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Super Cluster
Perspective on enhancing biopharmaceutical manufacturing employment opportunities in Massachusetts

The vision and the reasons for creating a Worcester based commercial Biopharmaceutical Manufacturing Accelerator.

October 2013

MassBio
Massachusetts Biotechnology Council

Foundation for the Advancement of Personalized Medicine Manufacturing

MBI
Massachusetts Biomedical Initiatives

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Training Center

Contents

A fundamental change is occurring in biopharmaceutical manufacturing which is embracing flexible, modular, molecule agnostic manufacturing platforms. This major paradigm shift is occurring for biologics, small molecules, vaccines, cell therapies, and novel classes of therapies still in the research phase of development.

These new flexible manufacturing platforms will be central to a future where personalized and regenerative medicines are part of patient centric treatment paradigms. With this shift an inspired Worcester based Public-Private Partnership can position the Commonwealth for development of a broader and deeper life science workforce.

Introduction

PwC

by Gerry McDougall

The promotion of Public-Private Partnerships to solve intractable problems or introduce new economic development into a region has a successful history in the United States and globally. The Commonwealth of Massachusetts has a robust life sciences R&D economy with over 550 companies, over 1,174 drugs in various phases of development and greater than 6% of the global biologics pipeline in development. Overall the life sciences employment has grown 40% from 37,490 to 56,462 from 2002–2012 quite an achievement.

One aspect of the Commonwealth's life sciences industry that has not exhibited robust growth is the biopharmaceutical manufacturing sub-sector. From 2002–2012 this sector grew by only 8% from 8,294 to 8,960 even though regional investment in R&D by the federal government and venture capitalists is always first or second in the nation as measured by any number of metrics. This dichotomy has employment implications: as more highly educated workers are joining the R&D biomedical workforce, there are fewer opportunities for "middle-skilled" workers who want to participate in one of the Commonwealth's most robust industries. Building on the challenges described in our 2008 report *"Super Cluster—Ideas perspectives, and trends shaping the global impact of the Massachusetts life sciences industry"* the authors have developed a perspective examining the ability of a Public-Private Partnership to overcome these still existing challenges to vitalize the biopharmaceutical manufacturing industry leveraging regional assets.

PwC has advised clients on over 100 public-private partnerships, some of which have been recognized with Thompson Reuters Project Finance International Awards. During these engagements PwC has developed an understanding of the principles that lead to the establishment of a successful Public-Private Partnership: define the role of the Public-Private Partnership; determine the lifespan of the Public-Private Partnership; decide upon the Public-Private Partnership model; establish and maintain Public-Private Partnership funding; and identify, select and engage Public-Private Partnership membership. They can be cultivated in biomanufacturing for the economic benefit of the Commonwealth, and the healthcare benefit of patients globally.

Gerry McDougall is a Partner at PwC and leads the firm's Personalized Medicine Initiative

Introduction

Massachusetts Biomedical Initiatives

by Kevin O'Sullivan

The Massachusetts Biomedical Initiatives (MBI) is a not-for-profit private, independent economic development organization dedicated to increasing job creation and innovative healthcare throughout Massachusetts by promoting the growth of start-up biomedical companies. MBI offers support to creative entrepreneurs with sound scientific business plans in an effort to commercialize their science. Through its MBI Incubator facilities located in Worcester, MBI lowers barriers to success for emerging companies by providing cost-effective, high quality laboratory space and support services. MBI is committed to collaborating with the academic, business, and government communities to promote Massachusetts as the world leader in the life sciences industry.

MBI, with our co-authors, have identified a unique area within the biomedical industry that is well suited for the historical strength in manufacturing that Worcester's economy was founded—biopharmaceutical manufacturing. With local assets like Worcester Polytechnic Institute's (WPI) Bioengineering Education & Training Center, contract manufacturer AbbVie, manufacturing equipment manufacturer General Electric Healthcare Life Sciences subsidiary Xcellerex, EMD Millipore, Thermo Fisher, and contract research organization Blue Sky BioServices, we have a unique opportunity to create a biopharmaceutical manufacturing infrastructure in New England's second largest city, to provide the Commonwealth's emerging biopharmaceutical industry with desperately needed access to state of the art commercial biopharmaceutical manufacturing equipment and expertise. This new focus will work to ensure that biopharmaceuticals with high potential are not only created here but also have the opportunity to be manufactured in the Commonwealth, commercialized here in-state, and supported by much needed stable "middle-skill" employment. The Massachusetts manufacturing sector's decline over the years must be reversed and we have assembled a top rated team and a solid vision to re-capture our state's prominence as reflected within this *"Perspective on Enhancing Biopharmaceutical Manufacturing Employment Opportunities"* report.

Worcester's abundance of potential biopharmaceutical manufacturing sites, a reasonable cost of living, and access to high quality human capital provides an ideal region for the formation of a public-private partnership to ensure a focused and successful approach to growing biopharmaceutical manufacturing jobs in the Commonwealth and fueling our life sciences industry's future sustainability!

Kevin O'Sullivan is President and CEO of MBI

Introduction

Worcester is prepared for biopharmaceutical manufacturing

by Michael O'Brien

Long a hotbed of industry in New England, Worcester is in the midst of a transformation from the traditional factory system of the 19th and early 20th century to the modern 21st century economy. With its traditional strength in manufacturing and "making things," Worcester is successfully competing as a biopharmaceutical manufacturing hub. The city is reinventing itself by providing an attractive climate for technology leaders, building the foundations for health care and medical research through strategic development, and instituting initiatives and programs to sustain future growth. As a center for commerce, industry, and learning, Worcester's success can be attributed to the low cost of housing, high quality of life, overall accessibility, and our growing knowledge-based economy. This change has transformed Worcester's economy—nearly 45% of all jobs within the city are in the educational and medical fields, attracting a young, highly educated workforce. Worcester has easy access not only to Boston and its western suburbs, but via I-90, I-495, I-84, and Route 146, quick connections to the North Shore, South Shore, Springfield, Providence, Rhode Island, and Hartford, Connecticut.

Nine colleges and universities and major teaching and clinical hospitals make Worcester the perfect location for research, discovery, pre-clinical testing, clinical trials, manufacturing and commercial production. The high concentration of intellectual capital and proximity to the region's best medical facilities, combined with an expedited permitting process and financial tax incentives, has helped to spur the expansion of the biotechnology and life sciences industry in the city. Supporting the infrastructure Worcester is putting in place to build new world leaders in life sciences related industries, Worcester Polytechnic Institute has opened a state-of-the-art training facility to prepare a new generation of biopharmaceutical manufacturing labor. Other companies, such as Abbvie, are manufacturing life-improving medicines in Worcester that are distributed around the world. We welcome the opportunity to become the "go to" place in the Commonwealth for the rapidly evolving biopharmaceutical manufacturing industry.

As a robust and vibrant community that is forging its own path, the City of Worcester is a smart city and a smart choice for investment.

Michael O'Brien is City Manager of Worcester

Executive summary

The long term goal is to have more of the Super Cluster's molecules discovered and commercially manufactured in the Commonwealth.

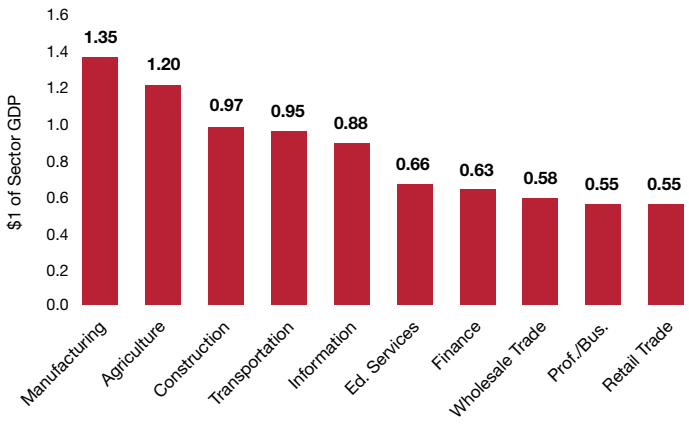
From the American Revolution to the Industrial Revolution, the city of Worcester has been seen as a leader of manufacturing not just within the Commonwealth, but in all of New England. Now Worcester has the opportunity to continue this history of leadership by developing a complementary industry segment for the Commonwealth's Life Sciences Super Cluster: biopharmaceutical manufacturing. With extensive research and development occurring at numerous institutions the Life Sciences Super Cluster is at the focal point of biopharmaceutical innovation for the industry. Worcester wants to support this winning position by becoming a leading region in biopharmaceutical manufacturing.

Over 1,174 personalized and traditional biopharmaceuticals treating a range of conditions are being developed by translational researchers and physicians within the institutions of the Super Cluster. The therapeutic areas include oncology, neurology, dermatology, lysosomal storage, gastro-intestinal, cardiovascular, musculoskeletal, central nervous system, sensory organs and systemic anti-infectives. As these therapies mature they will need to be manufactured to gain regulatory approval for clinical trials and potentially


Methanol

commercialization. Currently, most of these therapies will be manufactured outside the Commonwealth because there is a lack of economically viable biopharmaceutical manufacturing infrastructure in Massachusetts to support early stage production. As a whole, biopharmaceutical manufacturing is losing ground in the United States, with almost 40% of finished drugs, and almost 80% of active ingredients now obtained from overseas sources, however this does not need to be the case.[1]

Figure 1: Economic activity generated by $1 of secotor output, 2010



Source: AMP Steering Committee based on data from Bureau of Economic Analyss, Input-Output Tables available at www.bea.gov/iTable/index_industry.cfm.

This analysis was undertaken to understand the economic factors that could lead to the establishment of a biopharmaceutical manufacturing industry in Worcester. The Advanced Manufacturing Partnership (AMP) Steering Committee Co-Chaired by former MIT President Dr. Susan Hockfeld, showed that manufacturing creates more economic value per dollar spent than any other industry sector with biopharmaceutical manufacturing being identified as one of the key areas of future federal investment, **Figure 1.**[2] A paradigm shift is currently underway in pharmaceutical research, development and manufacturing as the medical field turns from large-scale production to smaller runs of biologics intended for a more specific patient group. This shift to more modular, flexible, single use manufacturing platforms provides an opportunity to retain and grow commercial manufacturing within the Commonwealth in alignment with the national priorities identified by AMP.[3]

This shift dramatically lowers the cost of creating infrastructure, and with Worcester's affordable cost of living provides two foundational elements for the creation of a Public-Private Partnership to establish a commercial biopharmaceutical manufacturing innovation zone in Worcester with the long term goal of having more of the Super Cluster's molecules discovered and commercially manufactured in the Commonwealth. Through a unique and flexible structure of a Public-Private Partnership, Worcester can fill the manufacturing innovation gap,

The manufacturing innovation gap for novel biopharmaceuticals, Figure 2, is an issue for the Commonwealth. A Public-Private Partnership focused on cultivating commercially sustainable manufacturing infrastructure can assist in resolving this gap.

1 http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf

2 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_amp_steering_committee_report_final_july_17_2012.pdf

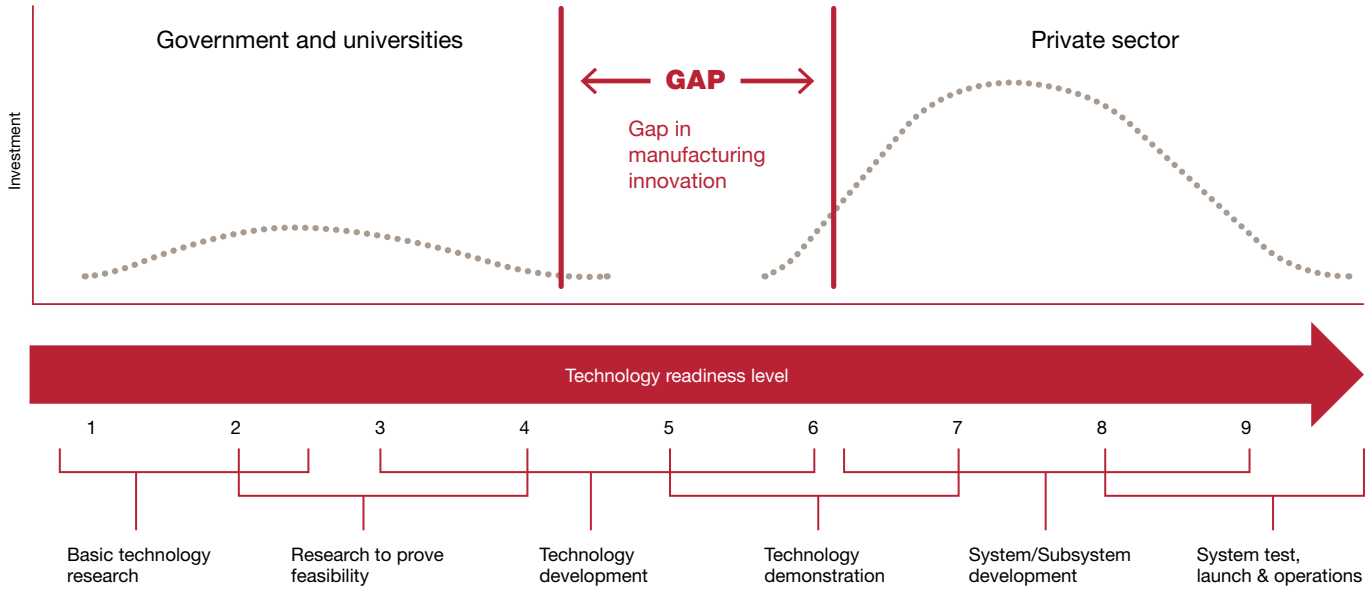
3 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_amp_steering_committee_report_final_july_17_2012.pdf

Figure 2, and will take the lead in biopharmaceutical manufacturing. With it Worcester can take the Commonwealth into the next era of biomedical innovation.

The Commonwealth has a history of supporting biopharmaceutical manufacturing with recent public investments. Facilities at UMass Dartmouth and UMass Lowell are expanding their biologics manufacturing footprint for training workers and testing manufacturing products and processes. MassBiologics in Boston is the only domestic non-profit and FDA licensed manufacturer of vaccines. Worcester Polytechnic Institute's Biomanufacturing Education and Training Center (BETC) is an example of the kind of innovative capabilities being created to train workers on modular, single-use equipment that will be pervasive in the future. The BETC provides customized, innovative workforce development solutions serving life sciences companies from across the region and the globe.

Only 45 miles from Boston, with an abundance of appropriately skilled workers, affordable cost-of-living, availability of manufacturing buildings, and numerous high quality educational institutions, Worcester is well positioned to form an innovative Public-Private Partnership to become a leading biomanufacturing region for the Commonwealth, country, and possibly the world.

Figure 2: Manufacturing innovation: Investment gap



Source: Report to the President on Capturing Domestic Competitive Advantage in Advances Manufacturing. Executive Office of the President: President's Council of Advisors on Science and Technology. July 2012.

The market analysis of the Greater Boston biopharmaceutical industry segment illustrates not only a significant opportunity for biopharmaceutical manufacturing, but also highlights a very fertile biopharmaceutical ecosystem where seed and early stage companies are not only garnering a large percentage of venture capital financing, but are also operating primarily in the Pre-Clinical, Phase I and Phase II stages of molecule development when "innovation spillovers"[4] from biopharmaceutical manufacturing knowledge could be most useful to the regional economy as a whole. The robust venture capital market in Greater Boston helps fund the development of these companies and their innovative medicines. Massachusetts biopharmaceutical companies received $838 million in venture capital financing in 2012, amounting to 21% of all U.S. venture capital for biotech in 2012. Over 80% of the companies located in the area are emerging, young organizations with a need for cost effective biopharmaceutical manufacturing.

The current rate of FDA approvals has been lack luster in the last decade; only 18 new biopharmaceuticals entered the U.S. market in 2012, roughly the same amount as FDA approvals from 2011 to 2009 (12 in 2011, 14 in 2010, & 18 in 2009). The smaller and modular biopharmaceutical manufacturing facilities built in Worcester can source key equipment locally (e.g. GE Healthcare's FlexFactory, EMD Millipore's Mobius, and Thermo Fisher's Hyperforma located in Marlborough, Billerica and Waltham respectively) and meet regulatory requirements of the FDA. Smaller, modular, biopharmaceutical manufacturing facilities can be readily adapted to continuous small molecule manufacturing, pioneered by MIT and Novartis.[5, 6, 7, 8] Continuous small molecule manufacturing can operate effectively under the same Quality-by-Design regulatory principles that govern the quality system of flexible modular facilities for biological molecule manufacturing. Conceptually indicating that modular physical infrastructure along with an integrated quality system is suitable for the portfolio of molecules under development in the Commonwealth. Additionally, many product failures during development are ultimately attributable to problems relating to the transition from laboratory prototype to industrial product. Keeping biopharmaceutical manufacturing near R&D helps ensure reliable, quality production and smooth transitions from lab to scale-up.

Massachusetts is well suited to sustain long-term growth in the biopharmaceutical manufacturing industry. The ~1,174 molecules being developed are like "diamonds-in-the-rough," and should be seen as the Commonwealth's "natural resources" which need to be carefully cultivated in order to yield positive economic outcomes. At the same time R&D is cultivating these precious resources, a large number of equipment providers for biopharmaceutical manufacturing, stationed in Massachusetts, have been bringing forth new technologies to streamline the biopharmaceutical manufacturing process. The Commonwealth has the ability to bridge the investment gap, **Figure 2**, in manufacturing technology and innovation, and bring forth the foundation for a unique economic opportunity.

4 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_amp_steering_committee_report_final_july_17_2012.pdf

5 http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=805483&sk=5d2504ec6a63343265847159bb809400

6 http://www.boston.com/business/articles/2007/09/28/novartis_to_give_mit_65m_to_find_new_way_to_produce_drugs/

7 http://web.mit.edu/press/2012/manufacturing-pharmaceuticals.html

8 http://novartis-mit.mit.edu/sites/default/files/images/2012%2011%2013%20Symposium%20on%20Continuous%20Manufacturing%20of%20Pharmaceuticals%20Notes.pdf

In summary, the following key points will be developed throughout this document:

- Support the formation of a Commercial Biopharmaceutical Manufacturing Public-Private Partnership for shared risk and responsibility of developing the physical asset of the facility and intangible asset of the Quality System required to manufacture clinical lots suitable for pre-IND and IND testing;
- Support the Establishment of a Commercial Biopharmaceutical Manufacturing Innovation Zone in Worcester;
- Support a regional focus on biopharmaceutical manufacturing job growth that collaborates with existing biologic manufacturing investments at UMass Dartmouth and UMass Lowell;
- Establish a Worcester regional biopharmaceutical manufacturing board that works with the existing Biomanufacturing Roundtable to ensure transparency, collaboration, and growth, led by WPI and MBI;
- Strive to ensure molecules developed in the Super Cluster have the opportunity for commercial manufacturing in the Commonwealth supported through outreach programs fostered by the Worcester Chamber of Commerce;
- Encourage participation of the City of Worcester, various State organizations and Federal Departments in this unique Public-Private Partnership to foster the expansion of biopharmaceutical manufacturing job opportunities in the Commonwealth.

Overview of the opportunity

Highlights

Biopharmaceutical manufacturing has and continues to move overseas.

Massachusetts leads in domestic research and development of biopharmaceuticals.

The Super Cluster's translational researchers are looking for modular, flexible, small-scale, multi-use production facilities.

A Public-Private Partnership will allow Worcester to leverage the local R&D talent and breakthroughs in biopharmaceutical manufacturing technology to keep biopharmaceutical production in the Commonwealth providing much needed jobs.

A paradigm shift is occurring in the biopharmaceutical manufacturing industry and there is a strategic opportunity for the Commonwealth's Life Sciences Super Cluster to maintain its position as an industry pioneer in biopharmaceuticals. As a whole, biopharmaceutical manufacturing is losing ground in the United States, with almost 40% of finished drugs, and almost 80% of active ingredients obtained from overseas sources.[9] Part of this is evident in the loss of jobs over the last decade in six of the top biopharmaceutical manufacturing states **Table 1**.[10]

Table 1: Job growth/decline in biomanufacturing states, 2002–2012

	Growth/ Decline	% Change
Texas	1033	11.6%
California	4329	10.8%
Massachusetts	**666**	**8.0%**
North Carolina	234	1.1%
New York	-1716	-8.0%
Illinois	-3231	-15.4%
Indiana	-4887	-25.0%
Pennsylvania	-7951	-29.3%
New Jersey	-12651	-32.1%
Michigan	-3982	-33.4%

Source: U.S. Bureau of Labor Statistics, Quarterly Census of Employment and Wages (QCEW)

9 http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugand CosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/default.htm

10 http://www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy1.pdf

Worcester's low cost of living, deep pool of talented labor, transportation infrastructure, tax incrementing financing and willingness to permit efficiently, provides an ideal partner city to locate biopharmaceutical manufacturing.

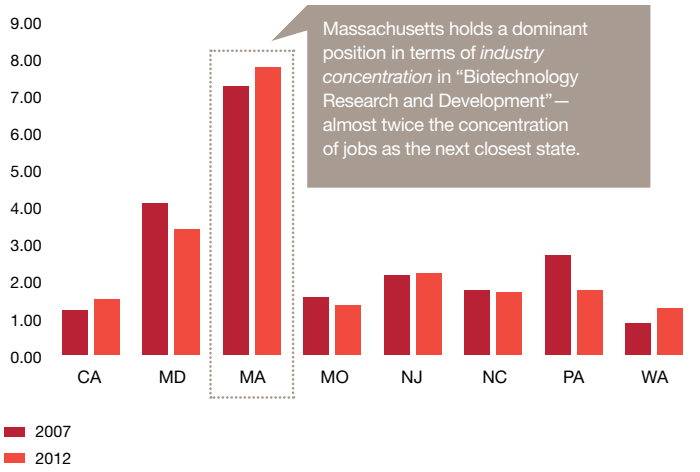
Massachusetts is a world leader in the research and development of biopharmaceuticals and possesses strong educational institutions, corporations, and foundations that all work to create life-saving biomedical products. However, the Commonwealth is at risk of passing up on the opportunity to leverage a unique position. Massachusetts needs to ensure that these biopharmaceutical innovations developed in the Super Cluster have the opportunity to be manufactured in Worcester. Focus on this will continue to encourage the growth of the larger biopharmaceutical industry, make it easier for researchers to gain FDA clearance for new drugs, produce employment opportunities for mid-level employees with a high school or associates degree, and ultimately save lives around the world. The paradigm shift from costly capital infrastructures to continuous process [11, 12, 13, 14] and flexible, molecule agnostic, single-use, disposable platforms provides an economic opportunity to change the direction of biomanufacturing in the Commonwealth. Through the use of a biopharmaceutical manufacturing Public-Private Partnership more molecules discovered in the Commonwealth can complete the biopharmaceutical product life cycle (discover, research, manufacture and commercialize) providing more employment opportunities for a wide array of people at various skill levels.

If Massachusetts does not act soon, it will witness biopharmaceutical manufacturing jobs being created overseas or in other states with lower labor costs and favorable government policy. Massachusetts could also lose out on future opportunities in the biomedical and life sciences field that are stimulated when R&D is located close to manufacturing, often referred to as the "spillover effect". High R&D concentration, **Figure 3**, leads to great potential for a modest biopharmaceutical manufacturing growth opportunity.[15] With the flexible option of a Public-Private Partnership the government and industry leaders who already have a presence in the region can come together to change this trajectory and make a long-term investment in the industry and the Worcester region. The biomedical and pharmaceutical industries as well as local research institutions have already demonstrated their willingness to work together as seen by the success of the Massachusetts Life Sciences Center and Massachusetts Biotechnology Council.

In fact, the local government has previously supported other initiatives within the biopharmaceutical industry to encourage growth and innovation. The missing link in the region is a flexible biopharmaceutical manufacturing infrastructure allowing new biopharmaceuticals to be quickly and safely manufactured in accordance with FDA guidelines, gain government approval, and rapidly increase scale for commercialization.

Previously, the standard biopharmaceutical manufacturing facility involved a massive capital investment in one factory for just a single drug. This created immense risk as only one in ten drugs makes it through clinical trials to gain regulatory approval. Innovative biopharmaceutical manufacturing design, equipment, and process automation have led to a paradigm shift in the industry with the introduction of products like Marlborough, MA-based GE Healthcare subsidiary Xcellerex's FlexFactory™, Billerica, MA-based EMD Millipore's Mobius platform and Waltham, MA-based Thermo Fisher's Hyperforma platform which can allow multiple drugs to be produced at one facility on a small or large scale and at a rapid pace without sacrificing quality

Figure 3: Industry concentration in biotech R&D



Source: U.S. Bureau of Labor Statistics, Quarterly Census of Employment and Wages (QCEW)

11 http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=805483&sk=5d2504ec6a63343265847159bb809400

12 http://www.boston.com/business/articles/2007/09/28/novartis_to_give_mit_65m_to_find_new_way_to_produce_drugs/

13 http://web.mit.edu/press/2012/manufacturing-pharmaceuticals.html

14 http://novartis-mit.mit.edu/sites/default/files/images/2012%2011%2013%20Symposium%20on%20Continuous%20Manufacturing%20of%20Pharmaceuticals%20Notes.pdf

15 http://www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy1.pdf

or safety. Coupled with commercial innovation of continuous process small molecule manufacturing pioneered by MIT and Novartis the Commonwealth is rich in biopharmaceutical manufacturing innovation.[16, 17, 18, 19] This revolutionary shift within biopharmaceutical manufacturing will lead to the future commercialization of exciting novel therapeutic modalities like nanomedicines, vaccines, cell therapies, as well as traditional small and large biopharmaceutical products and Worcester can be a key part of it. In addition to reducing the capital cost required per drug, the risk profile of investment is greatly diminished as the creation of even just one successful biopharmaceutical will more than pay for the investment.

In 2008, PwC published a report entitled *Super Cluster: Ideas, perspectives, and trends shaping the global impact of the Massachusetts life sciences industry.*[20] A perspective within the report articulated that despite these strengthening fundamentals, Massachusetts continues to struggle with various factors, including the high costs of living and labor, inefficient permitting procedures, and heavy taxation burdens. These factors play a crucial role in a company's decision of whether or not to establish commercial-scale biomedical manufacturing operations in the Commonwealth. Companies have pointed to Massachusetts' skilled work force as a primary reason for manufacturing in the state. Unfortunately, many of these same issues: cost of living, permitting challenges, and taxes, still exist but the climate is getting better. Particularly advantageous for the Commonwealth are some fundamental structural changes occurring in the biopharmaceutical manufacturing industry that can mitigate some of these factors.

In 2008, a majority of companies with manufacturing activities in Massachusetts planned to maintain or increase their manufacturing work force inside the state, while many planned to pursue cost-effective manufacturing alternatives elsewhere—a cause for concern for the Commonwealth that has changed little in the intervening five years. As with research and development, these companies are moving their manufacturing to Europe and Asia, as well as to other US states, for the same primary reason: access to lower-cost skilled labor and manufacturing infrastructure that is not available in the Commonwealth.

Despite hurdles, Massachusetts currently boasts a number of biologic manufacturers, with additional life sciences companies moving their manufacturing operations into Massachusetts. Bristol Myers Squibb's campus will eventually employ 550 people. Biomedical manufacturing companies here include AbbVie, Boston Scientific, Genzyme, Philips Medical Systems, Covidien, Shire PLC, Biogen Idec and Pfizer. Together these companies and others employ 8,900, but there are opportunities to grow this number.

MIT's Industrial Performance Center and Center for Continuous Manufacturing, the University of Massachusetts' BioManufacturing Center in Lowell, MA Accelerator for Biomanufacturing at UMass Dartmouth and the companies commercializing innovative single-use manufacturing technology, GE Healthcare's subsidiary Xcellerex, EMD Millipore's Bioprocess R&D Center, and Thermo Fisher, are all focused on developing services, process and products that operate within the paradigm shift occurring in biopharmaceutical manufacturing towards modular, single-use, disposable products for leaner more effective biopharmaceutical manufacturing. These and other resources will propel the industry into the future. With so many of these companies local, it provides a unique opportunity to strategically rethink how biopharmaceutical manufacturing capacity can be established in the Commonwealth.

16 http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=805483&sk=5d2504ec6a63343265847159bb809400

17 http://www.boston.com/business/articles/2007/09/28/novartis_to_give_mit_65m_to_find_new_way_to_produce_drugs/

18 http://web.mit.edu/press/2012/manufacturing-pharmaceuticals.html

19 http://novartis-mit.mit.edu/sites/default/files/images/2012%2011%2013%20Symposium%20on%20Continuous%20Manufacturing%20of%20Pharmaceuticals%20Notes.pdf

20 http://www.pwc.com/gx/en/pharma-life-sciences/super-cluster/index.jhtml

21 Industry Snapshot. MassBio. www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy2.pdf. 2013

Summary of local biopharmaceutical manufacturing

Highlights

The Commonwealth has a breadth of capabilities in drug discovery, development, and commercialization; however, there is a need for flexible, small-scale biopharmaceutical manufacturing capable of clinical production for early translational efforts.

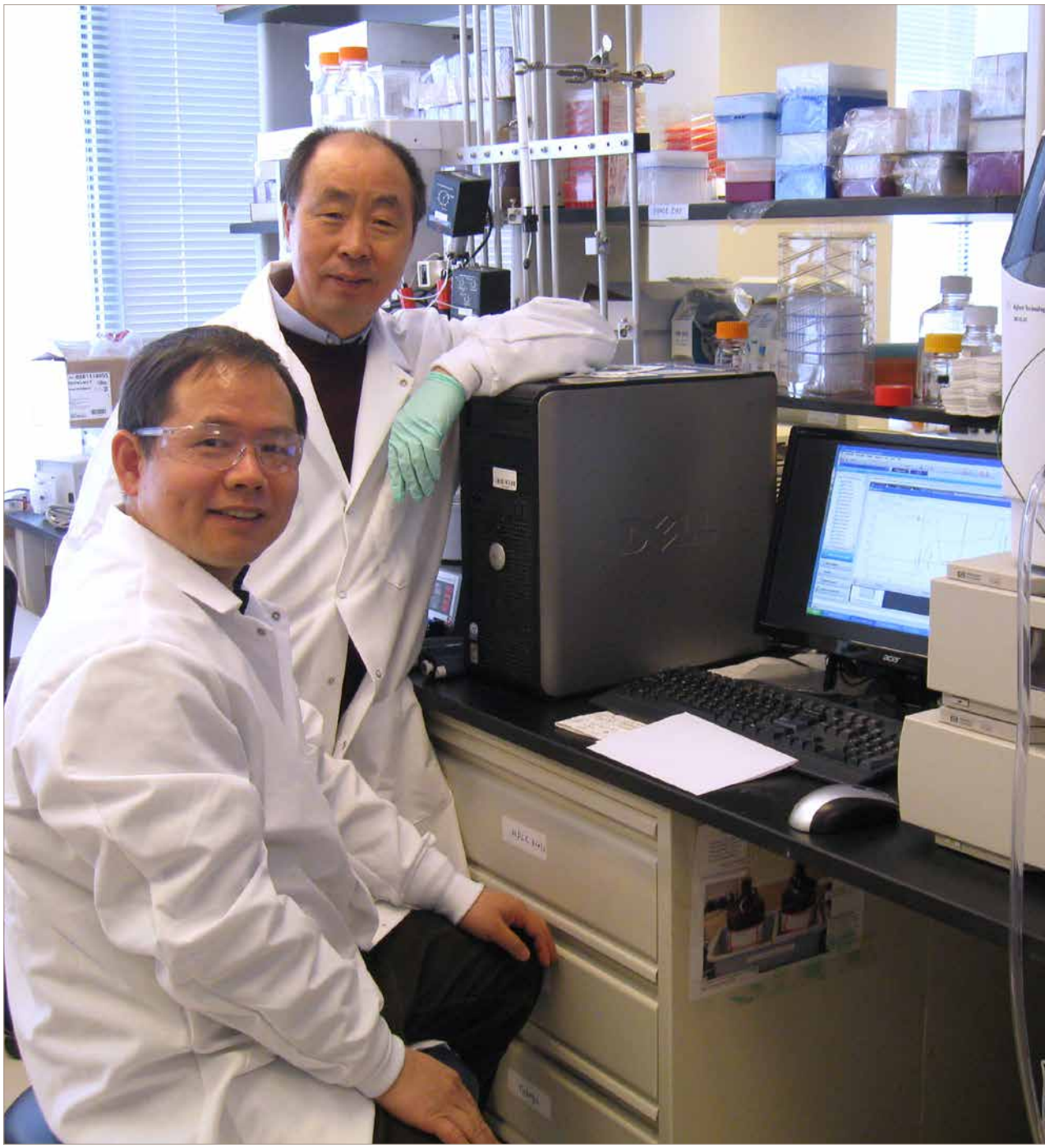
Worcester has a suitable environment for a biopharmaceutical manufacturing Public-Private Partnership due to its accessibility to drug researchers, trained workforce, and recent significant investments in life sciences.

Scientific advances in the niche products and personalized medicine fields are rapidly changing business models associated with traditional drug commercialization lifecycles. Higher yields, smaller markets, and revolutionary process development and manufacturing technologies are combining to accelerate the translation of drug development candidates to bedside drug products. The net result of this progress is that flexible biopharmaceutical manufacturing infrastructure can now be established in pre-selected locations at a significant reduction in cost compared to a decade ago. Such a flexible biopharmaceutical manufacturing capacity will not only provide manufacturing for in-state customers, but will also have the ability to attract customers on a national and international scale.

For example, Massachusetts has significant commercial biologics manufacturing capacity.[22] However, to meet the demand for small-scale biological clinical production, Massachusetts has precious few resources. There is no longer a need for more large capacity factories that specialize in one drug. Instead, today's world of personalized medicine requires flexible facilities that can quickly shift from producing one drug to another all while maintaining high quality

22 Massachusetts Biomanufacturing Roundtable Update. Mass Biotech Council. "http://www.massbio.org/writable/editor_files/biomanufacturing_roundtable_presentation.pdf". Dec 7, 2011

The numerous modular equipment manufacturing companies located in Massachusetts provide a unique opportunity to strategically rethink how biopharmaceutical manufacturing capacity can be established in the Commonwealth.



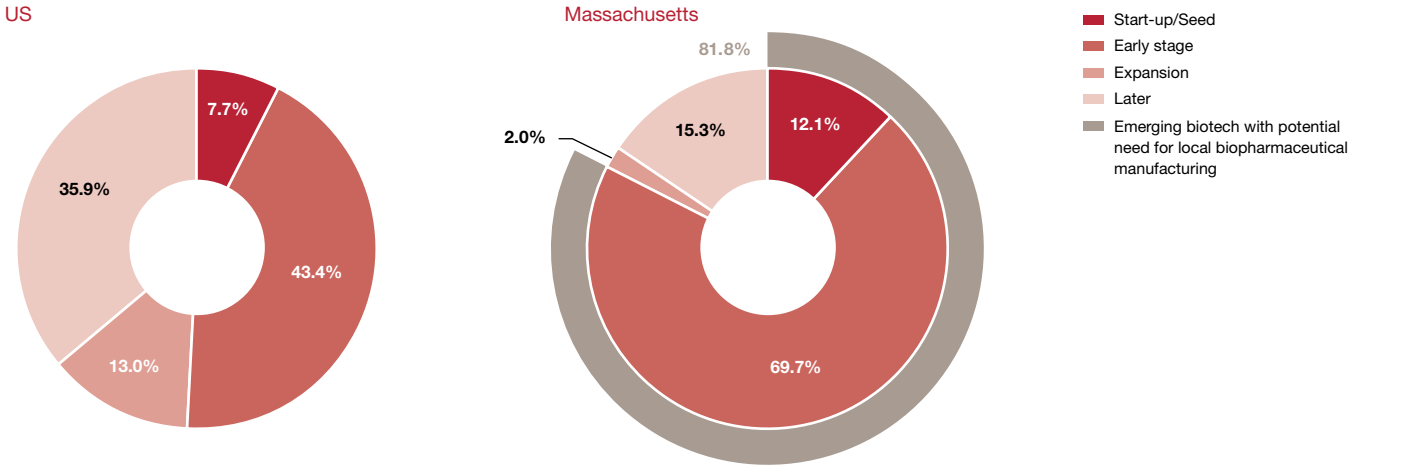
and safety standards and at a low cost. The solution to this issue is in regional growth: creating small-scale and flexible biopharmaceutical manufacturing facilities located near the people developing the drugs therefore allowing for a more effective cGMP ecosystem.

There is substantial investment and interest in biopharmaceutical manufacturing within Massachusetts as seen by the presence of contract manufacturing organization (CMO) companies such as AbbVie, Affinity, AMRI, and Gallus. However, in what could be a significant loss for the Commonwealth, Lonza recently announced that it will phase down production in Hopkinton as the company consolidates production in Switzerland, resulting in a loss of 200 in-state jobs.[23] There is a need to continue to strengthen the biopharmaceutical manufacturing community in the Commonwealth if the region wants to keep and facilitate the growth of emerging biopharmaceutical companies into mature employers.

A continuing strategy to invest in innovative solutions and infrastructure will go a long way to facilitate this reality. Though successful, current CMOs in Massachusetts only highlight the differentiated need to adapt to the new trends in biopharmaceutical manufacturing which are more suited for the Commonwealth's emerging biopharmaceutical industry. For example AbbVie, Affinity, AMRI, and Gallus facilities[24] provide a diversified range of services including large-scale production but are often not in a position to offer the affordable programs leading to small-scale production requirements needed for translating the Commonwealth's drug development pipeline to patients.

Often this inability to provide service is not because of a mismatch of capability (e.g. large batch infrastructure versus small batch need) but because the underlying client might be considered too financially risky at its current stage of financial development, i.e. potentially the exact stage at when transformational therapies need manufacturing services to produce clinical data to change the parent companies' financial outlook. As shown in **Figure 4** over 80% of biopharmaceutical companies in Massachusetts receiving venture investment in 2011 are in start-up/seed or early stage.[25] These emerging stage companies must find process development and manufacturing capacity for their molecules, most likely outside Massachusetts, to advance programs to value added milestones to garner further venture investment or a partnership. This process is always

Figure 4: Biotech venture capital financing indicates >80% of the MA life science companies are emerging portending an opportunity for local commercial manufacturing skills to promote an advantageous environment for growing more Commonwealth based commercial biopharmaceutical companies



Source: 2012 PricewaterhouseCoopers, National Venture Capital Association, MoneyTree™ Report, Historical Trend Data and Evaluate Pharma®

23 *Swiss drug company Lonza laying off 200 people in Hopkington.* www.bizjournals.com/boston/news/2013/07/26/lonza-closes-hopkinton-plant.html. July 26, 2013

24 Gallus is headquartered in MA, but manufacturers in St. Louis, MO

25 http://www.massbio.org/writable/editor_files/industry_snapshot_2012_final.pdf

time consuming and fraught with technology transfer risk, but the added dimension of not having manufacturing capacity within driving distance of R&D teams adds further time to the process to work through unforeseen technology transfer issues. The vision for biopharmaceutical manufacturing capacity in Worcester could mitigate several risks. A Public-Private Partnership would provide emerging biopharmaceutical teams with ready access to experienced personnel and tangible and intangible-infrastructure with reasonable economics that work with tight milestone driven budgets, leveraging the latest technology.

A Worcester based Commercial Biopharmaceutical Manufacturing Accelerator would complement existing public funding of therapeutic manufacturing resources to facilitate differentiated biomanufacturing in the Commonwealth.

The MA Biomanufacturing Center (MBMC) at University of Massachusetts at Lowell

Located in Lowell, MA, the MBMC serves as a center of research and development as well as education focused on biomanufacturing. In addition, MBMC partners with local biotechnology companies to pilot new drug manufacturing capabilities. This center was funded with a $10 million grant from the Massachusetts Life Sciences Center (MLSC)[26] and focuses on workforce training and development as well as new process development and engineering runs. Specific facilities include a cell culture lab, microbial fermentation lab, and a pilot plant for testing. The MBMC provides the opportunity to test new approaches within biomanufacturing although it is not designed for full-scale, flexible, commercial production. A partnership between the MBMC and Natrix Separations led to the discovery of a new process for purifying recombinant proteins resulting in significantly fewer steps, an increase in yield from 80% to 95%, a reduction in manufacturing time from 12 hours to 1.5 hours, and reduced production costs.[27]

MA Accelerator for Biomanufacturing at UMass Dartmouth (MAB)

The MAB, located in Fall River, is a $28 million 35,000 square foot facility with a 14,000 square foot cGMP-like biomanufacturing area. The center is anticipated to open in January of 2014 and has received $14.6 million from the MLSC.[28] The world-class MAB will include four production suites, quality control labs, a research and development suite, training lab, lecture halls, and presentation space. This innovative space will allow companies and researchers to come together and test new biomanufacturing processes while training current and future workers. Similar to the MBMC, the MAB is intended more for research and testing, not for clinical or commercial scale biomanufacturing production.

MassBiologics

Located in Boston, MassBiologics is the only domestic, non-profit, FDA-licensed manufacturer of vaccines. With over 100 years of experience (founded in 1897), MassBiologics currently manufactures and distributes the Tetanus and Diphtheria Toxoids, Adsorbed (Td) vaccine. MassBiologics is seen as the domestic leader for vaccine production which led Merck to sign an agreement in 2010 allowing for the exclusive distribution rights of MassBiologic's Tetanus-Diphtheria vaccine[29]. As of 1997, oversight of MassBiologics was transferred from the Massachusetts Department of Public Health to the University of Massachusetts Medical School. With a mission to discover and develop products that will significantly improve public health and multiple facilities housing vaccine production, cGMP manufacturing, laboratories for segregated culture, and research and administration, MassBiologic is seen as a leader in large volume vaccine production.

26 http://www.uml.edu/News/press-releases/2012/ETIC10Mgrant2012.aspx

27 http://www.uml.edu/docs/Shiga_Toxin_AN1000%5B1%5D_tcm18-46974.pdf

28 http://www.mass.gov/governor/pressoffice/pressreleases/2012/2012516-umass-dartmouth-mab.html

29 http://www.merck.com/licensing/news-and-events/massbiologics-press-release.html

Table 2: Differentiation of public biomanufacturing resources with proposed PPP Commercial Biopharmaceutical Manufacturing Accelerator

	Lowell	Dartmouth	Boston	Worcester		
	MBMC[1]	MAB[1]	MassBiologics	MBI/WPI BETC[1,2]	MBI/Blue Bky[2]	MBI/PPP Comm. BioMfg. Acc.[1]
Workforce development	●	●		●		
Cell culture development	●	●	●		●	
Process development and engineering runs	●	●	●	●	●	●
Pilot plant infrastructure	●		●			●
Scaled process validation			●			●
Fully integrated quality system			●			●
Fully integrated supply system			●			●
Clinical materials manufacturing			●			●
Sterile fill and finish operations			●			●
Build, operate and transfer manufacturing capability						●

1 The MA Biomanufacturing Center at UMass Lowell (MBMC), The MA Accelerator for Biomanufacturing at UMass Dartmouth (MAB), Massachusetts´ Biomedical Initiatives (MBI), Worcester Polytechnic Institute Biomanufacturing Education and Training Center (WPI BETC), MBI/Public Private Partnership Commercial Biopharmaceutical Manufacturing Accelerator (MBI/PPP Comm. BioMfg. Acc.)
2 MLSC awarded $5.15M in 2010 to develop Gateway Park, where the BETC and Blue Sky are housed

Worcester

Building on the resources available in Lowell, Dartmouth, and Boston, Worcester already plays a valuable role in MA biomanufacturing through Worcester Polytechnic Institute's Bioeducation and Training Center (BETC) and Blue Sky BioServices at Gateway Park. The state-of-the art $32 million facility at Gateway Center II provides incubator space for companies, educational institutions, and research laboratories. This new facility was funded in part by a $5.15 million grant from the Massachusetts Life Sciences Center.[30] Blue Sky BioServices, an MBI incubated company, also received an equipment loan for $300,000 from MassDevelopment to spur further growth.[31] With MBI providing access to economical infrastructure and access to a vast network, Blue Sky has been able to quickly ramp up services and now employs 40 people. Blue Sky is a successful example of how MBI can serve as a channel connecting public funding with private companies all working together for the improvement of healthcare locally and globally.

This $5.15M MLSC grant also allowed WPI to expand its BETC into a new 10,000 square foot wet lab in Gateway Park. MBI has worked closely with the BETC, particularly in the area of job training for biotechnology. Public investments in Gateway Park have linked non-profits like MBI, with training facilities like the BETC, to private companies such as Blue Sky, directly connecting students to future jobs and real-life training. MBI has led the way in facilitating the growth of biotechnology in the Worcester area by assisting in connecting the Massachusetts's Life Sciences Center and MassDevelopment to a variety of organizations, educational institutions, and companies. Because of this, MBI can help Worcester develop a Public-Private Partnership to seed the beginning of a new biopharmaceutical manufacturing community.

30 http://www.masslifesciences.com/docs/Gateway%202%20Dedication%20Media%20Release%20May12013.pdf

31 http://massbiomed.org/massdevelopment-loans-help-life-science-companies-grow-in-worcester

Table 3: Therapeutic classes ammenable to and functions that can be performed in a single-use, modular, molecule agnostic commercial manufacturing platform envisioned for Worcester

Therapeutic class**	Potential starting material examples	Upstream and downstream functions would be governed by a fully integrated commercial ready, auditable quality system								
		Upstream		Downstream operations (Can be performed and controlled environmental modules)						
		Cell Production	Harvest	Synthesis	API Pre-Processing	Concentration	Purification	Pre-Formulation Processing	Formulation	Sterile-Fill-Finish Suitable for Experimental Clinical Use
Biologics	Bacterial, yeast, mammalian	●	●			●	●	●	●	●
Vaccines	DNA vaccines, viral constructs (e.g., lentivirus), CHO-derived	●	●			●	●	●	●	●
Cell Therapies	Human and mammalian cells	●	●					●	●	●
Gene Therapies	Viral, trans-cell, nuclear transport compounds vectors	●	●			●	●	●	●	●
Nanomedicines	Organic/non-organic synthesis/formulation			●	●	●	●	●	●	●
Protein extracts	Protein API's				●	●	●	●	●	●
Oligonucleotides and Plasmid	DNA, RNA (those too large to synthesize generally produced in E. coli)	●	●		●			●	●	●
Pre-manufac-tured small molecules	API complex formulation, possible non-complex synthesis				●			●	●	●
Continuous small molecule manufacturing	Raw material to tablet production			●		●	●	●	●	●

**Other classes of therapies ammenable to this manufacturing platform could include: protein-protein conjugation, protein-nucleotide conjugation, protein-small molecule conjugation, natural products, and nutraceuticals

The Public-Private Partnership envisioned would provide emerging drug developers with economical access to manufacturing assets (tangible capital equipment and an intangible fully integrated Quality System) and experience that they can work with throughout the entire drug development process, including commercial development if a drug is approved, **Table 3**. This is the final piece in a system that will allow Worcester to go from a small but important player in the industry to a leader, complementing the hidden gems that already exist locally with the MBMC, MAB, and MassBiologics.

Biomanufacturing lesson

At the WPI BETC

The Commonwealth's biopharmaceutical manufacturing opportunity

Highlights

The Commonwealth has over 1,174 biopharmaceuticals in development.

There are over 728 compounds in Pre-clinical, Phase 1 and Phase 2, exactly the period when access to clinical lot manufacturing is critical.

Massachusetts has enough demand in the pipeline to warrant the development of flexible biopharmaceutical manufacturing facilities to bolster the Super Cluster as a whole.

For Massachusetts one of its greatest natural resources is the innovative economy of the biopharmaceutical industry and like any natural resource it needs to be cultivated to provide long-term employment opportunities. To do this it is imperative to make resource allocation decisions that assist entrepreneurial researchers to cultivate early stage molecules into life-saving therapies. The Commonwealth's biopharmaceutical industry currently has over 1,174 drugs, **Table 4**, with a majority of them in early stages of development (research projects to Phase II clinical trials). This pipeline continues to grow as more financial resources enter the region to support the development of therapeutic innovations.

Table 4: Massachusetts Pipeline by therapeutic area, 2012

Therapeutic area	Candidates
Gastro-urinary	20
Respiratory	21
Dermatology	26
Blood	35
Gastro-intestinal	41
Endocrine	44
Cardiovascular	47
Sensory organs	52
Musculoskeletal	58
Central nervous system	156
Systemic anti-infectives	186
Oncology	429
All other	59
Total (R&D)	**1174**

Source: EvaluatePharma®, July 2013

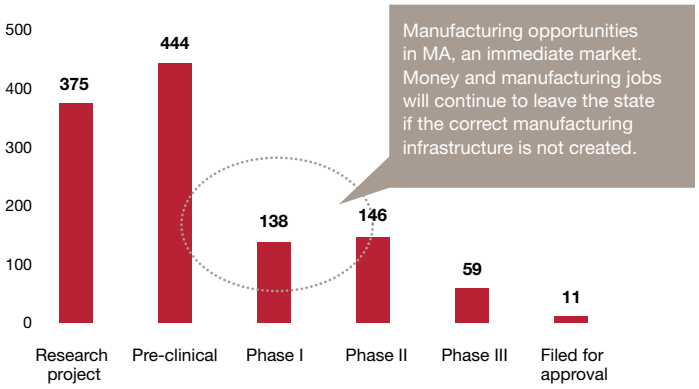
Currently Massachusetts has a dearth of the correct type of manufacturing that therapeutic innovators require. As a consequence most therapies are manufactured outside the Commonwealth.

Out of these 1,174 drugs, 469, **Figure 5**, are biologics with most of those in the pre-clinical and Phase I and Phase II development phases which might be readily amenable to a module single-use manufacturing platform.[32] Academic translational scientists and emerging biopharmaceutical companies developing these therapies will need access to quality manufacturing resources to secure the clinical inventory necessary to receive an Investigational New Drug (IND) status from the FDA and eventually clinical testing. Currently Massachusetts has a dearth of the correct type of manufacturing these innovators require so most therapies are manufactured outside the Commonwealth. Just a decade ago, building manufacturing capacity and operating it under current cGMP required a significant amount of financial resources which most emerging companies could not afford until a molecule had sound Phase II clinical data or partnered with an established biopharmaceutical company to support such activities. This significant financial barrier has potentially robbed the Commonwealth of opportunities to grow biopharmaceutical companies with the potential to commercialize their own molecules and help establish more Massachusetts headquartered, mature employers.

Much has changed in the biopharmaceutical manufacturing industry in the intervening decade with the evolution of modular technology, single-use, disposable technology, integrated component and reagent supply chains, and most importantly regulatory acceptance. Today much of the older biomanufacturing capacity remains under utilized, promoting a sense that there is an overcapacity of resources, however these types of resources are ill-suited for the needs of the Commonwealth's emerging biopharmaceutical companies. Massachusetts is not laden with over-capacity of high volume biopharmaceutical manufacturing that other regions suffer from and has an opportunity to seed the formation of biomanufacturing capacity that is flexible. These resources can be economical, molecule agnostic, and operated under cGMP to service the needs of the Commonwealth's Life Sciences Super Cluster. Once this unmet need is fulfilled, leading emerging companies can consider manufacturing their molecules in the Commonwealth rather than sending than producing them in other regions of the United States or other countries. With this need met and with time, the Commonwealth could experience a new generation of biopharmaceutical companies similar in economic impact as some of their forerunners: Biogen-Idec, Cubist, Vertex and Genzyme.

Of the 1,174 drugs under development in the Commonwealth a majority of which can be manufactured using single-use, modular, molecule agnostic manufacturing platformed envisioned by the PPP, MassBio was able to identify their phases of development, as well as therapeutic area as of July 2013, **Table 4**.[33] As can be seen in **Figure 5** most of these molecules are at the early phases of development. Eventually a portion of the drugs that are in pre-clinical and all of the drugs in Phase I and Phase II clinical trials will have to be manufactured under cGMP. According to FDA Guidance drugs in Phase I and Phase II can still have changes made to their manufacturing if the change improves the probability of achieving commercial scale therefore these compounds would be amenable to the described PPP manufacturing platform. Currently, a majority of this manufacturing activity occurs outside the Commonwealth.[34]

Figure 5: The Massachusetts' Drug Development Pipeline by phase



Source: EvaluatePharma®, July 2013

32 Industry Snapshot. MassBio. www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy2.pdf. 2013

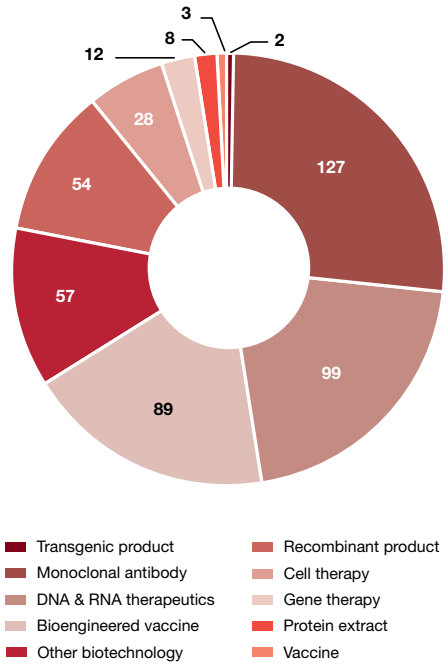
33 http://www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy1.pdf

34 MassBio Industry Snapshot. "http://www.massbio.org/writable/editor_files/industry_snapshot_2012_final.pdf". 2012

Further evaluation of the drug pipeline and a look at only the biologic candidates indicate that 479 fall into this category and are considered readily adaptable to the PPP envisioned manufacturing platform. MassBio was able to further segment these candidates by what type of biological therapy, **Figure 6**. The major categories of recombinant product, other biotechnology, bioengineered vaccines, monoclonal antibodies and some DNA therapeutics are major candidates for manufacturing in the Commonwealth while there is some expectation that DNA & RNA therapeutics segment can also be adapted to modular, flexible, single-use biopharmaceutical manufacturing paradigm.

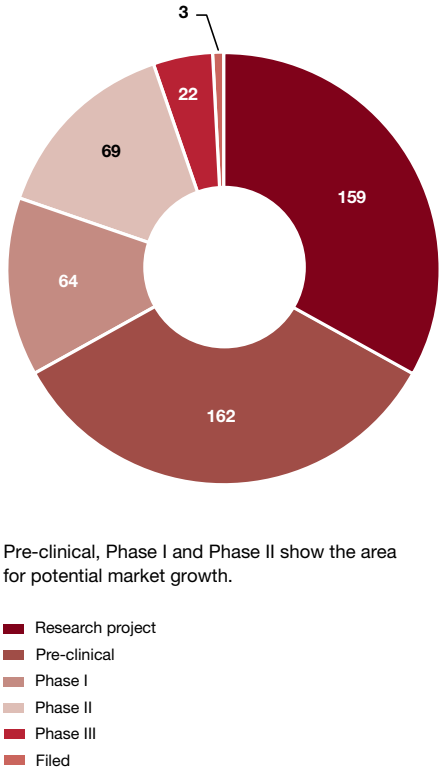
Of importance for the development of a robust biopharmaceutical manufacturing sector in the Commonwealth is that there will be local clients who could utilize a modular, single use-disposable configuration. MassBio was able to stratify the Commonwealth's biologics market by phase of development, **Figure 7**. Like the other data indicated, a majority of biologics are in the early stages of development (research projects, pre-clinical and phase I) which are ideally suited for experienced biopharmaceutical manufacturers to develop programs that assure effective scaling can occur on a modular, flexible, single-use biopharmaceutical manufacturing platform.

Figure 6: Distribution of the 479 Massachusetts based biologics candidates by technology area, 2012



Source: Evaluate Pharma Analysis—MassBio

Figure 7: Distribution of the 479 Massachusetts biologic drug candidates by phase ofdevelopment, 2012



Source: Evaluate Pharma Analysis—MassBio

Perspective

Biomanufacturing in the Commonwealth

by Robert Coughlin

Robert Coughlin
President and CEO
MassBio

The Massachusetts Biotechnology Council (MassBio) is a non-profit association of more than 600 biotechnology companies, universities, academic institutions and others dedicated to advancing cutting edge research, development and manufacturing. We are the leading advocate for the Bay State's world premier life sciences cluster. MassBio drives innovation by creating a forum for the biotechnology community to come together, educating the public and policy makers, influencing public policy, and advancing the economic interests of individual companies, as well as the sector as a whole.

Massachusetts is known as a global leader in biopharmaceutical research and development. Indeed, most observers outside of the region agree that Massachusetts is at the very forefront of the research and development. Less understood is that we are a leader in biopharmaceutical manufacturing of biologics as well. Massachusetts centers a region that has more mammalian cell culture capacity than any place in the world. Genzyme, Biogen-Idec, Pfizer, Bristol Myers Squibb and Shire are examples of global companies with significant biologics manufacturing operations in Massachusetts. They are here for the highly-skilled workforce and the connectivity to our tremendous research and development assets. Despite these notable operations, we have less capacity in the area of outsourced contract manufacturing. So, while our Massachusetts-headquartered companies have over 1,100 investigational drugs in development, the manufacturing of most of these clinical and commercial stage products is occurring elsewhere.

We need to shine a light on this tremendous opportunity—to not only develop new biologic products to meet unmet medical needs, but also to manufacture these products by creating more contract manufacturing capacity. This kind of capacity needn't exist at the higher cost core of the industry but can be grown in areas beyond Route 128, where close proximity to the research will still be available but at operating price points that ensure that we will be competitive with any region in the world. In the end, our focus must be on accelerating the flow of life-saving products from the bench to the bedside. Biomanufacturing here, in Massachusetts, can help our industry deliver on this critical promise.

Perspective

A new era of biomanufacturing equipment

by Parrish Galliher

Parrish M. Galliher
Founder and CTO
Xcellerex Inc.,
a GE Healthcare
Life Science Company

General Electric Healthcare's (GEHC) mission is to provide enabling, low cost, rapid deployment and flexible biomanufacturing technologies and facilities to the biotech, biosimilar, and vaccine markets worldwide. These include single use manufacturing systems, technologies and automation that can operate in a stand-alone fashion or be assembled into a fully integrated turnkey drug manufacturing production line platform called FlexFactory™, a breakthrough platform that was created in a Massachusetts biotech company. For the manufacturing facility building itself, GEHC, in collaboration with our engineering partner M+W Group provides custom turnkey facilities or alternatively the KUBio™ modular facility platform.

GE backs up this end to end offering by providing biomanufacturing services including manufacturing process optimization, training, and validation services: all critical to the success of our customers establishing their own manufacturing capacity. GE's global presence in 150 countries ensures stable support and service of its biomanufacturing technologies, providing local, same time zone technical assistance and consultation. GEHC's Massachusetts organizations are considered centers of excellence in single use bioprocessing expertise and technology. With a combined force of 200 engineers, technologists, biologists, biochemists at its Marlborough and Westborough sites, GEHC brings unparalleled leadership in bioprocessing to the Commonwealth and lowers the barriers to establishing cost effective biomanufacturing capacity.

The majority of the biomanufacturing capacity in the Commonwealth was built in the 1980's and 90's comprising of large complex stainless steel manufacturing facilities designed to make a single blockbuster drugs. Examples include Biogen Idec's Avonex facility, Abbot Bioresearch's (now Abbvie) Humira facility, Pfizer's Andover facility, BMS Devens facility, etc. These companies and their drugs are now facing biosimilar competition worldwide. In addition their new product pipelines are targeting smaller niche markets. These two trends are obsoleting many of the Commonwealth's large manufacturing facilities as well as their non-US satellite facilities worldwide (example Pfizer's Grange Castle facility, Ireland). Unfortunately these legacy facilities are the wrong type of capacity to meet the demands of the future: smaller niche markets, in-country for-country manufacturing, and multi-product flexibility.

What is missing in the Commonwealth is an installed base of flexible and agile biomanufacturing capacity commensurate with the impending trends in our industry: global competition, down pressure on drug pricing, smaller niche drug markets and loss of economies of manufacturing scale. These trends are spawning the need for a new generation of much more cost effective, efficient, multi-product and flexible biomanufacturing technology that is offered by GEHC.

Our goal should be to continue to lower the barriers to establish cost effective, efficient, multi-product, and flexible biomanufacturing capacity across the Commonwealth. Once this new infrastructure and capacity is in place, Massachusetts will most likely emerge as the industry leader in drug discovery R&D, development and manufacturing capacity.

Securing the future

by Blue Sky BioServices

Ted Marple
Chief Executive Officer

Paul Wengender
Chief Commercial Officer and Founder

Norman Garceau
Chief Scientific Officer

Blue Sky BioServices, Inc., is a ten-year-old contract research organization that specializes in custom protein manufacturing and screening for drug discovery in pharmaceutical and biotechnology companies and academic institutions. We employ 40 people in our new 10,000 square feet, purpose-built laboratory and offices in Gateway Park near the campus Worcester Polytechnic Institute in Worcester, MA.

The Cambridge-Boston metro region is the leading hub of global biotechnology innovation with hundreds of experimental drugs under development. However, the region lacks sufficient cGMP biomanufacturing capacity needed to support clinical trials and early commercial production. Although there is significant global large scale cGMP manufacturing capacity (>10,000 liters), there is much less mid-scale capacity (<1000 liters). With Lonza's recent announcement of its plans to close its Hopkinton site, the ability to meet the needs for biomanufacturing capacity locally from companies of all sizes in the metro-Boston area will decrease, leaving a gap that is not satisfied by existing alternatives at the present time. In addition, more efficient biotherapeutic production systems coming into common use today will reduce the need for large scale biomanufacturing. Furthermore, as personalized medicine continues to expand, the production scale necessary to meet demand for personalized drugs will be lower and be better served by smaller, mid-scale production facilities of up to 1,000L. Finally, it is well established that there is a competitive advantage to co-locating R&D and manufacturing and that innovation centers are frequently placed in proximity to manufacturing centers to facilitate technology transfer and enhance the product development cycle.

We believe that investors, biotech and pharma companies will favor working with local biomanufacturing companies if given the option, and that Worcester's proximity to the Cambridge/Boston area will offer a compelling competitive advantage for a company able to provide flexible, scalable, cost-effective manufacturing services. However, support from the Commonwealth will be vital to promoting development of biomanufacturing capacity which is necessary to secure a key aspect of the metro-Boston leadership for the future.


PALL
Life Sciences

Regulatory: A driver of innovation for biopharmaceutical manufacturing

Highlights

The FDA has specifically stated that start-up biopharmaceutical companies will struggle to get accelerated approval if they lack manufacturing capacity.

Flexible, modular biopharmaceutical manufacturing systems meet current and anticipated future FDA guidelines.

Per the Bayh-Dole Act, if federal funding was used during drug research and testing, a reasonable effort must be exerted to manufacture the drug within the United States.

The biopharmaceutical industry is regulated by the Food and Drug Administration (FDA) and any potential biopharmaceutical manufacturing expansion in the Commonwealth must heed close attention to both the current and future regulatory environment. The Commonwealth has numerous emerging biopharmaceutical companies that might have candidate therapies suitable for expedited approval pathway (see call out box Food and Drug Administration Safety and Innovation Act FDASIA 2012) but have a need to be responsive to biomanufacturing FDA regulations and guidance. In particular, the current Commissioner Dr. Margaret Hamburg stated at the Annual MassBio Meeting in March 2013: "No matter how good your data and how important the unmet need, approval hinges on whether you have a manufacturing facility ready to go and a plan in place for scaling up production so you can manufacture your new drug and do so in a high quality facility. Sadly too many start-up companies fail to recognize this fundamental fact and so approval is delayed."[35]

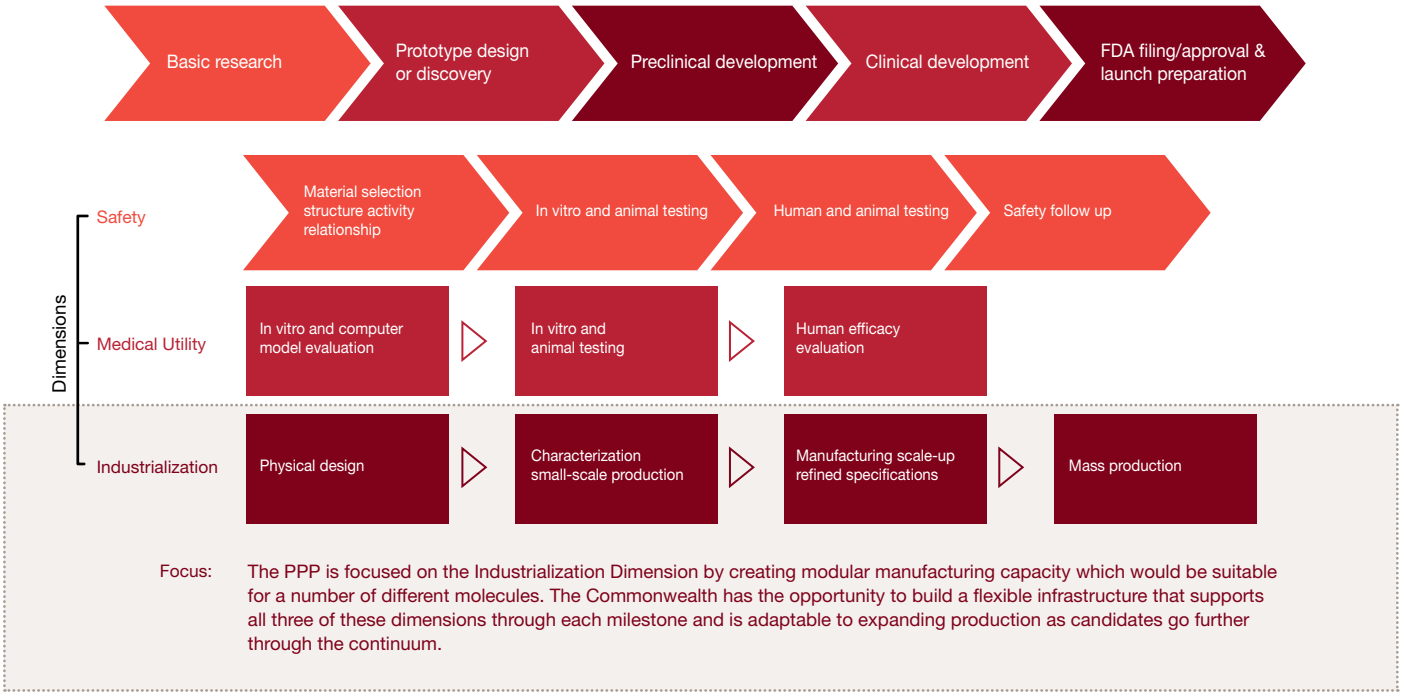
With the world's largest concentration of emerging biopharmaceutical companies a significant amount of time and energy will be committed to this new regulatory guidance. With technology transfer from bench to manufacturing

35 http://www.in-pharmatechnologist.com/Regulatory-Safety/Drugmakers-Seeking-Approval-Under-FDASIA-Must-Keep-Manufacturing-In-Mind-FDA

No matter how good your data and how important the unmet need, approval hinges on whether you have a manufacturing facility ready to go and a plan in place for scaling up production so you can manufacture your new drug and do so in a high quality facility. Sadly too many start-up companies fail to recognize this fundamental fact and so approval is delayed.

— Dr. Margaret Hamburg 2013

Figure 8: Regulatory: Three dimensions of drug development



Source: Innovation of Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. Food and Drug Administration. March 2004

platform not always as straight forward as many biomedical entrepreneurs believe it to be and a significant amount of early work with biopharmaceutical manufacturing personnel can alleviate many of the integration issues that can occur when biopharmaceutical manufacturing has to be performed according to FDA guidance to achieve IND approval and ultimately NDA or BLA approval.

The current rate of FDA biopharmaceutical approvals has been lacking in the last decade; only 12 new biopharmaceuticals entered the U.S. market in 2011, even lower than the amount FDA approvals in both 2010 and 2009 (14 and 18, respectively).[36] The recent passage of the FDASIA signed into law by President Obama on July 9, 2012, provides the industry with guidelines for how to best expedite approval and bring life-saving drugs to patients. FDASIA establishes a fast-track path for candidate therapies with promising preclinical data.

One key element the FDASIA considers: if a drug developer has a manufacturing facility prepared to scale up for full production, for many of the Commonwealths emerging biopharmaceuticals this new legislation is very helpful but it also means there will be condensed time line to bring biopharmaceutical manufacturing online. While regulation has always surrounded the biopharmaceutical industry, under this new law, drugs can be moved through the regulatory process faster, particularly if they involve breakthrough therapies or are for new medical treatments. While the government is working to ease the regulatory burden while maintaining high safety standards, they have also stated that it is imperative for the developer to have a manufacturing facility in place with the ability to rapidly scale up production.

The Critical Path Initiative (CPI) was launched by the FDA in March 2004, focusing attention on the challenges involved in the development of new drugs, and the lack of innovative development, evaluation and manufacturing processes. The FDA's report "Critical Path Opportunities: Innovation Stagnation" highlighted the widening gap between scientific discoveries and their translation into innovative medical treatments.[37] The FDA called for a national, collective effort to help modernize scientific and technical tools that would help predict the safety and effectiveness of manufacturing medical products, **Figure 8**. The collective effort required collaboration among federal agencies, patient groups, academic researchers, industry, and healthcare workers, among others.

36 MA Biomanufacturing Roundtable Update. MassBio. "http://www.massbio.org/writable/editor_files/biomanufacturing_roundtable_presentation.pdf". December 2011

37 http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf

A decade after the CPI report was released, manufacturing hurdles still remain, and the FDA is still struggling with how to address the manufacturing issues and how to integrate stakeholders appropriately in the biopharmaceutical infrastructure. A successful Public-Private Partnership could be the key to advancing the goals of the Critical Path Report in manufacturing. A Public-Private Partnership dedicated to expanding the infrastructure for flexible biopharmaceutical manufacturing in Worcester, combined with the available trained workforce located near the researchers and scientists discovering these breakthrough treatments, and with the support of expedited regulatory approval, lives will be saved. The technology behind flexible biopharmaceutical manufacturing supports the FDAs CPI acceleration goals and allows for rapid scaling up of production without sacrificing safety or quality.

Current FDA guidance suggests that drug manufacturers abide by the Quality by Design principles outlined in the following guidance documents and others:

- 2004: PAT–A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[38]
- 2006: Q8 Pharmaceutical Development[39]
- 2006: Q9 Quality Risk Management[40]
- 2009: Q10 Pharmaceutical Quality System[41]
- 2011: Process Validation–General Principles and Practices[42]
- 2013: Guidance for Industry: Expedited Programs for Serious Conditions–Drugs and Biologics[43]

The modular, flexible designs of new biopharmaceutical manufacturing facilities are capable of successfully responding to the diverse manufacturing needs of biopharmaceutical companies and engineered to comply with current FDA guidance. Leaner operating principles, environmentally friendly, modular biomanufacturing facilities which can be established in the Commonwealth that provide cost effective compliance with regulatory requirements for emerging biopharmaceutical companies dealing with the guidance issues associated with expedited reviews. Building on the Commonwealth's investments in manufacturing (UMass Dartmouth, UMass Lowell and WPI) issues with process development and the technology transfer process required to scale biomanufacturing often can be time consuming and delay approval can be mitigated with the development of a biopharmaceutical manufacturing capacity with an integrated quality system as is proposed for Worcester.

A facility with a quality system is an intangible asset that is one of our key observations that would move the states biopharmaceutical manufacturing forward and truly needs commercial level experience and operations to create biomanufacturing jobs in the Commonwealth. The pressure that comes with the potential for expedited FDA review for product performance is a double edge sword as many product failures during biopharmaceutical development can be attributable to problems relating to the transition from laboratory prototype to industrial product scaling. This risk can be mitigated somewhat by having biopharmaceutical manufacturing capacity in the Commonwealth that has the capacity to produce clinical material, such is the capacity envisioned.

A decade after the CPI report was released, manufacturing hurdles still remain, and the FDA is still struggling with how to address the manufacturing issues and how to integrate stakeholders appropriately in the biopharmaceutical infrastructure.

38 http://www.fda.gov/downloads/Drugs/Guidances/ucm070305.pdf

39 http://www.fda.gov/ohrms/dockets/98fr/2005d-0021-gdl0001.pdf

40 http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf

41 http://www.fda.gov/downloads/Drugs/Guidances/ucm073517.pdf

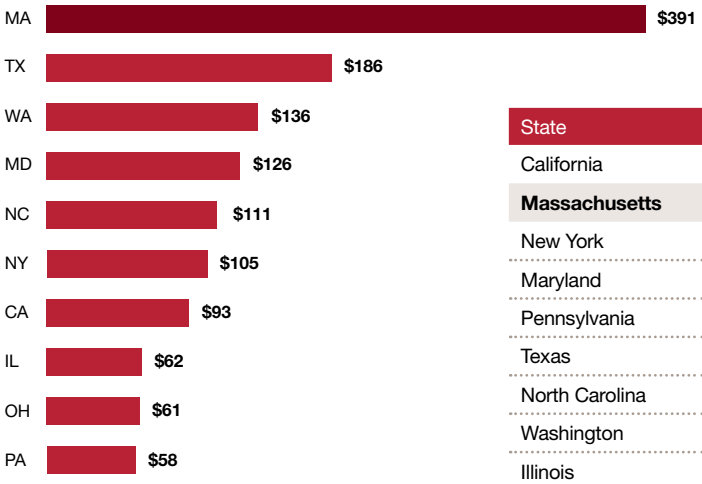
42 http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf

43 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Figure 9: NIH funding by state (total and per capita), 2012

Massachusetts trailed only California in total dollars in 2012.

On a per capita basis, Massachusetts leads all states, by far.



State	Awards	Funding
California	7,386	$3,474,549,212
Massachusetts	**4,991**	**$2,561,823,676**
New York	4,611	$2,042,139,008
Maryland	2,321	$1,597,575,211
Pennsylvania	3,369	$1,460,422,797
Texas	2,512	$1,076,636,178
North Carolina	2,183	$1,060,708,387
Washington	1,577	$917,530,811
Illinois	1,895	$798,049,640
Ohio	1,642	$707,599,023

Source: NIH, Research Portfolio Online Reporting, US Census Bureau

One other piece of legislation that impacts a significant number of the Commonwealth's emerging biopharmaceuticals developers is the Bayh-Dole Act of 1980.[44] Per the Bayh-Dole Act, if a company holds an exclusive license for a patent and the underlying technology received federal funding for part of its development, the company must make a reasonable effort to manufacture the a substantial portion of the product within the United States. Historically, the Commonwealth's Life Sciences Super Cluster has received significant federal funding (**Figure 9**: $391 per capita outpacing CA by $205) to fund the basic research many of the technologies local biopharmaceuticals are founded to commercialize. Therefore there could be a beneficial relationship for expediting the commercialization and compliance with Bayh-Dole within Massachusetts. By locating the biomanufacturing near the research centers located in the Greater Boston area, issues that would delay approval can be addressed and alterations can be made in a timely manner and federally funded drug patents can be manufactured in a cost-effective way within the United States.

44 http://www.gpo.gov/fdsys/pkg/USCODE-2011-title35/pdf/USCODE-2011-title35-partII-chap18.pdf

FDASIA implications for biopharmaceutical manufacturing

FDASIA–On July 9, 2012, President Obama signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA), Pub. L. No. 112–114, which will provide more than $6 billion in industry user fees to FDA over the next five years to help fund the Agency's review process for drugs and medical devices.

FDASIA includes a number of provisions that improve the regulatory process. First, by giving authority to collect user fees from industry for generic drugs and biosimilars, the FDA can ensure funding to continue critical review of new products. Second, a new drug development tool promotes innovation by expediting the development and review of new drugs in order to speed patient access. Third, the FDASIA incentivizes the development of certain drugs to address the diminishing pipelines of specific disease groups (e.g. antibiotics, antifungals, orphan diseases) or populations (e.g. pediatric). Fourth, FDASIA helps to encourage and provide significant patient input and stakeholder involvement in FDA processes. Finally, the FDA is committed to ensuring safety of the drug supply chain. Almost 40% of finished drugs, and almost 80% of active ingredients are obtained from overseas sources. FDA oversight is becoming increasingly important as counterfeit drugs and other illegal sales of medicine could mean a supply in the US that is of unknown safety and quality.[45] FDASIA allows for more effective communication and collaboration with foreign regulatory agencies by facilitating and sharing inspection findings of foreign manufacturing facilities. The act also mandates that manufacturers of life-supporting drugs provide notice of any supply discontinuation so that the FDA can more effectively monitor drug supplies and avoid shortages.[46]

40%

80%

Almost 40% of finished drugs, and almost 80% of active ingredients are obtained from overseas sources. FDA oversight is becoming increasingly important as counterfeit drugs and other illegal sales of medicine could mean a supply in the US that is of unknown safety and quality.

45 http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf

46 Memorandum: Summary of the Food and Drug Administration Safety and Innovation Act Drug and Device Provisions. Hyman, Phelps & McNamara. July 12, 2012.

Biopharmaceutical manufacturing workforce development

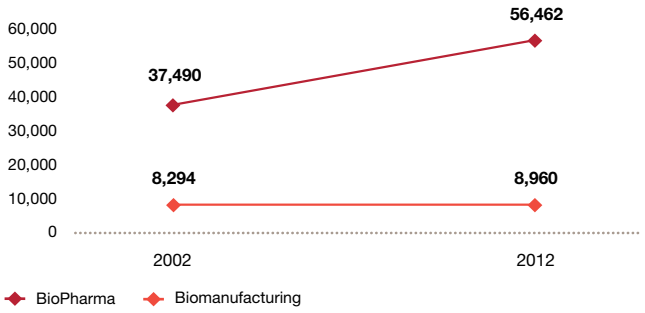
Highlights

The biopharmaceutical industry has led to job creation over the last decade in the Commonwealth; however, biopharmaceutical manufacturing job growth has stalled.

Worcester is known for its strong history in manufacturing and has been disproportionately affected by the 34% decrease in the Commonwealth's manufacturing industry over the last decade.

With more than 1,174 drugs in development in the Commonwealth, there is ample opportunity for biopharmaceutical manufacturing job creation in Worcester.

Figure 10: MA BioPharma vs. Biomanufacturing employment growth, 2002–2012



Source: US Bureau of Labor and Statistics, Quarterly census of Employment and Wages
http://www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy1.pdf

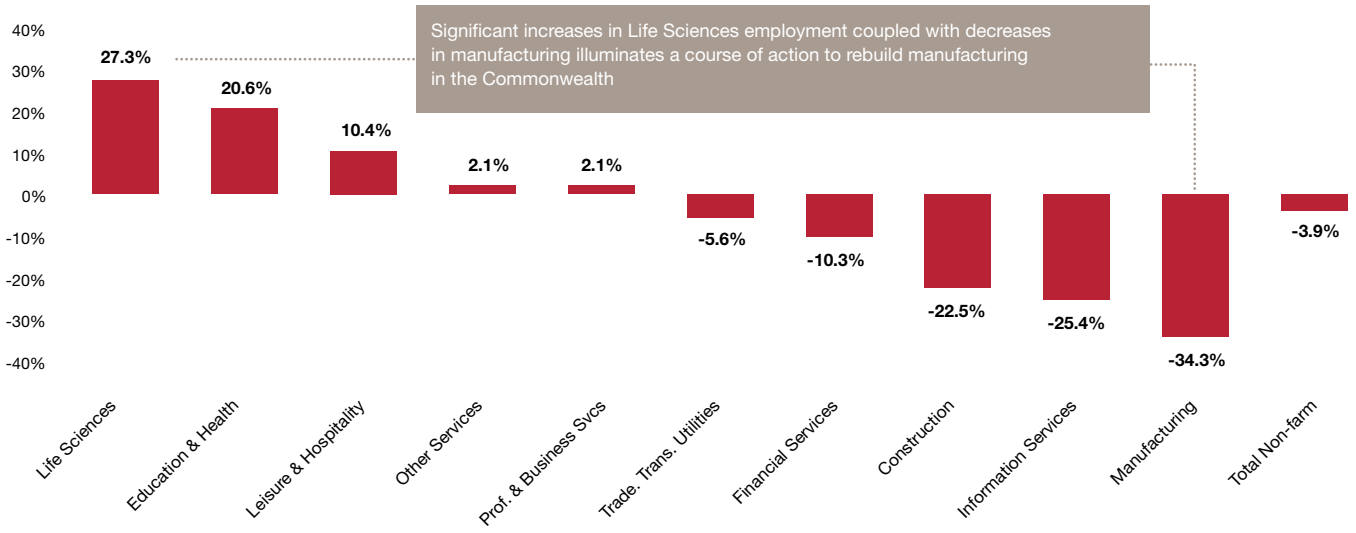
The people of Worcester have been the key asset in the city history from the American Revolution thru the Industrial Revolution. Citizens have proven time and again that they can adapt to new situations, are dedicated to improving their city and their circumstances, and can handle innovation. Now as the city faces the challenge of creating new manufacturing jobs to provide new opportunities to under or unemployed middle skilled technical workers, the time is right for Worcester to transform its key asset into a formidable biomanufacturing center of excellence to support the research and development efforts located in the Commonwealth's Life Sciences Super Cluster.

The Greater Boston area has seen strong growth in biopharmaceutical related jobs (over 18,900 new jobs between 2002 and 2012); however, the biomanufacturing industry has remained stagnant (an increase of only 666 jobs during the same period),[47] **Figure 10**. While this disparity continues the Commonwealth is allowing other states to benefit from investments made into Massachusetts' R&D Life Sciences Super Cluster. Massachusetts' upward trend of biopharmaceutical job growth coupled with its overall

47 MassBio Industry Snapshot 2013. www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy2.pdf. 2013

There are a number of converging trends in biopharmaceutical manufacturing and medicine that can provide the Commonwealth with a fleeting opportunity to turn some of the Super Cluster "molecular-franchises" into long-term sustainable employment opportunities in biopharmaceutical manufacturing.

Figure 11: Employment by sector



Source: BLS, Authors Analysis
*http://www.tbf.org/~/media/TBFOrg/Files/Reports/LifeSciences_f.pdf

significant decline in manufacturing employment, **Figure 11**, presents a call to action to integrate complementary investments in biomanufacturing into the Commonwealth's Life Sciences funding strategy.

UMass has devoted significant resources and made investments in manufacturing, leveraging university resources for regional economic development. By creating facilities in both Dartmouth and Lowell, UMass is supporting new business formation, job growth and training, and accelerating commercialization. WPI is also heavily investing: WPI's Biomanufacturing Education and Training Center at Gateway Park, a life sciences campus, provides innovative workforce development solutions. Serving life sciences companies from across the region and the globe, the center represents an innovative partnership of academia and industry. These investments are critically needed for the industry to grow. Job losses of over 34% in manufacturing need to be reversed.

Figure 11 shows significant loss of employment in the manufacturing sector, which represents a major loss of middle-skilled level positions from the Commonwealth's labor pool. There is an opportunity to strategically halt this erosion by focusing the creation of biopharmaceutical manufacturing employment opportunities that leverage existing life sciences investments made by the Commonwealth.

Massachusetts boasts the most concentrated life sciences R&D infrastructure in the country, which has led to the development of many lifesaving biopharmaceuticals. However, once these "knowledge-based" assets are commercialized they are often manufactured in other parts of the country. The Commonwealth has very few biopharmaceutical manufacturing resources for emerging biopharmaceutical companies to produce the seminal batches of clinical material in the Commonwealth. This puts the Commonwealth at a disadvantage because structural and financial barriers (e.g. regulatory, technology transfer, proven infrastructure etc.) mitigate an emerging biopharmaceutical company's ability to the repatriation of future manufacturing runs back to Massachusetts, even if they want to. Therefore, a key to workforce development is the creation of the "correct type" of biopharmaceutical manufacturing to complement the Commonwealth's emerging biopharmaceutical industry.

As of 2012, California is already far ahead of Massachusetts in terms of drug manufacturing — 44,229 jobs compared to just 8,960. Eight other states also have more people working in biopharmaceutical manufacturing than the Bay State, with NJ, NC and NY coming in second, third and fourth. CA is also growing that sector faster, by 10.8% in the past decade versus 8% in MA.[48]

Because the Commonwealth lacks the biopharmaceutical manufacturing infrastructure to perform seminal biomanufacturing runs for emerging biopharmaceutical companies, there is the potential for the Commonwealth to lose out on the commercialization phase of the product development life cycle. This loss could translate into forgoing 10–20 years of employment opportunities in biopharmaceutical manufacturing and the ancillary jobs associated with commercialized biopharmaceuticals. A single commercialized biopharmaceutical can be the catalyst for the creation of 100–400 revenue-sustained biomanufacturing jobs. With >1,100 biopharmaceuticals in development within the Commonwealth, there is ample opportunity to keep some of these home grown "molecular-franchise" here during the commercialization phase of their product life cycle. There are a number of converging trends in biopharmaceutical manufacturing and medicine that can provide the Commonwealth with a fleeting opportunity to turn some of these "molecular-franchises" into long-term sustainable employment opportunities in biopharmaceutical manufacturing.

As discussed in PwC's Super Cluster reports of 2007 and 2008 clustering of the correct type of resources (people, capital, technology, and knowledge) is vital to developing a successful self-perpetuating commercial ecosystem.[49, 50] Because of existing resources (see Galliher, O'Brien, Flavin, and Garceau perspectives) there is the opportunity to nucleate such a cluster for biopharmaceutical manufacturing in Worcester to create differentiated job opportunities than those found in the Life Sciences Hub inside Route 128. Additionally, it is widely believed by some in the industry that having manufacturing local provides researchers, regulatory, process development, manufacturers, and clinical personnel within proximity of one another provides better problem solving and more effective drug development. Thus the Commonwealth has an opportunity to develop an innovative type of biomanufacturing workforce locally that will be clustered with existing R&D resources potentially leading to a self-sustaining cycle of innovation, workforce development, and supports the growth Commonwealth HQ commercial biopharmaceutical companies.

In the Commonwealth, Worcester has the ideal socioeconomic environment, to host new investments in biopharmaceutical manufacturing. Unlike R&D positions in Boston/Cambridge, the salaries for biopharmaceutical manufacturing employment opportunities are more modest and Worcester's favorable cost of living, affordable housing, ready access to public transportation, 10 local colleges and universities are already enjoyed by the regions substantial life sciences and healthcare workforce. In a transformational event for the training of the future biomanufacturing workforce, Worcester Polytechnic University (WPI) recently established Biomanufacturing Education and Training Center (BETC), funded in part by the Massachusetts Life Sciences Center, which will train novice and experienced biopharmaceutical manufacturing staff in a fully functional Pilot-Scale Biomanufacturing Facility. The BETC will provide hands-on training for the multi-layered workforce needed to produce medicines and research compounds using engineered living cells. Training will include industry-standard process areas:

- Buffer and media preparation
- Equipment preparation and sterilization
- Environmental testing
- Fermentation and cell culture
- Laboratory analytics
- Protein capture
- Purification
- Validation

The tremendous potential of the BETC coupled with an existing biopharmaceutical manufacturing workforce at AbbVie of over 700 people provides ample opportunity for training and career laddering if additional biopharmaceutical manufacturing opportunities are developed locally to create a self-sustaining ecosystem.

48 http://www.bizjournals.com/boston/blog/bioflash/2013/08/california-beats-mass-in-biotech-rd.html

49 Super Cluster. PricewaterhouseCoopers. 2007

50 Super Cluster: Volume II. PricewaterhouseCoopers. June 2008

Perspective

Training enables success

by Stephen P. Flavin

Stephen P. Flavin
VP of Academic and Corporate Development
Worcester Polytechnic Institute

Given the complexity and sensitivity of the processes used for biomanufacturing human therapeutics, training people at every level of the organization becomes a critical enabler of success. Today, as the biotechnology industry matures and innovation enables new business models, the demand for effective biomanufacturing training only increases.

For more than 20 years, WPI has partnered with companies for bioprocess optimization projects and to deliver educational programs in the life sciences and business management. We have seen the evolution of the industry up close, which is why we made the strategic decision several years ago to create a new kind of training resource to help the biomanufacturing sector grow in Massachusetts and across the region.

With the support of the Massachusetts Life Sciences Center, WPI built the Biomanufacturing Education and Training Center (BETC) at Gateway Park in Worcester. The BETC, which opened in the spring of 2013, is a corporate-scale training facility unlike any other in the northeast. Spanning more than 10,000 square-feet, the center can train biomanufacturing employees with a range of skills from entry-level equipment operators, to production floor leaders, to advanced technical and management personnel.

At the core of the BETC is a pilot plant with microbial fermentation and mammalian cell culture capabilities (reactors up to 200 liters at this writing), standard process areas of equipment preparation, buffer and media preparation, product capture, purification, quality control and analytics. The BETC is configured for maximum flexibility with conventional and single-use technologies.

Our operating model is based on deep collaboration with industry partners. To date, Biogen Idec, AbbVie, Bristol-Myers Squibb, Pfizer and Shire Human Genetic Therapies have signed on as affiliates of the BETC, with experts from each company working with the BETC team to develop customized curricula and hands-on programs that support their specific business needs. These companies will use the BETC to train new employees, so they are productive from day-one, and to promote continuous improvement of their existing workforce.

Along with WPI life sciences faculty members and BETC subject-matter experts, professionals from these affiliated companies also serve as instructors and mentors for students enrolled in non-proprietary programs at the BETC which are open to the general public. These non-proprietary programs range from an entry-level fundamentals course that helps people transition into the biomanufacturing industry, to more advanced programs that will help employees in smaller companies that are now emerging in the biomanufacturing space as innovation and productivity gains lower the barriers to entry.

The BETC is also an important new core facility for graduate and undergraduate life sciences programs at WPI. Working in teams, students will conduct research and bioprocess development projects in the BETC, grounding their education with important operational experience.

Looking ahead, we know that 40 percent of all the drugs in the research and development pipeline today are biologics, many being advanced in laboratories across in New England. So to capture and retain the economic value of manufacturing clinical supplies of those new drugs, we need more and diverse biomanufacturing resources.

A major constraint to expanding those resources has been the availability of qualified people to run a process, capture the product, and to validate quality at every step of production. This is where WPI and the BETC will make a difference, providing effective education and training that enables success for companies and their employees.

AbbVie: An exemplar for growing biomanufacturing jobs

The success of the Abbott Bioresearch Center (ABC) over the past 24 years in Worcester's Massachusetts Biotechnology Research Park, illustrates the regions capability to not only support biomanufacturing facilities but to excel at it. The ABC opened in 1989 (then as the BASF Bioresearch Center) with strong support from Worcester and the local bioscience community. The region had many attractive factors for the center as well, Peter F. Moesta, divisional vice president of biologics manufacturing for Abbott, thinks that "Worcester could attract the same talent as Cambridge, but with a better commute and … quality of life".[51]

Abbott discovered its most successful product, Humira, in 1997 and by 2000 it had earned FDA approval to treat rheumatoid arthritis. In 2005 the FDA approved expanded use of the drug for use against early rheumatoid arthritis and psoriatic arthritis.[52] The commercial success of Humira prompted Abbott to expand biomanufacturing operations in Worcester and eventually spin-off AbbVie (the ABC included) in 2012 to focus solely on branded drugs.[53] Since opening, the ABC has expanded its facility and increased its staff from 70 to over 700.[54] This growth in staff with a new focus on branded drugs shows the potential for biomanufacturing expansion for each commercialized drug from the MA development pipeline.

70 to over 700

Since opening, the ABC has expanded its facility and increased its staff from 70 to over 700.[54]

51 *Central Massachusett's Life Science Industry Success.* Worcester Business Journal. 2009

52 *Feds approve expanded use of Humira.* Lisa Eckelbecker, Telegram & Gazette. October 5, 2005

53 *Abbott selects name for new drug company: AbbVie.* Associated Press. March 21, 2012 http://www.telegram.com/article/20120321/APF/303219875/0

54 Worcester Business Journal. 2009

Relevant biopharmaceutical funding

Highlights

The Greater Boston area is number one in both the number of biopharmaceutical start-ups and the amount of biopharmaceutical financing.

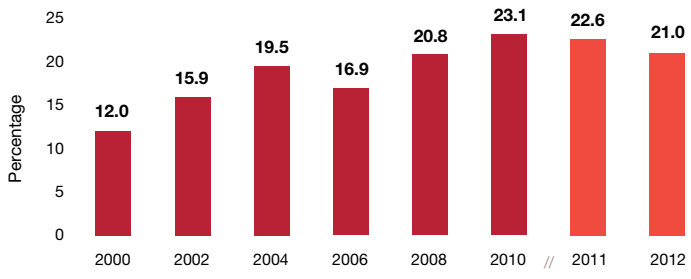
Financing is needed to fill the gap between funding from venture capitalists and self-financing after a successful drug reaches market.

Government supported financing and creative use of a Public-Private Partnership to focus the financing to help mitigate this gap.

Massachusetts is a national leader in financing early stage biopharmaceutical development, **Figures 12** and **13**. The challenge and the opportunity to grow the Commonwealth's global leading position as a biopharmaceutical innovator will be to identify the financial resources and policy choices to also become a global leader in biopharmaceutical production. According to figures from PwC and the National Venture Capital Association, New England, in the 2009–2010 period, New England surpassed the Bay Area in regards to the amount of biopharmaceutical financing and the number of startups. The Greater Boston Metro area has the necessary combination of educational research institutes and biopharmaceutical companies to be the key leader in early stage innovation.

Figure 12: Massachusett's share of the US biotech Venture Capital dollar, 2000–2012

MA received **21%** of all US biotech VC in 2012.

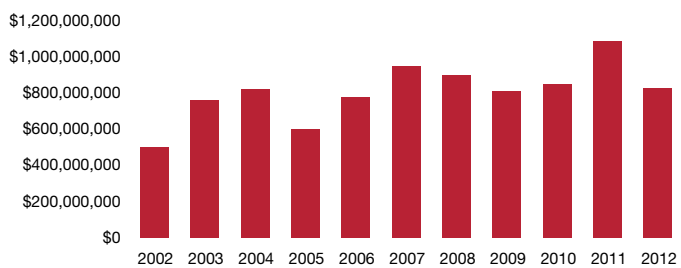


Source: 2013 PricewaterhouseCoopers, National Venture Capital Association, MoneyTree™ Report, Historical Trend Data

Figure 13: Venture Capital investment in Massachusetts biotech companies, 2002–2012

Venture investment in MA biotechs declined from an all-time high in 2011 to **$838 million** (national decline in VC biotech was 15% in 2012).

That makes **$8,892 billion** invested since 2002.



Source: 2013 PricewaterhouseCoopers, National Venture Capital Association, MoneyTree™ Report, Historical Trend Data

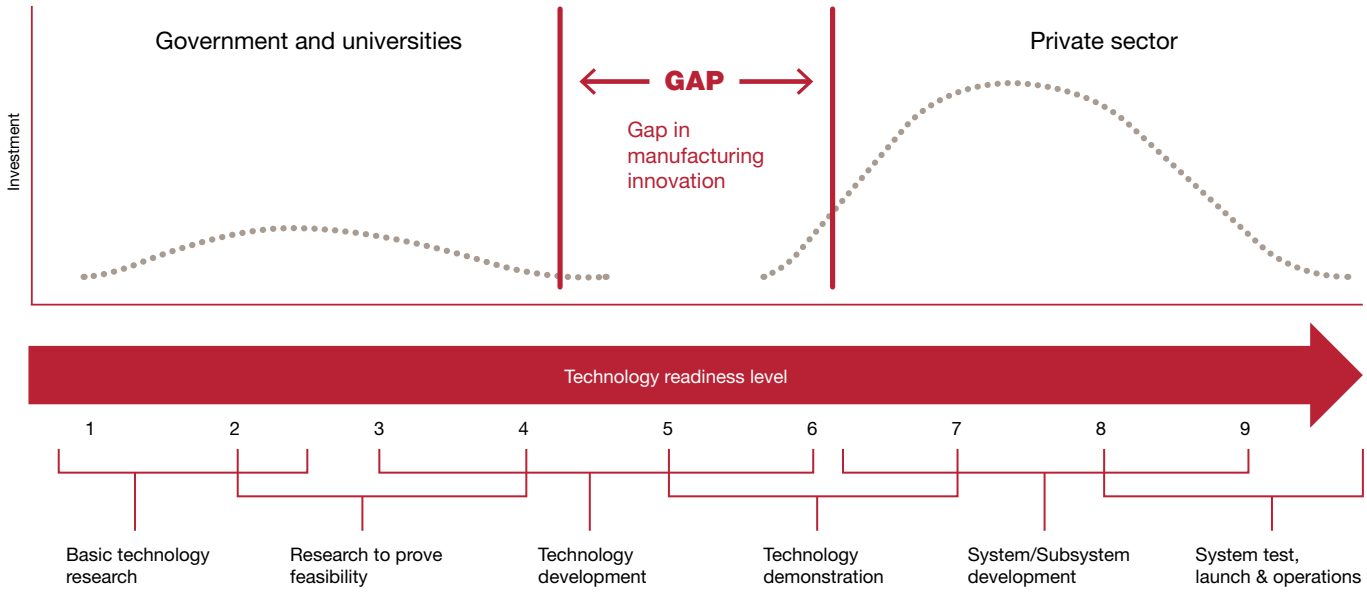
Massachusetts is a national leader in financing early stage biopharmaceutical development.

In fact, the Greater Boston area has started and funded 25% more early stage companies than any other region, including San Francisco, once known as the "birthplace of biotechnology." In California, Silicon Valley has been very successful at financing early technology stage companies and growing them into mature California headquartered companies. The Commonwealth has the opportunity to cultivate a similar environment for life sciences companies with a focus on trying to keep molecules in the region throughout the life-cycle, not just at the inception.

Such economic "structural" transitions require patient financial resources that are mindful of the long-term goal of the Commonwealth becoming net exporter of biopharmaceutical products to a global market not just underlying innovative technologies. While venture capital and Small Business Innovation Research (SBIR) money drive the research and discovery phases of innovative technologies other sources of funding will be necessary for cultivating biomanufacturing resources to facilitate achievement of a mature biopharmaceutical industry on whole. Even with budget cuts and sequestration some of these funds are still available from federal agencies such as the Department of Health and Human Service's National Institute of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA), and the Department of Defense's Defense Threat Reduction Agency (DTRA) and Defense Advanced Research Projects Agency (DARPA) are interested in manufacturing unique biologics and vaccines.

The Department of Commerce's Economic Development Administration (EDA) following the Advanced Manufacturing Partnership Steering Committee's release in July of 2012 of *"Capturing Domestic Competitive Advantage in Advanced Manufacturing"* report endorsed by the President's Council of Advisors on Science and Technology has started to make funds available[55] for capital investments in manufacturing.[56, 57, 58] The Steering Committee correctly pointed out that a significant gap exists in manufacturing "know how" created because of how this activity is financed, **Figure 14**. Coincidently it is the same

Figure 14: Manufacturing innovation: Investment gap



Source: Report to the President on Capturing Domestic Competitive Advantage in Advances Manufacturing. Executive Office of the President: President's Council of Advisors on Science and Technology. July 2012.

55 http://www.grants.gov/view-opportunity.html?oppId=208353

56 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_amp_steering_committee_report_final_july_17_2012.pdf

57 http://www.commerce.gov/news/fact-sheets/2013/04/17/fact-sheet-investing-manufacturing-communities-partnership

58 http://www.commerce.gov/blog/2012/05/29/26-million-competition-help-accelerate-growth-advanced-manufacturing-and-clusters

area of manufacturing capability which needs development as described by the FDA's 2004 Critical Path Initiative report (discussed later in this report).[59]

The US Treasury is continuing the use of the New Market Tax Credits (NMTC) program to stimulate economic development in low-income communities of which the three Community Development Entities (CDE) in the Commonwealth, Massachusetts Housing Investment Corp., a private nonprofit investor and lender that received a NMTC allocation award of $65 million. MassDevelopment, the state's finance-and-development agency, received a $40 million allocation under the program. NMTC investment can be utilized on both new construction as well as rehabilitation projects of historic and non-historic structures to stimulate job growth in low income areas.[60] MassDevelopment also has bond financing programs which offer a cost-effective way to finance real estate, manufacturing buildout, and equipment. Lower rates and flexible terms and tax-exempt bonds are available. And the Community Builders Inc., a Boston-based nonprofit developer of mixed-income housing, received a $25 million allocation; all totaled the Commonwealth received $130 million in NMTC capacity for fiscal year 2013.

As NIH and venture capital funded research moves forward, more and more biopharmaceuticals will need to be manufactured and Worcester will be the key desirable location.

The research and discovery work is already receiving heavy investments from Venture Capital groups. According to MoneyTree research, Massachusetts is second only to California in VC investments. As this research moves forward, more and more biopharmaceuticals will need to be manufactured and Worcester will be the key desirable location.

59 http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm113411.pdf

60 http://www.massdevelopment.com/financing

Biopharmaceutical manufacturing capacity and trends

Highlights

The biopharmaceutical manufacturing industry is shifting from the one-drug per facility model to a flexible model where a facility can produce numerous different drugs in small research or commercial batches.

An opportunity and environment exists to develop new flexible facilities, particularly in the Commonwealth to mitigate production is moving overseas.

The biopharmaceutical manufacturing industry is at a major juncture as it moves from the large-scale, one drug per factory model to a modular, single-use, disposable paradigm where multiple therapies can be produced within one facility early in development and with the ability to increase scale on the same platform after gaining regulatory approval. This paradigm shift is occurring for small and large molecules.[61, 62, 63, 64] For this perspective the biopharmaceutical manufacturing market capacity and trends of the biologics and vaccine segments are used as an exemplar. Greater in potential magnitude but similar trends are occurring in the small-molecule manufacturing segment.

Today there is a global excess of large-scale biomanufacturing capacity as well as significant overseas competition. More than 30 factories outside of the United States are manufacturing or will soon be prepared to manufacture biologics and vaccines that were initially developed in the U.S. Safety risks exist at many of these multi-use overseas facilities because of their use of mammalian cell cultures that have a higher risk of contamination and are a cause of concern to auditors and regulators.

61 http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=805483&sk=5d2504ec6a63343265847159bb809400

62 http://www.boston.com/business/articles/2007/09/28/novartis_to_give_mit_65m_to_find_new_way_to_produce_drugs/

63 http://web.mit.edu/press/2012/manufacturing-pharmaceuticals.html

64 http://novartis-mit.mit.edu/sites/default/files/images/2012%2011%2013%20Symposium%20on%20Continuous%20Manufacturing%20of%20Pharmaceuticals%20Notes.pdf

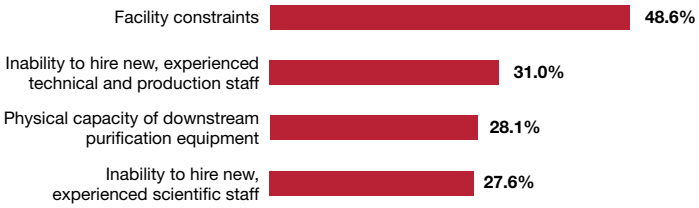
A Worcester based Commercial Biopharmaceutical Manufacturing Accelerator would complement existing public funding of therapeutic manufacturing resources to facilitate differentiated biomanufacturing in the Commonwealth.

A unique opportunity for growth in the biopharmaceutical manufacturing industry is in the creation of smaller scale facilities based on a modular design and operating within single use equipment. These smaller facilities can safely perform smaller clinical scale production runs and are flexible enough to be reconfigured for different biopharmaceuticals to support multiple programs simultaneously—all while being located close to the initial therapeutic developers and with easy access from a regulatory standpoint. Additionally, once regulatory approval has been achieved, these facilities can quickly scale-up production to commercial levels.

Articulated in this is a summary of biomanufacturing capacity, user outlooks for biomanufacturing needs, and the organizations that can support those needs. The number one reason given for upcoming biomanufacturing production constraints lies in existing facility constraints followed closely by the lack of educated factory workers, **Figure 15, 16.**[65] The Commonwealth has the capacity to address both of these issues. Of importance to the analysis is that there are few biomanufacturing facilities within New England that are prepared for the ongoing biomanufacturing paradigm shift.

Figure 15: Selected factors creating future capacity constraints

Which factors are likely to create biopharmaceutical production capacity constraints at your facility in 5 years (by 2015)?



Source: *8th* Annual *Report and Survey of Biopharmaceutical Manufacturing Capacity and Production:* BioPlan Associates, April 2011, 490 pages.

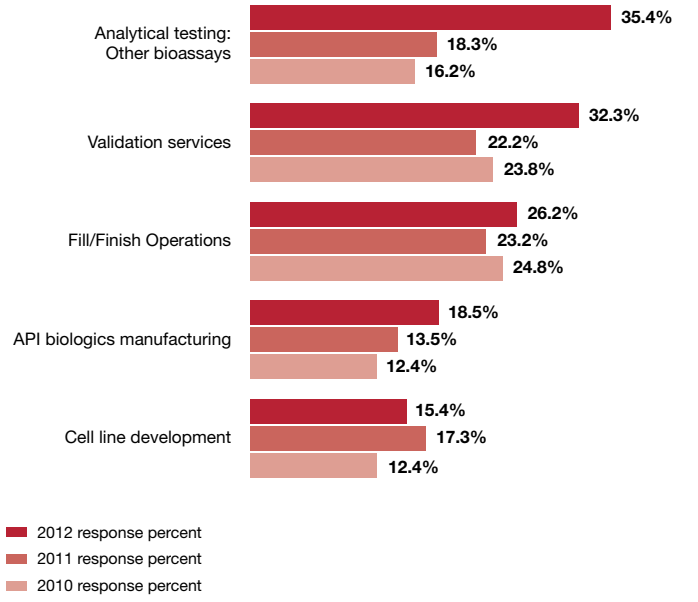
Exemplar: Biologic manufacturing market summary

Capacity for outsourced biologics and vaccine production world-wide, from small-scale through commercial production exceeds thirty (30) companies **Table 5** which could be considered a "going-concern", that is they appear active and operationally sound from a regulatory perspective.[66, 67, 68] Typically these companies offer one of two types of production microbial fermentation and/or mammalian cell culture.

It is worth noting that facilities that focus on microbial fermentation will often entertain both vaccine programs and recombinant protein production. The exceptions here reside with the types of pathogens employed. The more harmful a microbe is, for example anthrax or certain sporulating microbes, the more specialized the facility will become and the less likely it will be used for or have the capability of producing recombinant proteins.

Figure 16: Selected outsourcing activities projected to be done at "Significantly Higher Levels" in 2 Years, 2010–2012 trends

Which activities will be done at significantly higher levels at your facility over next 24 months? (Where will greatest changes occur? % indicating)



Source: Outsourcing Becoming More Strategic. Eric S. Langer. Pharmaceutical Technology. August 2012. www.bioplanassociates.com/publications/articles/2012/PharmaTech_Gauging-Outsourcing_Aug2012.pdf)

65 Pharmaceutical Outsourcing Trends. BioPlan Associates. bioplanassociates.com/publications/articles/2012/BioPharmIntl_PharmaOutsourcingTrends_Mar2012.pdf. January 2012

66 CMOLocator.com

67 2nd Edition Advances in Large- Scale Biopharmaceutical Manufacturing and Scale-up and Production 2007

68 Pharmacompare.com

Table 5: Examples of international early stage biomanufacturing capacity

Company	Location	Capacity/Capability
Vibalogics	Cuxhaven, Germany	Bacterial fermentation, Bioreactors, cell factories, roller bottles. Support e. coli and cell culture (also SPF eggs). Capacities greater than 5,000L.
CobraBio	Keele, UK	Bacterial fermentation, virus production to 250L scale. Also manufacture DNA for gene therapy or vaccines. Support to PIII.
Novasep	Charleroi, Belgium	Up to 250L cell culture in Batch, Fed-Batch, and Perfusion to support virus production. Up to PIII.
CSL Biotherapies	Melbourne, Australia	Manufacture flu at commercial scale.
DSM	Netherlands	Clinical and commercial scale microbial manufacturing.
BoehringerIngelheim	Vienna, Austria	6,000L bioreactors (multiple). Clinical and commercial manufacturing capabilities. Yeast, e.coli.
Vivalis	St Herblain, France	up to 100L in cell culture for vector manufacturing under cGMP conditions. Limited to PI/PII.
Innogenics	Ghent, Belgium	up to 100L in cell culture for vector manufacturing under cGMP conditions. Limited to PI/PII.
Biovian	Turku, Finland	200L bioreactor in batch, fed batch or perfusion to support e. coli, or viral vector production.
Bioreliance	Glasgow, UK	20L bioreactor for viral manufacturing to support PI/PII clinical trials.
Eurogentec	Eurogentec	Up to 500L fermentation supporting both clinical and commercial production. Supports protein and vaccine production.
Syngene	Bangalore, India	225L Bioreactors for fermentation supporting up to Phase III clinical trials.
SyncoBioPartners	Netherlands	270L Bioreactor Train to support through commercial production.
Biomeva manufacturing	Heidelberg, Germany	1500L Bioreactors for microbial fermentation supporting through Phase III trials.
Richter-Helm Bio Tec GmbH	Hannover, Germany	300Land 1500L Bioreactor scale supporting through commercial production of proteins, cell vaccines, and plasmid DNA. Supports clinical and commercial production.
Novozymes	Bagsvaerd, Denmark	Commercial production to 8,000L.
Hospira	Thebarton, Australia	500L bioreactor through Phase III production.
FujiFilmDiosynth	Billingham UK and Research Triangle Park, NC	1,000L and 2,000L bioreactors for microbial production. Support through commercial production.
Apotex Fermentation, Inc.	Winnipeg Canada	Up to 5,000L bioreactors to support through commercial production.
Scil Proteins Production	Halle, Germany	1500L Bioreactors for microbial fermentation supporting through Phase III trials.
WuXiAppTec	Shanghai, China	Active Pharma Ingredients (API's)-open access platform with "end-to-end" small molecule APIs/intermediates development and manufacturing capabilities from preclinical to commercial stages; Cell Banking (Many different species of mammalian or insect cell banks–ranging in size from 10 to 1200vials–can be manufactured GMP using a variety of media types); Cellular Therapeutics (cGMP clinical-and commercial-scale manufacturing. Large-scale expansion (up to 72 x 10 layer cell factory/lot experience). Autologous cell selection, expansion and processing. Cell expansion for allogeneic cell therapies and vaccines. Cell selection with GMP monoclonal antibodies. GMP cell bank production. Broad range of container/closure systems for final product. Controlled rate freezing. Short and long term Cryogenic storage).

Table 5: Examples of international early stage biomanufacturing capacity (continued)

Company	Location	Capacity/Capability
Florida Biologix	Alachua, FL	up to 100L in cell culture for vector manufacturing under cGMP conditions. Limited to PI/PII.
Omnia Biologics	Rockville, MD	up to 100L in cell culture for vector manufacturing under cGMP conditions. Limited to PI/PII. Employ both fed-batch and perfusion systems.
Meridian Life Science Inc.	Memphis, TN	up to 100L in cell culture for vector manufacturing under cGMP conditions. Limited to PI/PII. Employ both fed-batch and perfusion systems.
Cytovance	Oklahoma City, OK	Up to 100L for microbial fermentation supporting PI/PII.
KBI Biopharma	Durham, NC	140L Bioreactor (single) to support PI/PII clinical trials.
WaismanBiomanufacturing	Madison, WI	Up to 50L Cell Culture in Fed-Batch mode to support PI/{II vector production.
SAFC	Carlsbad, CA	130L scale capacity in cell culture for viral based therapeutics and vaccines to support PI/PII.
ABL, Inc.	Rockville, MD	400L bioreactor. Experience in Adenovirus, MVA, Lentivirus, Other retroviruses, Lytic and non-lytic viruses, Enveloped and non-enveloped viruses in batch, fed batch or perfusion to support e. coli, or viral vector production.
Aeras	Rockville, MD	BSL-2 for tuberculosis. Manufactures rBCG. Manufactures viral, protein and capsid virus.
Paragon BioServices	Baltimore, MD	Microbial Fermentation to 500L, virus production to 40L. Support PI/PII manufacturing.
University of Nebraska at Lincoln	Lincoln, NE	150L Bioreactor for microbial production supporting PI/PII trials. Yeast and bacteria.
Center for Biocatalysis and Bioprocessing, U of Iowa	Coralville, IA	1,000L microbial fermentation to support PI/PII.
VGXI, Inc.	Woodlands, Texas	500L bioreactor for plasmid DNA production. Through commercial.
Catalent	Madison, WI	For flexible cGMP production, from 10L up to 1000L, and non-GMP production up to 250L. Clinical Biomanufacturing, Mammalian Cell Line Engineering-Biopharmaceutical Development, Research through Clinical Phase I-II GMP protein production.

MBI Outreach

With MA Secretary of Housing and Economic Development, Greg Bialecki, (third from left), and Worcester City Manager, Michael O'Brien (center)

For mammalian cell culture, it is rare to see both virus production and recombinant protein production in the same facility. Even with single-use technology employed, the perception of risk is often too great to have both types of manufacturing occur in the same facility and will be an instant red flag to auditors (both from the company/consultancy and regulatory authorities). Therefore it is important for a new facility to match the intended market (to serve) to the facility design. Even with separated suites, process flows, air handling, and single-use equipment—customers are reluctant to entertain projects for mammalian cell culture generating recombinant proteins when there is also virus production in the same facility. Further, the scientific expertise required for virus production versus recombinant protein production may be different, in particular in the downstream aspect of the operation. Therefore most companies have "sister" facilities in separated buildings, sometimes in the same complex, to stay competitive.

Expression technologies implemented in mammalian cell culture facilities and microbial facilities also differ, but for development of processes and scale-up through Phase I they are often reasonably consistent across the board; that is, optimized around a few key cell types. Mammalian cell culture facilities producing virus or virus like particles (VLPs) use a wide range of host cells (e.g. BHK cells, HEK cells, Veros cells while VLPs can be produced in insect cells). Newer cell lines for virus production are also gaining favor (e.g. Per.C6 cells and CEVECs CEP cells). An example of the complexity of biologic manufacturing can be viewed through the commonly known Flu vaccine. The Flu vaccine has been grown in a variety cell lines such as MRC-5 cells, WI-38, FRhl-2, PER.C6, NIH-3T3, BHK, CHO, Vero and MDCK. However, According to WHO in the Initiative for Vaccine Research World Health Organization Report, the only cells that generate commercially sound titers have been Vero, PER.C6 and MDCK. Today, technologies used for virus production still includes roller bottles or T-Flasks but more production is being adapted to Wave bioreactors up to 100L scale, single-use bioreactors (GEHC-Xcellerex, Thermo Fisher Hyclone, ATMI, EMD Millipore, and Sartorius), small scale glass, and stainless-steel bioreactors. Therefore, having institutional knowledge of the most relevant production cell lines and current Good Manufacturing Practice (cGMP) practices for a class of biologics or vaccines is important for the success at early stages of development and post regulatory approval.

Companies offering microbial fermentation continue to employ glass at the process development scale and stainless steel at a much higher percentage as the adoption of single-use technology for microbial production is lagging as compared to mammalian cell culture. The economics of operational change over to modular, single-use technology for microbial fermentation suggest that adoption rates will be slower than mammalian cell culture. However, products such as the CellTainer® appear to be gaining a foothold beyond the seed train (e.g. the initial process step for growing microbial cells for biologic or vaccine production). For microbial fermentation at scales up to 25L and beyond 25L single-use bioreactors such as the BIOSTAT® CultiBag RM system (from Sartorius Stedim) or the GEHC Wave Systems appear to also be gaining in interest and use for development through clinical production.

The future: Much of the R&D and manufacturing of these new biosimilar products will be performed by CROs and CMOs that focus on productivity and cost-savings. Technological advances are making it easier and cost-effective to outsource manufacturing, including the use of disposable bioprocessing systems rather than more expensive fixed stainless steel systems. Advances in screening and analytical testing are also driving outsourcing to firms providing these increasingly specialized and resource-intensive services. As documented in the T*op 1000 Global Biopharmaceutical Facilities Index* (www.top1000bio.com), the increase in worldwide CMO and other biopharmaceutical outsourcing in the past decade will certainly continue through the next decade.

Data from this study shows that biopharma CMOs are expanding their manufacturing competence through the use of novel technologies, single-use/disposable bioreactors and other differentiated bioprocessing services. Expansions are resulting in increased adaptability, lower costs, faster turnaround and higher yields. For clients, this means that more CMOs will likely meet their needs (more competition, more choice) and the costs for using CMOs for product manufacturing are becoming at least slightly more competitive. Biologics manufacturing is inherently very complex, and companies are becoming more aware of the value of experienced CMOs as a provider of expertise, as well as a back-up manufacturer with 'flex' capacity.

Conclusion

Massachusetts has long been the leader in the pharmaceutical and life sciences arena. In a time of ground breaking therapeutics research and discovery, the requirements for the successful manufacturing of biopharmaceuticals have changed drastically. The one drug per factory model is no longer economically reasonable for smaller more niche products. Already states like New York, New Jersey, Illinois, Indiana, Pennsylvania and Michigan are experiencing reductions in the number of biopharmaceutical manufacturing jobs as the industry shifts to less capital intensive manufacturing platforms or manufactures material overseas.[69] For emerging biopharmaceutical companies smaller batches of drugs must now be made faster than ever before all while under tight budgetary and regulatory constraints. State-of-the-art flexible, modular biopharmaceutical manufacturing facilities meet the needs of researchers, regulators, patients, and investors all while creating new job opportunities for the local community. The convergence of innovative biopharmaceutical manufacturing technology commercialization and the 1,174 therapies being developed by Massachusetts based companies represent a significant amount of capability and demand for this new era of biopharmaceutical manufacturing to take hold in the Commonwealth.

Now as the biopharmaceutical manufacturing industry goes through a major transformation with from one drug per factory to modular, single-use platforms, the formation of a Public-Private Partnership to focus on manufacturing can help ensure that the Commonwealth remains the center

In a time of ground breaking therapeutic R&D, the requirements for the successful manufacturing of biopharmaceuticals have changed drastically. Single-use platforms and continuous manufacturing platforms are innovations available in the Commonwealth.

MBI Outreach

With MA Secretary of Housing and Economic Development Greg Bialecki (left), and MBI CEO and President, Kevin O'Sullivan (right)

of focus for the life sciences industry for decades to come. The Public-Private Partnership in collaboration with Worcester's economic stakeholders could transform the city and launch a sustainable biopharmaceutical manufacturing foundation that could support the regional growth of the overall manufacturing sector. A Public-Private Partnership is a preferred organizational structure and vehicle for accepting public funding for new manufacturing infrastructure as it brings together numerous stakeholders in a long-term investment and commitment to the field in this specific area.

Worcester's legacy of manufacturing excellence, the new Biomanufacturing Training and Education Center at Worcester Polytechnic Institute, the innovative single-use disposable equipment manufacturers (GE Healthcare, EMD Millipore, and Thermo Fisher), MIT's Center for Continuous Manufacturing, and the biopharmaceutical R&D strength in Greater Boston are the perfect foundational elements for a fundamentally new type of biopharmaceutical manufacturing industry to take root in the Commonwealth. Representing a point of nucleation, Massachusetts companies are developing over 460 biologics most of which are suitable for production in modular single-use biopharmaceutical manufacturing platforms. Financially Massachusetts is second only to California, with the second most amount of money invested in emerging biopharmaceutical companies by venture capitalists who want to see there innovative investments change the life of patients afflicted with disease. With so much of the drug research and development going on within Massachusetts, it makes strategic sense to keep the manufacturing local to broaden the type of employment opportunities the life sciences economy can provide. The biopharmaceutical companies in the Greater Boston area are committed to Massachusetts and some would like to commit to biopharmaceutical manufacturing here as well but the infrastructure has not developed to the point where that decision makes economic sense. Therefore biopharmaceuticals created and developed in the Commonwealth are manufactured in other states. The envisioned Public-Private Partnership could begin to break down this barrier and provide our local companies with in-state biopharmaceutical manufacturing resources for the production of clinical batches.

Worcester could be an ideal choice as a location for new modular biopharmaceutical manufacturing facilities with its affordable housing, access to public transportation, and buildings suitable for repositioning. With MLSC's existing investments in WPI's BETC to facilitate training of new workers, and Blue Sky's process development labs, the vision for a Public Private Partnership to facilitate the growth of biomanufacturing in downtown Worcester can leverage existing investments. Through innovative new technology, Worcester can provide drug researchers with the capabilities to manufacture small batches of drugs at the highest of quality to expedite regulatory approval and subsequently scale-up production in a multi-use facility for commercial production. With support from the federal government (NIH, DARPA, BARDA, DOD, Homeland Security, and CDC) in addition to local efforts through the Public-Private Partnership, Worcester can become the leader for domestic biopharmaceutical manufacturing. Together the operational experience and the state of the art facilities to will be the nucleus to support the entire cycle of drug development from workforce training, cell development through large-scale commercial drug manufacturing. The formation of the Public-Private Partnership will provide local biopharmaceutical manufacturing support to the research institutions in the greater-Boston area, employ middle skilled workers, keep biopharmaceutical manufacturing in the United States, and accelerate the time from discovery to patient treatment ultimately saving lives. This opportunity is truly a win for everyone: drug developers, residents of Worcester, the Commonwealth at large and eventually the global health population.

69 Industry Snapshot. MassBio. www.massbio.org/writable/editor_files/industry_snapshot_2013_final_copy2.pdf. 2013

- Support the formation of a Commercial Biopharmaceutical Manufacturing Public-Private Partnership for shared risk and responsibility of developing the physical asset of the facility and intangible asset of the Quality System required to manufacture clinical lots suitable for pre-IND and IND testing.
- Support the Establishment of a Commercial Biopharmaceutical Manufacturing Innovation Zone in Worcester.
- Support a regional focus on biopharmaceutical manufacturing Job growth that collaborates with existing biomanufacturing investments at UMass Dartmouth and UMass Lowell.
- Establish a Worcester regional biopharmaceutical manufacturing board that works with the existing Biomanufacturing Roundtable to ensure transparency, collaboration, and growth; led by WPI and MBI.
- Strive to ensure molecules developed in the Super Cluster have the opportunity for commercial manufacturing in the Commonwealth supported through outreach programs fostered by the Worcester Chamber of Commerce.
- Encourage participation of the City of Worcester, various State organizations and Federal Departments in this unique Public-Private Partnership to foster the expansion of biopharmaceutical manufacturing job opportunities in the Commonwealth.
- Encourage Worcester City Participation through the following programs:
  - City revolving loan fund to support bioengineering enterprises, funded by HUD 108 loans
    - This innovative $29 million program, funded by HUD and the CDBG program, is administered by the City of Worcester's Economic Development Division.
    - The Section 108 Loan Guarantee program assists projects that conventional lenders may consider as too high a risk to move forward.
    - The maximum Section 108 Loan Guarantee amount is 80% of the conventional loan to value amount (including bank financing), or the minimum amount required to make the project go forward.
    - The program does not provide equity financing and cannot provide a 100% guarantee.
  - Priority Development Site designation and associated **expedited permitting**.
  - Economic Development Incentive Program (EDIP)
    - An incentive program designed to foster job creation and stimulate business growth throughout the Commonwealth.
    - Participating companies may receive state and local tax incentives in exchange for job creation, manufacturing job retention and private investment commitments and tax increment financing (TIF) support for new real estate property investment.
    - TIF allows municipalities to provide flexible targeted incentives to stimulate job-creating development.
      - Negotiated Agreement between business and host municipality;5 year minimum, 20 year maximum or anything in between;
      - Business pays full tax rate on the "base value";
      - Exemption from property taxation on all or part of the increased value accrued as a result of development (the "increment");
      - Percentage of exemption may range from 5% to 100%;
      - Personal property tax exemption for both existing and new property;
  - EDIP personal property **tax exemption** for new real and personal property tax investment.
  - Workforce Central Career Center assistance in recruitment and job training for biomanufacturing activity.

- Encourage Massachusetts Life Sciences Center Participation through the following programs
  - Capital Program
    - The Capital Program is designed to provide grants for capital projects that enable and support life sciences workforce development and training, research and development, commercialization and/or manufacturing in Massachusetts. Applicants are academic organizations, research institutions, research hospitals, business incubators and other non-profit organizations. MLSC recognizes that investment in capital projects and infrastructure is required to create and sustain the attributes that make Massachusetts attractive to innovation clusters such as life sciences. This program is designed to help fund high potential economic development projects that promise to make a significant contribution to the state's life sciences ecosystem.
- Encourage MassDevelopment Participation through the following programs:
  - Tax-Exempt Bonds–Because they are exempt from federal taxes and in certain cases state taxes, tax-exempt bonds are usually the lowest interest rate option for real estate projects and new equipment purchases. Tax-exempt bonds can be sold in the capital markets or directly to your bank or another financial institution. Projects financed must be eligible for tax-exempt financing under the federal tax code and include:
    - 501(c)3 nonprofit real estate and equipment
    - Public infrastructure projects
    - Manufacturing facilities and equipment
    - Municipal and governmental projects
  - New Market Tax Credits–The NMTC Program[70] was created specifically to stimulate investment in designated low-income communities. The program is administered by the Department of Treasury but controlled locally by Community Development Entities (CDEs). MassDevelopment assesses potential NMTC projects for both non-profit and for-profit businesses, including, but not limited to, community and health centers, retail and office space projects, performing arts centers, mixed-use projects and light industrial use centers. For developers, NMTC financing can provide a valuable source of gap financing. NMTC investment can be utilized on both new construction as well as rehabilitation projects of historic and non-historic structures.
- Encourage Federal Government participation through the following programs:
  - Public Works and Economic Adjustment Assistance Programs
    - The Department of Commerce's Economic Development Administration (EDA) provides strategic investments that foster job creation and attract private investment to support development in economically distressed areas of the United States. Under Economic Development Assistance Program, EDA solicits applications from both rural and urban areas to provide investments that support construction, non-construction, technical assistance, and revolving loan fund projects under EDA's Public Works and Economic Adjustment Assistance programs. Grants made under these programs are designed to leverage existing regional assets to support the implementation of economic development strategies that advance new ideas and creative approaches to advance economic prosperity in distressed communities.[71]
  - Investing in Manufacturing Communities Partnership (IMCP)
    - IMCP is a new Administration-wide initiative that will accelerate the resurgence of manufacturing and help communities cultivate an environment for businesses to create well-paying manufacturing jobs in cities across the country. Through the IMC, the President is directing Federal agencies to provide coordinated assistance to manufacturing communities through a new partnership that will align Federal economic development resources and help U.S. localities make coordinated, long-term investments in their public goods in partnership with universities and industry. These investments will

70 http://www.cdfifund.gov/what_we_do/programs_id.asp?programID=5

71 http://www.grants.gov/view-opportunity.html?oppId=208353

72 http://www.commerce.gov/news/fact-sheets/2013/04/17/fact-sheet-investing-manufacturing-communities-partnership

ultimately help regions become more attractive for manufacturers and supply chains. The Partnership will be led by the Commerce Department with support from other federal agencies.[72]

- Advanced Manufacturing Technology Consortia (AMTech) Program
  - The President's Council of Advisors on Science and Technology (PCAST), entitled *"Capturing Domestic Competitive Advantage in Advanced Manufacturing,"* emphasizes this concern noting that the United States has been steadily losing research and development activities linked to manufacturing—and associated high skilled jobs—to other nations. The report warns that the continued loss of America's leadership in developing innovative technologies for advanced manufacturing will undermine our capacity to compete in global markets and includes sixteen recommendations including public-private partnership to foster ecosystems in advanced manufacturing technologies. As part of a proposed, comprehensive strategy to revitalize America's leadership role, the PCAST report recommend support for new applied research programs for advanced manufacturing. This includes efforts that support new public-private partnerships that would develop broadly applicable and precompetitive technologies, create and disseminate new design methodologies for manufacturing, and promote the development of shared technology infrastructure to support advances in existing manufacturing industries.[73]
  - In response Department of Commerce National Institute of Standards and Technology (NIST) is launching the AMTech Program to establish new and strengthen existing industry-led consortia to identify and prioritize research projects supporting long term industrial research needs. Thus, the AMTech Program provides funding to consortia that are focused on developing advanced technologies to address major technological and related barriers that inhibit the growth of advanced manufacturing in the U.S. and the global competitiveness of U.S. companies. Once fully implemented, it is envisioned that AMTech will provide funding in two broad areas: planning awards and implementation awards.[74]
- Healthcare and Threat Reduction Programs
  - With the advancement of novel vaccines, biologics, nanomedicines and cell therapies e.g. regenerative medicine the Department of Health and Human Service's National Institute of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA)[75], and Department of Defense's Defense Threat Reduction Agency (DTRA) and Defense Advanced Research Projects Agency (DARPA) will require manufacturing needs that are asymmetrical and require flexibility to bring new therapies to patients or National stockpile. There are annual calls to describe technology readiness levels (TRL) and the proposed capability should fall within the higher end of the spectrum (TRL5-TRL9) making it competitive for most federal solicitations.

MBI outreach to the NIH

With National Characterization Laboratory Deputy Director Dr. Anil Patri (left) and Dr. Piotr Grodzinski Director of the National Cancer Institute's Office of Cancer Nanotechnology Research (middle)

73 http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast_amp_steering_committee_report_final_july_17_2012.pdf

74 http://www.nist.gov/ampo/upload/2013_AMTech_FFO.pdf

75 BARDA-BAA-11-100-SOL-00001 designed to promote science and technology advancements of platforms applied to Medical Counter Measures (MCM) development for the Strategic Science and Technology Division

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