

Manufacturing Strategy for Diverse Biologic Pipelines of the Future



**Tufts Center for the Study of Drug Development,
Tufts University School of Medicine | Boston, MA**

October 2017

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About this White Paper

In October 2015, the Tufts Center for the Study of Drug Development hosted a workshop to explore innovative strategies for biologics manufacturing. The workshop was moderated by Abdullah Baaj, MD, PharmD, Parrish Galliher, MS, and Kenneth I Kaitin, PhD. This Tufts CSDD White Paper reviews the salient issues discussed and conclusions reached at the workshop.

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Introduction

The biotherapeutics industry is expanding rapidly across the globe, spurred by blockbuster biologics falling off the patent cliff, an uptick in orphan drugs, and the advent of biosimilars and personalized medicine. Where once biologics and orphan drugs were niche markets with few therapies in each space, more than 1,000 large molecules are in development today, and 250 orphan drugs have been approved in the U.S. Just nine years ago, only 11 drugs fit the definition of personalized medicine. By 2015, that number had grown 10-fold. It is expected that, within a few years, personalized medicines will have multiplied 100-fold. At the same time, the range of biologics is expanding at unprecedented levels. Once the domain of vaccines and simple proteins, biologics now encompass antibodies, immunotherapies, stem cell and tissue-based products, and even nutraceuticals.

Meanwhile, the biologics industry is facing epic globalization and decentralization of manufacturing processes. Just 20 years ago, biologics manufacturing was confined to a handful of plants in the U.S. and Europe. Today, the U.S. accounts for only 37 percent of the world's biopharmaceutical manufacturing. Asia has slightly outpaced Europe with more than 26 percent of global drug manufacturing, and other bio-clusters are springing up in Latin America, Eastern Europe and Africa.

Biopharmaceutical Activity



As recently as 1994..., the “bio” industry was exclusive to very few
As recently as 1994..., the “bio” industry had a limited talent pool
As recently as 1994..., the “bio” industry had concentrated expertise

Where are they today: Serono and Roche

Concentration of Global Biopharmaceutical Manufacturing



In the midst of such shifts, biologics have continued an upward trend in pricing, with some touting six-figure treatment costs in the U.S. Given the increased use of the drugs and growing competition, pressure is mounting to bring prices down. Consequently, biologics makers are looking more and more to manufacturing as the strategic driver of the commercial success of their products. They see manufacturing as a way to contain costs while increasing product quality and adapting to the demands of the 21st century biologics market. In the manufacturing plants of the future, flexibility will be key as drugmakers produce smaller runs of a greater variety of products in each facility.

To respond to the changing marketplace, the biologics industry will have to be as innovative with manufacturing technologies and processes as it is with the drugs it produces. The future of the industry rests on its ability to develop more cost-effective manufacturing technologies, tools and processes that can meet shifting demands of scale and product diversity while improving quality. New benchmarks, standards and best practices are needed to make manufacturing as efficient and flexible as possible to keep up with the dictates of a more diverse and global biologics pipeline.

To gain an understanding of the current state and future of biologics manufacturing, Tufts CSDD recently convened a roundtable discussion in which senior managers from biologics companies and officials from the U.S. Department of Defense and HHS' Assistant Secretary for Preparedness and Response shared thoughts, experiences and insights on biologics manufacturing. Highlights of that conversation are summarized in this report. Throughout the discussion, presenters stressed the need for industry to share technology and work together to develop the manufacturing platforms, standards and practices that will be required to meet the demands of tomorrow.

Industry Trends

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An increasing number of new biologics, coupled with biosimilar competition, is fueling a growing global demand for biologics, putting pressure on existing manufacturing capacity and forcing companies to invest in expanded capacity or new technologies to use their current capacity more efficiently. Part of that pressure is a push for quicker and more cost-effective biologics manufacturing that produces a consistent, high level of quality. As a result, time itself has gained incredible value.

With companies scrambling to secure market share in an ever-more competitive space that includes potential accelerated approval, breakthrough therapies, biosimilars and “hot” new discovery areas, time to market translates into enormous economic value, especially in fields such as oncology. Shortening or lengthening time to market by even a month or two can mean big gains or losses. Responding to that pressure, companies face a shrinking timeline for drug development, with much of the time compression focused on manufacturing.

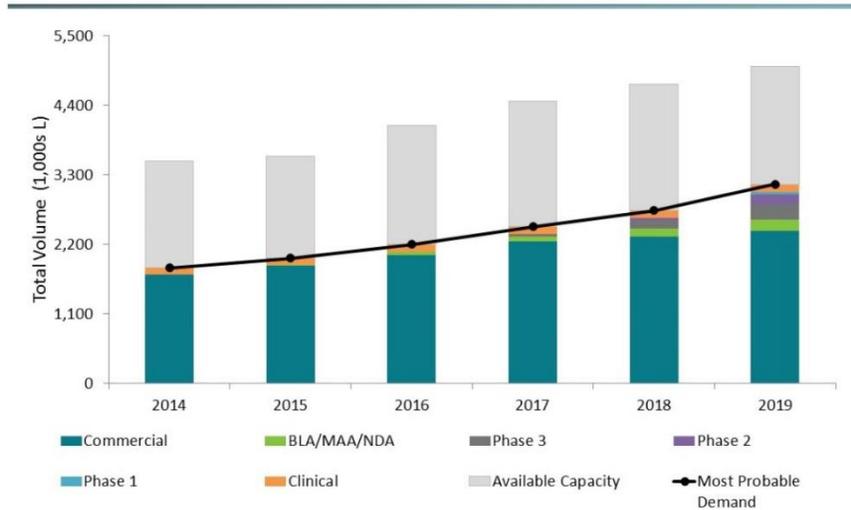
Another industry trend is the downward pressure on pricing. With biologics becoming the norm rather than a niche, that pressure will increase as the societal cost of healthcare rises. Global biopharmaceutical sales are forecast to exceed \$1 trillion by 2017, given the growing use of high-priced biologics. While biologics account for about 20 percent of global drug sales today, their share will continue to expand as more come to market. Currently, one-third of the drugs in the pipeline are biologics. More than 900 biopharmaceuticals are in development in the EU and U.S.; 78 percent of those are produced in mammalian systems. Recognizing that today’s pricing cannot be sustained at projected volumes, biologics makers are looking to reduce costs, especially in production.

However, the pressures to reduce manufacturing time and costs must not affect product quality. Consequently, manufacturers can no longer take what the biologic system delivers; they must design quality into the product. Developing products in accordance with Quality by Design (QbD) principles can require significant experimentation at every stage. While this may eat up time and investment, failure to adequately address such issues during development could increase the risks of regulatory or quality-related delays, which could be even more expensive and time-consuming in the long run.

Another industry trend impacting biologics manufacturing is a noticeable tightening of capacity utilization – a shift from the excess capacity that has been the norm for the past five to seven years. The change in capacity is occurring quickly, given the growth in biosimilars and biologics in the pipeline. Today, more than 70 percent of existing capacity is controlled by companies with marketed biologics, a fact that puts startups at a disadvantage. While bio-clusters are springing

up across the world, cell culture capacity continues to be dominated by Europe and the U.S. Many emerging markets are demanding that biologics makers build capacity in country for products intended to be distributed in that market. But building small capacity production lines in each country may not be efficient over time.

Capacity utilization is tightening noticeably



Perfusion capacity adjusted to equivalent fed-batch capacity where appropriate

6

From Clone to Commercial®

Product Companies Control >70% of Cell Culture Capacity



7

From Clone to Commercial®

To address such pressures and trends, the biopharmaceutical industry must develop novel manufacturing technologies and approaches. Yes, it could fine tune what it is already doing by adopting operational excellence initiatives, making improvements in materials and components, and tweaking its platform, particularly for antibodies. But given the growing diversity of biologics, the industry must move beyond the one-size-fits-all approach to manufacturing. It must expand and diversify its toolbox. Possibilities include:

- creative facilities and equipment concepts, such as ballroom design and single-use technologies (SUT);
- process intensification – e.g., continuous manufacturing and integrated unit operations;
- real-time quality through the use of process analytical technology (PAT) and real-time release.

While many of these tools are available, there are significant costs and risks in being the first to implement them in such a highly regulated industry. Given the value of time, the penalties for delays and unexpected setbacks in biopharmaceutical development programs are too severe for anything but success the first time out. But by nature of their newness, novel manufacturing technologies could create regulatory delays simply because regulators may be unfamiliar with them. There is no “good time” to implement new manufacturing technologies, as obstacles exist at all stages of biologics development. Another challenge is that most investment is aimed at drug R&D; relatively little is dedicated to new technology development and implementation.

The challenge that lies ahead is finding a way to improve the implementation of manufacturing innovations while minimizing the risks and avoiding delays of critical development programs.

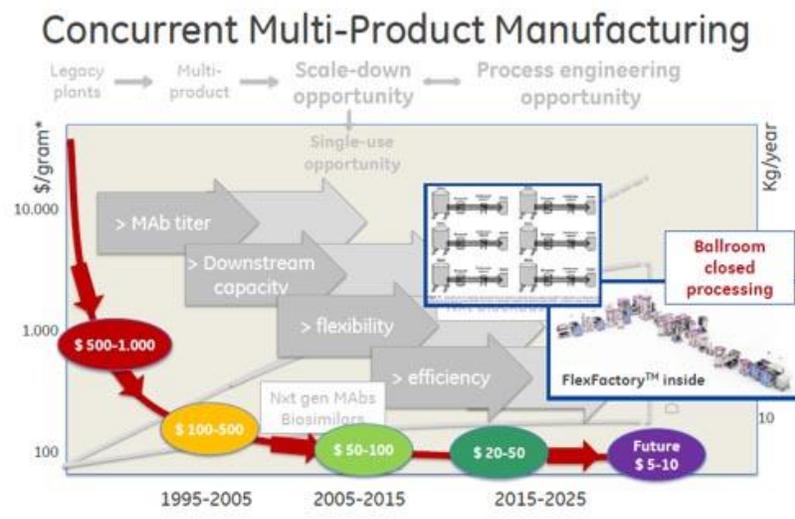
Innovation Strategies for Diversified Pipelines

Parrish Galliher

Chief Technology Officer

General Electric Healthcare Life Sciences

The cost of manufacturing biologics has fallen dramatically over the past three decades. In the early years, the cost of producing biopharmaceuticals in a “legacy” plant could hit \$1,000 per gram. Advances in technology reduced that expense in 1995-2005 to a per-gram range of \$100-\$500. Manufacturers have realized even more savings over the past decade, with the cost now ranging from \$50-\$100 per gram. To succeed in the future amid growing competition and pricing pressures, manufacturers will have to get those costs into the \$5-\$10 range while maintaining or enhancing the level of product quality. At the same time, expanding product diversity will demand smaller quotas and more flexibility – all at the loss of economies of scale.



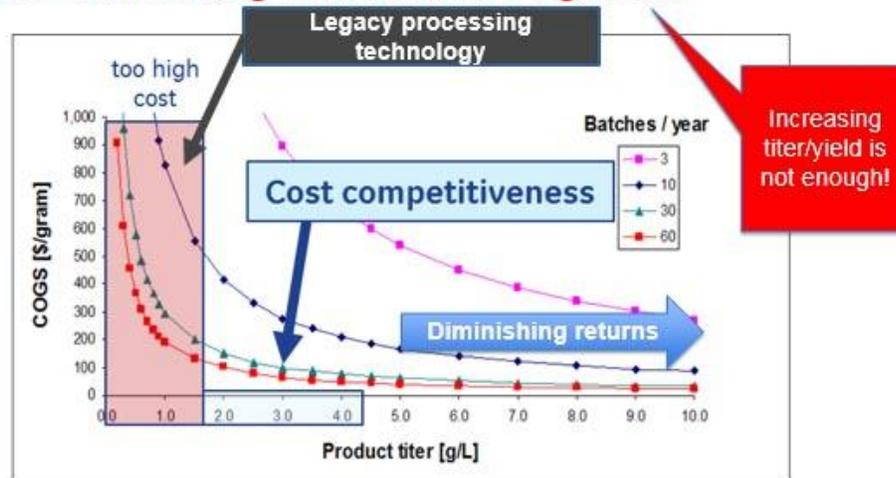
GE Confidential

GEHC P. Gallther June 2015

A number of innovation strategies are available to deal with diverse biologic pipelines. The most commonly used today is SUT plus a higher titer/yield, which offers advances in cost, quality and speed. While a fully integrated, single-use facility will see a sizeable increase in consumables, those costs are more than offset by savings in building size, operating costs, build-out time, cycle turnover time and energy costs. Over a five-year span, GE customers that switched from the traditional stainless steel bioreactors to SUT saw an average cost of goods (COGs) savings of 32 percent, even though the cost of consumables increased 194 percent on average. The biggest savings was an 85 percent reduction in water usage, followed by a 58 percent reduction in turnover time, 51 percent drops in energy use and facility capital costs, a 40 percent smaller carbon footprint, a 37 percent reduction in build-out time and a 33 percent drop in labor costs.

Technology has improved titer/yield to a point where CHO cells are producing 3-6 g/L, but the sweet spot for cost competitiveness appears to be 3-4 g/L for companies producing at least 30 batches per year. While the higher titer lowers the COGs for companies running fewer batches, they still are not as competitive. However, regardless of the number of batches they run, companies will begin to see diminishing returns beyond 5 g/L.

CHO cells are producing 3-6 g/L
but - diminishing returns above 5 g/L titer



Data courtesy Guenter Jagschies, GEHC



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GEHC P. Gallther June 2015

Put simply, SUT and higher titers are enabling significant improvements in COGs and efficiency, but they are not enough to respond to the pressures that accompany the increasing pace of innovation and meet the demands of the future. Biologics makers must look beyond SUT and high titers to more innovative approaches to reduce their manufacturing costs, enhance product quality and shorten the time to market. While there is lots of room for new COG and efficiency improvements in the future, the innovation toolbox already offers a variety of options for process development, facilities, and manufacturing and quality control:

Process Development

- HT screening, QbD, DOE, scale down modeling and metabolomics optimization
- Site-directed gene integration – landing pad expression cassettes
- Manufacturing-ready cell lines in R/D and microbial/yeast expression systems

Facilities

- SU futures – closed systems end-to-end
- SU friendly layouts for carry-in, carry-out SU operations
- Modular buildings and pods
- Liberal and aggressive open architecture facilities
- Concurrent multiproduct manufacturing

Manufacturing and Quality Control

- Single use, increasingly closed, SU microbial
- Intensified high cell density banks, N-1 or N stage
- SU perfusion of cells, cells+product, sensors
- Precipitation, flocculation, acoustic separations
- Continuous DSP enabling SU chromatography
- Pre-packed columns and DSP membranes
- Media or buffer concentrates, in-line dilution
- Reduction of raw material variability
- At-line, on-line analytics, near real-time quality control
- Multiproduct manufacturing – significant COG reduction, facility utilization

While it is not a panacea for all products and processes, continuous processing is an innovation tool manufacturers should seriously consider as it can significantly reduce time and some costs. The impact on COG in the upstream processes is still hotly debated, but the impact downstream is positive. Driven by their interest in consistent quality and the potential for lower prices that could increase patient access, regulatory agencies are generally supportive of continuous processing.

There is no right or wrong answer to whether companies should invest in manufacturing innovations or which new tools they should employ. It all depends on their manufacturing strategy. In updating their processes, manufacturers don't have to revolutionize everything at once. They should start with selected, "smart" implementation of innovations that will work for them, considering the impact each one will have on costs, time and quality. The "\$TUK" score is one way of evaluating whether a project is worth the investment.

\$ – The dollars (budget) available and the time for adopting the innovation. Can a business case be made for it? Has it passed the management decision process? Should it be in-sourced or out-sourced?

T – The technology drivers. What are the intended markets for the product? How big are they? Where will the manufacturing facility be located? What is the regulatory environment? The competitive landscape for that therapeutic space? The target COG vs. the current cost?

U – Understanding of the product and process involved. How stable is the product? What are the liabilities involved? The required dose? The capacity and scale that will be needed?

K – Knowledge required to develop the innovations and assess their impact. What manufacturing experience/expertise will be needed to implement the technology? Is it already in place? What automation experience will be necessary? Is there a sufficient skilled operator labor pool available?

SUT Risk Assessment and Facilities of the Future

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One of the key aspects of SUT facility design is a case-by-case, risk-based analysis of the design as a part of the quality system. The analysis should include the following key high-risk components:

- Operator error (receiving, storage, setup, operations, handling and qualifications)
- High pressure operations (> 5 psig) design review
- Client qualifications of outsourced vendor operations and dependence
- Leachable and extractable impact
- Design space definition, PAT development, automation
- Component failure and product impact assessment

Some clients have incorporated vision systems in the active portions of the process to provide online monitoring.

The single use design (SUD) assessment tool can document the sequential operations and match the evaluated risk against the operation. The failure modes effects analysis (FMEA) ranks the risk based on severity, probability of occurring and detectability. When these rankings (on a scale of 1-5, with 5 being the highest risk) are evaluated, the values are multiplied together to generate a risk priority number (RPN) that is the relative risk of that operation (the values will range from 1-125).

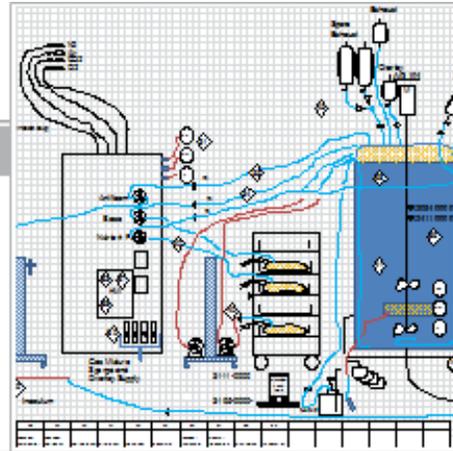
Single Use Design Assessment

PFD / FMEA / SUD

Define the process

Assess the risk

Correlate high risk with failure mode (FMEA) & processing (SUD template)



SUD Step	Step ID	Step Name	Step Description	Failure Mode	Failure Effect	Failure Cause	Control Design	Risk
1	1	1	1	1	1	1	1	1
2	2	2	2	2	2	2	2	2
3	3	3	3	3	3	3	3	3
4	4	4	4	4	4	4	4	4

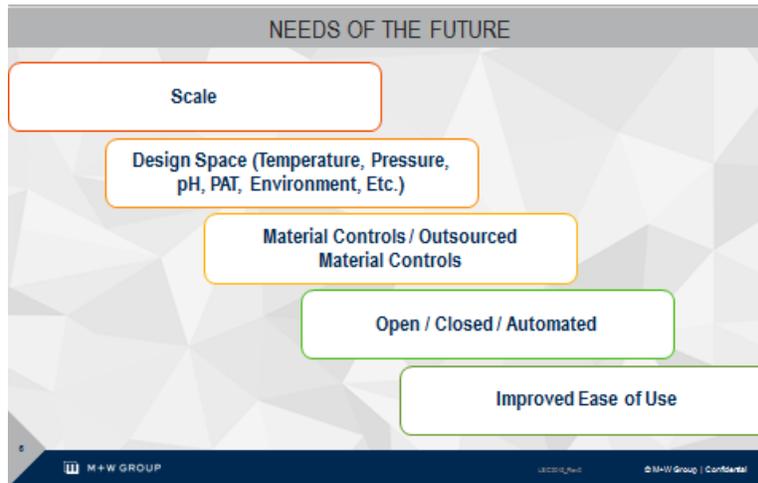


Using these studies, the typical high-ranking risks have been found to break down into the following categories:

- Operator error
- High energy
- Handling damage
- Instrument failure
- Equipment failure
- Leachable unknowns (BPOG, BPSA, FDA, etc.)

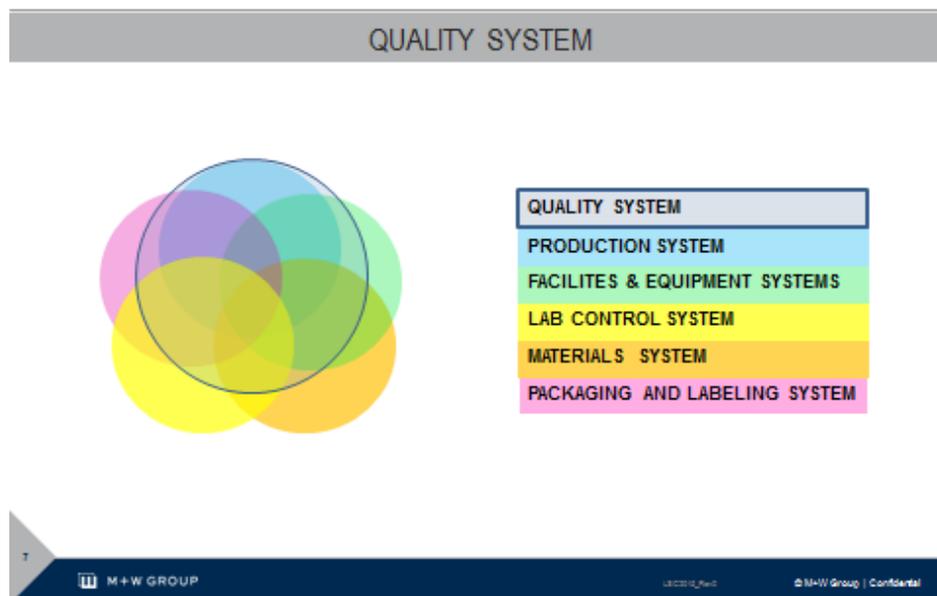
As product titers get better and volumes increase, the production needs of the future will be focused on improving the following areas:

Single Use Design Assessment

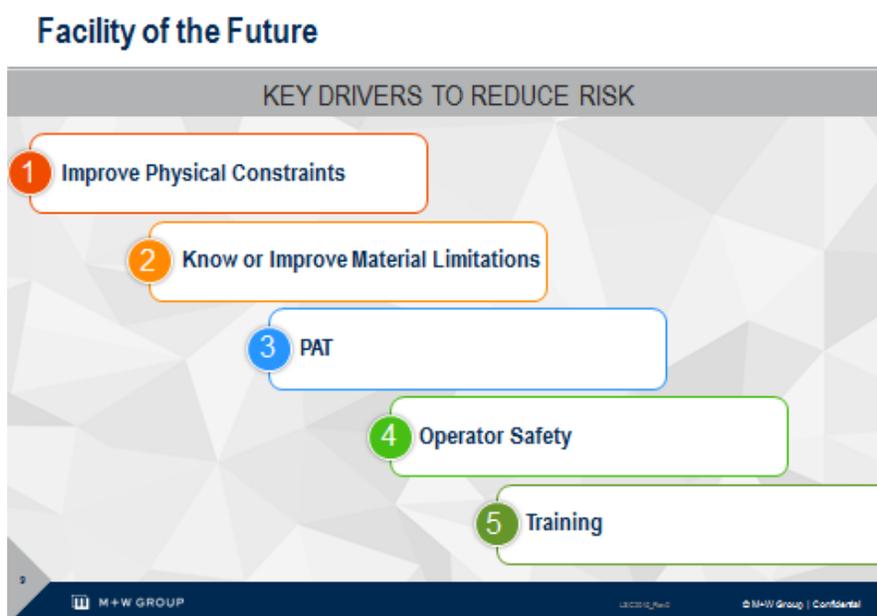


One can expand the risk evaluation beyond the production system to evaluate all aspects of the quality system. This evaluation would review all aspects of manufacturing within the product design space, including vendor audits, material life cycle, quality control operations, utility systems, facility layout, product delivery cold chain, and environmental control of the facility and support facilities.

Facility of the Future



In this way, the entire quality system can be evaluated for risk, and then the known risks can be mitigated using the best approach for the facility operations.



The facility of the future will incorporate a proactive review of the risks involved and the required scale limits for operator setup and operations. It also will optimize the facility flow and operational distances, provide closed systems where risks are high and improve automation to minimize operator error components.

COG Predictor of Efficiency

Jennifer Campbell
 Director Worldwide Biosimilars Program
 Merck Millipore

Evolving biopharma portfolios consisting of biosimilars, orphan drugs, more targeted therapies and personalized medicine – along with decentralized, local manufacturing – are driving reduced volumetric demands, enabling use of single use facilities at 2 kL or smaller. For instance, as biosimilars gain ground, the innovator is likely to retain about half the market share with three or four biosimilars splitting the other half. Consequently, instead of the innovator having one or two facilities to meet the global demand for that biologic, it will have a reduced demand, and each biosimilar maker will have its own facility to produce smaller quantities. Adding to the pressure to downsize volume will be the demand for manufacturing facilities in multiple markets.

The growing diversity of the pipelines also will result in more complex manufacturing processes and create a demand for multiproduct facilities and greater manufacturing flexibility. At the same time, greater regulatory expectations will require manufacturers to implement robust, well-controlled processes and minimize risks through a thorough understanding of those processes.

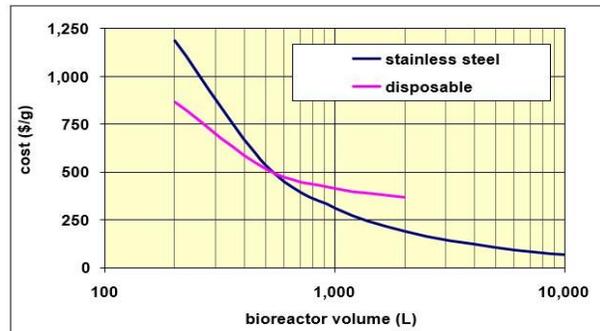
While switching to disposable SUT can be more expensive than maintaining an existing stainless steel system that has been fully depreciated, the implications of these major industry trends are forcing companies to adopt a more strategic view of bio-manufacturing. In responding to these trends, manufacturers have found that increasing bioreactor titers can lead to downstream bottlenecks and “facility fit” issues with tanks and floor space. Meanwhile, competition from biosimilars and other biologics in the same therapeutic space is spurring efforts to reduce the COG, making speed to market more critical and intensifying the importance of product quality.

All of these factors add up to the need to rethink biologics manufacturing. To do that, a company must first understand its cost contributors so it can appropriately target where changes are needed. BioSolve, a software tool that enables companies to model their manufacturing costs across platforms, can help provide a holistic view that assesses the impact of integrating new technologies and determines facility fit before investing in changes. In considering the choices, a company should keep in mind its scale of manufacturing, the level of flexibility needed, the number of biologics to be produced in the facility, the technology transfer required, the speed of operations, and facility constraints on utilities, water and skilled labor.

Scale is a significant cost factor that correlates with other system considerations. Reducing the scale of operation increases the cost per gram exponentially, with capital expenses increasing and consumables decreasing as a percentage of the total. How much those costs shift depends on the system. COG rises much more steeply for a scaled-down steel system than for a disposable SU system, as various elements of a steel system are more cost-sensitive to differences in scale. For example, water usage, which is a big consideration in countries where clean water is in short supply, varies greatly in steel systems. A 15 kL steel system would use about 30 liters of water per gram of MAb, but a 1 kL system would require about 110 L/g. The difference is in the amount of water needed for cleaning. A disposable system requires no water for cleaning, so it would be the most efficient at any scale in conserving water.



Effect of Scale



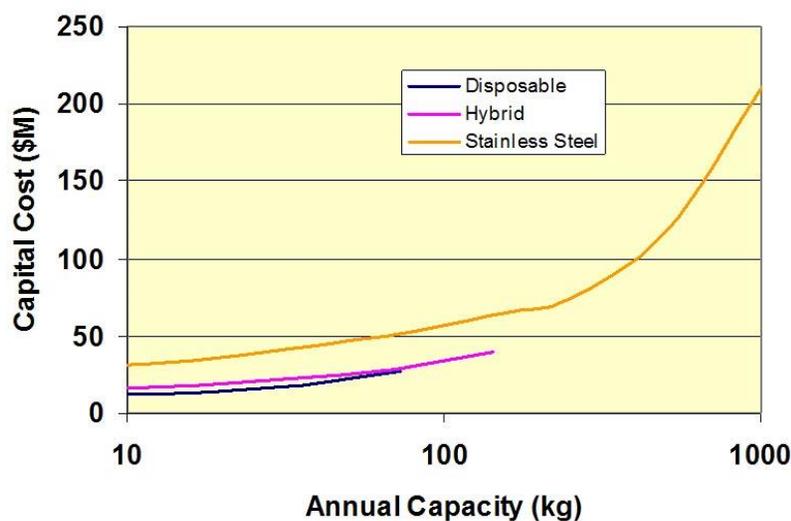
- Reducing the scale of operation increases the cost exponentially
- The lines cross, i.e. different advantages at different scales
- As the scale is reduced, capital expenses increase and consumables decrease as a percentage of the total

Scale also affects facility design costs and footprint, again impacting steel systems more so than disposable. Whether its annual capacity is 10 kg or closer to 100 kg, an SU system will require capital costs of less than \$25 million for facility design. The costs for a 10 kg steel system would be nearly double that of an SU system. At 100 kg, the costs would be upwards of \$50 million, and at 1,000 kg, they would exceed \$200 million. However, current SU portfolios present a COG challenge since SU benefits from greatly reduced capital expenditure, whereas the batch cost of consumables is much higher. On the other hand, SU combined with a flexible factory concept enables technology transfer of biosimilars by reducing the risk of facility design error, as well as the need for water.

A third choice would be a hybrid solution, which would be comparable to the disposable system in price but could offer greater capacity. Besides potentially improving efficiency, an SU hybrid system provides possible cost savings in capital investment and equipment, validation, energy, labor and maintenance/installation. Compared with a steel system, a hybrid also offers time savings in terms of startup and turnaround, as no cleaning is required.



Facility Design vs Capacity Requirement



Tufts CSDD 'Manufacturing Strategy for Diverse Biologic Pipelines of the Future' October 2015

Developing the Best Practices

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The biopharma industry is working to expand patient access to more affordable biotherapeutics. However, a number of challenges need to be overcome that are summarized in Table 1. In particular, it is increasingly difficult to predict the clinical and market needs for a given therapeutic area such as the oncology pipeline molecules. For example, Merck has broad clinical trials in more than 30 tumor types using Keytruda (pembrolizumab) and a range of combinations [1]. Any one of these candidates has the potential to achieve accelerated approval status from Phase I outcomes. Further complicating predictions is the expansion from traditional MAbs to a range of new molecule modalities, bispecifics, nanobodies and fusion proteins, each of which may require separate development and manufacturing platforms. The capacity demands also may vary. For instance for oncology, a highly potent, low dose agonist antibody may demand less than 50 kg/yr whilst an antagonist antibody for multiple indications may require more than 300 kg/yr. This combination of factors is driving the industry toward agile and flexible solutions necessary for quick responses and adaptability to change.

Table 1. Overcoming the challenges to support the oncology revolution

Challenges	Requirements
<ul style="list-style-type: none"> • Potential for accelerated approval • Difficult to predict clinical & Market Needs • Pipeline development • Patient accessibility • Global Presence 	<p>Be agile & flexible to quickly adapt to change</p> <ul style="list-style-type: none"> – Rapid to FIH paradigm – Fast development with high throughput development technologies – Flexible modular synchronised manufacturing & supply chain
<ul style="list-style-type: none"> • Evolving reimbursement environment • Global competition 	<ul style="list-style-type: none"> • Develop technologies for lower cost next generation manufacturing • Build high performance integrated organization <ul style="list-style-type: none"> – Coordinate technology to drive R&D continuum to manufacturing
<ul style="list-style-type: none"> • Potential High dose requirements 	<ul style="list-style-type: none"> • Develop high concentration formulation technologies

Rapid development from discovery to first-in-human clinical studies

The biopharma industry has been implementing initiatives to speed drugs into clinical studies. This comes from streamlining activities between discovery and preclinical development by integrating workflows between bioprocess development, safety assessment and clinical groups. This coordinated, streamlined approach has resulted in significant time reduction as shown in Figure 1.

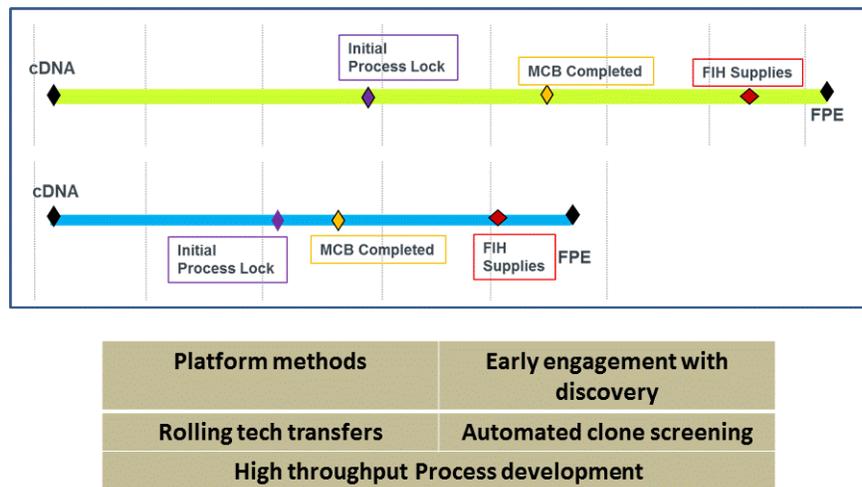


Figure 1. Acceleration of activities to accelerate from cDNA to human clinical trials

Bioprocess development has resulted in significant effort to implement high throughput technologies to speed process development. Figure 2 shows the end-to-end approach of automated SU disposable technologies used in process development. Such technologies provide

faster generation of data, allowing more throughput of pipeline projects into development. For example, laborious shake flask work for cell line development has been reduced with automated disposable spin tubes for cell passaging that use liquid handlers with automated tube capping and decapping. Automated disposable bioreactor tools now enable one scientist to simultaneously run a 24 bioreactor statistical DOE experiment that is three to four times faster than the conventional approach of 3 L glass bioreactors that required two or three operators [2]. The SU technology eliminates the need for laborious cleaning and sterilizing of glass or stainless steel bioreactors. In addition, the automated feeding and sampling systems expand capability by releasing the scientists to perform other activities.

Similarly for purification, 96 well slurry plates and miniature columns are used to accelerate chromatography resin selection and optimization. In addition, formulation excipient selection is accelerated with 96 well plate screening. These tools have associated scale-down models for line-of-sight to manufacturing, allowing the right first-time approach to minimize the duration for process development. In the coming years, further timeline improvement is expected as the new automated high throughput tools become further integrated with data management systems. This will allow statistical experiments to be expanded from 6-8 parameters to more than 15-30 parameters [3]. The streamlining of workflows will enable cell line development to be integrated with process development, shortening timelines but also resulting in more robust and potentially higher yielding processes.

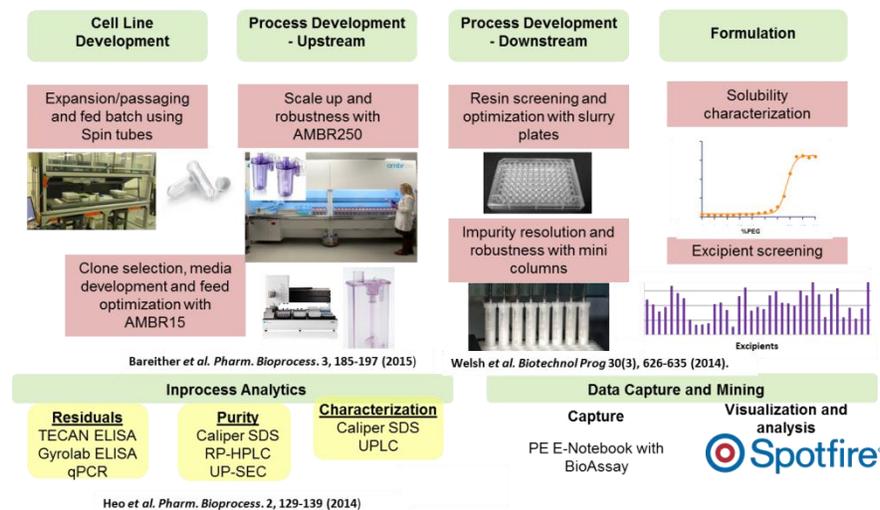


Figure 2. Accelerating bioprocess development via single use-enabled automation

Next-generation manufacturing process and modular facilities of the future

Lower cost processes in flexible manufacturing facilities that can quickly respond to changing market demands are necessary to support the oncology revolution. The flexible, low-cost modular facilities of the future (< \$100 million) can now be implemented with new lower cost biologics processing using disposable technologies. Expensive stainless steel manufacturing facilities – typically a 15,000 L scale bioreactor facility costing more than \$600 million – can now be replaced with lower cost SU-enabled technology. The fixed costs associated with conventional stainless steel facilities will transition to a variable expense cost structure. While delivering cost effectiveness and improved efficiency, it also will ensure product quality. The economic benefit can be seen in Figure 3, which shows multimillion dollar cost reductions in switching from traditional stainless steel bioreactors to SU fed batch and SU continuous processing [6].

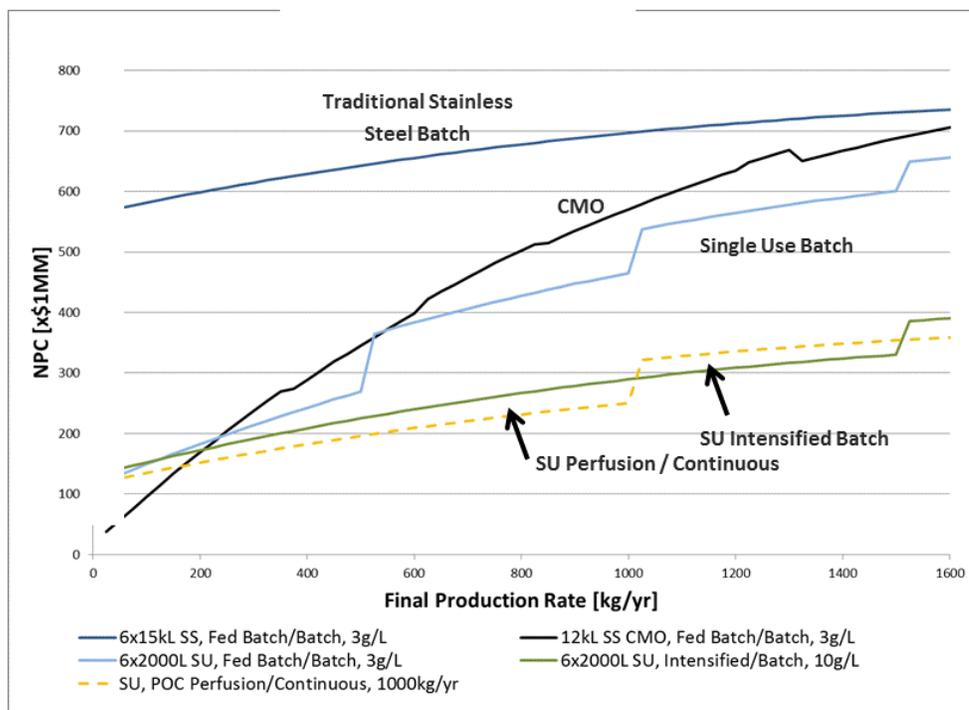


Figure 3. The Process Economic Cost Modeling of Next-Generation CHO Processing. The total cost of ownership cost-saving benefits (net present cost) of next-generation processes versus traditional stainless steel six-pack bioreactors. (NPC: net present cost is a total cost of ownership calculation including capital cost, operating costs and depreciation.)

The vision for the facility of the future is shown in Figure 4 in which an open ballroom concept of the small footprint facility (~60,000 sqft) allows a flexible design. A single facility based upon disposable technology with closed processing enables multiproduct handling. The facility's open ballroom design allows a toolbox of process platforms to be deployed according to the market capacity demands. For example, potent low dose molecules, less than 50 kg/yr, could be

supported by a conventional SU fed batch process, whereas high dose multi-attribute molecules could be manufactured via automated continuous processing.

Continuous processing allows for faster throughput processing than a conventional batch operation, eliminating interim product hold steps between unit operations. It is envisaged that process analytical tools will provide product attribute control of the molecule in real time as it is manufactured. The feasibility of continuous processing for drug substance manufacturing has been demonstrated [6] with three times faster processing than conventional batch processing at a significant cost reduction (Figure 3). This is enabled by new continuous chromatography technology [7] that allows efficient use of disposable columns with a single use flow path. Further improvements in throughput can be made by applying novel membrane technologies, such as membrane hydrogels [8]. Novel single use approaches combining the high throughput capacity of a membrane and the resolution capability of the resin have shown high loading capacity up to 10 times greater than conventional resin chromatography.

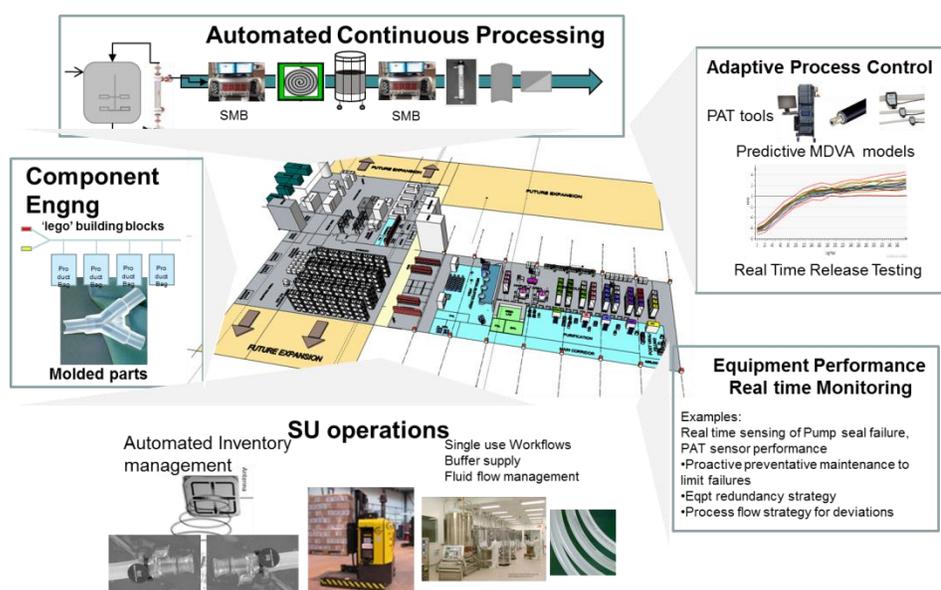


Figure 4. Potential facility of the future vision with capacity of up to 1,000 kg/yr within 60,000 sqft facility, using 3,000 L buffer bag locations with movable bags up to 500-1,000 L scale. Bioreactors in nonclassified space with 5 times media concentrates, online PAT and parametric modeling enable real-time release to minimize QC burden. Grade D air handling processing.

PAT tools in development include the multi-attribute method based upon peptide mapping and LC/MS [9]. This allows multiple attributes that support CQAs, such as glycan and charge variants, to be measured by a single method (Figure 5). This potentially eliminates at least five separate methods, reducing the QC burden and enabling real-time release of the drug. In addition, this work is being integrated with drug product and minimal inventory strategies to further streamline manufacturing.

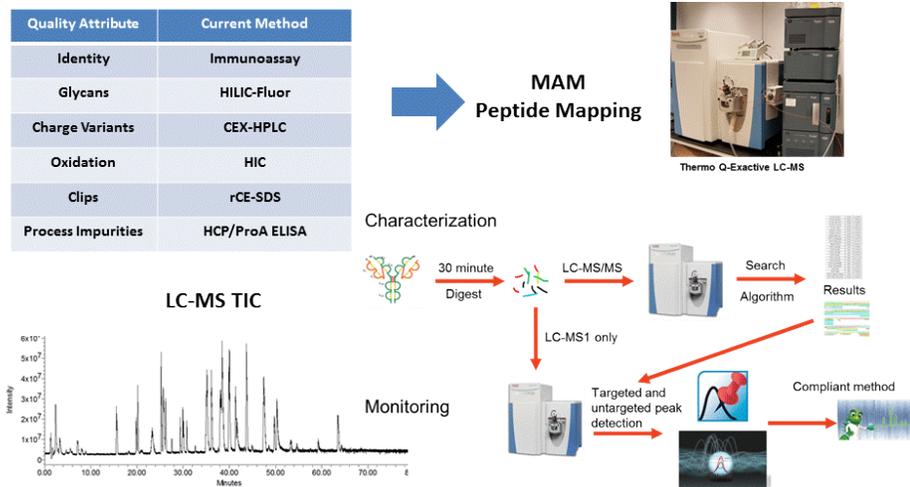


Figure 5. Multi-attribute method via peptide mapping/LCMS to deliver 90 percent of characterization assays

Developing high concentration formulation technologies

Development work continues to improve the ease-of-administration advantage of subcutaneous formulation for patients compared with the current IV approach. For syringe injection, a volume less than 1.5 mL is required so a high MAb concentration (more than 150 mg/mL) is typically required. The challenge is the MAb viscosity generally increases exponentially with concentration due to molecule-to-molecule interactions. Viscosities up to 200 cP have been measured for concentrations greater than 150 mg/mL. Therefore, development work is pursuing approaches to reduce viscosity such as novel excipients or crystallization to minimize viscosity to levels (less than 30 cP) that allow syringe injection.

Summary: Industry collaboration

It is anticipated that these new approaches will provide an agile and flexible low cost solution to handle the heterogeneous product portfolios and varying demand. The elements of success are summarized in Figure 6. The integration of continuous processing of drug substance and drug product with product attribute control should enable a synchronized manufacturing supply chain to the patient while maintaining product quality. The road to fully automated continuous processing is expected to be a stepping stone approach via semi-continuous processing. These approaches will likely require new regulatory pathways. End users are engaging with regulatory technology groups and collaborative working groups. In addition, the path forward requires close collaboration between suppliers of SU technology and end users.

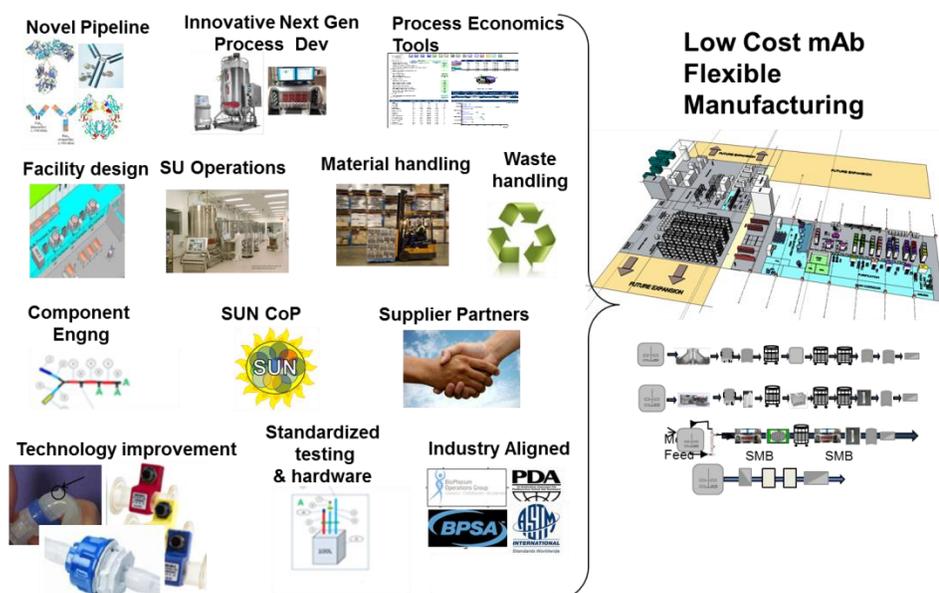


Figure 6. Elements of success for the next generation CHO mAb processing to modular facilities based upon single use technology: Key effort collaboration between suppliers and end users.

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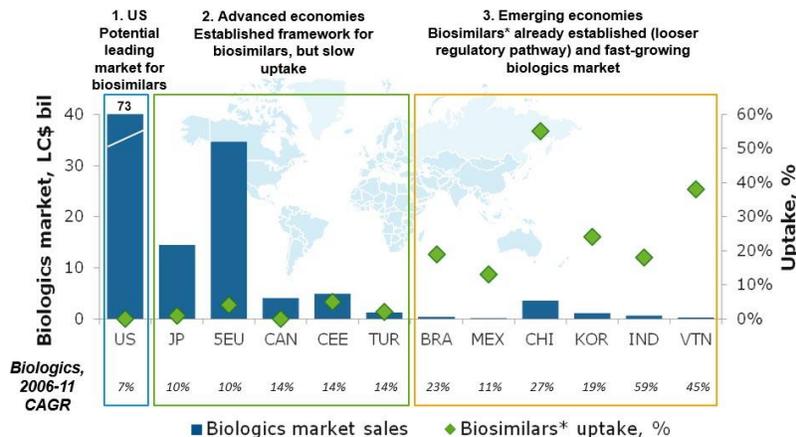
Emerging Market Strategies

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The advent of biosimilars, coupled with globalization and manufacturing decentralization, is creating an opportunity for companies like Boston Oncology that are willing to invest in biologics manufacturing in emerging markets. Such investment was not cost-effective when large stainless steel facilities were the only option, but innovative, cost-efficient manufacturing processes that allow for quicker startup, less investment, flexibility, low volumes, limited runs, and fewer resources are making it possible to respond to the need for biologics on a regional, if not country, level.

Given their lower cost, biosimilars are making biologic therapies available in some emerging markets for the first time and are spurring growth of biologics manufacturing capacity in those markets. While advanced economies have more established frameworks for biosimilars, uptake of the follow-ons is not as great as it is in emerging markets where the need for cheaper biologics is pressing.

Three geographical clusters arise Emerging economies anticipated to be a potential growth driver



Source: IMS MIDAS, 2006-11, *biosimilars in emerging economies have not gone through a thorough screening like in Europe

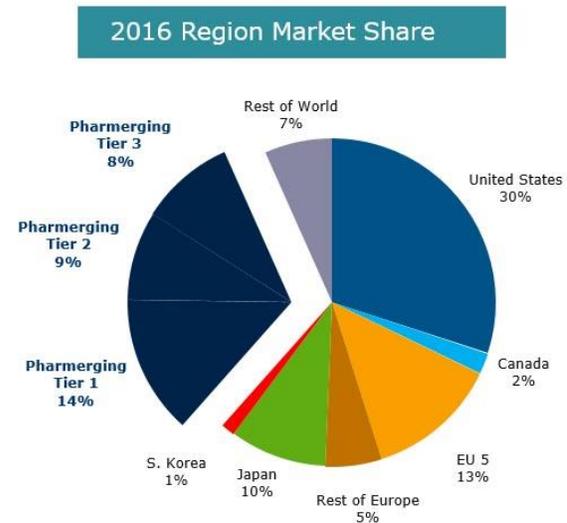
Given the unmet need and the economic growth in many emerging, or “pharmerging,” markets, the potential is great. With pharmerging economies accounting for 66 percent of global growth, those areas combined are expected to match the U.S. biopharmaceutical market this year and nearly double that of Europe.

Pharmerging will account for 66% of global growth Pharmerging to match US sales by 2016



Developed Markets CAGR 2012-2016	
US	1-4%
Japan	1-4%
Germany	0-3%
France	(2)-1%
Italy	0-3%
Canada	0-3%
Spain	(4)-(1)%
UK	0-3%
S. Korea	2-5%
Developed	1-4%

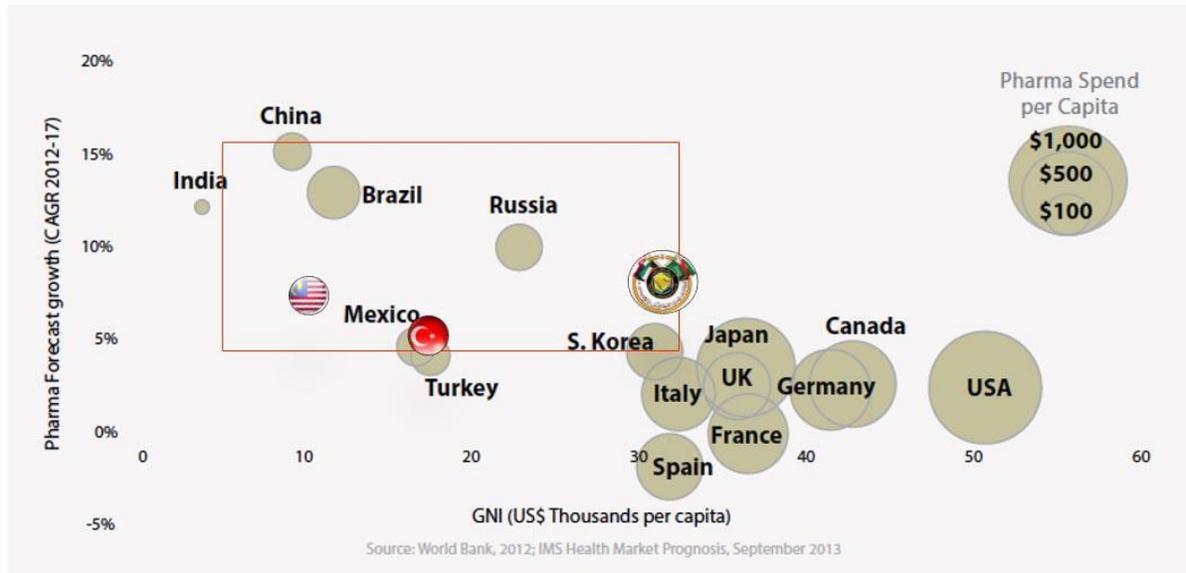
Pharmerging Markets CAGR 2012-16	
Tier 1 (China)	15-18%
Tier 2	12-15%
Brazil	12-15%
KSA	10-13%
India	14-17%
Tier 3	7-10%
Pharmerging	12-15%



- Growth opportunities lie in emerging markets
- These markets are difficult for multi-nationals to serve
- Boston Oncology provides solution for rapid-growth in emerging markets

In the past, the focus on emerging biopharma markets has centered on the BRIC countries – Brazil, Russia, India and China. But other pharmerging markets offer comparable opportunities, especially for biosimilar companies looking to invest in local manufacturing facilities. The key is to find markets in the “sweet spot” – that is, those markets with the income growth to sustain an increased biopharmaceutical spend. While most of the BRIC countries are in that spot, they are not alone.

Country Income vs. Country Growth shows a sweet spot



The demand in pharmerging markets will continue to grow as life expectancy and purchasing power increase. Along with a longer life and more affluent lifestyle, residents in the markets are experiencing a higher incidence of obesity, diabetes and cancer – often without access to life-saving biologics. Because of the unmet need, diseases like cancer are expected to place a heavier burden on the pharmerging markets than elsewhere. While the global death toll from cancer is predicted to double by 2030, it will triple in emerging markets such as the Kingdom of Saudi Arabia (KSA).

Worldwide cancer patients will double Yet will triple in KSA and GCC

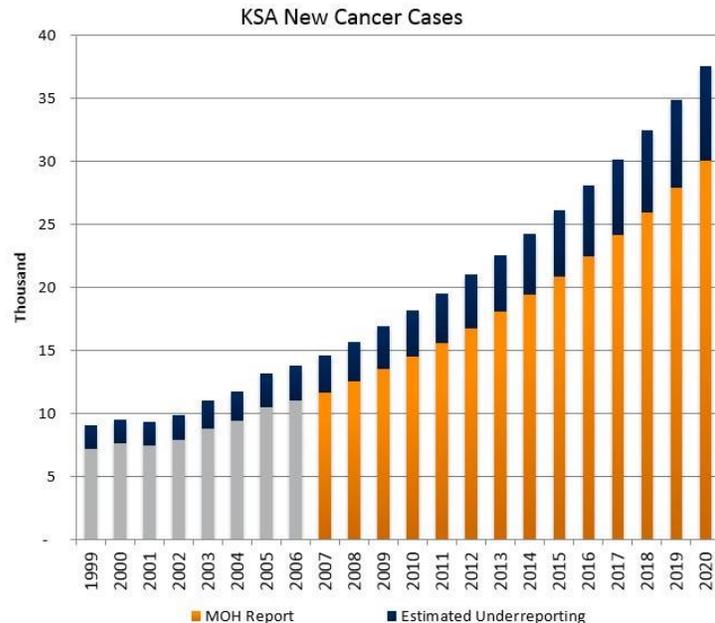


Global Burden:

- 1st most common cause of death
- 11 to 12 million people/year
- 24 million people live with cancer
- 8 million will die/year
- Developed countries: 50% fatality
- Underdeveloped countries: 80% fatality
- By 2030, Cancer incidence will double

KSA Burden:

- KSA: 3X annual increase



For a biopharma company to respond to the unmet need and the potential in emerging markets, it must develop a long-term strategy that starts with a look at its goals. If its goal is big profits with minimal investment, an emerging market would not be a good fit. Secondly, a company must consider which markets to invest in. Basic questions include:

- Is there a sufficient-sized commercial opportunity in the market?
- Can the company manufacture products that are affordable for the market? (Pharmerging markets generally have a smaller margin on drug sales.)
- Can the company make its biosimilars available to pockets of patients who have had no access to the innovator biologics?
- Does the company share the values of the specific market? This cannot be a one-size-fits-all approach.
- What is the geography of the market? Will access to clean water and other resources be an issue?
- How supportive is the government?
- What is the reimbursement system? Is there an advantage for having manufacturing facilities in country?

Developing EM Strategy



To achieve a defensible advantage, a company should target therapeutic areas that will have the biggest impact on patients in the market by treating the most prevalent and costly diseases there, especially when there are no competitors being manufactured in the area. To unlock access to the market, a company must evaluate the capabilities it will need in a given market. Then, it must consider whether to license its products, partner with a domestic firm, acquire an existing firm or manufacturing facility, or invest in building manufacturing facilities in the area.

Conclusion

In the future, innovative biologics manufacturing will fundamentally change the where, when and how life-saving drugs are produced while reducing the cost of their production. The global impact could be revolutionary, especially for emerging markets needing access to affordable biologics. But it also could transform the industry in developed markets by facilitating biosimilars, treatments for rare diseases and precision medicine.

As a further example of how the manufacturing of the future could impact the U.S., Christopher Earnhart, director of medical countermeasure integration advanced development and manufacturing capabilities and lead microbiologist at the CBR Defense Concepts and

Experimentation Branch of the Naval Surface Warfare Center and Dahlgren Laboratory, and Philip Ferro, director of special projects for the Assistant Secretary for Preparedness and Response at the Department of Health and Human Services, discussed how innovations such as continuous and real-time manufacturing could improve the government's emergency preparedness, making it more responsive to real emergencies and much more cost-effective. Instead of stockpiling massive quantities of pandemic vaccines and medical countermeasures "just in case" they are needed, real-time manufacturing would allow drug manufacturers to produce the drugs when they're needed. That capability would alleviate spending on drugs and vaccines that will never be used, the need for extensive storage facilities, and concerns about the expiration of stockpiled drugs and vaccines.

To fully realize the promise of the innovations that are within reach, a new paradigm of cooperation among biologics manufacturers is needed to deal with the regulatory, R&D and cost pressures facing the industry and to produce quality products in an intensely competitive and rapidly evolving space. Industry must work together to develop benchmarks, platforms and standards for the manufacturing tools that will be necessary to keep up with the demands of tomorrow. Biologics makers have several questions seeking answers. For instance, what is the role of continuous manufacturing? Or is there an algorithm that can be used to determine COGs and diminishing economies of scale for innovative manufacturing processes? The conversation must continue.

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About Tufts Center for the Study of Drug Development

Established in 1976, Tufts Center for the Study of Drug Development at Tufts University School of Medicine provides strategic information to help drug developers, regulators, and policy makers improve the efficiency and productivity of pharmaceutical research and development. Tufts CSDD conducts and publishes authoritative analyses that address the economic, political, scientific, and legal issues that affect the development and regulation of human therapeutics. In addition, Tufts CSDD hosts symposia and workshops, offers professional development programs, such as its annual *Postgraduate Course in Clinical Pharmacology, Drug Development and Regulation*, and publishes *Tufts CSDD Impact Reports*, a bi-monthly newsletter providing analysis and insight into critical drug development issues.

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