Asia Magazine, Vol 2, Issue 1

R.B. Holtz, D. Powers (2012), Integration of a *Single-Use Platform Process within an Innovative Facility Design*, BioPharm International Supplement, Vol 25, Issue 11

H. L. Levine, J. E. Lilja, R. Stock, H. Hummel, S. D. Jones (2012), *Efficient, Flexible Facilities for the 21st Century*, BioProcess International 10(11)

G. Hodge (2009), *The Economic and Strategic Value of Flexible Manufacturing Capacity*, ISPE Strasbourg Conference, 28–29 September 2009, Strasbourg, France

A. Shanley, P. Thomas (2009), *Flexible Pharma: Puzzling Out the Plant of the Future*, PharmaManufacturing.com

M.W. Jornitz (2013), *Defining Flexible Facilities: When is a flexible facility being flexible?*, Pharmaceutical Processing

P. Thomas (2012), *Biopharma's Future Facilities: Smaller Footprints*, Complexities, and Costs, PharmaManufacturing.com

M.W. Jornitz (2014), *Flexible Facilities of the Future – Examples*, PDA Europe Conference Modern Biopharmaceutical Manufacturing, Manufacturing of the Future 25–26 March 2014, Lyon, France

M.K. O'Brien, *Portable, Continuous, Miniature, & Modular (PCM&M) Development and Manufacturing: The Foundation for a Transformational Development, Manufacturing, and Distribution Model*, presentation at the 2015 PDA Annual Meeting, Las Vegas, USA

P. Almhem, A Gaasvik, J Lilja, *Modularisation in Biologics Manufacturing*, Pharma Focus Asia, http://www.pharmafocusasia.com/manufacturing/modularisation-biologics-manufacturing, accessed March 25, 2015

G-CON Manufacturing, *G-CON Manufacturing Announces Delivery and Operation of a Custom Made POD for PaxVax, Developer of Oral Vaccines for Infectious Diseases*, Press Release, Jan. 18, 2013

J. Markarian (2014), *Continuous Solid-Dosage Manufacturing Platform Nears Prototype Installation*, Pharmaceutical Technology

M.W. Jornitz (2014), *"Podified" Manufacturing Facilities and Risk Mitigation of Aging Pharmaceutical Facilities*, Pharmaceutical Online

PRWeb (2013), GEA And G-CON Announce PCMM Collaboration With Pfizer To Address The Rapidly Changing Requirements Of Pharmaceutical Development And Manufacturing, Pharmaceutical Online

M.W. Jornitz (2016), *The Changing Environment of Facility Planning, Design and Engineering – Flexibility being a Key Attribute*, Bioplan Survey

M.W.Jornitz, S.Backstrom (2016), *Evaluating the Benefits of Prefabricated Cleanroom Infrastructure Designs and Costs*, Pharmaceutical Engineering, IPSE, Vol 36, Number 3

10.0 Acronyms/abbreviations

Acronym/abbreviation	Definition
ADA	Americans with Disabilities Act
AMBIC	Advanced Mammalian Biomanufacturing Innovation Center
API	Active pharmaceutical ingredient
ASME	American Society of Mechanical Engineers
ASTM	American Society for Testing and Materials
BARDA	Biomedical Advanced Research and Development Authority
BL2	Biosafety level 2 (levels are defined from 1 to 4)
BPE	Bioprocess Equipment Group
BPOG	BioPhorum Operations Group
BTT	Bridge to transplant
BXR	Bioreactor
CAPEX	Capital expenditure
CHO	Chinese hamster ovary cells
CMO	Contract manufacturing organization
CPP	Critical process parameter
CQA	Critical quality attribute
DP	Drug product
DS	Drug substance
DSP	Downstream process
EMA	European Medicines Agency
FAT	Factory acceptance test
FDA	Food and Drug Administration
FDA ETT	Food and Drug Administration's Emerging Technology Team
FDA OBP	Food and Drug Administration's Office of Biotechnology Products
GMP	Good manufacturing practice
HVAC	Heating, ventilation and air conditioning
IBC	International Building Code
ICH	International Council for Harmonization
IP	Intellectual property
IQ	Installation qualification
ISPE	International Society for Pharmaceutical Engineering
mAb	Monoclonal antibody
MMCU	Modular mobile cleanroom unit
MHRA	Medicines and Healthcare products Regulatory Agency
MIT	Massachusetts Institute of Technology
NIIMBL	National Institute for Innovation in Manufacturing Biopharmaceuticals
NIST	National Institute of Standards and Technology

Acronym/abbreviation	Definition
NPI	New product introduction
OPEX	Operating expenditure
OQ	Operating qualification
PAI	Pre-approval inspection
PAT	Process analytical technology
PCMM	Portable, Continuous, Miniature and Modular (Pfizer/GSK collaboration)
PDA	Parenteral Drug Association
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PRIME	PRIority MEdicines (a European Medicines Agency scheme)
PQ	Performance qualification
QC	Quality control
R&D	Research and development
RM	Raw material
ROI	Return on investment
RTR	Real-time release
RTRT	Real-time release testing
RTU	Ready to use
SAT	Site acceptance test
SDD	Standardized disposable design
SU	Single-use
SUS	Single-use system
USP	Upstream processing
VHP	Vaporized hydrogen peroxide
WHO	World Health Organization

11.0 Appendix A – Antitrust statement

It is the clear policy of BioPhorum that BioPhorum and its members will comply with all relevant antitrust laws in all relevant jurisdictions:

- All BioPhorum meetings and activities shall be conducted to strictly abide by all applicable antitrust laws. Meetings attended by BioPhorum members are not to be used to discuss prices, promotions, refusals to deal, boycotts, terms and conditions of sale, market assignments, confidential business plans or other subjects that could restrain competition.
- Antitrust violations may be alleged on the basis of the mere appearance of unlawful activity. For example, discussion of a sensitive topic, such as price, followed by parallel action by those involved or present at the discussion, may be sufficient to infer price-fixing activity and thus lead to investigations by the relevant authorities.
- Criminal prosecution by federal or state authorities is a very real possibility for violations of the antitrust laws. Imprisonment, fines or treble damages may ensue. BioPhorum, its members and guests must conduct themselves in a manner that avoids even the perception or slightest suspicion that antitrust laws are being violated. Whenever uncertainty exists as to the legality of conduct, obtain legal advice. If, during any meeting, you are uncomfortable with or questions arise regarding the direction of a discussion, stop the discussion, excuse yourself and then promptly consult with counsel.
- The antitrust laws do not prohibit all meetings and discussions between competitors, especially when the purpose is to strengthen competition and improve the working and efficiency of the marketplace. It is in this spirit that the BioPhorum conducts its meetings and conferences.

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This roadmap report has been created, and is intended to be used, in good faith as an industry assessment and guideline only, without regard to any particular commercial applications, individual products, equipment, and/or materials.

Our hope is that it presents areas of opportunity for potential solutions facing the industry and encourages innovation and research and development for the biopharmaceutical industry community to continue to evolve successfully to serve our future patient populations.

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