Institutions, Public Policy and the Product Life Cycle: The Globalization of Biomanufacturing and Implications for Massachusetts

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ABSTRACT

Globalization has brought about a major shift in our understanding of how companies organize themselves and how they compete. The fragmentation of firms in their scope and structure, the vertical disintegration of firms through greater outsourcing, and the rise of global supply and value chains has led to new visions for companies ("metanational companies") and new models of production ("modular production networks") that "break free" from geography. In this global economy, many believe that manufacturing has little future in a high-skilled, high-wage region, given competition from lower cost countries. High-tech regions like Silicon Valley and Boston's Route 128 need to focus on design and innovation, and "let others produce what Americans think up."

Proponents of this vision dismiss classic models like product life cycle theory (Vernon 1966), which explain the location of manufacturing through the timing of innovation and the maturity of products. To these critics, this model no longer holds because of the ubiquitous nature of innovation, the growth of advanced markets in emerging economies, and the ability to move manufacturing offshore before a product is even standardized. In this view, it is almost inevitable that manufacturing beyond prototypes cannot survive in high-wage countries like the U.S.

This attitude, however, presents a false dichotomy between innovation and manufacturing. This thesis argues that in advanced manufacturing industries such as biotech manufacturing, it is precisely innovation that brings this complex manufacturing activity to high-skilled, high-wage, technologically advanced regions of the world. This research examines the geographic evolution of biomanufacturing and finds that product life cycle theory provides an excellent model for understanding the dynamics of the industry, albeit with some twists which add to the richness of the literature. These twists are first, the role that institutions, specifically regulation, play in shaping the product life cycle by providing patents that slow the entry of competition. Second, public policy, specifically competitive international tax policy, has become a new differentiator between countries that are seeking to attract high value-added, high-wage manufacturing through the use of tax incentives. Tax-Advantaged Locations (TALs) have become the new low cost destination for advanced manufacturing despite their high wages and costs.

Through interviews with 47 biomanufacturing executives and analysis of the geography of biomanufacturing investments made by 96 companies between 2002 and 2013, I find that technologically advanced regions such as Massachusetts retain the most innovative aspects of the industry, including early stage manufacturing as well as the first stage of commercial manufacturing. Massachusetts has a significant opportunity to retain and grow the industry, though the economic development impact is not in a large number of

jobs, but in the building of a "regional system of innovation" based in human capital and companies that can usher in new technologies and emerging industries.

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Chapter 1
Introduction

In the spring of 2009, the president and CEO of the Massachusetts Biotech Council said in his annual address, "It is time to focus on encouraging innovation among Massachusetts biotech companies rather than luring biotech manufacturers [to the state]." His attitude toward the opportunities for manufacturing in Massachusetts capture a pervasive attitude found in many corners of the country.

That line of thinking argues that manufacturing has little future in a high-skilled, high-wage region, given global competition from lower cost countries. Automation, the offshoring of manufacturing jobs, and the government bailout of major auto companies has created an impression among the general public that the U.S. is unable to compete globally for manufacturing jobs. The only hope for growing industries in the U.S. is to focus on knowledge-intensive, research-intensive industries that thrive on innovation like biotech. This attitude is prevalent in both the U.S. and many other advanced, industrialized countries that are importing increasing volumes of goods from China and elsewhere. One German executive sums it up: "We need to put money in places that create knowledge, not things…Silicon Valley isn't a factory anymore; it's a think tank." Regions like Silicon Valley and Boston's Route 128 need to focus on design and innovation, and "let others produce what Americans think up."

Globalization has brought about a major shift in our understanding of how companies organize themselves and how they compete. The fragmentation of firms in their scope and structure, the vertical disintegration of firms through greater outsourcing, and the rise of global value chains has led to new visions for companies ("metanational companies") and new models of production ("modular production networks") that seek to leverage knowledge from every corner of the world and reap efficiencies by maximizing global production networks. By leaving only high-value-added activities in the home country (R&D, product design, marketing, strategy), a company can focus on its "core competencies."

In this paradigm, companies have broken "free of geography." The most enlightened are investing outside of their home base where for too long executives have been "blinded" by the power of clusters. In particular, proponents of this vision dismiss classic theoretical models like product life cycle (Vernon 1966), which explain the location of manufacturing through the timing of innovation and the maturity of products. To these critics, product life cycle represents a "traditional" view of global competition in which innovations take place in a company's home country and are then "projected" outward to the rest of the world in order to tap into new markets. Ultimately, production is moved to cheaper locations. For some, this model no longer holds because of the ubiquitous nature of innovation, the growth of advanced markets in emerging economies, and the ability to move manufacturing offshore before a product is even standardized. In this view, it is inevitable that manufacturing beyond prototypes will not survive in high-wage countries like the U.S. ~~it~~ This helps explain the comments of leaders like those quoted above who see investments in manufacturing as a dead end for advanced economies.

This view, however, presents a false dichotomy between innovation and manufacturing. In advanced manufacturing industries including biotech manufacturing, it is precisely innovation that brings manufacturing to technologically advanced regions such as Massachusetts. For over two decades, much has been written about the important link between innovation and production (manufacturing) and the risk to U.S. innovation, among other things, of losing the ability to make products (Cohen and Zysman 1987; Uchitelle 2006). A number of empirical industry studies illustrate this link and identify many of the reasons manufacturing continues to exist in higher wage, highly skilled, advanced economies (Herrigel 1993; Pisano 1997; Bluestone, 2007), including institutional factors and external economies.

This research contributes to these industry studies with an examination of the geographic evolution of biomanufacturing and how product life cycle (PLC) theory helps to explain this evolution. In particular, despite the debunking of product life cycle theory in many empirical studies of other industries, it provides an excellent model for understanding the

dynamics of this industry, albeit with some twists which add to the richness of the PLC literature (Antras 2005). These twists include the role that institutions such as regulation play in shaping the PLC, as well as ways in which public policy, specifically tax policy, have become the new differentiator between countries, replacing low wages as a driving force in location decisions.

1.1 Rationale, Research Questions, and Findings

At a time when there are concerns over the U.S.'s ability to maintain its position as a world leader in innovation and worries that a polarization of the labor market is leading to the loss of "middle-tier" jobs, this research examines the dynamics of a highly innovative, advanced manufacturing industry that creates middle-tier jobs and in which the U.S. is the global leader. This is also an industry that, starting five years ago, began heading offshore. For reasons outlined in greater detail below, biomanufacturing exhibits many of the "sticky" qualities that characterize industries in which the U.S. should be able to compete: complex, innovative, highly skilled labor, significant regulation, a high degree of tacit knowledge; and an integral rather than modular development process.

But despite these characteristics, global competition is increasing, and high-tech regions that are leaders in the industry, such as Massachusetts, are trying to determine how to hold on to their competitive advantage in the field. While many regions around the world are expending significant time and effort to develop the biotechnology industry in their area, a different set of challenges exist for places like Massachusetts and California that are pioneers and leaders in the industry. Specifically, how do regions that are "leading technology states" maintain and even enhance their lead while being high-skilled, high-cost locations? Massachusetts is second only to California worldwide in terms of mammalian-based biomanufacturing capacity (the most complex type of biomanufacturing), and thus, provides an excellent case study for understanding how places at the technological frontier of an industry can stay at that frontier, even as global competition increases and the industry matures. In addition to changing the ways companies compete, the new realities of global competition create different expectations and strategies around regional economic development. Gone are the days of

manufacturing plants that employ tens of thousands and provide a job for life. While it doesn't provide a large number of jobs, (12,000 in New England), biomanufacturing may be one of the best types of niche manufacturing in which a high cost location like Massachusetts can compete. As leaders in Massachusetts grapple with how to promote and sustain innovation in the region, some have asked, if the state can't compete in this type of advanced manufacturing, can it compete in any?

My research questions draw from two related fields: industrial organization, including theories of the firm, product life cycle, and modular production; and regional economic development, including agglomeration economies, new growth theory, and the geography of innovation. Four primary questions drive this research:

1. What explains the location of biomanufacturing investments, and how does the geography of the industry change over the product life cycle?
2. What is the importance of biomanufacturing to the overall biotechnology cluster and to the innovation process?
3. How does the U.S. in general, and a "high-tech" region such as Massachusetts in particular, compete in a global advanced manufacturing industry such as biomanufacturing?
4. What is the economic development opportunity, if any, for Massachusetts in this industry, and what should the strategic priorities be for retaining and growing the industry?

The U.S. retains the most innovative parts of the biomanufacturing process, which occur at the early stages of the product's life cycle during pilot and clinical trial production and, to a lesser extent, at the commercial launch of a new product. Due to the benefits of proximity to upstream R&D, companies prefer to locate their early stage manufacturing near their process development teams. Likewise, as product life cycle theory would predict, many companies locate their first commercial manufacturing facilities near R&D, as they launch their first product or develop new processes for more complicated products.

However, for more standardized commercial production of well-established products, after a few years of production onshore, investments are starting to head offshore. This is particularly the case for growing companies with at least one "blockbuster" drug. Companies' second and subsequent facilities are heading offshore, and in some cases, "killing two birds with one stone" by locating in new markets (Europe) while moving production to a low-cost location. This is possible because of a new twist to the PLC theory in which these manufacturing jobs are not heading to low-wage, low-cost countries, but instead, are heading to high-wage, high-cost countries (Ireland, Switzerland) that are ultimately cheaper because of tax advantages (tax advantaged locations or TALs). As countries move up the skills ladder and compete for higher value-added and higher skilled jobs, tax policy becomes a new differentiator among countries and regions eager to seed and grow an industry that is not easily moved to cheaper locations.

Another important twist to the PLC theory provides context to the evolution of the life cycle. Institutions, in particular, regulation that protects intellectual property (IP) in the form of patents is critical to understanding the dynamics of the location of biomanufacturing. In an R&D intensive, complex industry that has been described as a "competitive oligopoly," patents provide on average 12 years of monopoly profits to biopharma companies, slowing down the product life cycle by reducing competition. In addition, companies are loath to expand their operations into countries that don't have strong IP laws. Only in the case of biosimilars (biotech's equivalent to generics) are companies locating facilities outside of the "triad" (North America, Europe, and Japan) and producing what is essentially a commodity in traditional low-cost locations (primarily in Asia). The product life cycle has still been accelerated considerably over the decades despite these unique aspects of biomanufacturing. The first approved biotech drugs in the mid-1980s stayed onshore for 20 years before production was moved to a low-cost location. Today's approved drug might be moved offshore within four or five years, if not in some cases, immediately.

While the US pioneered this industry and is still a global leader, there are some important changes taking place in the industry that will challenge this predominance: technological innovations that are increasing productivity, and the rise of Asia in biomanufacturing, specifically contract manufacturing. While half of the top ten locations for biomanufacturing in the world are in the US, two of them will be in Asia by 2013. That being said, the current risk from an economic development point of view of losing the industry as it globalizes is more likely the loss of some of the 300,000 high-skilled, high wage jobs in mature manufacturing, rather than losing the innovative aspects of the industry. Innovation in the industry continues to take place in the early stages of manufacturing and despite the offshoring of commercial manufacturing, neither biotech R&D nor process development within biomanufacturing have been "pulled" by these investments.

Like the U.S. as a whole, Massachusetts must compete in the early stage of innovative manufacturing work, which is fed in part by the strong R&D and the entrepreneurial biotech base in the region. However, there is also an opportunity to retain and grow commercial manufacturing. For companies who are building their first commercial facilities or are involved in complex production processes, keeping a facility near R&D helps to ensure reliable, quality production. In addition, sunk costs and economies of scale play an important role in the economics of biomanufacturing, so companies who have established facilities in the region are more likely to expand those facilities (as Genzyme and Shire have done recently in Massachusetts). Finally, with new technologies that are bringing down the overall cost of manufacturing and a desire for smaller, niche production as well as continuous improvement, the cost of setting up commercial production in the U.S. may be decreasing relative to manufacturing overseas. In the case of Massachusetts, since the state cannot compete on national tax policy to keep commercial facilities in the region, it must compete on talent and innovation and the benefits that come from proximity to biotech R&D. While the industry generates only approximately 10,000 jobs in the state, fewer jobs may be more the rule than the exception for advanced manufacturing industries in the U.S. More important than the number of jobs, however, are the kinds of jobs (high skilled and high wage), the skills

base that is embedded in the region, and the innovative work that companies engage in. These help contribute to the region's "system of innovation" and help generate the next wave of ideas, companies, products, and services.

1.2 Biomanufacturing in Context

There are a number of reasons why biomanufacturing is a compelling case study for understanding how the U.S. and innovative regions like Massachusetts compete in an advanced manufacturing industry. It also raises interesting questions about what strategies regions can pursue to retain and grow an industry that is both highly innovative but also maturing and becoming more global. The following four points underscore the value of this case.

First, biomanufacturing is part of biotechnology, an industry that has served as an exemplar of a "new economy" industry. It is deeply rooted in the sciences, is research intensive, and is highly innovative. Since its emergence in the 1970s, many have heralded life science in general — and biotechnology in particular — as the industry of the twenty-first century, where research into biological processes will dominate the research agenda and lead to cures to a range of illnesses. While biotechnology can be applied in a wide range of industries (agricultural, industrial, medical devices), this research focuses on the application of "biotech" to the health care industry and, specifically, biopharmaceuticals. Biotechnology is currently an $80 billion market, has great growth potential and is currently experiencing double-digit growth (16%, twice the rate of pharmaceuticals). It has become, to a fault, the "holy grail" of economic development strategies for cities and regions around the world that want to build a biotech cluster in hopes that it will bring high-skilled, high-paid, research-intensive jobs, as well as the wealth generated by entrepreneurial spin offs. Like biotech, biomanufacturing is also highly innovative. But in the face of the decline of traditional manufacturing industries such as textiles and automobiles, will new manufacturing industries such as biomanufacturing be able to replace the lost jobs of the traditional industries? Examining the location dynamics of biomanufacturing sheds light on how manufacturing in a knowledge-intensive industry

occurs today and what the implications are for retaining and growing this industry in the U.S.

Second, biomanufacturing is one of the most complex and technically and financially risky types of manufacturing that exists today. Despite the emergence of biomanufacturing over 25 years ago, there are a number of factors that have kept the industry located primarily in the biopharmaceutical "triad" — North America, Europe, and Japan. It is much more difficult to make a drug from a biological process based on living cells than a chemical process, which is the basis of pharmaceuticals. Because of the biological nature of the product, it is technically impossible to make a generic version of it. For this reason, the term "biosimilar" is used. In addition, because of the public safety issues involved, biomanufacturing is strictly regulated by the FDA and other world regulatory bodies, and any changes to the manufacturing process can lead to regulatory delays, which cost a company time and money. The fragmentation of the regulatory system across different countries also presents companies with added costs. As a result, companies like to keep strict control over manufacturing processes, and when they build a facility (with a cost typically between $450 to $750 million), companies are loathe to change the facility or move it for fear of FDA penalties. The cost of failure is high, not only potentially in terms of public health issues but also in operational costs. A bad batch of drug material can set a company back at least a month (the time to ramp up) in their production line, which, given the long and costly timeline of bringing a drug to the market (eight to 10 years and over $1 billion), can be costly. For all of these reasons, biomanufacturing has more "sticky" qualities than other types of advanced manufacturing, as companies want to keep close watch over the process.

Third, proximity matters in the biomanufacturing process. There is a period between the hand-off of the molecule from research to the process development team to the second phase of clinical trials, in which there is high uncertainty and little predictability. This has led to locating manufacturing facilities, both clinical and commercial, near biopharma research teams, many of which are U.S.-based. The production process at this stage is more "integral" than "modular," meaning that the technology has not yet been

standardized. Knowledge that is shared between research teams and the process development and manufacturing teams is more tacit than codified. Unlike in other industries where process innovation is largely about cost-savings (commodities such as chemicals, steel, and paper, or mature industries such as apparel, processed food, and shipbuilding), the biomanufacturing process is part and parcel of product innovation (Pisano, 1997).

The benefits that arise from the proximity of upstream biotech research activities to downstream manufacturing activities underscore the importance of the interface between product and process innovation. In addition, innovation in manufacturing can lead to tremendous cost-savings (unlike in drug research, for example) by speeding up the time to market and the time it takes to ramp up production. For these reasons, companies often want to keep biomanufacturing in-house once there is a successful drug. This underscores the debate that has arisen around how important knowing how to make a product is to overall innovation in a company and industry. As John Zysman asks, "Under what circumstances is the lack of in-house world-class manufacturing skills a strategic vulnerability?" (2005). This question resonates for the biopharmaceutical industry. For most large biopharma firms, having core competence in biomanufacturing has been seen as critical both to ensure quality control and to capture the benefits of process innovation, such as accelerating the time to the market and ramping up production.

Finally, biomanufacturing today is highly dynamic and innovative in virtually all aspects of the industry. The FDA set the stage for this by creating a new approach to regulating the industry in 2002, which allowed firms greater flexibility in changing their processes without risk of penalty. New technologies are emerging that are helping increase productivity as well as give companies greater flexibility in locating and building new bioreactors. There are also new business models that are emerging in which the classic distinction between manufacturing in-house and contracting out (to contract manufacturing organizations or CMOs) is evolving. Companies are partnering with CMOs to achieve their biomanufacturing goals, and in some cases where companies have extra capacity, they are engaging in CMO activities. On top of all this, the nature of

biomanufacturing demand may be changing with the emergence of more personalized medicine, which requires smaller, niche volume production, which in turn changes the design and layout of new facilities. All of these factors suggest again an industry that is engaged in continuous change and innovation, and this plays to developed countries' competitive strengths.

These characteristics — a knowledge-intensive, growing industry; a risky and complex process integral in nature; and a highly dynamic and innovative industry — represent exactly the type of industry in which the U.S. in general and Massachusetts in particular should be highly competitive.

1.3 Outline of the Dissertation

The dissertation is divided into seven chapters. The following provides an outline of each chapter.

Chapter Two provides an introduction to the biotechnology industry. I outline the long, costly, and complex process of bringing a drug to the market, the importance of the regulatory process, and the trends that are currently influencing the industry, all of which make it highly dynamic. Overall, the chapter underscores the high risk and high uncertainty that exists in biotech. In Chapter Three, the biomanufacturing process is explained in detail, including the different phases, costs, role of contract manufacturing, and regulatory environment. The challenge of biomanufacturing and the high risk and cost of failure highlight how this industry is still more "art than science." The chapter sets the stage for understanding the unique aspects of the industry, its complexity, and why it is an industry in which many countries want to compete.

In Chapter Four, I present the theoretical framework that supports my propositions for what drives location in the biomanufacturing industry. I find that product life cycle theory, far from being irrelevant, is highly applicable to this industry, albeit with some distinctive features. I also discuss the role of agglomeration economies and the geography of innovation to understanding the concentration of the industry. I also discuss some

additional factors that help explain location and how these add to the theoretical frameworks.

Chapter Five presents my data analysis, which supports the propositions outlined in the previous chapter. Global trends in biomanufacturing facility investments (measured in volume) from 2002 projected to 2013 are presented, followed by data that support the linkage between strong biotech R&D and biomanufacturing, as well as the importance of proximity to R&D for the industry. Finally, I show how drug sales, company growth, and a company's overall drug portfolio can influence the location of commercial manufacturing facilities. Since 2004, 10 product companies and one CMO have built or are in the process of building commercial facilities in a tax-advantaged location. This constitutes one of the major emerging trends in the industry and provides insight into how countries and regions are using public policy to compete for advanced manufacturing investments.

Chapter Six delves deeper into some of the trends around technological innovation in biomanufacturing. What role does innovation currently plays in the industry and what role it could play in the future as it relates to the location of biomanufacturing investments? I review how new technologies and innovations are affecting the current and future location of the industry and discuss the balancing act companies must manage between taking risks with new technologies and being consistent with their processes and final products so the FDA does not question the quality of work. I review four major innovations occurring in biomanufacturing today, all of which help explain why many believe there is a "revolution" occurring in the industry. I then take this question of the future location of biomanufacturing and outline some possible scenarios based on new technologies and also factors external to biomanufacturing that will impact how the industry evolves geographically over time. Finally, I compare and contrast the location of pharmaceutical operations with biotech and draw some conclusions about what we can learn from the pharma industry. Ultimately, this chapter outlines where the "sweet spot" for the U.S. lies in terms of competing in the biomanufacturing industry.

In Chapter Seven, I turn to the question of biomanufacturing as an economic development opportunity. In previous chapters, I outlined industry dynamics and how these affect where the industry locates. In this chapter, I ask the following question: Given what we know about these dynamics, how does biomanufacturing contribute to economic development? I also review the economic development impact of biomanufacturing in terms of jobs and skills development, innovation, and taxes to determine what the current contribution is to the U.S. and what is at risk if the industry moves off shore. Before examining the opportunity for Massachusetts, I review some of the strategies that are being employed in other parts of the world (Ireland, North Carolina, Singapore, and the United Kingdom) to seed and develop the industry.

In Chapter Eight, I turn specifically to the economic development possibilities for Massachusetts, the second largest location for biomanufacturing globally (based on volume). The Massachusetts economy has been referred to as a "boutique" economy, a description that accurately portrays this kind of niche manufacturing. After reviewing the competitive advantages and disadvantages for biomanufacturing in Massachusetts, I make recommendations in four key areas in which the state should invest in order to retain and grow the industry in the region and conclude that this is exactly the kind of industry in which the state should be competitive. Additionally, I make recommendations to support that goal. In Chapter Nine, I conclude my argument and suggest areas for further research.

Chapter 2
Introduction to Biotechnology

2.1 Background on the Industry

This chapter provides a brief introduction to the complex science and business of biotechnology. The discussion focuses on aspects of the industry that are most relevant for understanding the dynamics of biomanufacturing, such as the drug development process, timeline, costs, and regulation. Biotechnology is defined broadly as the application of cellular and biomolecular processes to develop and make useful products. While these products can be in a wide range of industries (agricultural, industrial, medical devices), this research focuses on the application of "biotech" to the health care industry and, specifically, biopharmaceuticals.[1]

This industry was born in the 1970s, and many pinpoint the date of origin to Genentech's (the first biotech firm) founding in 1976. It emerged with a number of scientific breakthroughs, the most significant being the development of recombinant DNA technology — genetic engineering — that allows for making proteins such as human insulin.[2] Recombinant DNA technology has had a profound effect on the pharmaceutical industry (Walsh 2007). First, by making proteins that are naturally produced in the body *in vitro* the proteins can be extracted from external sources in large quantities. Second, this process avoids the transmission of disease and can be safer to develop because the proteins are produced in a controlled environment rather than in native biological sources that carry disease or are hard to obtain. Finally, some of the engineered therapeutic proteins can be more effective than the natural protein product, acting faster or slower than natural proteins.

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[1] Definition from the Biotechnology Industry Organiztion (BIO), 2008. "Bioscience" or "the life sciences" encompasses a broad range of biologically related industries beyond drugs and pharmaceuticals, such as agricultural production, medical devices, industrial production, or research, testing, and medical laboratories. See Battelle Technology Partnership Practice and SSTI, *Growing the Nation's Bioscience Sector: State Bioscience Initiatives 2006*, under "Section Title," http://www.bio.org/local/battelle2006/battelle2006.pdf (accessed June 30, 2009).

[2] The discovery was published in 1973 by Stanley Cohen of Stanford and Herbert Boyer of UCSF. (Boyer went on to found Genentech).

The development of genetic engineering as well as monoclonal antibody technology gave birth to an industry that has to date created more than 200 new therapies and vaccines, with an additional 400 drug products and vaccines currently in clinical trials. These drugs treat a wide range of diseases such as cancer, diabetes, HIV/AIDS, autoimmune, and neurological disorders. Biotech drugs represent approximately $80 billion of the total $800 billion global pharmaceutical market, and while it is a relatively small part of the market, it is growing faster than conventional pharmaceuticals, whose margins have been reduced considerably due to the introduction of generic competition. As of 2007, there were 1,450 biotech companies in the United States, of which approximately 330 were public.[3]

But as thirty plus years have demonstrated, biotech is an extremely risky and costly business. "[There is] a fundamental and deep struggle between the conflicting objectives and requirements of the science of biotechnology and the business of biotechnology." (Pisano 2006, 6). Bringing a new drug to the market costs on average over $1 billion and takes an average of 10 years. More than half-way through the process, close to half of all drug candidates fail. While a patent is granted for 20 years, companies may spend half of that time developing a new drug, getting Food and Drug Administration (FDA) approval, and commercializing it. And assessed purely from a business point of view, the biotech industry has on the whole performed poorly. An analysis of the aggregate profitability of publicly traded biotech companies between 1975 and 2004 shows rising revenues but profits that have hovered around zero (*Ibid* 116). The "profound and persistent uncertainty" of biotech creates a challenging situation for commercializing this science.

2.2. The Biotech and Pharmaceutical Industries

Today, the differences between biotech companies and pharmaceutical companies have blurred, as the science and the business of biotech and pharmaceutical drug production have become more integrated. Prior to 1980, however, very few pharmaceutical companies had in-house biotech research and development (R&D) programs. To

[3] Biotechnology Industry Organization, "Biotechnology Industry Facts," Science for Life, http://www.bio.org/speeches/pubs/er/statistics.asp (accessed July 1, 2009).

understand the rising importance of biotech in the "biopharma" world, one needs to understand the scientific processes behind these industries.

The distinction between biopharmaceuticals and pharmaceuticals lies in how the drugs are produced (Walsh 2007). In traditional pharmaceuticals, drugs are made from small molecules (low molecular weight organic chemicals) and produced from direct chemical synthesis using raw chemical ingredients and producing pharmaceutical products in bulk quantities. These are then formulated into the final pharmaceutical products such as pills. Biopharmaceuticals are fundamentally different in that they are derived from large molecules and are produced from biological sources. A "biologic" refers to products derived from these sources. Biotechnology is the process by which biological systems (cells, tissues) or biological molecules (enzymes, antibodies) are used to make commercial products.

The term "biopharmaceuticals" was first used in the 1980s to refer to types of therapeutic protein that were produced using biotech technology, specifically genetic engineering. Many of the new therapeutics developed for application in a wide range of areas (oncology, inflammation, bone disease, neurology) are protein-based. The first drugs approved were replacement proteins like erythropoietin or EPO, and human insulin (the first biotech drug therapy approved by the FDA in 1982). More recently, engineered therapeutic proteins have been developed. These recombinant proteins are produced using living cells such as bacteria (*E. coli*), yeast (*S. cerevisiae*), or cultured mammalian cell lines (Chinese hamster ovary cells [CHO] or baby hamster kidney cells [BHK]).

Biotech has made the landscape for drug development larger, more diverse, and more complex. There are more therapeutic agents to work with, more possible permutations to discover, and the development of a biologic drug is on the whole a more complicated process than that of pharmaceuticals because of its roots in molecular biology. The variability that arises when working with living cells is much greater than what arises with chemical compounds. Also, more scientific expertise is required in the development process, including the emerging fields of bioinformatics, genomics, protein chemistry,

etc. Biotech has created all this without replacing traditional pharmaceuticals or the ways drugs are discovered. The same amount of uncertainty exists in drug discovery, and biotech drugs success rates have not proven to be any higher than chemically synthesized drugs. Overall, there is no "dominant paradigm for drug discovery," and no paradigm shift has taken place in the drug industry with the introduction of biotechnology (Pisano 2006, 70).

The drug discovery process, unlike other goods-producing industries such as electronics, maintains a high degree of uncertainty through much of the development process. This is largely due to the fact that the product that is being made is interacting with the human body, our knowledge of which is limited. With high uncertainty comes high risk. Most of what comes out of the drug discovery department of a company will fail. Compounds going into Phase I clinical trials (the first year of testing in humans) have an 8% chance of making it to the market, and as much as 50% of all drugs in Phase III (the fourth to sixth year of testing in humans) will fail.[4] "Drug R&D is inherently an iterative and inductive process in which high levels of uncertainty persist throughout the process"(*Ibid* 59). Along with being a highly risky business, it also demands a high level of integration across multiple fields, specializations, and technologies. The increased complexity that biotechnology has introduced to the drug development process requires more interaction, not less, across different disciplines that develop drug compounds. With each of these compounds comes distinct and particular knowledge in how to design clinical trials or manufacture the compound. The drug R&D process is ultimately becoming more challenging, requiring more, not less, integration across disciplines and expertise.

2.3. **The Business of Biotech**

As stated earlier, biopharmaceutical drugs represent approximately 10% of the $800 billion global pharmaceuticals market and are growing at 16% annually, over twice as fast as the pharmaceutical drug market (Levine 2009). Biopharmaceuticals now represent approximately one quarter of all new drugs coming on to the market (Walsh 2007, 8). There are a number of reasons why "biopharma" drugs are becoming more prevalent and

[4] FDA Deputy Commissioner, Dr. Janet Woodcock, IFPAC speech, January 30, 2007; Pisano 2007, 57.

why large pharmaceutical companies — "big pharma" — have been taking note. First, biotech as a percentage of "blockbuster" drugs (drugs with sales over $1 billion) is growing. In 2000, three of the 36 blockbuster drugs (or 8%) were biotech drugs. In 2006, 18 of the 101 drugs (or 18%) held this status (Lawrence 2007). And that number is predicted to grow. Second, as the patents begin to run out on pharma drugs and generics cut margins severely, big pharma is looking for ways to fill its pipeline and its purse. The controversy over "biosimilars" (see below) may give biopharma drugs more cover for longer periods of time against imitations. Third, the trend toward personalized medicine plays to the strengths of biopharma in terms of finding therapeutics that address diseases with smaller affected populations. Biotech companies often target smaller, more specialized diseases because there are fewer barriers to entry into these markets. Big pharma, on the other hand, have traditionally been interested in creating "blockbuster" drugs that will treat a large population and help the company achieve higher growth rates. This reality has led all of the large pharmaceutical companies to build their biopharma capacity, in most cases through the acquisition of companies with strong biotech drugs or pipelines. Table 2.1 below shows some recent examples.

Table 2.1

Recent Acquisitions of Biotech Cos by Big Pharma

Year	Pharma Co.	Biotech Co.	Amount ($b)
2009	Pfizer	Wyeth	60
2008	Eli Lilly	Imclone	6.5
2007	Schering Plough	Organon	14.4
2007	AstraZeneca	Medimmune	15

Partnering or acquiring biotech firms has become the norm in the industry, given the need for cash to support the drug R&D process.

The costs of developing a drug have increased over the years. The costs are estimated at approximately $1.2 billion over an eight-plus year period.[5] The costs are roughly divided into one-third for R&D, one-third for clinical trials, and one-third for launch, marketing,

[5] This most recent estimate comes from *Volume 8 Number 6: November/December 2006*, Impact Report: Analysis and Insight into Critical Drug Development Issues (Tufts Center for the Study of Drug Development, 2006),

and sales.[6] For publicly traded biotech companies, it takes on average 11 years for the company to see a positive cash flow, which has led some to question whether the model of a publicly-traded biotech firm is feasible (Pisano 2007, 117). But while the risks are high, the rewards can be great. Biopharma products generate approximately 85% gross margins.

2.4 Trends in the Biotech Industry

There are a number of significant trends and factors that will influence biotech and biomanufacturing in the coming years. While the industry was considered to be in a relatively strong position in 2007 ($29.9 billion raised by U.S. and European companies, one of highest years on record, increased venture financing, increased revenues by 17%, and as close as ever to aggregate profitability in the U.S. [still negative, however]), 2008 was a much more difficult year due to the recession (Ernst & Young 2008). One of the most obvious impacts of the financial crisis has been consolidation in the industry and the acquisition by a number of big pharma companies of other biopharma companies with strong biologics products and/or pipelines (Lilly of Imclone, November, 2008; Pfizer of Wyeth, January, 2009, Merck of Schering Plough, March 2009; Roche of Genentech, March, 2009). As Joe Jimenez, head of Novartis' pharmaceutical division, said, "In the 90s, everybody won." That will not be the case in this [2000] decade.

There are a number of challenges that the industry faces long-term:

Pressure to Improve Productivity: With patent expirations looming and more pressure on the pricing and efficacy of drugs (the United Kingdom had the first case in which a company agreed to refund a payer for the cost of treating patients that did not respond to the medication), pharma companies need to restructure and create incentives "to improve productivity of their innovation efforts." Drug R&D spending has increased significantly since the 1990s ($37 billion in 1994 to $94 billion in 2003), yet this research spending has not been reflected in the number of new drugs brought to market. That number has in fact gone down.

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[6] Tom Ransohoff Bioprocessing Technology Consultants, interview by author, Spring 2009.

2004 marked a 20-year low in the introduction of new medical therapies on the market. "We are spending more but getting less" (Pisano 2006, 118). This is largely played out in the phases between preclinical development and drug launch. As stated earlier, compounds going into Phase I have an 8% chance of reaching the market (compared to 14% in the early 1990s); and Phase III failure rates are up 30% from a decade ago. While there are a number of factors that play into this challenge, overall it is suggested that the failure lies in the lack of investment in the medical development process — the post-drug-discovery phase of drug development. "The development process — the critical path to patients — becomes a serious bottleneck to delivering new products...we continue to use the tools and methods of the 19th and 20th century to evaluate 21st century technology."[7] Too little "evaluative science" is being used to address product performance in the areas of safety, efficacy, and manufacturing. The FDA is pushing the biopharma industry to make processes less based on empirical evidence or trial and error and more science-driven. Figuring out how to translate research into successful drug therapies in a cost-effective manner is the challenge facing all biopharma companies. As CEO Severin Schwan of Roche said to the Wall Street Journal on December 8, 2008, "Those who fail to bring sufficient innovation [to their drug development process] will be squeezed out of this market."

Personalized Medicine: Personalized medicine, the effort to provide more customized therapies to patients, has become more available to doctors as diagnostic testing has improved. Rather than using the traditional trial-and-error testing with patients to find out the right drug and dosage, personalized medicine uses more refined testing to determine from the outset the physiological makeup of a patient and whether a particular drug will be effective. This is possible today because of a better understanding of the sequencing of the human genome and how particular genes manifest into diseases. For example,

[7] Cited by FDA Deputy Commissioner, Dr. Janet Woodcock, speech given to the IFPAC meetings, January 30, 2007. Woodcock outlines a number of additional reasons cited for this difficulty in developing new therapies: the failure of some types of new science (genomics) to deliver what was hoped for, the reduction in the number of easy targets and the challenge of developing drugs for chronic diseases, the increasing costs and complexity of developing drugs (such that there is a disincentive for companies to see candidates through the clinical trial process), and finally some blame the slowness of the FDA.

researchers now have identified 38 types of leukemia and 51 types of lymphoma, whereas 60 years ago, they only knew of five types total (Aspinall and Hamerash 2007).

A number of studies show that most drugs that are prescribed in the U.S. today are effective in less than 60% of the treated patients, leading to significant waste in treatments and saving fewer lives. Pricing pressures and safety concerns are increasing the pressure and interest in personalized medicine. This goes against the pharmaceutical industry's blockbuster-drug model, in which billion-dollar drugs are developed for a large population and are effective for the majority of patients but not all of them. However, many predict that this model of developing drugs is losing momentum as the number of drugs approved by the FDA has steadily declined, even in the face of increased spending on R&D. This trend will have a profound effect on the competitive landscape, creating greater interest and potential markets for smaller and medium-size companies that are developing drugs for smaller subpopulations.

Biosimilars/Biobetters: The other critical difference between biotech drugs and pharmaceuticals is the ability to create generic drugs from the original. Small molecule drugs (like Pfizer's Lipitor [which treats cholesterol], the best-selling drug in the world [$13 billion annually]) are easily copied because they are chemically based, and a generic drug company can prove it has made an exact copy of the drug. Once a drug like Lipitor comes off the market (2012), generic companies will be able to make the drug and sell it for perhaps two-thirds of its current cost initially and for less over time. This is not the case for a biologic drug. Large molecules are hard to replicate since they are coming from living molecules. In fact, the term "biosimilars" is used instead of generics because one cannot prove that an imitation drug is identical to the original compound of a biotech drug. They are not "interchangeable" in the way that chemically based drugs are. The FDA to date has not allowed biosimilars to be sold in the U.S. market (though Europe has approved some). A bill has recently been introduced in the U.S. that outlines a pathway for allowing biosimilars to be sold. Another trend, "biobetters," also creates a challenge for biopharma companies. Rather than making a biosimilar, which attempts to replicate a particular biotech drug, biobetters try to improve upon a drug, altering it slightly so that it

is more effective in treating the ailment. The drug may improve treatment only marginally, but it is enough to make the original drug obsolete.

Integrity of the Supply Chain: Given some high profile and fatal situations that have occurred in recent years due to the contamination of biopharma supply chains, regulators are becoming more stringent about holding companies responsible for the quality and safety of their supply chains and have recently issued guidance on the subject. The complexity of the supply chain, the number of environmentally sensitive products, and the increasing number of sophisticated counterfeiters of drugs has made this a topic of increasing focus and concern. For a biotech company, transparency along the supply chain can be challenging when a drug has up to 90 separate raw materials in it. The Heparin crisis of 2008, in which the supply chain was contaminated in China and resulted in 100 deaths, highlights the enormous damage such a problem can cause a company, as well as public health at large.

Globalization: Big pharma and biotech companies have been focused on lowering drug development costs to compete, but as the industry becomes more global, the real opportunity lies in developing products to suit emerging markets, most likely partnering with local companies. Most biotech companies to date have had a "two-market" strategy — North America and Europe. But they will need to go to other markets and create multi-divisional structures that can tap into the growing market in emerging countries. [8] The biopharma market in "pharmamerging" countries including Brazil, India, South Korea, Mexico, Turkey, and Russia is growing at 14-15% and represents approximately $110 billion.[9] Few companies will be able to ignore these growth markets.

These trends present significant challenges but also great opportunities for the biopharma industry going forward. For many years, supporters of the industry have said that its heyday is just around the corner. While the size of the industry is relatively small compared to other industries (under 500,000 FTEs worldwide and revenues of about $80

[8] Discussion at the "The Future of Biomanufacturing" Summit, MIT CBI, February 3, 2009.
[9] Charles Cooney presentation, at MIT's Biomanufacturing Conference, March 11, 2009.

billion), the growing global demand for biotech products is expected to increase as the world's population grows in size and continues to age overall (Herman et al. 2008).

2.5. The Drug Development Process

The drug development process, as explained earlier, is a long and expensive process, wrought with high risks and uncertainty. The following provides a simple overview of the various steps in the process:

Figure 2.1 The Drug Development Process

Research and Discovery. The first step in developing an effective drug is to find the particular entity that provides a point for intervening in a disease process. This could be through a particular protein or gene or a biochemical pathway. The research team, made up of molecular biologists, cell biologists, biochemists, and molecular geneticists, are all searching for a place in the process of a disease's development in which the introduction of a drug could inhibit its growth. The research team tries to identify specific genes that are involved in the disease. Once they have a number of drug targets (target identification), protein chemists attempt to synthesize and characterize the target proteins and find those that will be receptive to a drug intervention. The potential drug molecule must bind to the target, among other things, to be a successful "hit."

Once the team has narrowed its focus to one target, it then begins "target validation," making sure there is a statistical relationship between the presence of this protein and the disease the team is trying to address. If the target is validated, the chemistry team then works to find the potential molecule or drug that would inhibit the protein in question. The team comes up with candidate compounds and uses high throughput screening to see

how the compounds affect the target. Tens of thousands of molecules are tested at this stage and only those that "hit" are considered. This "lead identification" process generates a number of potential molecules — drug candidates — that are then tested to find the one with the best properties to fit to the target and keep their structure. This is the "lead optimization" process. Once the team settles on one compound, it brings it into the preclinical development stage where teams from both research and manufacturing start to work with the compound. At this stage, there is a 1 in 5,000 chance that the molecule will be commercially produced.

Preclinical Development. Once the research and discovery team identify a compound they believe has potential, the drug goes through a series of tests before it can be submitted to the FDA for approval to be tested in humans. The drug candidate must be tested for quality, safety, and efficacy. Pharmacological and toxicological tests take place both in the lab (*in vitro*) and *in vivo* in animals (primarily toxicity studies). If the compound passes these tests and proves to be safe and effective in animals, then the company files an IND (investigational new drug application) to receive approval to test the drugs in humans and commence clinical trials. The FDA will inform the company of its ruling within 30 days. It is at this point in time that the company also usually files a patent and the 20-year patent clock starts to tick. Preclinical studies can take up to three years or more and cost between $10 to 30 million.

Clinical trials. Clinical trials test the safety and efficacy of new drug candidates. They are divided into three consecutive phases, each emphasizing a different aspect of the testing.

Table 2.2 Clinical Trial Phases

Phase	Evaluation Undertaken	Ave. No. of Yrs
I	Safety testing in healthy human volunteers (20-80)	1
II	Efficacy and safety testing in small number of patients (100-300)	2
III	Large-scale efficacy and safety testing in larger no. of patients (1000-3000)	3

Phase I studies test a drug's safety in a small number of volunteers. If the drug passes this test, then it moves into Phase II, which also tests safety as well as the effectiveness of the drug at different doses. A control group is created during this phase, which only takes a

placebo. Phase II-b studies are often conducted to further test the drug at different dosages. During these two phases, the manufacturing team is figuring out how to make the drug cost-effective and in increasing amounts. If the drug proves effective at a certain dosage in Phase II, is able to be manufactured at a reasonable cost, and the competitive landscape for the drug is promising for the company, then the drug moves into Phase III. Hundreds and thousands of patients are used in Phase III clinical trials that take place in multiple locations and follow patients for a longer period of time.

Once clinical trials are completed, all of the information about the trials are compiled in a dossier and submitted to the FDA as part of a Biologics License Application (BLA). The FDA takes approximately one year to render a judgment on a drug candidate. Clinical trials can cost approximately $300 to $400 million.

Commercialization. If the drug is approved, it is registered with the FDA, and the product is launched. This marks the commercialization stage in which the drug is produced at a commercial scale at a facility that has been preapproved by the FDA. The company's sales and marketing team aggressively tries to sell the drug to doctors and patients. Commercialization and launch of the drug can cost between $300 to $400 million.

This process is very well established, and while different companies may organize their teams slightly differently or differ on what they keep in-house or outsource, the protocol for developing a drug is highly regulated. There is significant transparency within the industry as to how drugs candidates are proceeding through the various stages. Particularly for publicly traded companies, drug pipelines are tracked closely to determine the company's future prospects.

2.6. Regulation and Intellectual Property in Biotechnology

Regulation: For obvious reasons of public health and safety, the biopharma industry is highly regulated. The FDA regulates food, medical devices, drugs, cosmetics, and toiletries, whose total annual value in the marketplace is approximately $1 trillion. It does this with a budget of approximately $1 billion. Two centers at the FDA handle all

biopharma drug approval and regulation, including the inspection and regulation of manufacturing facilities. These two centers are the Center for Drug Evaluation and Research (CDER), which oversees pharmaceuticals, and the Center for Biologics Evaluation and Research (CBER), which oversees the regulation of biologics. The core responsibilities of the FDA with respect to drugs are:

- Reviewing preclinical data on drug candidates to determine whether a drug is safe to begin clinical trials
- Protecting the rights of patients participating in clinical trials
- Assessing preclinical and clinical trial data to decide whether a drug should be approved
- Inspecting manufacturing operations to ensure they follow "good manufacturing practice" (GMP)

A company may have a number of interactions with the FDA as it shepherds a drug toward approval — the IND application at the preclinical phase, inspection of manufacturing facilities (for Current Good Manufacturing Practices [cGMP] approval) where drugs will be made for clinical trials or for commercial production (inspected every two years), and the BLA, a biologics license application once trials are completed and the company is looking for FDA approval for commercial production of the drug.

The European regulatory framework is consolidated for all European countries under the European Medicines Agency (EMEA), based in London. The EMEA was created in 1995 to help streamline the drug approval process in Europe. In Japan, the largest pharmaceutical market in the world on a per capita basis, the Pharmaceutical Affairs Bureau (PAB, a division of the Ministry of Health and Welfare), regulates the drug market. Unlike the other agencies, the PAB sets an official price for a drug. Significant efforts have been made to harmonize these different regulatory bodies, and they are more similar than dissimilar. The International Conference on Harmonization (ICH) is an international body based in Geneva that assembles experts from all three regions in the world to create more seamless processes for drug registration in these regions. While this

is an important body, only seven countries have signed on to the ICH, and it is renowned for taking a very long time to rule on matters. Every country has its equivalent of these bodies; however, in terms of approving drugs, they usually take their lead from the three main agencies in the world because that is where companies are seeking approval first because of the large markets. Having said this, one biomanufacturing executive expressed frustration with the process: "The ICH provides guidelines, but they are only guidelines. Each country can decide to slightly modify how they want to sell a particular drug in their country."

Intellectual Property. It is important to understand the basic dynamics of how companies protect their intellectual property since it is a critical driver in the business and economics of biotech drugs. The rise in the use of intellectual property rights (IPRs) in biotech has led to a vociferous debate as to whether IPRs are actually helping advance research and the social benefits that should be derived from that research, or hindering it because of the effects of "privatizing" the scientific discoveries (Hermans, et al, 2008). Once a company develops a lead drug candidate in the R&D phase that they believe holds great promise and is original work, the company will file a patent with the U.S. Patent and Trademark Office (USPTO). Once the patent is filed and granted, the company has 20 years of protection from anyone using the patented innovation without the company's approval. Given the long timeline to develop a drug, this can leave a company with anywhere from five to 12 years of a monopoly once the drug is on the market. Once the patent is filed, it is made public 18 months later.

To develop a drug, a company may use multiple patents that could be held by the company itself, other companies, or a university. A patent might protect a product or a process — the process one uses to make a protein, for example. A company that wants to use another company's or entity's patent will license it from that company. They will pay a licensing fee (upfront) and possibly more money based on milestones in the development of the drug. If the drug actually makes it to the market, typically a company will charge royalties for use of its patent, which can run from between a quarter of a percent to 5% of the final drug profits depending on the importance of the patent. If the

patent is an important one and the company has the resources, it will apply for patents in a number of other countries (obtaining patents in all of the European countries costs a company between $150,000 to $200,000).[10] Some companies might choose to make a drug in a country where the product or process is not patented in order to avoid paying the licensing fees or royalties. However, this strategy will become problematic if it wants to sell its final product in the U.S. The U.S., as well as a few other countries, has laws prohibiting the sale of a product in the country if it is protected by U.S. patent law that has not been made in a country that also protects the patent. Thus, a company cannot make a drug elsewhere to avoid patents and then re-import it into the U.S.

2.7 Discussion

This brief introduction has provided an overview of the biotech industry, the drug development process, and the business of commercializing drug discoveries. It is important to understand how biotech differs from most industries because of the enormous costs involved, high risks of uncertainty and failure, and significant regulation. While introducing an extraordinary range of possibilities for addressing human diseases, biotech has also created a more complex and multifaceted drug development process. This process is more integrated than before, introducing new techniques and disciplines that must be called upon to help develop effective drugs.

At the same time, biotech has not changed the business of drug making. It is still extremely time-consuming and expensive (8 to 10 years and over $1 billion to bring a drug to the market) and is fraught with high risk and uncertainty. A company will spend almost half of its patent time of 20 years developing and commercializing a drug. Despite these challenges, the industry is growing in the double digits, twice the rate of chemically based pharmaceutical drugs, and big pharma companies see smaller biotech companies as a critical part of their future (which explains the many acquisitions recently). A number of trends will shape the biopharma industry going forward, including the pressure on prices caused by a desire to control health care costs in places like the U.S., and the introduction of biosimilars, pressure on drug R&D productivity, personalized medicine,

[10] Biotech patent lawyer, interview by author, January 6, 2009.

ensuring the integrity of the supply chain, and the increasingly global market for biopharma drugs.

Because of the significant R&D requirements, public safety concerns, the highly regulatory nature of the industry, and the pressure to innovate to both create new discoveries and reduce costs, biotech has grown in high-wage and higher cost locations primarily in North America and Europe. But the combination of a maturing of some of the biomanufacturing processes, growing talent around the world, and emerging markets is leading to an expansion of the biotech footprint to more countries. The "rise of the rest" has significant implications for places like Massachusetts and California, which have been home to the industry for 30 years. While these places are still home to innovative biomanufacturing, they are becoming less likely places to build commercial facilities for established new drugs. The unique dynamics of the industry listed above will be referred to repeatedly in the subsequent chapters as the dynamics of biomanufacturing and the locations of the industry are explored.

Chapter 3

Introduction to Biomanufacturing

With some general background on the biotechnology industry, I now turn to the subject of this research — biomanufacturing. But before examining the dynamics of the industry and presenting findings from the research, I will outline the research design and methodology used to collect and analyse data on the industry.

3.1 Research Design and Methodology

This research engages in "grounded"-theory building, which is the process of building theory inductively through the qualitative analysis of data (Glaser and Strauss 1968; Strauss and Corbin 1990). Grounded theory is a common research method in the social sciences and uses empirical findings to develop testable and valid theories about social phenomena. In many areas of the social sciences, "mixed methods" or hybrid methods of research are becoming more accepted, combining qualitative and quantitative methods to get at the answer to a research question. Particularly in fields of research that are not well understood or where not a great deal of research exists, adding qualitative data to quantitative analysis can shed light on the meaning of the data. In the field of industry studies, qualitative methods are a particularly useful form of theory-building because of the challenge of finding quantifiable data regarding firm-level behavior.

In the case of this research, a data set provides descriptive statistics about the geography of the biomanufacturing industry over a period of 11 years. Qualitative research in the form of semi-structured interviews, focus groups, and documentation research provides the context in which to interpret the quantitative analysis. This research analyzes one industry — biomanufacturing — and uses the firm as the unit of analysis to understand the location of biomanufacturing investment decisions. Once a global picture is presented, I then provide a case study of Massachusetts to determine how a technologically advanced region within the U.S. competes in a global advanced manufacturing industry. Unlike comparative case studies where variables are analyzed

across cases, within-case analysis we examine the causal path in one case to provide in-depth understanding of the factors that influence our "dependent variable," in this case, the location of biomanufacturing.

3.1.1 Quantitative Data Collection and Analysis

A data set on global mammalian-based capacity was provided by BioProcess Technology Consultants (BPTC), a biopharmaceutical consulting firm based in Acton, Massachusetts. BPTC are experts in process and product development, manufacturing, as well as quality and regulatory affairs for biologic products. BPTC works with all of the major biopharma firms as well as midsize companies in the US and abroad. The company also publishes an annual industry report outlining global supply and demand for biomanufacturing as well as trends in the industry[11]. On the supply side, BPTC tracks all public announcements regarding global biomanufacturing capacity, both when additional capacity is created or when current capacity comes off line. They have collected and tracked this information since 2002, their baseline, and project global capacity volumes through 2013. On the demand side, they also maintain a demand database, which tracks biological recombinant drugs that have been approved and those currently in clinical trials. Through both of these databases, BPTC is able to predict demand for both microbial and mammalian bioreactor capacity year-by-year and five years into the future. BPTC cautions that the high level of risk and uncertainty in the drug development process makes their predictions on the demand side more unreliable the more years one goes beyond the current year's demand. The supply side, however, is highly robust, not only based on the tracking of announcements but also because of the firm's deep knowledge of the companies in the field and the relatively few new investments that are made year to year. If there is a weakness in the data, BPTC believes it is in Asia (primarily China), where some small facilities, primarily making biosimilars, are located.

The data set provides the following information about new bioreactor capacity: company type (whether a product company or a contract manufacturing organization [CMO]);

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[11] Ransohorr TC, et al. (Bioprocess Technology Consultants Inc., Acton MA) "Cell culture manufacturing capacity: trends and outlook throught 2013". Springfield (VA): *PharmSource Information Services*; December, 2008.

location of new or additional investment; whether it is a commercial or clinical facility; whether the facility is online, in construction, in planning, or in the validation stage; the year the facility went into operation (or year estimated to be online); the number and size of reactors (in liters); and finally total volume in thousands of liters. The data set also identifies the type of processing used at the facility: batch-fed, perfusion, roller bottle, or disposable. Because of the difficulty of tracking the volume of the latter two processes, these were not included in the analysis. However, these represent a small fraction of the total volume globally. Fed-batch is the most commonly used method of cell culture (where the medium in a reactor is fixed) and represents 89% of the total volume tracked in the data set. The perfusion method in cell culture is less commonly used and differs from fed-batch as the volume of medium used in the cell culture process exceeds the physical reactor size. Medium is added into the reactor and removed from the culture at an equivalent rate. Thus, because of this "increase" in reactor capacity, one must apply a multiplier of five to equate the perfusion reactor volumes to fed-batch. (This multiplier was confirmed by several industry experts.) Perfusion processes represent just over 10% of the volume tracked in the data set.

The data set is comprised of investments made by 96 companies — of which 63 are CMOs — between the years of 2002 and projected to 2013. There are 238 separate data points, and each represents a company's investment in added (almost all of the time) capacity, either to a new facility or to an existing one. The investments are made in 21 different countries and in 117 different cities.

The information provided in the data set by BPTC was gathered from public sources including trade magazines, corporate documents and newspapers. Because of the transparency about drug pipelines and drug production in the biopharma industry, companies are quite forthright about their production processes and investments. This is particularly important to ensure a comfort level about the company's ability to deliver a drug to the market on time and safely. With a timeline for building commercial facilities somewhere between four and seven years, companies usually announce plans to build years in advance to forecast when their capacity will be online and available. These plans

can always be put on hold, but they give as robust an account as possible of planned investments.

In order to test some of my hypotheses about the importance of proximity to R&D activities, as well as the size and stage of development of the company, I augmented the data set and added a number of other variables including parent companies; location of company headquarters; company R&D centers; the city, state, and country if appropriate of the biomanufacturing investment; and the distance between clinical and commercial facilities and R&D centers. All of the information I collected was publicly available and collected primarily from annual reports or trade publications. This additional information helped illuminate patterns in the data (for example, where clinical and commercial facilities are located relative to headquarters) as well as outliers.

Descriptive statistics were performed using pivot tables in an Excel database. In this analysis, I cut the data in multiple ways, including geographically (continent, country, state); by size in terms of facility and volume (clinical, commercial, greater than 5KL, 50KL); by type of company (product companies vs. CMOs); and by number of facilities. The data set was updated twice in 2008 with new information from BPTC such that the data is considered complete for 2008. The BPTC database shows no new additions in 2009. This squares with my analysis which shows no new additional capacity added as of 2010.

3.1.2 Qualitative Data Collection and Analysis

In addition to the database, I also conducted semi-structured interviews to provide the context and interpretation of the quantitative data. Between the winter of 2007-8 through the winter of 2008-9, I conducted 47 interviews with 28 senior executives in 20 companies, as well as with three expert consultants and two lawyers in the field. I had multiple interviews with several people. These interviews took place primarily in Massachusetts but were also conducted in Research Triangle Park, North Carolina, and in Copenhagen, Denmark. I met with the heads of biomanufacturing or engineering and then often followed up with an interview with the plant manager or head of facilities.

Initial access to biomanufacturing experts in the area was made possible through introductions provided by MIT contacts. These interviews created a "snowball effect," in which each interviewee offered the name of one or two other people to interview. Because the industry is fairly tight and there is a lot of moving between firms, a high percentage of those interviewed knew each other, at least those in the Massachusetts region. The companies break down into nine big or medium-size pharma companies, four large biotech companies, and seven small-to-medium-size biotech companies.

The interviews covered a range of topics, including the background of the person I was interviewing, the history of the company and its biomanufacturing capabilities, the reasons for the location of the company's facilities, and the interface between the various teams involved in manufacturing from pilot to commercial (if applicable). I also focused many questions on new technologies and how they are changing the use and configuration of the plants, where innovation in the process occurs, the team structure, and future ideas about the facility of the future and how drug substance is produced.

In addition to face-to-face interviews, I held three focus groups, sponsored jointly by MIT's Industrial Performance Center and the Massachusetts Technology Collaborative. The meetings were held in February and November of 2008 and May of 2009. I facilitated the meetings, and my research served as the basis for discussion. These roundtable discussions were particularly fruitful because they provided a forum for industry leaders to respond to my research and to one another, in some cases challenging each other's assumptions. The differences in points of view on current trends, the direction the industry is heading in, and the competitive position of Massachusetts helped highlight some of the most interesting questions about biomanufacturing.

All of the first interviews with a particular executive were transcribed, as were two of the three focus group meetings. Notes were taken and later transcribed for second and third interviews. These were usually held to help clarify a point made in the first interview. I coded the interviews across a range of topics including proximity to R&D, regulation, role of pharma in biotech, trends in the industry, product life cycle, labor, new

technologies, innovation, future scenarios, and economic development. Overall, this process yielded a very rich set of data to analyze and interpret. The process of using focus groups to provide feedback to the data was also extremely valuable for challenging my work and assumptions.

3.2 Background on Biomanufacturing

Murphy's Law as Applied to Biologics Production

"Under the most rigorously controlled conditions of pressure, temperature, volume, humidity and other variables, the organism will do as it damn well pleases."

The birth of biopharmaceuticals represented the birth of the biomanufacturing industry. Big pharma companies and growing biotech companies built their first facilities as biotech drugs became more promising and ultimately gained FDA approval: insulin in 1982 (Eli Lilly licensed from Genentech and manufactured in Indiana and Liverpool, England); human growth hormone in 1985 (Genentech, made in California and slurped up by Roger Clemmons); and interferon in 1991 (Schering Plough, made in New Jersey). Like biotech technology itself, this was completely new territory. While drawing on the traditional fields of microbiology, biochemistry, and chemical engineering, new and more specialized fields emerged in the 1970s such as molecular biology and biochemical engineering. Biomanufacturing represented the cutting edge of research and attracted the best and the brightest to try and tackle many of the challenges presented by this new field.

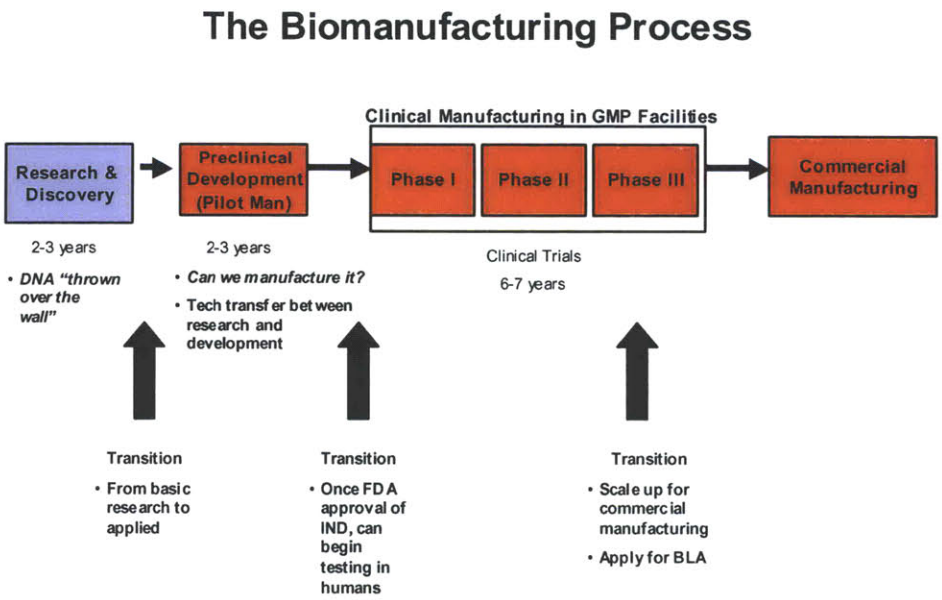
The biomanufacturing process is complex and has been referred to more as an "art rather than a science," though it is becoming more science than art as time goes on (UBS 2003)."There was no knowledge out there on how to do this [in the late 1980s]. We had to figure it out ourselves." (HF) Growing the drugs from living cells and bringing the product to scale for human consumption presents significant challenges. While some of these challenges have been largely tackled (expression systems and yields), many of the

challenges of 25 years ago are still challenging scientists today (cell viability, purification). Nevertheless, an enormous amount of progress has been made in the field as companies push for greater innovation to save time and money, and the regulatory agencies have become more of a partner rather than an impediment to this process.

3.3 The Biomanufacturing Process

Like in pharmaceutical manufacturing, there are two types of drug manufacturing, often referred to as primary and secondary manufacturing. Primary manufacturing refers to the making of the drug substance or "bulk production" (known as Active Pharmaceutical Ingredient [API] in pharmaceuticals). This is the most complicated part of the manufacturing process. Secondary manufacturing refers to the making of the drug product (i.e., how the substance is formulated for human consumption, either as a pill, a liquid form, an injection, etc.). In this stage, the drug is produced in its final dosage form and then moves on to the fill, finish, and packaging stage. The secondary stage is the more routine and mobile of the two manufacturing types. The following provides a basic outline of the biomanufacturing process for primary manufacturing (i.e., the making of drug substance for monoclonal antibodies):

Figure 3.1



Preclinical Development (Pilot Manufacturing)

As stated earlier, the preclinical development stage is concerned with developing a cell line that is safe and effective and can be used in humans. Research develops a number of stable cell lines that are next handed to the process development (PD) team to test and obtain the one that has the highest "expression," that is, the one that produces or expresses the particular protein of interest most robustly in a cell-based system.[12] The types of cells used, such as CHO, are combined with the protein therapy to produce an expression cell line. This cell line has to be "stable" (i.e., hold the DNA [genetic stability] for the antibody and produce the drug at a consistent yield). Once the protein is expressed in the cell, it is secreted into the culture medium and then recovered later following the bioproduction run. Once a stable cell line is created and characterized, the cell line is expanded, and a master cell bank is created. These cells are preserved for indefinite periods of time by freezing them in liquid nitrogen.

Upstream Processing –Fermentation

Upstream processing technically begins once some cells are thawed and are used to grow laboratory-scale starter cultures of the producer cell line (five-liter scale). This is then used in tens of liters of media in a small bioreactor and subsequently used in several thousand liters of media in a large-scale bioreactor.[13] The conditions to promote optimal

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[12] This discussion focuses on mammalian cell-based expression systems, but bacteria such as *E. coli* is used as well to produce proteins. However, it is usually only used on a pilot scale. While microbial-based systems are lower cost because bacteria is easy to grow and does not need an expensive culture medium and is easy to scale up, most biopharmaceuticals use cultured mammalian cells. This is based on one primary drawback of microbial production: bacteria cannot produce proteins that are modified with sugars (glycosylated). This prevents bacteria being used to produce full-length antibodies or proteins. A number of products on the market are produced in bacterial expression systems (Neupogen, Intron A, and Nutropin), but these are in the minority. This is not to suggest that animal cell-based systems are easy to work with. To the contrary, they are highly complex, grow slowly, and are vulnerable to physical damage while being cultivated. See Walsh, 2007.

[13] Multiple types of processing exist for cell culture manufacturing, but the two primary processes used to seed a bioreactor are batch fermentation and continuous perfusion. The former requires that the starter batch of cells are continuously grown and split into multiple batches that seed the bioreactor at a high density. The latter introduces new growth medium throughout the process, rather than relying solely on the starter batch of cells. Batch fermentation is used more by biomanufacturers because it results in a density of cells that can be harvested more quickly. To equate the bioreactor volumes used in batch fermentation and perfusion, a multiplier of 5 is used with perfusion volumes (i.e., 20KL of perfusion would be equivalent to 100K batch-fed).

cell growth are developed during the preclinical product development stage. The process is then highly repetitive as production is increased. It takes approximately 30 days in the "seed" reactor once the tanks have been "inoculated" with the culture to generate any product. It takes an additional 10 to 14 days to harvest the cells in a terminal batch (i.e., the final product).

The scaling up of the cell lines is a highly complicated process that brings many skills to bear:

> "You're talking live cells here...every cell has the same metabolism as we do ...You need to make sure that each is getting enough oxygen and breathing enough. You need to make sure that enough solutes are in there. How does it scale up? So there's chemistry, biology, physics, engineering. And they are all coming together. So this move, transition, is hard."

Once the cells are harvested, they then move into the downstream phase.

Downstream Processing –Purification

At this point, the cells are harvested and separated from the culture medium by centrifugation and/or filtration. The protein now must be purified to homogeneity. Purification is usually achieved using column chromatography. Column chromatography refers to "the separation of different protein types from each other." A number of different chromatographic techniques have been developed to separate the proteins based on their different "fingerprints" (Walsh 2007, 140).This process removes unwanted proteins and other potential contaminants and isolates the protein of interest on the column. After several additional purification steps, the protein is ready. High-resolution chromatography will yield a protein that is 98 to 99% pure. This is after losing 25 to 50% of the initial starting material in the process. The purification protocol developed in the preclinical phase of development is highly scrutinized because it is at this stage that the protocols are developed for subsequent clinical manufacturing. Purification takes only about a week, but it represents the bulk of the cost of the entire production process, approximately 50 to 60%. While progress has been made in harvesting higher and higher yields (i.e., product per liter [increasing "titers"] in the upstream process), little progress

has been made in the downstream phase, and purification has not seen similar increases in output.

The Interaction Between Process Development and Manufacturing

The PD team conducts the preclinical development work, scaling up cells first in five-liter beakers and then up to possibly 200-liter reactors. It is during this testing that interactions between the PD team and the manufacturing team will ideally begin. In recent years, companies have placed a greater emphasis on creating a more seamless exchange between the development and manufacturing teams. While the PD team is focused on process and manufacturing is focused on getting operational (i.e., producing quality batches), you need a team "that marries them together…you want a team that really understands the science and the manufacturing," said one plant manager. This bridge is built by what some companies call the manufacturing science teams (MS; also could be called manufacturing science and technology or technical operations). The MS team asks the PD team questions like "What does this [the cell line] look like? Can we scale it up?" What it learns in the early stages of development will pay off greatly in the scaling up of the product.

The PD team may take approximately six months to complete their testing, but half-way through the stage, the teams are often already talking and interacting closely (face-to-face) to ensure that manufacturing is prepared to work with the material they will be handed. The tech transfer between these two teams "is the most important part of the [manufacturing] process, " said one plant manager. In most cases, these teams are working in the same location, potentially with MS people "on the bench" with the PD team in the same lab. But even in cases where the PD team is in one city and the MS team in another, the MS team will travel to the PD location and can spend up to several months working with them to ensure a smooth tech transfer to the manufacturing part of the process. "It certainly helps a lot [to be in the same location] but it's not critical," said one MS executive. This scenario doesn't happen as much as it should, according to some experts in the field. But it is here that significant time and money can be saved as the two teams work collaboratively. The potential cost savings in improving the production

process are enormous. One company cut its preclinical development time from 12 months to six because of these interactions. "This is where the knowledge is mainly held."

> " We don't want walls [between process development and manufacturing]. We're not throwing stones over walls. How accepting would you be if development folks were saying 'This is gonna make your life so much easier,' and they throw it (the cell line) over the wall, and you have no idea what it's gonna do. You have to change all your documents, you have to retrain everyone on it, and you have no idea what's going to happen. There's no buy-in there. *Now*, manufacturing science are *in* the lab, they understand the science, they're part of the decision-making process. So new technologies are so much more accepted in manufacturing because they have a say in what technologies are chosen and why."
>
> "It used to be linear, from PD to manufacturing, but it's not anymore. The whole paradigm has changed because ...[we] are getting faster and faster into the clinics...and this is more efficient. It's so important for everybody to talk to each other because everybody's needs are different. PD might think, 'Oh it's great, it's workable,' but manufacturing might say operationally, 'Absolutely not, I can't do that.'"

Once PD is satisfied with the cell line, it then hands it off to the manufacturing team, which begins the upstream and downstream processing again to produce the product at scale. This begins once a vial of the working cell bank system is taken from storage and thawed. This next phase of upstream and downstream processing can take from 9 to 18 months before production of clinical material. It is here that the team will try and "optimize" production, learning everything about the material and how best to scale it up. "You want to get your optimization tests done early in the process because it gets very expensive to run engineering runs later on." At this point, the drug substance is in the hands of the manufacturing team.

Clinical Manufacturing: Phase I and II

Before beginning clinical trials, the company must file an "IND," an investigational new drug application with the FDA. But before applying for an IND, the drug must be made successfully in a Current Good Manufacturing Practices (cGMP)-approved clinical facility for six months to ensure stability. GMP facilities are those that have been approved by the FDA. This approval is the primary difference between pilot

manufacturing and clinical manufacturing. These two types of facilities will most likely be in the same location, but they do not have to be. Based on the many batches that have been run in development at five-liter and 200-liter scales, manufacturing will begin to scale up production to produce enough drug substance to complete Phase I, Phase IIa, and possibly IIb clinical trials. The development team, the MS team, and the manufacturing team are all "on the floor during execution" to troubleshoot any unforeseen variations that arise during the scale up.

Phase III and Commercial Manufacturing

During Phase IIb, the company will decide whether to move into production for Phase III clinical trials. This is based on the success of the drug in previous clinical trials and the overall market for the drug. Phase III production is at a much greater scale than previous clinical trials and at times can be at the same scale as commercial production would require. As a result, it will take place at a facility where the company, assuming no problems in the final clinical trials, will plan to make the drug commercially. Phase III production could be just another campaign similar to the previous ones but at a larger scale (a "resupply campaign"), or if the company believes it is ready to begin commercial production, it will begin process validation (in other words, testing all aspects of the commercial production process for submission to the FDA). Once the company has conducted the testing it needs for FDA approval, it files a Biologics License Application (BLA). The FDA will take approximately a year to render judgment on the drug. Before a facility can commercially manufacture a product, it must be approved with a preapproval inspection (PIA) from the FDA.

The processes used to produce material in clinical trials should not deviate greatly from those used for final-scale commercial manufacturing, particularly in Phase III trials. "You want Phase III as close to verbatim as possible; you can't afford to do a lot of optimization… the process may not be perfect, but enough is known after Phase I, II, and III that you get a predictable standard yield." Changes could potentially alter final product characteristics. This increases the importance of the early development work and "getting it right" in preclinical trials. Commercial manufacturing commences once a drug has received FDA approval. A GMP commercial facility can be from 2K- to 25K-liter

bioreactors. The manufacturing science and manufacturing teams are both involved, as well as the process development teams, though this is a more recent trend. Companies are looking for high success rates, which can be defined narrowly around how many of their batches were successfully run or more broadly to include getting the drug successfully to the patient. By the time of commercial production, success rates are very high, above 95%

Final Analysis and Fill/Finish

In the final phase, the purified antibody is tested through a series of analytical tests that ensure the integrity and consistency of the product — quality control (QC) tests. This includes analysis of identity, posttranslational modifications, product purities and impurities, and quantity and potency (efficacy). If the product passes these tests, it can then be packaged in the fill/finish stage. Whether the product will be sold in liquid or powder form is often determined by how stable a protein is in solution. Before being shipped, vials must be quarantined and retested for stability and product consistency. All of these tests, as well as those taken throughout the process, must be documented, and the information must be submitted to the FDA as part of the approval process.

3.4 The Business of Biomanufacturing

While on a cost basis, manufacturing represents a relatively small part of the entire biotech drug development process (15 to 20% of the cost of sales), it is a critical part of the process for a number of reasons that often compel companies to want to manufacture themselves. Safety issues are paramount. If the manufacturing process is not safe and secure, it can present enormous dangers to the public with significant cost implications for the company. An example like Baxter Pharmaceutical's Heparin crisis in 2008 presents the worst-case scenario, in which 100 people died from contamination of the drug from a Chinese manufacturer. The product was recalled worldwide (Laurencin and Nair 2008). But even in less dire situations, the cost in terms of time and money of poor manufacturing processes can add up. As outlined earlier, developing a batch of product for commercial production can take several months. If a virus spreads on day 50 of a 120-

day process, then the process must start again, and you lose those 50 days plus the additional 30 it takes to seed the reactor. Every hour can cost as much as $40K.[14]

Second, getting the manufacturing process working effectively is essential to getting needed drugs to patients and maximizing the benefits of a patent. There are significant opportunity costs that arise when a production process does not meet deadlines or overshoots or undershoots its capacity needs. It is well understood that the cost of being "short" (or not having enough manufacturing capacity) is far greater than the cost of being long (too much capacity).[15] It can also pose challenges for patients if they cannot get life-saving drugs. According to one executive, having two months of inventory of a particular drug on hand is "troublesome."

Finally, manufacturing presents a critical opportunity for a company to save time and money in the drug development process if it can improve its cycle times. Companies are hard-pressed to cut costs during R&D or clinical trials, where in the latter case, once they've started on a path, it is hard to deviate from it. But in manufacturing, any innovations that lead to a shorter time frame can represent hundreds of thousands of dollars. " Where we gain margin is in manufacturing. Cutting it in half over time is all profit to us. If you really want to increase margins, you need to be making the product yourself." This, in the end, could be the biggest driver for companies to keep manufacturing in-house. "If you can squeeze one more batch a year out of the process, then you are doing great. It is a constant game to lower costs." But this is not your average cost-cutting game, where savings are gained in trying to find cheaper inputs. Cost-cutting arises from being more innovative and developing new technologies:

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[14] Figured provided by executive at a large biotechnology company, interview by author, November 29, 2007.

[15] In a hypothetical analysis, T. Ransohoff estimates the cost of inaccurate capacity planning for a typical oncology monoclonal antibody. In the case of being too long (50% underutilization of the facility), a company would have carrying costs of approximately $2 to 3 million a year. In the case of being short (50% under capacity), the loss of operating profit to the company could be $40 to $50 million a month. See Tom Ransohoff, "Considerations Impacting the Make v. Buy Decision," *American Pharmaceutical Outsourcing,* (March-April 2004), 4.

> "Instead of trying to figure out how to save a certain amount of money on sample tubes, we're gonna be trying to figure out, 'Is there an instrument we can install online that would eliminate the need for sample tubes?...the typical lean, cost-cutting guys who figure out how we can reduce the number of paper clips we're using — that's not our mentality."

And it's not just the ability to innovate with the process; it is also the ability to innovate with the product:

> "We want to learn how to make it ourselves. First there is the risk involved, but second, we learn more about our product. You can't expand your product and grow it if you don't know what it is about."

For all of these reasons, a company that can afford to manufacture its own product will most likely choose to do so. For those who become proficient at manufacturing, there are significant gains to be made in terms of time and money. It also can send a signal to the market that a company that perhaps is relatively new, or new to biologics, takes the business seriously and is in it for the long-term.

General Costs and Risks of Biomanufacturing

While the cost of producing drugs differs greatly, a general estimate of operating expenses for manufacturing breaks down as follows:[16]

Capital	30 to 40%
Materials	20 to 30%
Labor	30%
Utilities and Waste	5%

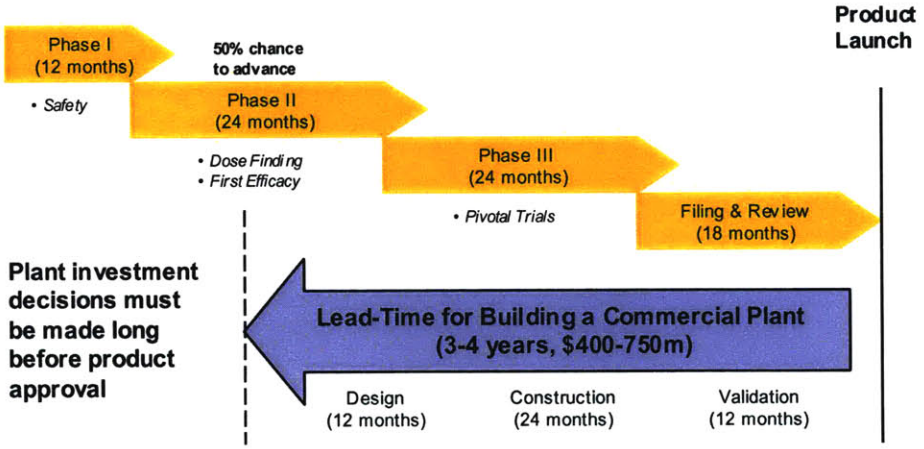
The major investment decision a company will make regarding its biomanufacturing is whether to build its own facility. The cost of building a commercial plant can run from $200 to $750 million, depending on the size. A rough benchmark in the industry is that construction costs run at approximately $4,000 per liter of installed bioreactor

[16] This applies to a facility producing monoclonal antibodies at 1000kg/yr. For smaller quantities, capital outlays would be greater. See Ransohoff, 2004.

capacity.[17] A pilot plant might be less than one tenth of this cost ($10 to $15 million). While the cost of a commercial facility is substantial, what is most challenging is the capital at risk for a company that builds a commercial facility. They take approximately four years to build, which means construction needs to begin while a company's leading drug candidate may only be in Phase II of clinical trials, with a 50% chance of being launched. Companies with sufficient scale and capital must determine whether their pipeline is promising enough to justify building their own plant or whether they should use a contract manufacturing organization (CMO) to make their product for them. Once built, a facility is rarely "mothballed"(abandoned because of the cost of building as well as the importance of receiving FDA approval for a facility).[18]

Figure 3.2

Cost and Timing of Building a Commercial Facility



Pilot manufacturing facilities require roughly half the time and are a tenth of the cost

Source: T. Ransohoff, 'Evaluating Strategic Options for Biomanufacturing", IBC Biopharma Manufacturing and Development Summit, December 2006

Raw materials are another significant expense. Unlike a pharmaceutical product that might have five ingredients, a biotech drug might have up to 90 different ingredients that

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[17] Tom Ransohoff, "The Rise of Biopharmaceutical Contract Manufacturing," *Biopharm International,* 20(11), 165 – 174 (2007).

[18] Because these facilities are costly and must meet FDA regulation, they are rarely completely abandoned by a company. Many commercial biomanufacturing facilities will be owned by several different companies over time or refitted to adapt to newer technologies. Centocor, for example, built its plant in New Jersey in 1987 and continues to produce biotech drugs in it today.

must be obtained from multiple sources. This is a costly endeavor, particularly as companies feel greater pressure to ensure the safety and integrity of their supply chain. Labor represents a relatively small part of the overall costs of the manufacturing process. With labor costs at 30% of the total cost of goods and overall manufacturing approximately 20% of the total cost of sales, then manufacturing labor represents only 6% of total sales. This fact plays into an important dimension in the cost structure of biomanufacturing — the role of economies of scale. As the scale of a facility increases, the cost of labor as a percentage of the cost of goods sold decreases, while costs skew upward for raw materials. The cost of labor can drop to as little as 2.5% of the total cost of goods sold. This becomes important as one analyzes firm behavior in building new facilities. Once a company has a blockbuster and needs to expand capacity, there is a good chance it will build a much larger facility. The costs of labor and infrastructure decrease relative to the costs of raw materials. Thus, there is little incentive for a company to seek out low-cost locations based on labor or infrastructure. As evidenced later on, tax policy begins to play a more significant role at this stage of a company's growth.

3.5 Contract Manufacturing

Another dimension to biomanufacturing that has not yet been discussed is the role of outsourcing and contract manufacturing organizations (CMOs). CMOs became more popular in the 1990s after the FDA Modernization Act (1997), which loosened regulatory procedures and allowed biopharma companies to use CMOs more easily.[19] Today, there are approximately 63 CMOs worldwide that produce clinical and commercial drug substances for almost all products. They hold approximately one-sixth of the total global

[19] Before the Modernization Act, the FDA required companies to submit two license applications for the commercialization of a new drug — a product license application (PLA) and an establishment license application (ELA), which, according to the FDA, had to be held by the same company. To hold an ELA, the company had to either do many of the manufacturing steps itself or be responsible for the clinical testing and the final manufacturing steps of the process. This made it difficult to outsource the manufacturing without giving up some control of the product. To make any changes to the process, the company had to submit a new license application. The complexity of the regulatory process, as well as the importance of the manufacturing process to developing a successful drug, led companies to develop in-house capacity. In 1997, the FDA created a single licence application, the Biologics License Application (BLA), which allowed companies to retain control of their product, even if they outsourced the manufacturing.

mammalian-based biomanufacturing capacity. As discussed earlier, the capital put at risk when building one's own commercial manufacturing facility is enormous, and just running manufacturing operations is an expensive proposition. Companies must justify why they want to make a drug themselves rather than outsource it to a third party (the "make or buy" decision). The stage of a company's development is a critical factor in determining this. Start-up companies tend to have expertise in research but little knowledge of the operations side. They have "all their eggs in one basket,"so to speak, with one drug candidate or a very small pipeline, and often they are under pressure to meet milestones to obtain additional funding. "What I care about in choosing a CMO is their track record," said the CEO of a start-up biotech company. " The larger, more established CMOs cost more because they often want some royalty, but you get more assurance. The smaller newer CMOs can cut costs and use new technology and often aren't looking for a royalty. But we can't afford to get this wrong. We'll go with the more established company."

As a company grows and possibly has multiple drug candidates in the pipeline, either approved or in Phase III trials, it might consider switching from a CMO to in-house manufacturing, in part for the ability to control the process and the timeline. But the risks are high. "The industry is just littered with people who've tried to build facilities and then nothing ever gets in it." Larger firms are more likely to turn to CMOs when they are capacity constrained, for fill/finish, or as they wait to see whether a drug will sustain sufficient demand over time. BMS followed the latter strategy for its biologic Orencia, using CMOs in South Korea and New Hampshire until the drug proved to have legs. The company then decided to build its own commercial facility in Massachusetts (coming on line in 2011). One of the large, established CMOs confirmed this pattern when outlining where its business comes from as a percentage of the biomanufacturing process: 30 to 40% at the point of cell line development, 30 to 40% between Phase 1 and Phase 111 of clinical trials, and approximately 20% from commercial manufacturing. Companies may also create close relationships with CMOs — like Genentech has with Lonza — such that the CMO becomes almost an extended arm of the company, and significant biomanufacturing R&D is shared between the companies.

There are a number of factors beyond company size and stage of development that impact a decision whether to make a product in-house or buy it (i.e., outsource the manufacturing to a CMO). These include:[20]

- *Feasibility:* Does a CMO meet the technology requirements, the scale, and have the capacity at the right time for the company?
- *Strategic Fit*: Is there a competitive advantage to developing the expertise in-house, particularly given what is in the company pipeline?
- *Risk Management and Assessment*: Has the company accounted for all of the risks associated with biomanufacturing such as product failure, delays in construction, and difficulties in the manufacturing process?
- *Financial Considerations:* If it manufactures, a company needs to determine whether its return on capital will be greater than its cost of capital. Given the amount of capital at risk when building one's own commercial facility, this type of analysis comes with significant discount rates.

The benefits of outsourcing (preserving capital, optimizing new technology, keeping up-to-date with FDA requirements) also come with challenges (lack of in-depth technical expertise, turnover of key personnel, extended or longer timelines). Some experts in the field predict CMOs will become more competitive over time. "Because CMOs are working on thinner margins, they tend to push harder on operational excellence. They may provide the best value over time." In conversations with companies, it is clear that most companies use CMOs at one point or another but on the whole do not want to hand over their manufacturing *in toto* to them for the life of a successful drug. The lack of control has costs, as highlighted earlier. But as the data presented in later chapters shows, CMOs are the only companies that are adding significant capacity beyond 2010. They clearly believe they will have the customers to fill that capacity.

[20] Drawn from Ransohoff 2004.

3.6 The Regulation of Biomanufacturing

The FDA regulates the manufacturing and packaging of biopharmaceutical drugs to ensure the drugs are safe, pure, and effective. Manufacturers must follow "Current Good Manufacturing Practices" (CGMPs or GMPs), emphasizing the fact that company manufacturing technology must be up-to-date and employing recent developments in safe and effective manufacturing practices.

Beginning in the 1990s, there was growing pressure to reform the FDA's pharmaceutical manufacturing regulatory process. This subsequently has applied to biomanufacturing as well. For many years, the FDA was criticized for stifling innovation in the field. The FDA's approach to regulation focused on any changes to the established manufacturing process, requiring companies to report any and all minor and major changes to the process. This approach created disincentives for companies to change anything that deviated from what the FDA approved originally in the manufacturing of the drug. Not surprisingly, companies hesitated to change anything in their bioprocessing that might risk FDA scrutiny or worse, the shutting down of operations, so the tendency was to produce a drug as it had always been produced, no matter how inefficient this process might be. By the end of the 1990s, "It was virtually impossible to implement any changes to the process," said one biomanufacturing executive (PM). The FDA ultimately agreed: " Fear of regulatory consequences impedes adoption of new sciences." (Woodcock 2007). A report commissioned by the FDA later confirmed that there was significant waste in the pharmaceutical manufacturing industry, to the tune of $50 billion a year (Macher and Nickerson 2006). While this is true, a number of company executives said that cost-cutting imperatives have led companies to innovate in their biomanufacturing processes regardless of the stifling presence of the FDA. Ultimately, the FDA has followed the lead of innovative "bioman" companies in reforming the regulatory process.

The FDA announced a new initiative in 2002, *Pharmaceutical CGMPs for the 21st Century*, to investigate how the agency could enhance and modernize the regulation of

pharma manufacturing and product quality. FDA regulations for pharma manufacturing had not been updated since 1978. The objectives of this initiative were to:

- Encourage the early adoption of new technological advances by the pharmaceutical industry
- Facilitate industry application of modern quality management techniques, including implementation of quality systems approaches
- Encourage implementation of risk-based approaches that focus both industry and agency on critical areas
- Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
- Enhance the consistency and coordination of FDA's drug quality regulatory programs, in part by further integrating enhanced quality systems approaches and not the agency's business processes and regulatory policies concerning reviews and inspection activities

The third point, in particular, introduced a radical change in the FDA's regulatory approach. Rather than spend its time and limited resources inspecting all facilities and processes equally, the FDA began to discuss a risk-based approach that would support innovation and focus the agency's efforts on those processes that are the most critical and highest risk (i.e., those which present the most danger to consumers of the drug). The risk-based approach emphasizes the importance of outcomes rather than processes. To address many of the other objectives, the FDA also launched a process analytic technology *(PAT)* initiative, which emphasizes the importance of understanding and controlling the manufacturing process throughout. As biopharma manufacturing has moved from being more of an art to more of a science, analytical tools have been developed that help identify and explain variability in the manufacturing process. By understanding variability in the process, it can be better managed and explained. This produces an inverse relationship between the level of process understanding and the risk of producing a poor quality drug. PAT "moves from empirically derived trial and error methods to rigorous, mechanistically-based and statistically controlled processes"

(Woodstock 2007). PAT has led to significant innovation in the biomanufacturing process, including new approaches that incorporate continuous improvement and "Quality by Design."

In 2004, the FDA released its final reports on GMPs for the 21st Century and PAT and also launched its Critical Path Initiative (CPI). As mentioned before, the CPI's basic premise is that the significant investment and progress that has been made in basic medical science through R&D investment has far surpassed the investment and progress that has been made in the drug development process. Both the leveling off of drug candidates in the pharma development pipeline and the decreased chances of success for new products in the pipeline have motivated the FDA to focus its attention on how to translate the significant amount of investment in drug discovery into successful therapeutics for consumers. One of the bottlenecks to advancing the drug development process is that public funding has not supported research in clinical trials or manufacturing science, and private companies keep their advances in these areas proprietary. Thus, a company can gain significant competitive advantage in time and cost with successful manufacturing processes, for example.

All of these changes in the biopharma manufacturing field have generated a tremendous amount of innovation in recent years in the field — "a revolution," as the executive from Wyeth put it. With the FDA now as a partner, companies are in a better position to innovate and experiment, as long as they are continuously monitoring and evaluating their processes. This has required a significant change in the culture of biomanufacturing, from one that discouraged risk or experimentation to one that encourages and rewards it. At the same time, changes in established manufacturing processes can still bring about inquiries from the FDA, something all companies want to avoid. As a result, companies are walking a fine line between encouraging innovation and experimentation and enforcing a consistent protocol. Overall, there are large incentives for a company to both control its own manufacturing process and excel at it.

3.7 Discussion

Unlike the manufacturing process for many goods, biomanufacturing is a complex, highly regulated process that, by its very nature, cannot be made into a commodity. It is integral within each of the stages of manufacturing and modular also between them, producing both a need for greater proximity within the value chain at some points and the ability to separate the chain across distances at others. It is also a critical part of the biopharma drug value chain because of the safety concerns, productivity, and profit margin improvements that can be made, as well as significant innovations that can impact the time and costs of the process. As a result, companies on the whole prefer to keep the manufacturing in-house when feasible. Because of its complexity, the skill set required of the workforce, and its link to biotech R&D (process development teams), biomanufacturing presents a type of advanced manufacturing that many Western countries, as well as developing countries, would like to compete in. The globalizing of the industry due to its growth overall as well as new markets (and combined with the aggressive tactics of some regions and countries to attract biomanufacturing investments) is leading to a shift in biomanufacturing production and a change in the industry's footprint geographically. The following chapter outlines the theoretical frameworks that I use to explain the drivers of locations of biomanufacturing and how my research supports these theories.

Chapter 4
Theoretical Frameworks and Evidence on the Drivers of Location in Biomanufacturing

My research draws from and brings together two distinct but related literatures: industrial organization and economic geography. While these fields share similar subject matter, primarily firm and industry behavior, they have differed in the central preoccupations of their respective fields. Industrial organization has been primarily concerned with firms and markets – why do firms exist and what determines their scale and scope? This has led to research across a broad array of fields – sociology, management, political science – that examines the relationships within and across firms and industries, and the variety of business relationships that exist to deliver products and services to the market. Economic geography is also concerned with firms and industry, but its primary focus has been on how they influence the "spatial and locational foundations of economic life" (Scott 2000). The latter is fundamentally interested in how place affects economic activity. As a result, it has been mainly concerned with factors that influence the structure of a place – its history, institutions, social relationships, and the dynamics that are created within a place, including agglomeration economies, social networks, path dependence, and increasing returns (Whitakker et al. 2008). In recent years, there has been a convergence between these two fields as industrial organization has become more preoccupied with factors external to the firm such as relationships and networks between firms. This has led to greater focus on the external economies created by firms, a subject at the heart of economic geography (Sturgeon 2002).

In this chapter, I take two important concepts from each of these literatures, external economies and product life cycle, and show how they help explain the location dynamics in biomanufacturing. Alfred Marshall's agglomeration economies provides a theoretical framework for understanding the original location of biomanufacturing. The emergence of the biotechnology industry, and with it biomanufacturing, in the Boston and San Francisco areas is largely the result of specialized knowledge and talent found in the universities and research centers in those two locations. As explained below in detail, access to talent is a precondition for the location of biomanufacturing operations. Another

benefit to agglomeration economies, emphasized by Michael Porter in his work on industry clusters (1990), is the efficiency gained by proximity to customers, suppliers and various elements of the cluster. For industries that are time sensitive, of which biomanufacturing is one, locating in proximity to other parts of the industry value chain as well as to similar companies is beneficial.

While agglomeration economies help to explain the original location of biomanufacturing, product life cycle theory (PLC) provides a more dynamic theoretical framework to explain the evolution of the industry as it progresses from early to late stage manufacturing through the life cycle of the product. In this highly innovative industry, PLC helps to explain why we see most clinical production near R&D, and later-stage commercial production off shore.

This chapter outlines each of these theoretical frameworks and the research findings that support these theories. Because of its primary importance to industry location, I begin with a review of the agglomeration economies literature and the important role external economies, particularly specialized labor, play in biomanufacturing. I follow with a brief review of the industrial organization literature and then discuss in depth product life cycle theory, which provides the other primary theoretical framework for understanding location dynamics in biomanufacturing. I then apply the different stages of biomanufacturing to the product life cycle model. I end with a review of secondary factors that influence location: drug sales, company portfolios, and capital outlays for facilities.

4.1 Economic Geography

Since the early 1990s, there has been a revival of literature linking geography, firm performance and economic development. Revived research fields such as the "new economic geography" and the "geography of innovation." (Porter 1990; Krugman 1991; Henderson and Jaffe 1999) have emerged to understand the link between firms and their physical environment and specifically how important that environment is to a firm's ability to innovate. The emergence of new models of economic growth in the 1980s

brought geography back into the equation of firm performance and economic growth. New economic growth theories emphasize the role of human capital in generating long-run growth such that knowledge accumulation becomes a form of investment that can generate social externalities (Romer1986). One of the paths to these increasing returns to knowledge is agglomeration economies in which concentrations of knowledge help facilitate a number of transactions in terms of information searches and coordination. The concentration of knowledge in the form of people and firms is thought to create knowledge spillovers, which enhance the generation of innovation and thus increase technical progress and economic growth[21].

The importance of agglomeration economies was recognized by Marshall (1890) when he outlined the three primary external economies that are derived from firms locating in proximity to one another: 1) a specialized labor pool 2) specialized buyers and suppliers and 3) knowledge spillovers. Marshall described these areas as "industrial districts", which, as envisioned by Marshall, were locally based production centers of small, locally owned firms where scale economies are relatively low. Today, industrial "clusters"[22] are the term and concept more widely used (Porter 1990) which are regionally based and encompass large and small firms. While the benefits of clusters have historically revolved around lower costs of factors of production (search costs for human capital, or transportation costs) their benefits are now understood more in terms of their social and economic organization (Pyke and Sengenberger 1992). The strong networks that exist between firms through specialization and subcontracting define the cluster and are reinforced by high levels of inter-firm cooperation, trust and entrepreneurial dynamism. This speaks to the importance of clusters in an era in which innovation is so critical to firm performance and economic growth.

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[21] Research in this area has focused on the relationship between R&D investments in regions and economic growth and finds a positive correlation. This led to a modification in the knowledge production function that includes specifications for both space and the product being produced (Jaffe 1989).

[22] Porter defines clusters as ""geographic concentrations of interconnected companies, specialized suppliers, service providers, firms in related industries, and associated institutions in a particular field that compete but also cooperate." (1990).

Geography and Innovation

One of the major areas of inquiry in cluster development today is the role of knowledge sharing, knowledge creation and learning within and among firms. How do firms increase their knowledge and learning and thus increase innovation and productivity? Does the specific spatial arrangement of firms within a geographic area influence the creation of knowledge? Because of the benefits of proximity, knowledge developed in a cluster is thought to flow more easily between people and firms, and lose its value as it travels outside the cluster. "Tacit knowledge," as opposed to "codified knowledge" (Polanyi 1966) requires proximity and face-to-face interactions, whereas codified knowledge can be more easily communicated across greater distances. Research in recent decades has confirmed that innovation is "geographically mediated", that is, rates of innovation (often measured by patents) are highly affected by localized knowledge. While we may not be able to point to one single factor that leads to innovation - institutions, star individuals, networks - empirical evidence shows that innovative activity is regionally clustered, particularly where there are industries with high R&D levels, university research and skilled labor (Feldman 1999). Thus, despite the globalization of knowledge and talent, clusters are more important, not less important, to innovation.

All of this points to the importance of finding talent that can generate new knowledge. The importance of talent in biomanufacturing cannot be underestimated and explains the concentration of the industry in a limited number of locations. The following provides an outline of the role human capital and a specialized labor force plays in the industry.

4.2 Biomanufacturing's Specialized Labor Pool

Many have documented the fact that there is an increasing demand for skilled labor in the 21st century, due to technological change and increasing global competition (National Academy of Sciences, 2008). For decades, terms such as "the knowledge economy" and "knowledge workers" have been used to convey the changes taking place in the economy. The significant technological component of many jobs in the 21st century places particular emphasis on skills in Science, Technology, Engineering and Math (STEM), and strengthening these in the US has become a top priority for business and

policymakers alike [23] In addition, the kinds of tasks that workers are required to perform has changed. For skilled jobs, "nonroutine" tasks are in demand such as abstract and expert thinking, and complex communication, which involve building understanding or trust (Levy and Murname, 2004). All of this has led to a skills bias in labor force demand, which has contributed to the growing "polarization" of the US labor market (Autor, 2007). Employment and wages are growing both at the higher-skilled and lower-skilled levels. This translates into lower paying low-skilled service jobs as well as higher paying, high skilled service jobs, but a loss of jobs in the middle (those that are "routine") due to computerization, automation and offshoring. This has led, in part, to the characterization of the 21st century by some as the era of *The World is Flat* (Friedman, 2005), in which the concern is less about finding talent than about the offshoring of highly paid professional and technical jobs to other countries (Finegold 2007). While these trends have been emerging over decades, there is a growing sense of concern and urgency about the US's ability to compete with the "rise of the rest"(Bhide 2008).

Biomanufacturing is a good example of an industry that produces the kinds of jobs that are coveted in the "innovation economy." The industry employs workers with a science background, and the tasks involved, while potentially routine in and of themselves, require expert thinking and judgment to manage the process and problem-solve when unexpected events occur. Many of these are also jobs that can move offshore, once a firm has built up internal expertise and can find the skilled labor in another country. The primary concern for biomanufacturers is finding skilled workers. As discussed in the previous chapter, unlike the manufacturing of widgets, manufacturing a biotech drug incorrectly can have significant consequences, both in terms of public safety and for the time and cost of production. As a result, companies need to ensure they can find the quality workforce that can be relied upon to operate their facilities. "Talent is most important," says one executive about the location of his biomanufacturing facility. "You need the demographics working for you – a good number of bachelors degrees, in particular."

[23] This agenda received a great deal of attention after the publication of the National Research Council's Report "Rising Above the Gathering Storm", 2007, which highlighted the number of ways the US is falling behind in STEM education. Congress responded with the passage of the America COMPETES Act in 2007.

The number of workers employed in a biomanufacturing facility depends on a range of variables. The scale of production is the critical driver, whether it is a small pilot plant or a larger GMP facility (the latter requires more documentation for the regulators because the drugs will be consumed by humans). What is the potency of and demand for the drug and thus how many batches do you need to make per year? How many shifts does the facility run? Pilot and clinical facilities can range in volume from 100 to 500 liters for pilot operations and up to 10K liters for clinical. Employment numbers can range from 25 to 50 people for a pilot plant, to 400 with GMP clinical production. For commercial plants, again the range can be wide in terms of volume (from 5K to 120K liters) and employment (anywhere from 250 to 1,200).

Biomanufacturing operations draw from two types of labor pools. Approximately 20-25% of the workforce for a commercial facility will draw from a highly educated group of Masters and PhD graduates who will engage primarily in process development work (the Manufacturing Science team) and the intricacies of scaling up the substance. These higher degrees may be in molecular biology, biochemistry, and chemical engineering, as well as MBAs for their project management skills. The rest of the workforce, from 75 to 80%, will have either a four-year degree in the sciences (over half of the group), or a two-year associates degree, or a high school degree with some work experience. The BA might be in biology, chemistry or engineering, or the associate degree could be a two-year certificate in a science-prep or biotech course. The BA workers are involved in program management, engineering, QA/QC and some technical operations. The associate and high school degree employees work as technicians or operators and are involved in monitoring and operating the manufacturing equipment, preparing media for the various stages of production or transferring material from one stage of the process to the next.

Table 4.1: Range of Positions, Education Requirements and Salaries

Position	Education	Wage/Salary Range
Dept. Heads, Manufacturing Science, Project Management	PhD MA	$60K - $200K+
Supervisors, Engineers	BA/MA	$60 - $130K
Technical Operato Supervisors	BA Ass. Degree High School	$17 - $34 an hour

A number of changes in the biomanufacturing process, particularly around facility design and process evaluation techniques, are changing the nature of the work and how it is organized. On one hand, the change in the structure of facilities is going to require a workforce that can multi-task:

> "We're transitioning from a place that makes a single product to a place that makes a couple of products so we gotta be flexible, we gotta have people cross-trained. Now we gotta take risks on people, and on their development and we've gotta have them grow and continuously improve how we do things. Otherwise we're going to need 10 times as many people in order to add three more products."

On the other hand, the increased use of monitoring and evaluation techniques through Process Analytical Technology (PAT), means there has been greater automation and computerization of the process. The newer generation of workers relies more heavily on these to perform tasks and report what is going on. As a result, the "pioneers" in the field complain that the next generation does not have a deep understanding of the process or first-hand experience in diagnosing problems.

> "The difference is, is that when you do a startup, you have to do far more than the job role that you're hired to do now. So in an established facility, you come in and you do your box job of whatever it is, as that's been defined over time, and, you don't get exposure to the challenges you have when the building's not working, or is just starting. . . They don't get that broad exposure early, and you don't get it in, in the firefight mode. And when you start up a building, you get both . . .that experience is just invaluable.

These changes speak to the ways the work is becoming both more complex, specifically at the early stages, and more routinized at the later stages, as a way to manage the complexity.

Because of the demands for highly educated workers as plant managers, manufacturing scientists as well as project managers, the industry tends to locate where there is already some base of science-related activity, most likely in the form of colleges and universities. This ensures that the company can find the Masters and PhDs it needs. " For the first 10

years after a PhD, people want to be where the interesting work is. That's often where the universities are," said one bioman executive. In a field that is constantly looking for new and innovative ways to manufacture biotech drugs in a more timely and cost-effective manner, there is a premium placed on being in and near centers where the talent can be found to develop these new technologies. In addition to highly skilled workers, the number of college or two-year degree graduates (in the sciences) a company's needs can be significant (in the case of Wyeth in North Andover, MA, approximately 1,000). Thus, locations that have multiple colleges and universities help fill the demand at this level. "You need to be somewhere where you can find a good percentage of BS and advanced degrees," confirms one plant manager. "You're not going to find this business out in the middle of some agricultural area."

As highlighted earlier, manufacturing labor represents a relatively small part of the overall costs of producing a drug, anywhere from 15 to 30% of the operating costs of manufacturing, which represents only 20-30% of the total costs of goods sold. Ultimately, manufacturing labor represents a small part of the total cost of sales (3 to 9%). Because the costs of labor are a relatively small part of the equation, locating in places with relatively cheap labor is not a strong pull for companies.

> " If you go through many of these facilities, and you see the complexity of it, and the investment in it, and the technologies involved, and the skill level of the people involved, and the cost of making it, it's just not about cheap labor."

Further, the labor costs do not differ greatly between locations. Salaries in Europe and the US are approximately the same. And even in lower-cost locations such as Singapore and Puerto Rico, labor costs, at least for the more highly educated workers, do not differ greatly because most of these workers at this point in time are imported. Despite the tax breaks provided by these places (discussed below), they are often lacking skilled labor. Puerto Rico, a major center for pharmaceutical manufacturing, has relatively few biomanufacturers who are producing drug substance, in part because of the short supply of skilled labor. In the case of the few that are there (Abbott and Amgen, for example),

they hire their top talent from within the company, and in the case of Abbott, from their existing pharma manufacturing operations in Puerto Rico. Singapore is aggressively trying to build its capacity and attract investment through recruiting top talent and offering substantial grants to companies that will train the local workforce. One company that chose to locate their facility in Ireland over Puerto Rico or Singapore (all providing tax benefits) chose Ireland because they could draw from across Europe for their skilled labor.

Rather than seeking out low-cost labor, biomanufacturing centers are relatively tightly bound to centers of biotech research and a STEM skills base. Clearly, a specialized labor pool of workers with a science-based background is a necessary condition for biomanufacturing. The external economies generated by locating where there are other biotech companies and research leads to a concentration rather than dispersal of biomanufacturing centers. However, skilled labor, while necessary, is not sufficient for completely explaining the location of biomanufacturing. Other issues, such as the product's life cycle, also come into play. The following section outlines product life cycle theory and the role it plays in determining the location of biomanufacturing.

4.3 Industrial Organization

Research in industrial organization over the past 80 years has focused on fundamental questions about why firms form, their scope and size, distinctions between firms and markets, and ownership and employment relations (Putterman and Korszner 1996). A number of models of firm behavior have emerged over time to address these issues: first neoclassical and principal-agent models, followed since the late 1930s by transaction-cost models (Coase, 1937, Williamson, 1985) and variations of this including theories around the cost of monitoring and property rights models. Efforts to integrate economics and organizational theory have led to the behavioral theory of the firm (Cyert and March 1963) and the evolutionary theory of the firm (Nelson and Winter 1982). More recently, a

knowledge-based theory of the firm has emerged, in which creating and utilizing knowledge is the central source of a firm's competitive advantage (Grant 1996). [24]

Throughout most of this time, the dominant concept that grounded industrial organization was the "modern corporation" as defined by Chandler in the mid-1970s (Sturgeon 2002). However, the challenges faced by US firms in the 1970s and 1980s, and changes in the way firms organize themselves, internally and externally, have since led to a shift in the industrial organization paradigm. Two aspects of the late 20th century, early 21st century economy have fundamentally changed the way firms innovate and produce goods and services. The first, the globalization of production and trade, and the second, vertical disintegration of multinational firms, have changed our understanding of the modern corporation. The vision of a large hierarchical, multinational enterprise with subsidiaries around the world has been largely discarded for a more flexible model of companies that outsource significant portions of their value chain and only focus on their "core competencies." Networks between firms emerge to meet the innovation and production needs of the company. Some argue that a new paradigm for industrial organization and economic development is emerging in which the economy is dominated by "the modularization of production." (Sabel and Zeitlin 2004, 388.) In this model, the production process, while remaining integral where knowledge is tacit, can now be broken into modular pieces that can be separated and produced by multiple different firms in multiple different locations around the world (for instance, in the electronics industry). This gives rise to new production networks that, it is argued, are more adaptable to change in highly competitive markets. This new model of production has raised questions as to whether older models of industrial organization of production such as product life cycle, are still relevant today. Below I discuss in fuller detail the product life cycle theory and why, even in the face of these dramatic changes in industrial organization, the model is still useful to understanding the geography of production in certain industries.

[24] See Connor, 1991, for a summary of some of the schools of thought within industrial organization economics.

4.4 Product Life Cycle Theory

One of the central theories to emerge in industrial organization in the 1960s was the concept of the product life cycle, which was one of the first theories to explain the early phases of the globalization of production. Vernon (1966) showed how the natural life cycle of a product goes from innovation to the codification of knowledge, and ultimately to the shift of production processes to low cost locations. New products are invented "to satisfy new wants" in the industrialized "North" (the United States in Vernon's example), and are initially manufactured in the country where they are first invented because of the degrees of freedom it offers the producers, the relative unimportance of the cost of production at this early stage of the product's life cycle given the assumed monopoly, and the general uncertainty that exists about the product and its market and a desire to keep production in proximity of buyers, suppliers, etc. The market the firm is producing for also matters. "The creation of new products and processes depends on the existence of a large market to bear the high cost and risk involved in the supporting R&D expenditure." (Cantwell 1989, 55). As a product matures, the production processes become standardized, economies of scale are achieved through mass output and investments are made into fixed assets. At this stage, cost begins to be an issue for the company, even if price competition is not yet present, as the ability to begin to predict costs becomes increasingly important. Assuming demand for the product increases in other advanced countries, the company will decide whether it should take the risk of setting up a facility in the countries where the market is expanding. Ultimately, the company will shift the location of production from the higher wage North, to the lower wage "South," and the product is finally imported into the US. "The US [exports] high-income and labor-saving products in the early stages of their existence, and [imports] them later on. (Ibid,p. 201).

As early as 1979, Vernon suggested that the product life cycle theory was losing some of its relevance as globalization increased (Vernon 1979). The convergence of advanced country markets, namely between the US, Europe and Japan, and the speed with which technologies were being diffused, including to developing countries, made the theory less relevant in explaining how some industries evolved. Japan provides a number of examples in the 1970s and 1980s where continuous innovation became part of the

country's production processes in motor vehicle production and televisions. While Vernon agreed the model was less useful in explaining the relationship between advanced industrialized countries, he believed there were a number of cases where the model would still be relevant. This includes the innovating activities of smaller firms that do not have the capacity to immediately move manufacturing to offshore locations. He also predicted that there would be a tendency for companies to site their first production facility near their home base as they continue to develop and improve their production processes. At this earlier stage of getting a product to market, companies are less likely to be fixated on a least-cost location. Finally, Vernon argued that while the gap between developed countries in terms of income, market size and factor costs was diminishing, this gap was still wide between developed and developing countries. This would still put the latter at a disadvantage in terms of becoming innovators for anything but their own economies.

Along with these cases that are more applicable to the PLC theory, Vernon also suggested modifying the model to account for oligopolistic industries (Cantwell 1989). Oligopolies refer to market structures in which there are a relatively small number of sellers in the market as well as limitations on the entry and exit conditions in the market (Craig and Malek 1995). These limitations may be caused by barriers to entry into the market such as economies of scale, in which, for example, the specialization of labor and large capital expenditures in particular equipment deter new entrants from entering the market. Another important barrier to entry is "product differentiation" that can provide a company with "first-mover advantage". Patents, which provide a company with a temporary monopoly, can help increase a company's advantage by allowing the company time to promote its product and develop brand loyalty. These factors can lead to higher prices since there is no perfect competition in the industry, as well as suboptimal outcomes for social welfare. In the case of oligopolies, the PLC model shows how companies maintain ownership advantages of their new products not so much because of some technological advantage, but because of barriers to entry in the form of scale economies. This barrier allows firms to "adopt non-innovative strategies in the later stages of the cycle." (Cantwell 1989, 59).

Product life cycle theory has continued to be elaborated upon in case studies of certain industries such as petrochemicals, where economies of scale play a role in location (Auty 1984). More recent research into product life cycles has added more "richness" to the model, for example, in the recent work by Antras (2005), where technologies are transferred to the South through a number of inter-firm arrangements such as subcontracting, licensing and arm-length arrangements, and even if a product is relatively new and not fully standardized, it may still be moved to the South, but produced within firm boundaries.

While the model has certainly become richer, many argue it has been debunked and become obsolete in the face of the expansion of globally integrated multinational corporations (MNCs), the globalization of talent and innovation, the speeding up of the product life cycle, and the growth of new markets in emerging economies. PLC theory represents a "traditional view" of how MNCs have operated, in which companies innovate in their home country, "project" their products and homegrown advantages internationally by expanding into markets that have the requisite disposable income for their products, and over time, move production to countries with lower costs factors, usually labor-intensive operations (Doz et al. 2001). Today knowledge is increasingly diverse and dispersed and as such, companies need to seek out innovative ideas beyond their home base. Thus, it is argued, the development of innovative products is not necessarily tied to the market they are invented in. In addition, as the product life cycle shortens, and its spread across global markets becomes more unpredictable, "riding the life cycle of a standardized product through waves of international expansion, as successive countries develop, becomes less and less tenable." (*Ibid* 41).

There are clearly examples where PLC has been "reversed" and turned upside down in cases where markets in low-cost locations have evolved to the point of being "innovator" locations. The low-cost locations where products were sent to be manufactured have become some of the most advanced markets in the industry as innovation in the industry has been taken up by the "follower country." In some more recent cases, local demand has increased and become more sophisticated. US firms are now investing heavily in

R&D in these markets in order to develop the most advanced products, in industries such as software, flat panel displays and personal computers (Macher and Mowery 2008). As continuous process innovations become part and parcel of most industries, production that is moved abroad can in some cases bring upstream R&D innovative activities with it. This underscores the dynamic nature of these global industries and the potential importance of the location of production to geographic distribution of the cluster over time.

Despite these variations on the product life cycle theory and the fact that, for many industries today, non-standardized production processes are moved immediately to low cost locations, product life cycle is still relevant for understanding the production dynamics of a highly complex, highly regulated industry such as biomanufacturing. Despite some twists, the model still holds. First, there are some unique characteristics about the biopharma industry that speak to Vernon's modified model. Biopharma has been described as a "dynamic oligopoly with substantial competition" (Craig and Malek 1995, 321). Significant barriers to entry in the form of economies of scale (capital expenditures) as well as product differentiation (patents) prevent easy entry and exit into the industry. These factors, along with the complexity of the process, have resulted in biotech products still being initially manufactured in the country where they are first invented. Most companies, whether small or large, keep early stage manufacturing close to the home base R&D, and first commercial facilities are also built near by, as Vernon predicted. At these early stages, finding a low-cost location is secondary to getting the product right and out on the market as quickly as possible. In addition, since these facilities are expensive and need to be approved by the FDA or the equivalent in Europe and Japan, companies are very careful about assuring approval and thus often want the first facility nearby. While the companies are under tremendous time pressure to get products to the market, given the development costs, patents help alleviate some of this pressure and put the emphasis on quality rather than cost at this early stage. Second, the largest market for biopharma products is in the US, followed by Europe and Japan (in that order). Companies are keeping R&D, and production, near their largest customers. Convergence within "the Triad" has led to introduction of new products almost

simultaneously in some of these markets. Today, biomanufacturing production of a drug in the US can easily meet demand in Europe and vice versa. However, there are often political reasons why it might be expedient for a company to locate some production facilities in certain countries if they want a favorable price for their drug.

Once a production process becomes more standardized (after several years) later stage commercial manufacturing of a product may move offshore to a lower cost location if demand can justify a new facility. But in the case of biomanufacturing, low cost does not equate to low wages or low cost infrastructure since the difference in cost of these factors between North America, Europe or Asia is minimal. Low cost locations in this industry translates into tax-advantaged locations, i.e., places that offer lower corporate tax rates. While patents protect a company's profits on a product for a number of years, the downward pressure on drug prices is such that companies are still looking for low-cost locations for production. But with a highly complex process and intellectual property to protect, companies still prefer to keep production within North America and Europe. A "middle station" has emerged between high cost locations within the US and low cost production locations like China and India. This new middle station includes countries and regions such as Ireland, Switzerland, Puerto Rico, and Singapore, more recently, that are aggressively pursuing biomanufacturing through tax breaks and subsidies to companies. This is Vernon's new "South" for low-cost production. As Asian markets grow and begin buying innovator drugs, companies will move production to that region of the world. However, it will not be for low-cost production reasons but for expanding markets. For the few biosimilars that have been approved, production of these is moving to Asia, resembling the "South" in Vernon's original vision.

One final point to address in critiques of product life cycle theory is the issue of time, specifically the speeding up of product life cycles. There is no question that the speed with which innovation occurs has increased at a phenomenal rate, and subsequently, the rapid replacement of one technology with another as well. One of the results of this is that technologies are being diffused rapidly, which has led to growing talent and capabilities within countries around the world such that the ability to off-shore complex

production processes has become easier earlier on in the product life cycle. This dynamic is not just due to a process of technological diffusion, but also to a new dynamic in development ("compressed development", Whittaker et al. 2008) in which the off-shoring of leading edge production processes provides the receiving country with an opportunity for rapid learning and market entry into a new industry. Over time, off-shoring becomes easier as the skills and capabilities are developed in more locations. Biomanufacturing provides an excellent example of this. The first mammalian-based biologics were approved in the mid 1980s and the production of three of the four did not move off shore to a low cost location for 20 years. Today, due to technological advances, changes in regulatory requirements, and increased talent around the world, drugs that are approved and launched are being off-shored to low cost locations within three to four years. The product life cycle model still holds, but over a much shorter time period.

With this background on product life cycle theory, I now turn to the actual dynamics of the product life cycle of drugs and how this translates into the manufacturing life cycle.

4.4.1 The Product Life Cycle of Drugs

What is the product life cycle of a drug? Patent protection largely drives the cycle, since the introduction of generics to replace patented pharmaceutical drugs will significantly cut sales. In the case of a pharmaceutical drug, the product life cycle begins at the R&D stage. As discussed earlier, it can take 8-10 years to develop a drug before it is launched commercially. Once a pharma drug has been approved for the market, companies assume a 20-year life cycle. Most importantly to the company, it can expect on average 12 years of sales before patents run out.[25] By year 9, the drug is expected to be in the mature portion of its product life cycle, and in year 12, when the drug goes off patent, sales begin to decline. Across all drugs that went off patent between 1994 and 1997, the entry of generic competitors led to average percentage sales declines of 31, 28, 20 and 20% for the first four years off patent. This holds primarily for products with significant sales. For drugs with less sales (under $40 million), generic competition may not arise, which leads

[25] Henry Grabowski, John Vernon and Joseph DiMasi, "Returns on Research and Development for 1990s New Drug Introductions", *Pharmacoeconomics*, 2002; Supplement 3; pgs 11-29. The analysis is based on data between 1990 and 2000 with 7 to 11 years of worldwide sales for "new chemical entities" (NCEs).

to a much more moderate decline in sales. For the truly blockbuster drugs, the rise and fall in the product life cycle can be much more pronounced because of their steep incline in sales and rapid descent once generics are introduced.

The product life cycle for a biopharma drug is somewhat different because of the unresolved nature of biosimilars. As explained earlier, because of the molecular nature of biopharma drug substance, two products may be considered similar but not identical or interchangeable. For this reason, the term generic is not used. For purposes of patient safety and to protect their investments, biotech companies and others argue that biosimilars must conduct clinical trials (at least Phase III) and meet FDA standards before they can be sold to the public. This leads to development costs of $10 to $40 million for a biosimilar, compared to $1 to $2 million of the development of a pharma generic[26]. This is a highly contested debate, particularly because four major biotech drugs that represent 50% of all biotech drug sales will be off patent by 2010[27] . Legislation that would pave the way for biosimilars in the US has recently been introduced in Congress.[28]. In the meantime, the EU has approved five biosimilars (two of human growth hormone, three of EPO), and India and China are positioning themselves to compete in this space, largely in domestic and emerging markets, where biosimilars are already approved. The approval of certain biosimilars reflects the fact that biologics differ in their complexity in terms of molecular weight and the extent of post-translational modification of the molecule during synthesis (Pore, et al, 2008). Insulin, for example, is characterized well enough that it is approved for manufacturing by a number of companies. The case of insulin is instructive. Eli Lilly received FDA approval

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[26] Global Business Insights, *The Future of Biosimilars*, 2007.

[27] EPO, insulin, interferons and G-CSF (granulocyte colony stem factor).

[28] On March 11, 2009 Representative Waxman introduced legislation in Congress that provides for the approval of biosimilar products, defined as " no clinically meaningful differences between the biological product and the reference product" as well as "interchangeable" biosimilars, defined as a product that can be "switched one or more times" with the reference product "without an expected increase in the risk of adverse events." The bill also provides incentives for brand companies to continue to develop new therapies. Specifically, similar to the current structure for approved drugs, it would provide five years of exclusivity for a novel molecular structure before any biosimilar could be approved. It also provides for a three-year exclusivity for certain modifications of a previously approved product (such as a new condition of use) and a six-month pediatric exclusivity period. The bill also provides first biosimilar applicants with at least six months of exclusivity if an interchangeable biosimilar product is approved. (Foley & Lardner Newsletter, March 13, 2009).

for the first insulin drug, Humulin, in 1982. That drug went off patent in 2001. However, there were no biosimilar drugs developed to replace Humulin for a couple of reasons. First, Lilly developed an insulin analog, Humalog, which was a better version of its first drug and captured part of the insulin market for a second time. Its patent runs out in 2012. Such "biobetters", improved versions of a drug that has already gone off patent, are often the reason biosimilars have not been developed. Second, the FDA, while promising to produce guidelines on the use of generics or biosimilars for insulin and human growth hormone in 2001, decided in 2006 that it would not issue guidelines just on these products and would instead try to develop guidelines for the whole of the biotech industry. Needless to say, nothing has yet been forthcoming, though legislation has recently been introduced in Congress.

All of this suggests that the product life cycle for biopharma drugs might differ slightly from that of a pure pharma drug. It may be a longer life cycle, beyond the 20 years. This lack of clarity or direct and immediate threat from biosimilars may have historically given biopharma companies some cushion in terms profit margins and the need to move production to low-cost locations as soon as possible. But all the executives interviewed believed biosimilars would be a part of the industry landscape eventually. Some products may be challenged by biosimilars, others may be challenged by biobetters. Given the costs of developing a biosimilar, it may be more cost effective to go after the creation of a biobetter. In either case, such developments will put pressure on biotech drug profit margins, which influences where companies choose to manufacture. Assuming at the least a 20-year life cycle for a biotech drug, we now can address the question of where manufacturing occurs across this 20-year span.

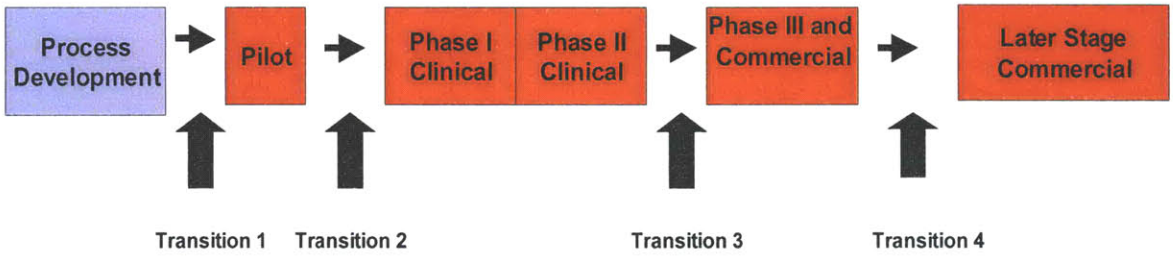
4.4.2. Product Life Cycle and the Biomanufacturing Process

The product life cycle of a biotech drug maps on to four different stages in the drug's manufacturing process (see Chart 5.1)[29]. To understand the manufacturing process and

[29] When I refer to the manufacturing phases of the drug, I am referring to the manufacturing of the drug *substance*. Manufacturing of the drug *product* refers to the fill/finish phase of manufacturing which takes place at a small scale during clinical trials and a much larger scale for commercial production. The manufacturing of drug product is not included in this analysis.

location of each phase, it is important to understand the kinds of knowledge, whether tacit or codified, that are used. As discussed earlier, biomanufacturing involves complex technologies and tasks that are not easily codified. The tacit knowledge that is exchanged in the process, particularly in the beginning of the manufacturing process, creates a highly integrated and non-linear production process, which makes separability difficult. However, once a technology or technological process becomes more standardized, it becomes more "modular", and thus is more easily produced at a distance or outsourced.

Figure 4.1: Four Stages to the Manufacturing Life Cycle



In the case of biomanufacturing, there has indeed been a "modularization of production" (Sturgeon, 2002). As Figure 4.1 shows, there are four different points in the manufacturing process where a company can transition the compound in a technology transfer ("tech transfer") between different entities within a company or to a third party. These represent points in the production process where the manufacturing can also move locations. However, while this modularity has allowed for greater flexibility in the location of production and movement of the drug substance between multiple locations, the complexity of the task still keeps most companies of scale (i.e., not start-ups) producing in-house and not outsourcing to a third party. The following outlines the manufacturing life cycle for a biotech drug and what occurs at each of these transitions.

Early Stage Manufacturing

Given the complexity of making the drug substance once it is received from Process Development (Transition One), as well as getting it to scale, the knowledge needed to grow mammalian cell cultures is not codified at these early stages. Pilot manufacturing, which happens in non-GMP facilities, and early clinical manufacturing (Transition Two) which requires GMP facilities, still involve significant trial and error before stable manufacturing processes are in place. This was echoed in numerous interviews:

> "There is a huge advantage to having the clinical facility close by to R&D. In cell therapy, there is so much back and forth [between the early stage manufacturing and R&D]. You learn about surprises and problems. For example, we're learning about stem cell preparation today in the same way we were trying to understand mammalian cell culture 20 years ago."
>
> "It helps [to have the manufacturing near R&D]." It's not 100% necessary but it helps. The teams need to be really closely connected. But that doesn't have to be physically proximate. Teams can understand the issues completely and talk daily from distant locations."
>
> "We take the product from R&D here at our site, or from our European R&D, or from licensing situations. It's probably a little slower when it comes from someplace else. But we have groups here that liase with the research folks. So you always have people on site with project familiarity."

As discussed earlier, once R&D hands off the compound to the process development team (PD), the interactions begin between the PD team and the Manufacturing Science (MS) team. The R&D team is still heavily involved at this early stage.

However, while many believe it is beneficial to have these teams in close physical proximity, and most companies do, it is not absolutely critical that the pilot and early clinical manufacturing take place side by side with the R&D and PD teams. A tech transfer across distances *can* take place between the PD team and the MS team, as long as there is significant communication between the two. This usually involves the MS team meeting with the PD team months before Transition 1 occurs, and once it does, having members of the PD team join the pilot manufacturing team for a number of weeks (from two to six weeks) while the manufacturing process is initiated. For large biopharma

companies with multiple research sites, manufacturing is usually centralized. Pfizer, for example, which has biologics R&D centers in many locations (St. Louis, California, New England and England), has only one pilot and clinical manufacturing facility in St. Louis. Likewise, Novartis has a relatively small biologics research team in Cambridge, MA but all of its manufacturing, including pilot, is done in Switzerland, where its headquarters and main R&D team is located. Thus, while the manufacturing process at this early stage is highly *integral* and involves a lot of tacit knowledge exchange with the process development team, it can also be transitioned to other locations at Transitions One and Two if need be. Start-up companies engage in this type of tech transfer when they outsource their manufacturing to CMOs. "It's not my first choice [using a CMO], but I don't have another option," said one CEO of a biotech start-up. "I try to have strong PD people and some MS people on my side to work closely with the CMO." The ability to cross geographic distances with knowledge that is tacit points to the importance of what some call "communities of practice." (Gertler 2003, 86). While geographic proximity is important for the generation and transmission of tacit knowledge, some argue that in fact, more important than this is the organizational proximity and context in which tacit knowledge flows. If biomanufacturers within the same company, or even across firms, work closely together and share experiences, expertise and commitment toward a common goal, tacit knowledge can be shared across distances without risking losing the knowledge. In the case of biomanufacturing, most of these transfers of knowledge are happening within firms, within a tight knit network of manufacturers, which makes such transfers possible. While most firms still want their pilot and clinical manufacturing physically close to R&D, it is possible to separate the two.

Phase III and Commercial Manufacturing

At Phase III clinical trial production, companies are engaged in process validation and stabilizing the manufacturing at a larger scale, with the intention of manufacturing at a commercial scale at the same location. This is due to the fact that it is in Phase III that the larger scale manufacturing process is validated, a BLA (Biologics Licensee Application) submitted, and FDA approval obtained. Thus, Transition 3 is an important decision for the company because it is choosing the location where it will most likely be producing its

commercial product (if successful) for several years. Over the past 15 years, production at this stage of the process has become more routine. "Phase III and commercial manufacturing are pretty much well understood. While in the early 1990s, it was still a bugaboo, by the late 1990s, we had conquered the process." While the product still could not be called a commodity, the manufacturing process is more linear than early stage production, since it is almost entirely separate from R&D. By the time a product is launched, enough batches of the drug have been produced successfully that the process could be characterized as standardized. At this stage of the manufacturing process, the knowledge is codified, and while it may still be internal to the firm ("trade secrets"), it is much easier to convey across distances.

However, one is still making something from a biological substance with significant "micro-hetereogeneity". Despite all of the testing and good success rates, post-commercial issues with production do arise. While commercial production may be routinized and the process codified, it does not prevent random and unexpected changes to occur in production. "There's no such thing as zero risk and people are starting to realize that." This view was expressed from a number of different companies:

> " All these inputs are coming in…from vendors, from people, from assays..from raw materials, from disposables…I don't know...the atmosphere!…These variables are ever changing"
>
> "Even after making something for a long time, it changes because it's a biological process. It goes wrong and we can't explain it. A new generation of workers may never have seen it … The human factor is usually the reason things go wrong. You want to take the human factor out of the process."
>
> "There's always a challenge. One raw material out of a thousand and you suddenly have a slightly different sugar configuration of the molecule and you don't know what that means. And your clinical trials weren't done with that slight difference. Probably means nothing, but it might. We've been making our product for 10 years and I'm still working on some issues right now."

The risks of the "human factor" are in part why there has been a great emphasis placed on developing Process Analytic Technology (PAT). "Process success rates, PAT. . . we need to systematize the scale up because it's largely tacit ... we need to put a process behind it. It sits in people's heads...you can't read a book about it," said one executive. But even with PAT in place and knowledge codified to the greatest extent possible, the very nature of the product prevents it from becoming, strictly speaking, a commodity. Nevertheless, the improvements made in bioprocessing, particularly in PAT, in the last decade have shifted production from more of an art to a science such that, while there is always some element of tacit knowledge involved, the processes themselves have progressively become more routinized. Thus, while there is always risk, companies have been successful at managing the probabilities of something going wrong. "Risk is reduced through better management of the probabilities."[30]

By the time the drug is being produced commercially, the process has been standardized to the extent possible, and while there are still risks, and always will be, the drug can be produced in multiple locations if a company has multiple facilities. In the case of one company, the goal has been to make its three commercial facilities (two in the US, one in Europe) "seamless:"

> "All of our teams and platforms are the same across the three locations so it becomes easy to transfer the processes between the different sites...Everything is compatible. There's nothing that's unique so to speak. Where a drug is manufactured depends upon how I want to use my capacity."

Transition 3 is the final manufacturing step before launching a product and as such, is critical to the commercial success of the drug. While commercial manufacturing is more standardized and can be more easily located at a distance, depending on the stage of growth of the company and its experience with commercial manufacturing, often it chooses to manufacture closer to its central campus. First and sometimes even second facilities are often located nearby or "onshore" to ensure that no glitches develop in those critical first years of production. But as companies grow and the demand for

[30] Charlie Cooney,. MIT The Future of Biomanufacturing Conference, March 10-11, 2009,.

biomanufacturing capacity increases, they tend to locate new commercial facilities further a field, whether to enter a new market, seek a lower cost location or because of an acquisition of another company. In addition, companies do not want to tie up their only facilities near HQ with the production 24/7 of one drug, preventing them from using the site for pilot, clinical or smaller batch commercial production. Once a product becomes successful, dedicated facilities are needed to continue to produce the drug without distraction.

Later Stage Commercial Manufacturing

Transition Four represents the mature phase of the manufacturing life cycle. At this point, after a company has been manufacturing a drug commercially for several years, it may find an opportunity to move production to a lower-cost location if faced with increasing demand for capacity. Confident in the manufacturing process at this stage, the tech transfer involved at this point is perhaps the easiest of all of them. For companies with the market share and the resources, locating commercial facilities farther afield makes good economic sense. Since 2004, most large biopharma companies have built facilities in lower-cost locations. This has accelerated the globalization of the industry. In almost all of these cases, the company has kept production in-house and not outsourced to a CMO. However, there are two interesting directions that companies take with respect to the use of CMOs at this point. Companies that have used CMOs up to this stage have waited to see how the drug performs on the market. If it has been successful and demand looks likely to grow, companies often decide then to get in the business of biomanufacturing for all of the reasons outlined in the previous chapter: control brings better opportunities for cost savings and innovation, as well as security in terms of the public health concerns. This has been BMS's strategy, a relative newcomer to biomanufacturing. In contrast, if a company has extensive experience in manufacturing and needs more capacity but does not want to build another facility, it may also decide to outsource production of its most standardized drugs. Genentech's relationship with Lonza in Singapore is an example of this[31]. On the whole, however, the risks involved and the

[31] In 2006, the Swiss-based CMO Lonza, announced it would build the first commercial-scale biomanufacturing facility in Singapore, which is expected to be online by the end of 2009. In 2006, Lonza

potential benefits of control still tend to keep manufacturing within firm boundaries. Genentech has outsourced relatively little of its manufacturing. Almost all biopharma companies that have had a successful biotech drug have ultimately ended up building their own facility and bringing manufacturing in-house.

It is perhaps surprising in an industry that has been around for 30 years, that until recently, few companies had moved production of mature drugs to low-cost locations. Product life cycle theory would predict that as a drug matures, production naturally moves to low-cost locations. Four mammalian –based biologics were approved in the 1980s. But only one of those was produced in a low-cost location before 2006. For approximately 20 years, three of the four drugs were made in the US or Europe. While this provides a window into the geography of biologics manufacturing historically, it is clear that prospectively, the timeline between the launch of a drug and locating its production in a low-cost location has been shortened. As outlined above, it was not until the late 1990s that Phase III and commercial manufacturing became more standardized. This, plus the fact that the regulatory process is now more supportive than obstructive to biomanufacturers, has given biomanufacturers more flexibility earlier in the manufacturing process to decide where to manufacture. A number of companies have moved production of their blockbuster drugs to low cost locations at a much earlier stage in the drug's lifecycle. For example, Abbott received approval for Humira in 2002, which it had produced through Phase III and launched out of its Worcester, MA facilities. The same year the drug was approved, Abbott began building a new commercial facility in Puerto Rico, and by 2006, the facility was on line and Humira production moved to Puerto Rico. Similarly, Genentech's Avastin was approved in 2006, and made in California. The same year, Genentech entered into an agreement to have Lonza produce the drug in its new facilities in Singapore, which come on line in 2009. This shortening of the timeline from the launch of the product to production in a low-cost location is driven by one critical factor: demand. When it is determined that a new product has a strong and growing market, then the company must develop a plan of action to expand capacity.

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entered into an agreement with Genentech to produce Avastin, in a new dedicated 80,000 liter plant in Singapore. The partnership between Lonza and Genentech stipulates that Genentech has the right to exercise an exclusive option to purchase the plant anytime between 2007 and 2012 (Genentech website).

4.4.3 Product Life Cycle and Entering New Markets

According to PLC, as the product matures, one would expect to see commercial production move first to new markets, and second, to lower cost locations.

In the first case, Vernon believed that there is a "triggering event" that pushes a company to consider creating a manufacturing facility in a new market, often a threat to a monopoly position. In the case of biopharmaceuticals, it is more likely the approval of a drug and the benefits that can come to the company if it manufactures in the new market. One would expect to see biopharma companies expanding most likely from the US, the largest drug market in the world, to Europe, the second largest (followed by Japan). The reality today is that companies are often seeking regulatory approval in multiple locations simultaneously, or within a very short period of time. In the case of expansion in Europe, given the relatively seamless nature of US and European regulatory environments and the low transportation costs for drugs, locating a facility in Europe is not essential to selling drugs on the continent. However, there are a few hoops companies must jump through before their drug can be sold, as well as some very practical benefits to locating production on the continent. First, a Qualified Person for Pharmacovigilance (QPPV), somewhat like a Quality Assurance professional in the US, is responsible for assuring the drug is ready for public consumption. This "QP" role, introduced in the mid-1990s, must be a European resident employed by the company, who takes responsibility (including liability) for the safety of the drug and deems it ready to be licensed. The company must also conduct release trials in Europe, ensuring that the drug has been successful with patients within Europe.

Besides these technical points, which can be accomplished in some cases by hiring third parties, there are other practical benefits to locating production in Europe. A European location can impact the company's top line since each country is responsible for the pricing of drugs in that particular country. Several countries will look favorably on the pricing of a drug (ie, price it higher) if the company manufactures it in their country. There is also a follow-on effect once a drug is priced in one country because others will follow the "price leader" country. Thus, if a company wants to help ensure a healthy

price for its drug, it may well decide to open a production plant in a particular country. This practice is becoming an unwelcome *quid pro quo* in some countries (Brazil and Turkey) where the governments have insisted on the manufacturing of some aspect of the drug in their country before they will allow it to be sold. While this requirement may be satisfied by a packaging plant or some aspect of the final stages of production, this could be a worrying trend for companies because of the challenges it presents for developing an efficient and safe manufacturing network.

In terms of locating production outside of "the Triad" of the US, Europe and Japan, demand has not developed enough in other parts of the world, particularly Asia, for many companies to invest in production in those markets. An exception to this is a company such as Sandoz, which makes biosimilars, and announced an investment in Singapore (via its parent, Novartis). In this case, there is a growing market that could be well served by production in the region. There may also be reasons (discussed below) other than emerging markets to locate in Southeast Asia.

4.4.4 Product Life Cycle and Low Cost Locations

Product life cycle theory predicts that after expanding into new, growing markets, as a product matures, companies will seek out low-cost production locations based on lower wages. Ultimately, as the product becomes a commodity, it is imported to the country in which it was originally produced. In the case of biomanufacturing, as technology has improved, regulation has loosened, and companies have become more comfortable making biologics, they have indeed moved production to lower cost locations, even if the product is not quite a commodity. However in this case, it is lower tax rates, not labor costs, that are driving the cost advantages, and they are found not only in "the South" or regions and countries in developing countries, but also in the "North" in a few European countries. In fact, offering a lower tax rate has been part of a concerted effort by a few countries and/or regions in the world to build up world-class biomanufacturing operations. This "middle station" between production in the innovator country such as the US, and production in the low cost country such as China or India, has emerged because of some of the unique attributes of the biomanufacturing industry. While a drug is under

patent and no biosimilars exists, a company has on average 12 years of monopoly profits for its drug. Given the desire to be closer to major markets, and the relative lack of qualified, lower-cost manufacturing options in Asia that will provide solid IP protection, companies preferred to locate their facilities within the Triad. Knowing this, a number of countries and regions have differentiated themselves within the Triad by using tax breaks to attract biomanufacturing investments.

Tax Policy and Incentives

Tax policy plays an increasingly important role in the location of biomanufacturing. For a company that has a billion dollar product, reducing a corporate tax rate on manufacturing from, say, 38% to 2% can represent hundreds of millions of dollars on the bottom line. A number of countries have tried to build their biotech capabilities on a foundation of downstream investments rather than upstream, that is, attracting investment that focuses on the production process rather than R&D. With fewer barriers to entry than R&D and a more standardized process, these activities are more mobile. The plan and hope for some of these countries and regions is that expertise in the downstream manufacturing will over time help build a critical mass that might attract investments in upstream R&D. For some places like Ireland and Singapore, they are simultaneously trying to develop both downstream and upstream activities in their countries. Attracting foreign direct investment (FDI) through favorable tax policies has long been a strategy of some countries, particularly targeting the manufacturing of multinational corporations (MNCs). Ireland began aggressively recruiting electronics manufacturers in the 1950s, and subsequently focused on biopharmaceutical manufacturers in the 1980s. Singapore has always focused on large-scale manufacturing and developed clusters in electronics, precision engineering and chemicals. As the electronics industry began to head to cheaper production locations in Asia in the 1990s, both countries targeted higher-value added manufacturing, like hard disk drives (in which Singapore became the largest exporter in the world) and biopharmaceutical manufacturing. Given the more complex, higher paying work in biomanufacturing, this industry became the logical follow on to pharmaceutical manufacturing, but requires a more skilled workforce, something Ireland and Singapore have invested heavily in since the 1990s (Breznitz 2007; Pereira 2006).

"Tax-advantaged locations" (TALs) have become well known and effective in their use of tax policy as a way to seed industries in their country or region. Along with Singapore and Ireland, Puerto Rico (PR) is another TAL whose favorable tax policies have attracted significant amounts of pharmaceutical manufacturing. Unlike Ireland and Singapore there is virtually no biotech research being conducted in PR. Another TAL in Europe is Switzerland, where a number of cantons are reinforcing the already strong biopharma company presence in both R&D and manufacturing, through favorable tax policies. While favorable tax policies exist in many other countries (and certainly are used at the state level in the US), these four locations emerge as the most prominent and clear-cut TALs for biomanufacturers. They also have been most effective in attracting investments.

These countries offer a tax rate of anywhere from 0 to 13% on products manufactured in their country, compared to the US federal tax rate of 38% (see Table 4.2). To understand the significance of this system as it relates to manufacturing, it is useful to take an example. Assume a company has sales of a drug of $100 in the US and after the cost of goods sold (COGS), it is left with $75 in gross profit. If all of the R&D, manufacturing and sales and marketing are in the US, then the $75 will be taxed at the US federal tax rate of 35% (offset by R&D tax credits given to the company for R&D, including Phase I and II clinical trials). If, however, the drug was manufactured in Ireland, and manufacturing represents approximately 15% of COGS, then $11.25 will be taxed at the Irish rate of 12.5% rather than the US rate of 35%. The company will pay $1.40, rather than $3.94 in tax, a savings of $2.54. The savings are much more dramatic if one applies a 2% or 0% tax rate.

In Singapore and Switzerland, companies can operate in the country tax-free for 20 years before they will be taxed. In addition, places like Ireland have a graduated tax rate so that the rate decreases the more "at-risk" operations are located there. Thus, the tax rates are lower for Phase III clinical production than they are for commercial production. In this way, the government hopes to attract more of the research-related operations that might lead to intellectual property (IP) developed in the country. The more IP in the country,

the more knowledge-intensive work, which translates into higher skills, incomes and ultimately standards of living.

Companies, in turn, can claim a lower tax rate if they can prove that "at-risk" operations were conducted in the TAL. This practice, called "transfer pricing" is " the art of attaching a monetary value to trademarks, patents, research and other intangibles that one arm of a multinational company transfers to another". Transfer pricing apportions costs across different arms of a multinational company and thus determines what profit is allocated to which country. As the CFO of Glaxo said, "It's probably the most complicated area of taxation in the world. It's not like buying a TV, where there is a market price," he said. "There isn't a market price within a company."

Table 4.2: Tax Rates Available to Biomanufacturers in Select Countries

Country	Tax Rate (%)	Comments
Singapore	0	First 20 years tax free; negotiated thereafter; training
Switzerland	0	First 20 years tax free; tax rate thereafter negotiated upfront;
Puerto Rico	0-4	Training and infrastructure subsidies
Ireland	0-13	Depends on stage of manufacturing; training and infrastructure subsidies
US	38	Corporate tax rate; tax breaks and subsidies provided at the state level

Tax policy has become paramount for many companies when considering their manufacturing strategy. "Going forward, it is all about tax rates," said one manufacturing executive. "That's all we hear about from headquarters. We must manufacture in a tax haven." Many executives interviewed called the decision to manufacturer offshore in TALs "a no-brainer." Other companies, smaller in size, call this issue a "red herring:" "In

a high margin business, these costs are really far down the chain. We'll invest some of our operations in TALs, but not all of it," said one executive at a FIBCO.

Clearly, TALs make the most sense for those who are most concerned about margins, for example, CMOs (Lonza's move to Singapore, for example). In addition, for companies who expect to be in the business of biosimilars, such locations make sense because of the lower margins. Novartis announced in 2007 that it will be building its next biologics manufacturing facility in Singapore, in part because its generic manufacturing subsidiary, Sandoz, is in the biosimilars business (those plans have been put on hold for the moment). But as biosimilars develop and the biopharma industry experiences greater pressure on its margins, TALs are going to make sense for many biopharma companies.

Subsidies

In addition to the tax breaks, countries or states/regions also offer other subsidies around land, infrastructure and training. While these alone won't attract investments in TALs, they help sweeten a deal, particularly when comparing packages from different countries or regions. These may include grants for land, buildings, physical infrastructure, or training the workforce. Singapore has been very aggressive in this area, for example, offering Lonza hundreds of millions of dollars to build its newest facilities, as well as offering to pay for the training of its workforce, both in the US and in Singapore.

These sorts of sweeteners are familiar in the US as well, though on a smaller scale. While states can do little to change the federal tax rate, they can provide grants and other types of investments to attract or retain companies. North Carolina has been very aggressive in biopharma manufacturing, offering millions of dollars to companies to build in the state, where historically there was little life sciences R&D. "They rolled out the red carpet for us. Their attitude was, 'what else can we do for you?'", said one executive who built a commercial facility in the state. Massachusetts, whose particular strength lies in upstream R&D, has more recently focused on the value of biomanufacturing to the regional economy, and offers its own set of incentives, though they fall more within the range of "public investments." In 2005, in the largest package ever assembled, the state offered

BMS $33 million in tax credits and issued a $34 million bond for physical infrastructure investments to locate its commercial facility in Devens[32]. The details of the subsidies provided are often not made public so it is difficult to assess the final package for any company.

Overall, manufacturing in low-cost locations is clearly becoming more attractive to biomanufacturers and is an important driver in location decisions at the later stage of production. Product life cycle theory helps explain this dynamic, just as external economies, particularly specialized labor, helps explain the origins of the cluster. While these are the primary factors that explain the location of the industry, there are secondary factors that help explain some of the anomalies that appear in the data provided in the next chapter. Drug sales, the company's stage of growth and portfolio, and the sunk costs of facilities all help to explain the location of biomanufacturing.

4.5 Other Factors That Drive Location

The factors presented thus far as critical to determining the location of biomanufacturing (skilled workforce and product lifecycle) explain important parts of the story. A skilled workforce is a precondition to any biomanufacturing investment. However, while a skilled workforce is necessary, it is not sufficient to explain why companies locate where they do, given the number of possible locations that can provide a skilled workforce today. Likewise, product life cycles clearly influence where clinical manufacturing and early stage commercial manufacturing facilities are located, but they do not tell the whole story as to why some companies choose to locate in low cost locations and others don't. There is a third critical factor that drives location decisions: demand. Despite cheaper locations in which to manufacture, companies will not move production unless there are sufficient drug sales to justify it. Demand, combined with the company's stage of growth and portfolio, help explain the final phase of the manufacturing life cycle.

[32] The state also changed its investment tax credit rules to allow the company to claim a 5% refund on its investment in the facility. http://www.pharmaceutical-technology.com/projects/bristolmyers/

4.5.1 Drug Sales

Aligning the supply of biomanufacturing capacity with the demand for a drug is another challenging aspect of the business of biomanufacturing. "Companies...still cannot predict how well a given therapy's market will grow" (Kamarck 2004). At the same time, companies want to maximize profitability as quickly as possible: "The market with novel biologics is usually difficult to predict so we usually look to optimize profitability early," said one executive. As discussed in the previous chapter, companies walk a fine line between trying to maximize utilization rates and ensuring enough capacity to meet current and future demand. Once a drug becomes successful and demand is predicted to increase, a company must quickly figure out how to increase capacity, given that it can take at least four years to build a new commercial facility.

A company that needs to increase capacity has a number of options: expand at its current location, outsource some of the manufacturing to a third party, acquire a new facility, or build a new facility. One of the key factors for the company will be current and predicted drug sales, for one or multiple products. For example, all of the companies that have bulk production in low-cost locations have at least one blockbuster drug. The decision to build in a TAL was driven in almost all of these cases by the need for greater capacity. As one executive said:

> "People will not proactively seek out a tax advantaged location just to move something offshore. Its not from the NPV or the IRR that you decide you are just going to move [production]. It is prompted by the need to expand. You've got a successful product and you've got to spend $150m to expand your existing facility. It's opportunistic. If you need to have a shovel in the ground and you're going to drop $150m, why don't you get the tax advantage, too..."

In today's biomanufacturing landscape, if a company decides it is time to build a new facility, then the decision where to build a second (or more) commercial facility will be heavily influenced by the tax advantages the company can receive by locating production in a TAL. A couple of examples help underscore the importance of drug demand to manufacturing location decisions.

Enbrel, the wildly successful arthritis drug, illustrates both the importance of manufacturing to a company's success, as well as how demand can drive much of the location decisions for a company. Enbrel was developed by Immunex and approved by the FDA in 1998. The drug was initially manufactured by a CMO, Boehringer Ingelheim. But the company was soon overwhelmed by demand. Within six months of the launch of the drug, US sales had already surpassed the company's worldwide sales projections for the year (*Ibid*). It quickly bought existing facilities in Rhode Island, (built by Wellcome and Genetics Institute in the late 1980s and sold to American Home Products in 1999). The Rhode Island facility was, for a while, the world's largest cell culture manufacturing center. Immunex sold the European rights to the drug to Wyeth, which immediately began building its second commercial facility in Ireland for Enbrel production. The inability of Immunex to meet the production needs of the drug ultimately contributed to the company's sale to Amgen in 2002. Amgen had the resources to immediately add another facility to the Rhode Island site. Until the Wyeth site came on line in 2006, there was a shortage of Enbrel such that there was a week or less of supply on the shelf in any one location. Wyeth's decision to manufacture in Ireland was both driven by tax advantages and the fact that it was producing for the European market. Currently, the tax benefits of manufacturing in Ireland saves the company hundreds of millions of dollars a year.

Likewise, disappointing sales of a drug can scuttle expansion plans. Amgen acquired Abgenix and its drug Vectibix (a colon cancer drug) in 2006, the same year the drug was approved by the FDA. Anticipating increasing sales of the drug (sales were $170m in 2007), the company did a worldwide site search for a new facility and decided upon Ireland as a second commercial facility for the drug (the first is in Fremont, CA). But ongoing clinical trials of the drug found it to be ineffective and cause negative side effects, which have led to declining sales. Amgen subsequently dropped the plans for its Ireland facility.

4.5.2 Company Stage of Growth and Portfolio

Given the capital outlays that are required for a biopharma company to manufacture its own drugs, clearly the company's size and resources are critical to whether it will be conducting its own manufacturing. As discussed earlier, start-up companies or those with just a few drug candidates in early stage clinical trials are going to outsource their manufacturing to a CMO. Until a company has a certain degree of confidence about its pipeline and the chances of having a successful drug candidate, it is unlikely to engage in its own manufacturing due to the expertise required and the capital outlays.

Thus, most of the biopharma companies that are building their own clinical and commercial facilities are companies of a certain scale with capital resources. They (and their investors) will not take on the risk of building biomanufacturing capacity unless there is sufficient capital at hand. This is particularly true for companies deciding to build facilities abroad. Aside from sufficient drug demand, the company must have a large enough base of manufacturing expertise that it can take on the enormous task of building a facility abroad. To build a facility that will maintain a company's culture and standards requires significant investment of the home team's time. One company that built a facility in Ireland had an "expat" team of 20-30 people move to Ireland for six months to a year to ensure a successful transfer of knowledge, expertise and cultural practices. "The goal is to make it a domestic plant in that foreign location."

However, scale and resources do not automatically lead companies to manufacture offshore in lower-cost locations. As discussed in the last chapter, the business model of biopharma has evolved over time from one in which there was a clear distinction between biotech firms and pharmaceutical firms, to one in which companies engage in both aspects of drug development, thus are often referred to as "biopharma" companies. Having said this, the big pharma companies have slowly been building up their biologics capacity, largely through acquisition, and differ in some fundamental ways from the traditional "FIBCOs" – fully integrated biotech companies, like Genentech, Amgen, and Biogen-Idec. The business culture between biotech and big pharma are often described as polar opposites: biotech is the entrepreneurial, innovative, casual and somewhat

undisciplined start-up industry, while big pharma is the slow, top-heavy behemoth that stifles innovation. Until recently, some argue, biotech companies did not think in terms of costs or margins. "Biotech is not driven by a business model," said one executive. "Cost is not a significant issue in this industry." The different history, experience and culture of big pharma and biotech companies may influence decisions regarding where to manufacture. Aside from a greater sensitivity to margins, pharmaceutical companies have been making drugs offshore in low-cost locations for decades and thus may have a greater comfort level in moving biologics production offshore to countries where they already have pharmaceutical manufacturing operations At the same time, the relative newness of biologics to a big pharma company's portfolio might make it more comfortable with keeping manufacturing closer to home, even if it has the resources to build abroad. In the next chapter, we will see examples of both strategies.

4.5.3 Capital Outlays and Acquisitions

Finally, while all of the factors described above are the primary drivers of biomanufacturing investments, companies may often end up with facilities that are not near their R&D or company headquarters as the result of an acquisition. As stated earlier, the significant capital outlays and time commitment ($200m to $800m and four to seven years) that are required to build a commercial facility, and the value of FDA approval of a site, make these facilities valuable to new owners who rarely "mothball" them. Often, they continue production of the drug or drugs they have acquired, or will renovate the facilities for their own uses. Many facilities have had multiple owners over time, and have been used for decades. Centocor's St. Louis commercial facility has had four owners since it was built in the early 1990s. Similarly, Amgen's Rhode Island facilities, built in the late 1980s, have had three owners over its thirty-year life.

4.6 Discussion

In this chapter I propose two driving factors that explain the location of biomanufacturing, outlining the theoretical frameworks and supporting qualitative evidence to support these propositions. From economic geography and in particular, the geography of innovation, we understand the importance of clusters, particularly for knowledge creation and innovation. In innovative industries like biomanufacturing,

external economies generate a specialized labor pool that helps provide the most critical factor for operations, a skilled workforce. With a relatively high percentage of post-graduates employed in the industry (20 to 25%) but labor representing a relatively low percentage of total costs (3-9% of total sales), biomanufacturing clusters arise in places where they can find talent. Low-cost labor is not a real factor.

While skilled labor is a necessary condition for the location of biomanufacturing, it is not sufficient. Product life cycle theory provides a dynamic model to explain the manufacturing process along the life cycle of a product. Biomanufacturing follows a classic product life cycle trajectory, though patents and tax policy add some twists. Early stage manufacturing, and first commercial facilities stay close to R&D. When a company expands into new markets, it is often killing two birds with one stone: expanding into a new market such as Europe, but also locating in a new "middle station" lower cost location, namely tax-advantaged locations (TALs). These middle stations, places such as Ireland, Puerto Rico, and Switzerland, are taking advantage of the fact that companies want to stay close to their markets and do not have options today to send complex, patented biomanufacturing processes to lower cost locations based on wages or infrastructure. They use tax policy and subsidies to attract the most standardized biomanufacturing. Even though companies can have a temporary monopoly due to patents, many are moving operations to TALs at an increasing rate to optimize profitability. For biosimilars, the product life cycle is complete, as companies locate these lower-cost products to cheaper countries in Asia. Finally, other factors can play a role in determining where a company makes its biomanufacturing investments. If drug sales become substantial, a company has an incentive to find a low-cost location for its manufacturing. However, it depends on the company's stage of growth and general business culture and portfolio as to whether it will make this move. Companies with many several approved drugs, or a history of pharmaceutical manufacturing abroad, are more likely to seek out TALs than companies that do not fit this profile.

This chapter has proposed two key factors, talent and product life cycle, to explain the location of biomanufacturing. The next chapter will provide more quantitative data to support these propositions.

Chapter 5

Data Analysis of Trends in the Location of Biomanufacturing

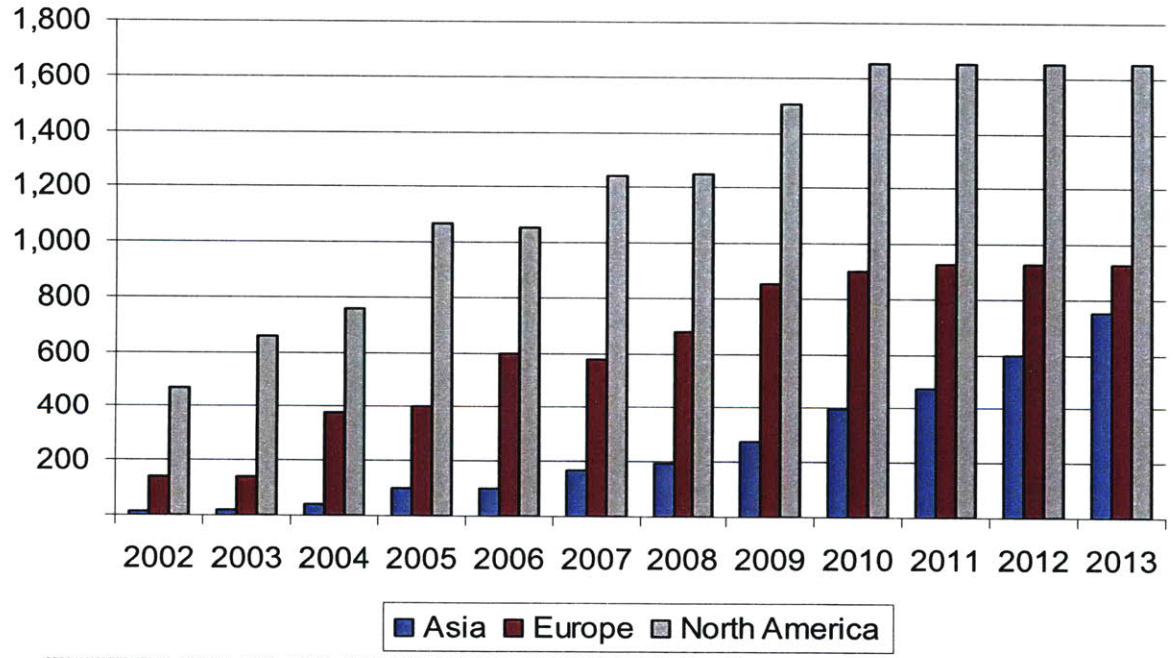
The previous chapter proposed that two key factors, skilled labor and product life cycle, are the primary drivers of location, with drug sales and company growth and portfolio secondary factors. This chapter provides data to support these three propositions, as well as data on overall trends in biomanufacturing investment.

5.1 Global Trends in Biomanufacturing Investments:

5.1.1 Investments by Continent

Figure 5.1 provides an overview of recent trends in global investments in mammalian-based biomanufacturing capacity.[33] A number of observations can be made from this chart.[34]

Figure 5.1: Global Biomanufacturing Capacity, 2002 projected to 2013



investments up to that date. Data represents biomanufacturing capacity based on when it is projected to go online. Thus, for example, investment projects announced in 2005 do not appear in the data until 2009, when the facility is expected to go online. Given it takes approximately four years to build a facility, the data account for all announcements made up to December, 2008.

[34] As a reminder, this data covers only mammalian-based GMP clinical and commercial facilities. I also only include batch-fed and perfusion processes when referencing volume of capacity since it is difficult to accurately know the volume for other processes such as disposables or roller bottles. However, in references to number of companies or sites, I do include those companies engaged in processing other than batch-fed or profusion. Projects that are in the planning, construction or validation phase are also included.

US Predominance : In terms of volume, the US has more volume than any other continent. This is no surprise given the prominence of biotech in the country, and the importance of proximity between R&D and production,. The industry was pioneered in the US and significant investments were made in large bioreactors beginning in the mid-1980s (Genentech's 8x12K reactors were approved in 1985). Given the capital outlays involved in building facilities, most of those built in the last two decades are still in use today.

Productivity and Pipeline: While there has been relatively steady growth in volume from 2002 through 2009 and projected into 2010 in North America and Europe, as of 2010, growth is predicted to level off through 2013, the latest year forecasted. These trends were projected well before any global economic downturn so they are not related to changes in the demand for biopharma products. Instead, they are primarily due to productivity gains in the industry. Overall process yields or "titers", have increased at an extraordinary rate in the past decade such that companies have gotten rapidly increasing amounts per liter. For monoclonal antibodies for example, it was common to achieve titers of 100 to 200 mg per liter. "If you were between 100 and 500mg per liter, you were happy," said one executive. Today, companies regularly achieve three grams per liter, and it is thought that some companies are producing at four grams per liter for some commercial production. Other companies are developing cell lines for certain antibodies that are heading toward 10 grams per liter. [35] This not only leads to producing more with existing capacity, but also may lead to smaller facility footprints, potentially moving away from large 20kl tanks. This trend raises concerns about excess capacity in the short- and medium-term. In addition, utilization rates are predicted to increase from the current

[35] These estimates come from interviews with biomanufacturing experts from several companies. No one would give exact numbers on their titers, but provided a range. Most agreed that titers would reach 5-10 grams in the next decade. The Dutch company, Crucell, is pointed to as one company that is developing technology that increases titers to between 10-20 grams per liter.

level of 50%, to around 70% by 2010.[36] All of this will occur with a larger pipeline of drugs.

Growth in Asia: The final point to make about Figure 5.1 is the steady growth of capacity in Asia over the past seven years, and importantly, the projected growth from 2010 to 2013. This too, plays a role in the flat growth projected in Europe and North America. The increase in biomanufacturing capacity in Asia can be explained by several factors. First, a number of Asian countries are targeting the biomanufacturing industry as a growth industry and thus have made a concerted effort this decade to grow and develop capacity (Singapore is a prime example). Their strategy has involved both attracting FDI through lower tax rates and subsidies (discussed in the product life cycle section), and also developing internal contract manufacturing capacity. CMOs are highly sensitive to costs because of the pressure on their profit margins, and thus will be among the first to seek out low-cost production locations. Not surprisingly, the growth in Asia is being driven by CMOs (see Figure 5.2). Sixteen of the 19 companies manufacturing in Asia are CMOs. These investments suggest CMOs expects significant growth in their business even if productivity is increasing.

The second reason capacity is growing in Asia is because of the growing market in the region. Locating production in Asia is an important first step for those companies that want to serve the emerging biopharma market, currently dominated by biosimilars. Except in the case of Japan, the drug substance being made in Asia is not for "innovator drugs". Production is largely for more mature products with high volume. Table 5.1 below shows the additional capacity coming on line in Asia between 2010 and 2013. The investments each year are largely driven by one company, all of which are CMOs but for Novartis. If any one investment falters (such as Novartis' plans in Singapore, which have been put on hold), the growth in Asia looks less dramatic. While Asia is still not as large as some might expect, biomanufacturing is clearly becoming a global industry.

[36] Estimates provided by BioProcessing Technology Consultants, December, 2008. The 70% estimate is dependent upon two variables: overall process yields (titers) and how many products in the pipeline gain regulatory approval.

Figure 5.2: Contract Manufacturing Organization Capacity, 2002 to 2013

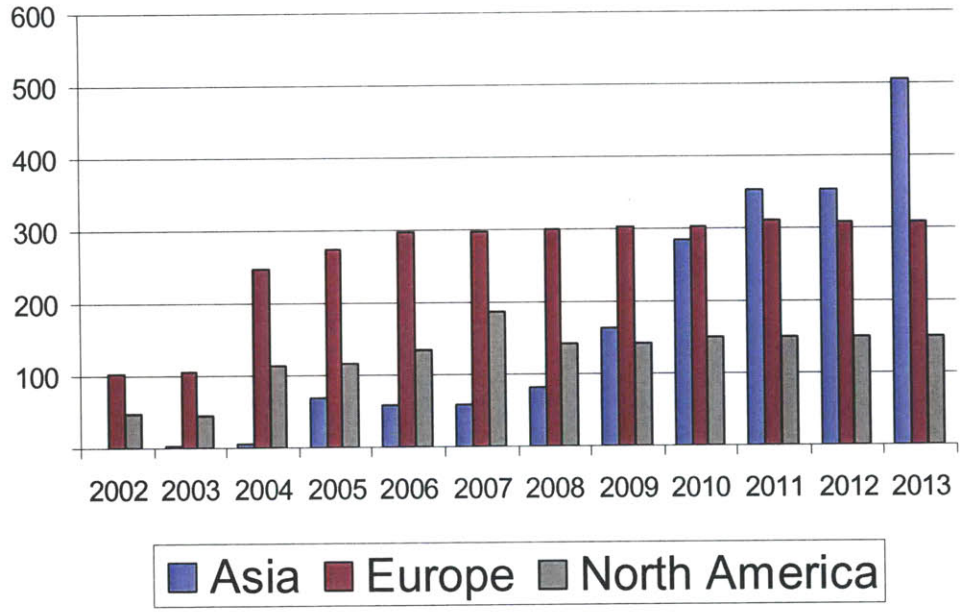


Table 5.1: Projected New Capacity in Asia, 2010-2013

Year	Added Capacity	Of Which	Invested By	In Country
2010	121,500	90,000	Celltrion	South Korea
2011	84,000	80,000	Lonza	Singapore
2012	120,000	120,000	Novartis	Singapore
2013	153,000	108,000	Celltrion	South Korea

Total volume of capacity is one way to measure the presence and concentration of the industry by continent. Other descriptive analytics gives more context to the biomanufacturing going on in each of these parts of the world (see Table 5.2). First, not surprisingly, when it comes to total number of companies conducting biomanufacturing, the US has the most number of companies and the smallest percentage of CMOs. This means there are more product companies, which are engaged in making "innovator" drugs. In contrast, Asia, home of a growing biosimilars market, has the highest percentage of CMOs. Second and related to this previous point, are the significant number of clinical biomanufacturing sites in the US and Europe, which speaks to the amount of clinical research going on to develop new drugs. Third, the number of commercial sites with capacity over 5kl underscores the entrepreneurial strength of the

US. Sites of this level of production are most likely first commercial sites for growing companies or companies engaged in producing for niche markets. The fact that there are twice as many sites of this size in the US relative to Europe may point to Europe's challenge in translating research into commercial ventures. Finally, the relatively small difference between the US and Europe when it comes to the number of commercial sites with greater than 50kl shows that well established companies have invested at a significant level in both continents, investments that are not easily moved or made obsolete.

Table 5.2: Descriptive Statistics on Biomanufacturing by Continent

Continent	No. of Companies	No. of CMOs	Percent of CMOs	No. of Clin. Sites	No of Comm. Sites	Comm. Vol > 5kl	Comm. Vol> 50kl
North America	50	28	56%	46	32	17	12
Europe	41	30	73%	33	23	8	10
Asia	19	16	84%	16	7	9	4

5.1.2 Top Locations Globally

Figure 5.3 below shows the top 10 regions for biomanufacturing in the world by capacity. Five of the 10 are in the US, three are in Europe, and two are in Asia (for the top 10 locations on each continent, see Appendix Z). Of course, the top two locations in the US, California and New England, are sizable geographies when compared to some of the other geographies (Singapore or Maryland, for example).[37] In total, biomanufacturing investments have been made in 117 cities and 22 countries (of which there are 24 states or provinces within North America).

[37] The regional clustering of the top US locations, New England (MA, RI, NH) and the Northeast (NJ/NY/PA/CT) are based on well established industry clustering of the biopharma industry nationally (see Biospace.com). Connecticut is included in the descriptive statistics but not presented in Chart Y because it has insignificant capacity.California, while often divided into Northern and Southern California, was kept as one state for purposes of data analysis. Maryland is usually grouped with the "Mid-Atlantic" region including Delaware, DC and Virginia, but these three areas have no biomanufacturing capacity. North Carolina stands on its own. The grouping of Ireland/UK was based on their geographic proximity.

Figure 5.3: Top Biomanufacturing Locations by Volume, (projected through 2013)

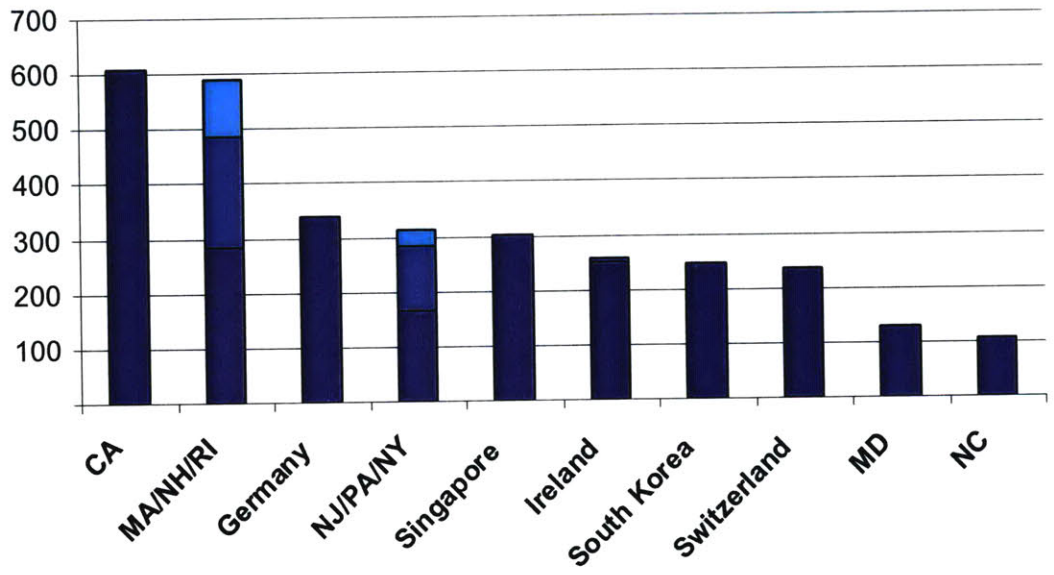


Table 5.3 provides some of the descriptive statistics. While volume is an important indicator of industry presence, as mentioned before, the number of companies in each location also indicates the dynamic nature of the cluster, i.e., whether there are more start-ups or growing companies that are reaching a scale in which they engage in their own manufacturing. The top locations by number of companies speak to this dynamic. New England, Ireland/UK, the "Northeast" (NJ/PA/NY/CT) and California all have well established, large biopharma companies, but also a number of small-to-mid-size growing companies. In addition, the scale of commercial facilities speaks to the extent to which established companies are invested in the area. Again, New England, the Northeast and California dominate in this category when we look at number of investments that are greater than five or 50kl.

Table 5.3: Descriptive Statistics of Top Locations for Biomanufacturing Globally

Continent	No. of Cos.	No. of CMOs	No. of Clin. Sites	No of Comm. Sites	Vol. > 5kl	Vol. > 50kl
New England	13	2	9	9	5	4
Ireland/UK	11	7	7	6	2	2
CA	10	6	9	9	4	3
Germany	9	6	7	4	1	3
NJ/PA/NY	11	4	9	6	4	2
Switzerland	5	3	2	3	1	2
Singapore	3	2	1	3	1	2
MD	3	2	3	2	1	1
South Korea	2	2	1	1	0	1
NC	2	1	1	1	0	1

What is perhaps surprising about these 10 locations is how concentrated the industry is, how few companies there are in some of the locations, and the presence of relatively new "players" on the list. North Carolina, with just over 100kl in volume, has only two companies engaged in mammalian-based production and only one commercial site (though with greater than 50kl). This is also the case for South Korea, which, along with Singapore is on the list prospectively (based on facilities that should be online by 2013). If these and Maryland, with three companies and less than 130kl, are taken off the list, that leaves six locations in the world with biomanufacturing concentrations, each with five to 13 companies. This suggests that biomanufacturing is specialized enough that centers are few and far between, but also that, given the right conditions, other regions have entered the industry by attracting or growing a few companies that make significant investments. In the previous chapter, I proposed that talent, proximity to biotech R&D, and lower costs were all critical drivers of biomanufacturing location. This next section looks at whether the data supports these propositions.

5.2 The Importance of Talent and Proximity

5.2.1 R&D Centers and Manufacturing

Biotechnology is one of the most "knowledge intensive", high-skilled industries of the 21st century. Much has been written about the high percentage of highly educated workers in the field, and its co-location with regions that have research universities and solid STEM education (Cortright and Mayer 2002). The life sciences is one of the more education-intensive clusters, with a higher than average percentage of workers with advanced degrees. (Mass Inc, 2007). To the extent that biomanufacturing is co-located with biotech R&D, it is drawing from the same highly skilled labor pool.

Table 5.5 presents a comparison of the top global biotech R&D centers by employment and global biomanufacturing centers by volume. At the country level, seven of the eight top countries for R&D in biotech (countries with greater than 4,000 employees) are also within the top eight countries globally for mammalian–based biomanufacturing[38]. This

[38] Because biomanufacturing employment data is difficult to separate from pharmaceutical manufacturing data, I use volume of capacity as a proxy for employment. For example, if one ranked US states/territories

suggests there are benefits to co-location, which as the previous chapter outlined, relate to talent within a biotech center, and proximity to biotech R&D. Two exceptions stand out on the list: Canada, which is ranked fifth in research but does not have significant manufacturing, and Singapore, which is ranked 3rd prospectively in biomanufacturing center but does not yet have significant R&D employment. In the case of Canada, one can assume they benefit from proximity to major biomanufacturing centers in the US, much in the same way the UK benefits from proximity to Ireland. In the case of Singapore, while investing in both R&D and manufacturing, the downstream manufacturing is more easily developed due to lower barriers to entry.

Table 5.5:Top Global Biotech R&D Centers by Employment, 2003

		R&D Total	Global Bioman Ranking	Volume (kl)
1	US	73,520	1	1,736
2	UK	9,644	4	250
3	Germany	8,024	2	337
4	Korea	6,554	5	249
5	Canada	6,441	NA	11
6	Denmark	4,781	7	96
7	France	4,193	8	80
8	Switzerland	4,143	6	234

Source: R&D data from OECD (2006) as presented in Hermans et.al.(2008). Biomanufacturing data from author.

When one examines the US state by state (Table 5.6 below), there is more divergence between US centers of biotech research and biomanufacturing. Three states that are centers for biotech R&D employment are not centers for biomanufacturing: Florida, Texas and Illinois. Obviously the proximity between states with biomanufacturing capacity as well as the presence of CMOs around the country makes it entirely possible to develop R&D without manufacturing, though not necessarily preferable. In the case of Florida and Texas, their R&D capacity has been acquired relatively recently (Florida provided $300m in grants for the Scripps Institute to locate a facility in Florida), and there are efforts underway to develop biomanufacturing capacity (Texas A&M just

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by pharma manufacturing employment, Puerto Rico would be ranked 4th due to the high concentration of small molecule pharma manufacturers located there. For further information, see discussion in Chapter X on economic development. See Battelle Technology Partnership Practice and SSTI, *Growing the Nation's Bioscience Sector: State Bioscience Initiatives 2006*, under "Section Title."

provided $50 million to develop a vaccine facility in College Station. Demand for biomanufacturing may be generated over time. The only US region that is strong in biomanufacturing but not strong in R&D is Puerto Rico, which has focused primarily on becoming a low-cost biopharma manufacturer.

Table 5.6: Top US Biotech R&D Centers by Employment, 2006

	State	2006 Employment	US Bioman Ranking	Volume(kl)
1	California	75,616	1	607
2	Pennsylvania	32,855	5	119
3	New York	27,672	10	32
4	Massachusetts	25,637	2	286
5	New Jersey	24,880	4	164
6	Florida	22,466	NA	1
7	Texas	21,238	NA	0
8	Maryland	16,457	5	128
9	North Carolina	16,005	7	105
10	Illinois	13,262	15	2

Source: Employment numbers from Battelle, (2008); Includes jobs in research, testing and laboratories in the life sciences.

While there is no way to prove any directional causation, my research suggests that it is R&D that pulls the manufacturing, and not the reverse. Because of the importance of proximity to R&D (discussed below), biopharma companies often locate manufacturing near R&D. In contrast, in places where manufacturing exists without the R&D, such as Ireland, Singapore and Puerto Rico, little R&D investment has followed.

5.2.2 Distance Between R&D and Manufacturing

Drilling down a bit deeper on the co-location of these activities, one discovers a relationship between biotech R&D, biomanufacturing and product life cycle. As was outlined in the previous chapter, product life cycle plays a role in biomanufacturing location. Particularly in the early stages of a drug's development, when a compound is being scaled up in the pilot and early clinical manufacturing, the tacit nature of the work keeps this manufacturing closer to the R&D teams. Many companies have co-located their primary biologics research centers with the company headquarters, but this has been

changing. Increased vertical disintegration in pharma R&D since the mid-1980s, and the acquisition of biotech companies to gain access to the R&D, has led to a greater expansion and geographic dispersion of some R&D activities.[39] Boston has benefited from this trend, for example, with the location of R&D teams from Merck and Novartis. As with many other large biopharma companies, they have multiple R&D centers, as well as European and US headquarters.

In an effort to determine how important proximity to R&D activities are for clinical and commercial biomanufacturing, I analyzed the distance between a company's R&D center and its biomanufacturing facilities, for both clinical and commercial facilities. [40] The benefits of proximity for clinical manufacturing are borne out by the data (Figure 5.4). An analysis of all clinical production facilities (42 sites) finds that 80 percent are within 100 miles of R&D teams and all but one of these are the companies' first clinical facility (the exception is a second). An additional 17% are within 1,500 miles (the distance between Chicago and Boston, for example), of which 70% of these are second, third or fourth facilities. Thus, the vast majority of clinical manufacturing facilities are kept close to R&D, and as a company grows and adds additional clinical sites (often through acquisition), these too are within a reasonable distance of the research teams (a couple of hours' flight).

Whereas clinical biomanufacturing facilities are used for relatively short campaigns of small batches, and ideally continually replenished with new drug candidates that are just going into clinical trials, commercial facilities require scale, continuity and repetitive, non-stop production. As discussed in the previous chapter, a commercial facility is used for Phase III scale up and the launch of a product. By this point in time, the drug has

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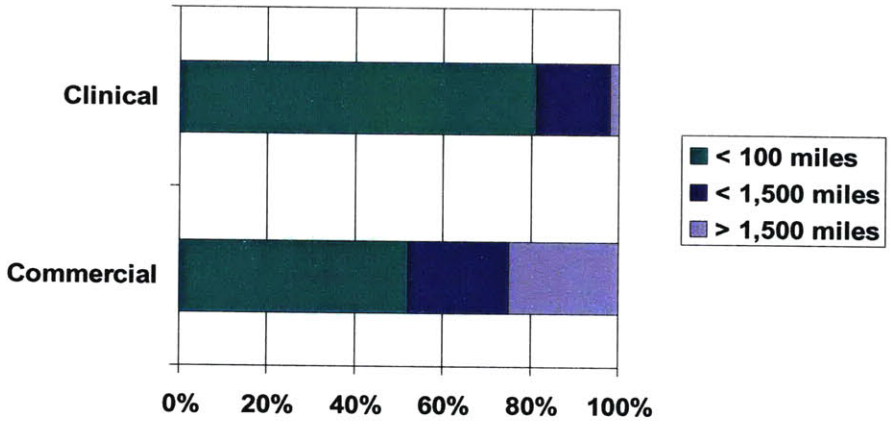
[39] Ian Cockburn, "Pharmaceuticals." Chapter in D. Mowery, J. Macher and S. Merrill (eds.) *Globalization of Innovation:US Firms Comp Innovation in Global Industries: U.S. Firms Competing in a New World* (National Academies Press, Washington DC. 2008), 207.

[40] I did not attempt to determine exactly which drugs were researched in which locations and where those particular drugs were manufactured because of the complexity of tracking the numerous drugs each company is developing. If there is R&D being conducted in a location where there is also manufacturing, I have used that R&D center for this analysis.

passed proof of concept, the manufacturing process is well understood, and the facility is validated for commercial production.

Figure 5.4: Distance Between R&D and Biomanufacturing



With less interaction between upstream R&D and the downstream commercial manufacturing, it is perhaps a bit surprising that just over half (51%) of all commercial facilities (44 sites) are still within 100 miles of company R&D. The vast majority of these (78%) are the first commercial facilities for the company, a finding that fits with Vernon's predictions about product life cycle theory. As a company begins commercial production of most likely its first approved drug, it wants to keep a close eye on production. While the more codified process allows companies to locate production further a field, three-quarters of all commercial facilities are still within 1,500 miles of R&D centers. Importantly, close to 90% of these are either first or second facilities for the company. This suggests that commercial production, while more established and well understood, still presents enough complexity that companies find it beneficial to keep it nearby, either within a couple hours drive or flight. It is also important to remember that some of these facilities were not built but acquired, and preserved rather than mothballed because of the capital investment already made.

The 11 facilities located greater than 1,500 miles from company R&D highlight some of the other factors that influence location, specifically drug demand, company size and portfolio, and lower costs. Product life cycle theory would suggest that facilities built

farther away would reflect the maturing of the product, with companies either entering new markets or finding lower cost locations for production. This is the case for most of the 11, but surprisingly, three of the 11 are first commercial facilities. The rest are either second (3), third or fourth facilities (5).

Table 5.7: Companies with Commercial Facilities More than 1,500 Miles from R&D

Company	# Facility >1,500miles	Bioman Location	Location Driver
Genmab	1st	Minnesota	Acquisition
Lilly	1st	Ireland	TAL
Pfizer	1st	Ireland	TAL
Abbott	2nd	Puerto Rico	Demand/TAL
Novartis	2nd	Singapore	Demand/TAL
Wyeth	2nd	Ireland	Demand/TAL
Amgen	3rd	RI	Acquisition
Amgen	4th	Puerto Rico	Demand/TAL
Biogen	3rd	Denmark	New Market/TAL
Centocor	3rd	Ireland	Demand/TAL
Genzyme	3rd	Belgium	Acquisition

Table 5.7 above shows the 10 companies (11 sites) and the primary factor that drove the decision to locate a facility in that region. Acquisitions explain three of the 11, including one of the first facilities. Drug demand and tax-advantaged locations largely explain the rest. The next sections will speak to these important drivers of location.

5.3 Drug Sales, Company Growth and Portfolio

As explained in the previous chapter, increasing demand for a drug puts pressure on a company's manufacturing capacity. In order to meet demand and achieve economies of scale, companies will look to expand production, and in doing so, take greater account of cost-effectiveness.

Table 5.8 presents all 28 companies with approved mammalian biologics along with variables that give some indication of company size (market capitalization where appropriate), drug sales (for approved mammalian drugs only), number of commercial facilities, and whether they have built facilities in a tax-advantaged location. The data suggests that there is a difference in manufacturing strategy and location depending on

the size of total drug sales and stage of company development in biologics production. Companies with less sales, fewer approved drugs and fewer commercial facilities tend to keep commercial manufacturing near R&D, while companies with greater sales, more approved drugs and more facilities tend to locate production farther away, in low-cost locations.

For the 14 companies that have sales of under $500 million, almost half are using CMOs for their production, and the rest are manufacturing at or near their R&D HQ. This includes both Novartis and Lilly, which are planning or in the process of building facilities in TALs to accommodate production of their future biosimilars and pipeline and/or drugs obtained through acquisition. Ten of the 14 companies have only one drug approved and either one or no commercial facility (they use CMOs). Nine of the companies have market capitalizations under $10 billion or are privately held. In addition, 75% of the drugs were approved after 2002, so they are relatively early in the drug's sales lifecycle, with an average approval year of 2002. This profile fits with the product life cycle theory presented to date. Smaller, emerging companies with just one approved drug do not have the resources to build their own manufacturing facilities so they outsource production to CMOs. Even large, established companies, such as Lilly, outsource when they are relatively new to biologics production and have few approved drugs with insignificant sales. Medium to large-size companies (from $1- $40 billion in market cap.) that decide to manufacture their drugs themselves are locating their first commercial manufacturing facility near to their R&D headquarters, and in some cases, may choose to even locate their second facility nearby (such as BMS), to gain comfort with the manufacturing process. Overall, these companies have a wide range of market capitalizations if any, an average of 1.3 approved drugs, which have been on the market for an average of seven years, with average annual sales of under $130 million. For all of these companies, the emphasis is on quality and getting the product to market, and less on cost savings.

Table 5.8 Biopharma Companies with Approved Mammalian Biologics:

Number and Location of Commercial Manufacturing Facilities

	Company	Mkt. Cap ($b, 3/09)	No. of App. Drugs	Year(s)	Sales ($m, 2007)	No. of Sites	TAL	Location State/Country
	SALES < $500M							
1	Regeneron	1.1	1	2008	0.0	1	No	NY
2	Zymogenetics	na	1	2008	0.0	1	No	WA (CMO)
3	Alexion	2.9	1	2007	0.1	1	No	RI
4	Halozyme	0.4	2	2005, 2005	0.6	0	No	CA (CMO)
5	Cytogen (EUSA Pharma)	na	1	1996	9.6	0	No	NJ (CMO)
6	Astellas	na	1	2003	18.7	0	No	NC (CMO)
7	Novartis	106.5	1	1998	30.0	2	Yes	FRA, SING
8	Stryker Biotech	13.3	1	2004	30.0	1	No	NH
9	Biomarin	2.0	1	2005	86.2	1	No	CA
10	BMS	43.7	1	2005	231.0	2	No	NY, MA
11	Xoma/Genentech	na	1	2003	242.0	1	No	CA (Genentech)
12	Shire	8.2	3	2006	339.9	2	No	MA, MA
13	Organon (Schering Plough/Merck*)	37.4	1	1997	342.0	2	No	NC (CMO), NLD
14	Lilly	35.3	2	1994, 2001	440.5	0	Yes	CMO
	Average:	***NM***	***1.3***	***2002***	***126.5***	***1***		
	SALES > $1B							
1	NovoNordisk	37.7	1	1999	1,076.7	1	No	Denmark
2	Bayer	37.8	1	1993	1,121.3	1	No	CA
3	Medimmune (AstraZeneca)	49.8	1	1998	1,125.0	1	No	MD
4	Wyeth (Pfizer)*	50.8	4	1997-2001	1,265.0	2	Yes	MA, Ireland
5	Imclone (Lilly)*	6.5	1	2004	1,296.3	1	No	NJ
6	Baxter	33.1	2	1993, 2003	1,714.0	2	Yes	CA, CHE
7	Roche	92.2	3	1997, 1997, 2007	1,775.4	3	Yes	DEU, NJ, CHE
8	Genzyme	18.0	6	1994 - 2006	2,078.0	3	No	MA, MA, Belgium
9	Biogen	14.4	3	1996, 2002, 2004	2,114.6	3	No**	MA, NC, DNK
10	Merck KgA	59.8	6	1996-2006	2,613.3	3	Yes	DEU, FRA, CHE
11	Abbott	76.0	1	2002	3,000.0	2	Yes	IL, PR
12	Centocor/ OrthoBiotech (J&J)	142.5	4	1998 - 2009	7,905.0	4	Yes	NLD, PA, MO, IRE
13	Amgen	60.0	4	1989-2006	11,547.6	5	Yes	CA, CO, RI, PR, CA
14	Genentech (Roche)*	88.4	8	1993 - 2004	13,390.4	4	Yes	CA, CA, CA, SING
	Average:	***54.8***	***3.2***	***1998***	***3,715.9***	***2.5***		

* Acquisitions that had not closed as of March 31, 2009

** Biogen built a commercial facility in Denmark under the assumption there were tax benefits to conducting R&D in the country; th

For subsidiaries, market capitalizations are for the parent company.

For the 14 companies that have "blockbuster" drugs (drugs with greater than $1 billion in sales), the appeal of low-cost locations increases significantly. The majority of these companies (eight) have expanded in locations that provide some kind of tax advantage.[41]

All of these companies are large, publicly traded biopharma companies and in most cases have more than one drug approved and more than one commercial facility. The averages of all 14 companies are: market capitalization of $55 billion, 3.2 drugs approved, approval date of 1998, $3 billion in sales, and 2.5 commercial facilities.

The six companies with blockbusters that have *not* expanded in TALs share a number of similarities. Aside from Genzyme and Biogen, the four other companies have only one drug approved, with sales just above $1 billion. They also have only one commercial facility. Again, this data supports the theory that companies like to keep their first commercial facility nearby, even in the case of significant sales. When demand starts to grow for a blockbuster drug, then a company may look to a TAL for their next facility, as in the case of Abbott and its drug Humira, which currently earns $3 billion a year.

But again, drug sales do not explain the whole picture, as becomes clear when one looks at which companies have invested in TALs. Another important variable in this analysis is the composition of a company's "portfolio" of biologics and pharmaceutical drugs. As discussed before, for many of the "big pharma" companies, biologics is a new and relatively small but growing part of their portfolio. Big pharma's long history of manufacturing in tax-advantaged locations, as well as the pressure on pharma drug margins, makes them much quicker to seek out the low-cost location. Many of these companies already have some kind of pharma manufacturing operations in TALs, either for small molecule manufacturing, or fill/finish. Of the 14 blockbuster companies, eight

[41] Merck and Roche's expansions in Switzerland are counted in this category despite the fact that they already had investments in the country (Merck acquired a commercial facility through its purchase of Serono, and Roche is headquartered in Basel). The companies chose Switzerland for major commercial manufacturing investments (for Merck, 120KL coming on line in 2010, for Roche, 75KL coming on line in 2009.) when they already had additional commercial sites (two each) and multiple approved drugs (Merck, 3; Roche, 6). While they had more incentives than other companies (such as Baxter) to locate commercial facilities in Switzerland, they also had incentives to invest in TALs, which made further investments in Switzerland highly attractive.

are either big pharma or subsidiaries of big pharma and of these, six have invested in TALs. [42] Large biotech companies like Amgen and Genentech also have eventually invested in bulk manufacturing operations in low-cost locations, though only in the last couple of years. Medium- size companies like Genzyme and Biogen (market capitalizations of $14 to $18 billion) have not yet made such investments, though they acknowledge in interviews that tax plays some role in location decisions.[43] However, unlike the big pharma companies, tax rates are one among a number of important factors such as a talented workforce and developing state-of-the-art manufacturing – taxes are not the first and foremost consideration.

While this analysis can't prove causation, it does support the proposition that drug demand is an important factor in location decisions for biomanufacturing. Without "blockbuster" sales, and even in some cases with them, companies tend to keep production near R&D, particularly if it is their first approved drug and first facility. Once a company reaches blockbuster sales, and particularly if they are expanding from their first facility, they will seek out a low-cost location. This pattern is supported by product lifecycle theory, which emphasizes the importance of cost reduction as demand increases and companies look to gain economies of scale in production and lower costs. Likewise, a biopharma company's portfolio and history with manufacturing drugs will influence location decisions and the readiness with which the company seeks out low-cost locations.

5.4 Tax-Advantaged Locations

Manufacturing biologics in tax-advantaged locations has clearly become a new trend in biomanufacturing. Since 2004, 11 product companies and one CMO have built, or are in

[42] I include in the list of "big pharma" Bayer, Medimmune (AstraZeneca), Wyeth, Baxter, Roche, Merck KgA, Abbott and Centocor/OrthoBiotech (Johnson and Johnson). I am not including Imclone or Genentech since the transactions with Lilly and Roche have not been completed.

[43] Biogen picked Denmark as the site for its third commercial facility, its first outside of the US (online in 2010). While Denmark is not known as a TAL, there were tax benefits for R&D that made the country attractive for investment, given Biogen's long-term plans to eventually make Denmark an R&D center as well as manufacturing center. The tax law was changed in 2008, much to Biogen's dismay.

the process or planning stage of building, commercial facilities in TALs (see Table 5.9).[44] As discussed earlier, a number of factors have made manufacturing at a distance more acceptable, including improved technology and routinization of the process, a more supportive regulatory environment, and the maturing of products into later stage commercial manufacturing. But for a few exceptions, the companies that have invested in TALs share similar characteristics. They are large, established publicly traded biopharma companies with market capitalizations ranging from $33 billion to $140 billion. Of the 11 product companies, 10 have multiple approved drugs, and eight have at least one blockbuster (four with sales over $3 billion). In addition, the drugs they are manufacturing have been on the market for an average of 11 years. In all but two of the cases, the facility in the TAL is a second or later facility.

Table 5.9: Companies Building Commercial Manufacturing Facilities in TALs

Year	Company	Market Cap.	Number of App. Drugs	Years	Drug Sales ($m, 2007)	TAL Country	No. of Facility
2004	Baxter	33.1	2	1993, 2003	1,714.0	Switzerland	2
2006	Abbott	76.0	1	2002	3,000.0	Puerto Rico	2
2006	Wyeth	50.8	4	1997-2001	1,265.0	Ireland	2
2008	Amgen	60.0	4	1989-2000	11,547.6	Puerto Rico	4
2008	Centocor (J&J)	142.5	4	1998 - 2009	7,905.0	Ireland	4
2009	Lonza*	5.3	NA	NA	NA	Singapore	3
2009	Pfizer*	93.5	0	NA	0	Ireland	1
2009	Roche	92.2	3	1997, 1997, 2007	1,775.4	Switzerland	3
2010	Merck	59.8	6	1996-2006	2,613.3	Switzerland	2
2011	Genentech (Lonza)	88.4	8	1993 - 2004	13,390.4	Singapore	4
2011	Lilly	35.3	2	1994, 2001	440.5	Ireland	1
2012	Novartis	106.5	1	1998	30.0	Singapore	2
	Average	***70.3***	***3.2***	***1998***	***3,971.0***		***2.5***

* Denotes company does not have an approved mammalian-based drug.

It is worth examining the exceptions in this list because they may foreshadow emerging trends. Unlike all of the other TAL investments, Pfizer and Lilly's facilities are their first commercial biologics facilities in the world. In addition, until their recent acquisitions, Pfizer had no approved mammalian-based biologics and Lilly had two, with combined sales of under $500m. These companies are building facilities assuming they will have successful drugs, either from their pipeline or their newly acquired companies, which will

[44] As stated earlier, Roche and Merck's investments, while technically in a TAL, are also building on sunk costs and economies of scale, given their existing investments in Switzerland.

require greater biomanufacturing capacity. In the case of Pfizer, the company spent close to $7 billion between 2004 and 2008 buying biologics companies and currently has four drugs in Phase I clinical trials, eight in Phase II and one in Phase III.[45] For Lilly, the acquisition of Imclone at the end of 2008 gives the company a blockbuster drug, Erbitux, a mammalian-based drug approved in 2004 and made in New Jersey. Thus, the drug will be made commercially for seven years in the US before Lilly's new facility in Ireland goes on line (2011).

Both Pfizer and Lilly have leap- frogged over the first step of building their first commercial facility near their R&D centers in the US and immediately moved commercial manufacturing further a field to a low-cost location. In conversations with a Pfizer executive about this unprecedented move, he said "A lot of people like to talk about the magic and mystique of the bioman process – that "the process is the product". But I think that overstates things. We're pretty confident about our antibody production and our tech transfer capabilities." The behavior of these big pharma companies could foreshadow future investments by other big pharma companies. The importance of the tax breaks to these companies is such that they are willing to take on the added risk of manufacturing new drugs at a distance from R&D.

In addition to Lilly and Pfizer, which have little or no drug sales for mammalian biologics, Novartis stands out for its insignificant sales in biologics. However, as stated earlier, Novartis' subsidiary Sandoz is one of the leading generic drug and biosimilar manufacturers and thus their Singapore facility will be able to serve the growing biosimilars market in Asia and elsewhere.[46].

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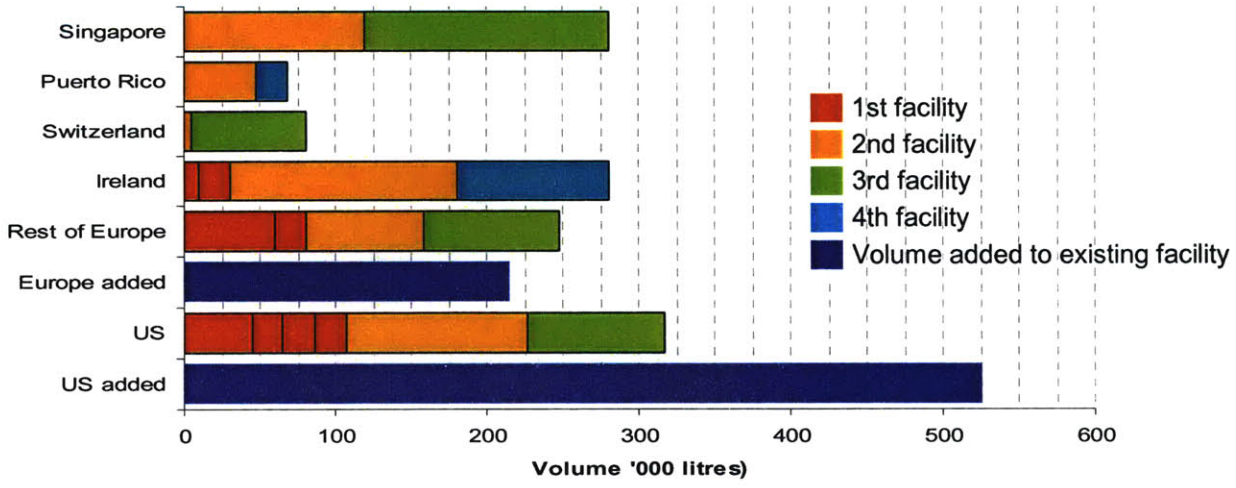
[45] Pharmaceutical-technology.com: The Website for the Pharmaceutical Industry, http://www.pharmaceutical-technology.com/ (accessed July 17, 2009).

[46] Sandoz introduced its first biosimilar on the market in 2006, Omnitrope, a branded copy of Pfizer's Genotropin growth hormone, after it received European approval, and eventually US approval. Sandoz had to bring a lawsuit against the FDA in 2004 for not approving the drug. A court eventually ordered the FDA to approve the drug in 2006. Sandoz sells Omnitrope, at about a 25% discount from the original price. It's biosimilar, Biocrit, was approved by the EU in 2007 but has not been approved in the US. See Andy Stone, "Pharmaceuticals," *Forbes* (March 2007), under "Business," http://www.forbes.com/2007/03/14/biotech-generics-drugs-biz-cz_as_0315biotech.html (accessed July 18, 2009).

Commercial facilities, as opposed to clinical facilities, are much larger facilities and more substantial investments for companies. In an effort to maximize drug profitability, particularly if a company is building a second or more facility, paying lower corporate taxes on output is highly attractive, and has led many companies to locate commercial facilities in TALs. Since 2006, practically every large biopharma company has invested in a new commercial facility in a TAL. This is driven significantly by drug sales, but also by big pharma's insistence in some cases, on locating any new commercial manufacturing facilities in TALs, regardless of sales. However, with significant demand and the resources to expand, moving production to a TAL, in the words of many executives I spoke to, "is a no-brainer."

While investments in TAL's clearly represent a trend, this must be put in context with the all investments occurring in this time period. If one looks at all commercial facility investments since 2004, one finds that investments in TALs do not tell the whole story. As Figure 5.5 shows, a significant number of first, second, third and even fourth facilities were built in the US and the rest of Europe during the same time period as the investments in TALs. In addition, adding additional capacity to existing facilities is also occurring. The value of proximity to R&D for first facilities, and the importance of sunk costs as well as the economies of scale that can be derived from larger plants are still important factors in the location of commercial facilities. Still, TAL investments represent a disproportionate share of overall investments.

Figure 5. 5 Investments in Commercial Facilities, 2004 to 2013



5.5 Discussion

This chapter presents trends in investments in biomanufacturing capacity from 2002 projected to 2013. The trends globally and regionally show an industry in transition in a number of ways. First, biomanufacturing is experiencing significant productivity gains such that yields that were unthinkable a decade ago are now being achieved and surpassed. This may lead to excess capacity globally in the short- to medium-term. Second, there is a changing geographic landscape. While the US and Europe have historically dominated in this industry, Asia is growing in prominence, making this a global industry. Third, unlike many industries where there has been a complete geographic decoupling of R&D from manufacturing, proximity still matters in biomanufacturing. The majority of the top R&D biotech centers in the world (by employment) are also the top biomanufacturing centers (by volume). Most clinical sites, and over half of the commercial facilities have been built within 100 miles of company R&D operations. Companies tend to locate their first commercial facility nearby. However, as companies grow and there is pressure to expand capacity, companies are investing farther a field. Finally, in the last five years, almost every major biopharma company has invested in a tax-advantaged location, saving millions of dollars a year. For companies with significant drug sales and growing demand, building a commercial facility in a TAL makes good business sense. However, TALs don't represent the entire story around new commercial facilities. Significant investments are still being made in non-TAL locations within Europe and the U.S, highlighting the fact that proximity to R&D, sunk costs and economies of scale play an important role in this industry.

Chapter 6
Innovation in Biomanufacturing and Implications for the Future

Today, innovation is understood to be the key driver of economic growth and company success in a global economy. Companies that can innovate in their processes, products or organizational structure will ultimately find ways to deliver a better product or service. How companies generate new knowledge and innovate is of primary concern to companies and is a rich and growing topic in the management literature (Lam 2005; Lazonick 2005). Likewise, how regions promote innovation is also of great interest to states and countries. Fostering national and regional "systems of innovation" has become central to many countries' and regions' public policy agenda (Asheim and Gertler 2005). Retaining and growing innovative industries is considered the most effective way to build a high-skill, high wage economy that is less susceptible to downsizing and offshoring.

As shown in the previous chapter, technological innovations are clearly having an impact on the industry's productivity. In this chapter, I look in greater depth at the technological innovations taking place in the biomanufacturing industry to understand their impact on where innovation takes place, both within the company value chain, and geographically. I look at four new technologies that are having a significant impact on the industry and how these may or may not affect the location of the industry. Given that advanced industrialized countries such as the US must compete on innovation, I combine these new innovations with outside factors to look forward and map out the geography of the industry in the future. I close with a brief comparison with the evolution of the pharmaceutical manufacturing industry and whether this might shed light on the future evolution of biomanufacturing.

6.1 Innovation in the Biomanufacturing Industry

For the 30 years since its inception, the biomanufacturing industry has been overall, highly innovative, particularly in process innovation. However, the industry has had to walk a fine line between taking risks with new technologies and altering its processes and final products to the point that the FDA questions the companies' practices. Due in large part to the regulatory environment, the biomanufacturing culture has historically been

driven more by fear of change than by the opportunities created by developing new technologies. As one executive described it:

> "There's a lack of innovation in the industry because there's so – there's so much risk around change. The time scales are *so* enormous. The – the dollars involved are *so* enormous. The risks, therefore, from a business standpoint, are just doubly enormous..., the FDA is *very* tight on changes – *any* changes – scale, types of systems, process architecture – you know, the recipe. If you change any of that stuff, generally, you have to go back and repeat some of the, potentially, in the worst case, the clinical trials, which everybody tries to avoid."

However, by the new millennium, a "revolution" began taking place in the industry as the FDA embarked on a revamping of its regulatory process for biopharmaceutical manufacturing (with the publication of *cGMP Pharmaceutical Manufacturing for the 21st Century*), and companies began to reap the benefits of improving biomanufacturing processes, products and technologies. As described earlier, while it is difficult to gain margin in other parts of the drug development process, manufacturing offers enormous opportunities for cost savings if you can become more efficient and cut down timelines. The importance of time and getting a product to market is paramount in this industry, probably more so than in many industries because of the enormous product development costs. As one executive said, "You *have* to have new technologies, if I want to do this, and I want to do it *quickly.* Because in the manufacturing world of biotech, it's *time* that costs you everything."

While time and cost pressures have driven the innovation process in biomanufacturing, the desire to innovate must confront a culture that has been, up to now, fairly risk-averse:

> "We've *got* to innovate! If you innovate – you've got to innovate while you're still being successful, or else it's too *late*. If people start doing it after the fact – you know, when they start to get in trouble, you'll *never* have the money to do it. And the paranoia will go up, and the conservative views will go up, so you'll never *move* ahead."
>
> "If through innovation we can get better control over what we do, we can improve quality, we can tighten up and reduce variation, we can predict output more accurately. We can take care of quality issues in advance, not from testing three

> months later. We can take care of things in real time. And we can get data into hands of people that can make a difference and empower them at a low level. The output of that which is good for the company is we increase our success rates. And we reduce cost. These are not antithetical at all, between quality and innovation."

This may explain in part why the innovation taking place in biomanufacturing is characterized more by *sustaining technologies* than *disruptive technologies* (Christensen 2000). Sustaining technologies "improve the performance of established products, along the dimensions of performance that mainstream customers in major markets have historically valued." (Ibid). Most new technologies in an industry are sustaining in nature, improving and developing an existing industry with well-established products. Disruptive technologies, on the other hand, radically change the value-proposition of a particular product on the market. This may be through the introduction of a product that is cheaper or simpler, and taps into a new customer base. The introduction of the personal desktop computer, small off-road motorcycles and health maintenance organizations all describe what could be called disruptive technologies.

The new technologies that are creating a "revolution" in biomanufacturing are decidedly of the sustaining type. They are incremental in nature and, while significantly changing how biomanufacturing is done, they have not diverged dramatically from the final product or customer demand. The regulatory nature of the industry helps explain much of this." There's an intersection between innovation and technology that is getting to the point where if you make some pretty incremental improvement in your biomanufacturing, from a cost standpoint, it is worthwhile and you should go after it," said one executive, from a company that is considered a leader in biomanufacturing.

Just as some new technologies can be disruptive and lead to the decline of one industry while replacing it with a new one, new technologies can also create a new geographic map for an industry, making some locations more accessible and amenable to an industry while diminishing the advantages of the industry's existing locations. Improvements in communication technology, for example, have made offshoring of many services easier,

for example, locating call centers in emerging countries such as the Philippines, India, or Eastern Europe has become standard practice for companies today.

The next section reviews four of the most important technology-related trends that have emerged in recent years in biomanufacturing and hypothesizes how these either currently or in the future may affect location of the industry over time. These innovations affect productivity, facility design and operations as well as organizational behavior, and are dramatically reducing costs and timelines in the biomanufacturing process.

6.1.1.Four Technological Innovations in Biomanufacturing

1) Increased Productivity: Higher Titers: As discussed briefly in Chapter 6, one of the major drivers of productivity in biomanufacturing is the efficiency with which biomanufacturers are manufacturing mammalian-based cell lines. "Titers" represent the amount of grams per liter of material that a bioreactor produces. Most facilities in operation today were built in the 1980s assuming production of approximately .01 grams/L.[47] Productivity has increased over 100-fold to an industry standard today of 1-2 g/L, with some industry leaders producing as much as 3-6 g/L. And, the tens of grams per liter in mammalian systems is clearly in sight (Rosin, 2007). These improvements are due to new technologies in cell line development and expression levels, as well as improved media composition and process control.

This increase in productivity, along with possibly smaller-volume, niche products, means that future commercial products will not need as much capacity as current products do, thus, companies will be able to produce more with the same or less capacity (though this does not change the downstream purification process, which has not seen the same productivity increases). Some have predicted that a two-fold increase in industry-wide productivity will result in a reduction of overall biomanufactuing capacity requirements of approximately 25% by 2013 (Levine et al. 2007). This decrease in demand leads to fewer new facilities and potentially smaller footprints when building. " If you can now get three times the output per batch, it's the equivalent of building three half a billion

[47] This is based on producing monoclonal antibodies, which represent the bulk of biotech manufacturing today. See Howard Levine, "Challenges and Solutions for Biopharmaceutical Manufacturing" (presentation, Cambridge HealthTech Pep Talk Conference, January 15, 2009).

dollar facilities, and all you've done is a year's worth of work in development," said one plant manager.

The implications of this increased productivity is clear. There will be less need for large-scale bioreactors and fewer plants built because of increased yields per batch. "The days of the big tanks are possibly over, such as Genentech's 8x25K bioreactors. It's possibly back to the future with small reactors and smaller facilities," said one plant manager. The data supports the fact that less capacity will be coming on line in future years. The desire for a smaller footprint will also diminish the difference in size between pilot and commercial facilities. This could lead to continuous production in one place, though most likely not in one facility, given the different demands on a pilot versus a commercial plant. Some firms are already doing continuous production, from pilot to commercial, at one site. The potential efficiencies gained in continuous production might persuade companies to keep pilot through commercial near their research operations, particularly if they are not building large-scale bioreactors. Still, when the economics of manufacturing a blockbuster drug abroad are compelling, commercial manufacturing will be separated from early stage manufacturing to capture the cost savings

2) Single-Use Technology: Introduced in the early 2000s, single-use technologies or "disposables" refer to the use of disposable technologies, that is plastic bags and tubes that can be thrown away once they are used for fermentation. Disposables allow biomanufacturers to make a product in a plastic liner inside a bioreactor and use plastic tubing rather than steel in the manufacturing process. Rather than having to clean the bioreactor once it is used to ensure there is no contamination, disposables limit the amount of contact between the bioreactor and the material, as well as the contact between humans and the bioreactor. They are currently used in pilot and clinical manufacturing since the largest disposable bags are 2,000 liters. While commercial manufacturing may some day be feasible using disposables, there seems to be little interest in the idea from companies, given the significant weight involved in moving around the disposable bags (a 500 liter bag weighs 1,100 lbs). As titers increase and the size of bioreactors decreases,

disposables have become more popular, such that virtually every company is now using them.

Because disposables involve plastic tubing rather than stainless steel, facilities can be built in 12 to 15 months, rather than the multiple years it can take to build facilities in steel. This buys companies more time during clinical trials to see how their drug candidate is doing, reducing the company's overall risk and capital outlays. These "flex factories" reduce the costs of building the facility as well as operation costs by approximately 50%. Using plastics rather than stainless steel also makes the production system more portable and easily transported across distances. Another advantage, particularly in areas that are not rich in water, is that disposables run on electricity and do not need significant amounts of water to generate steam, thus they use 70% less waste water.

Overall, disposables have a number of advantages to them that result in rapid deployment, greater flexibility and lower costs, including:[48]

- Increased speed to proof-of-concept and commercial launch
- Reduced capital investments and improved return on capital
- Increased facility utilization by reducing change-over time between drugs
- Reduced cleaning and cleaning validation costs in multi-product operations, i.e., those making more than one drug in a location
- Improved process mobility

One company that built a pilot plant in 2001-2 in 14 months uses disposables and describes their value:

> "The disposables give you flexibility. But also it gives you speed to initiate your operation. So here, we don't have any process piping. It's all disposable. We have some tanks that we use, and the bioreactors are obviously stationary. But all the connections between are all flex. And the

[48] Levine, 2009.

> reason we do that is it's easier to switch products, and, it's easier to clean it. Especially in the early stages, you have to show cleaning verification. It's not validation, but verification, to show that your surfaces are clean. The less surfaces you have, the faster it is. So, we took that approach very consciously in the design of the building.

In terms of impact on the geography of biomanufacturing, disposables may radically alter the landscape. Disposables make the biomanufacturing process, at least in the pilot and clinical phases, more modular, creating a "plug and play" turn-key operation that companies can easily move. A CMO that is spearheading the use of disposables expects clients to take the production systems home with them once they have developed a compound in the early clinical phases of development. "This is a technology that you can locate in any tax haven, any IP haven, any labor market, " he said. Another executive describes what some companies are already envisioning:

> "If you can stick a facility up for $20 million, then it hardly matters where you stick it and it hardly matters if you get it wrong. There are companies, like GE, that are talking about putting together a truck that they would basically drive up and drop off at somebody's door that would have all the plastic bioreactors, disposable clones, filters and then once the guys were finished with it, they'd drive it back."

Disposables are clearly more mobile, so without "steel in the ground", companies are less wedded to a particular location and can move facilities around more easily. While the flexibility expands the options geographically, the cheaper cost and delayed timeline to build may play to the advantage of smaller companies, who may be able to afford building facilities with single-use technologies. For smaller companies, and for smaller scale, niche production, disposables might offer a chance for more companies to control their production. As discussed earlier, it is more likely these smaller companies will prefer to keep manufacturing nearby and thus this technology could offer a way to grow early stage biomanufacturing near emerging biotech companies.

3) Multi-product Facilities: With the introduction of disposables, companies began to experiment with making more than one product at a single site. In the beginning, this was considered highly risky because of the risk of contamination between drugs and concern

about creating problems with the FDA. But companies have become more comfortable managing multi-products such that facilities just coming on line now are designed to handle up to six or seven separate products at the same time. That being said, no one facility will fit all products or processes, such as antibodies, recombinant proteins, mammalian and microbial production. But they can handle any scale of production, whether it is milligrams/L, gram/L or kilos/L, from preclinical to commercial. A multi-product facility provides greater flexibility for companies and less of a need for multiple plants. The design of facilities is driven in part by the volume and titer of the product. For low volume, low titer products, large manufacturing operations that can handle multi-products will be appropriate. For high volume, high titer products companies may stay with dedicated plants but with smaller bioreactors.

Multi-product facilities have fundamentally changed the skills required to run these plants and the demands on the workforce. Two executives described the changes in their operations and how multi-product facilities create new challenges in training the workforce:

> "When you're in a single-product facility, you don't spend a lot of time changing. You get people into a very high throughput mode and you worry primarily about efficiency, quality and efficiency. Now, with a multi-product platform, you're worried about how you do changeovers faster. How do you run two products simultaneously and insure that there are no mix ups. How do you do tech transfer more quickly without using 10 times as many people to pull it off? How do you process four different products when you used to process one, and not completely overwhelm your documentation system and have four times as many people?"

> " The workforce that you need for the facility that makes *one* product is different than the one for six or seven. The *one* product, you can take a less skilled workforce, and condition them to perform these tasks over and over and over again. . . What you're not going to get from that situation is process improvement, continuous improvement. You're *not* going to get the innovation that you want. When you go to multi-purpose facilities, and you have people who run those, and you use smarter people, then it becomes much easier to bring in new techniques, new innovation."

This is a good example of how technology upgrading is leading to skills upgrading for the workforce. Currently, all new facilities that are being built have multi-product

capacity. In terms of influencing location, to the extent that these facilities demand a more highly skilled workforce, this may steer companies away from places that are not perceived to have a highly skilled workforce (Puerto Rico, for example).

4) PAT and Quality by Design: One of the other major trends in biomanufacturing is the improvement being made in understanding the process in greater detail, largely from better measurement processes. Introducing PAT, or Process Analytical Technologies, into biomanufacturing has been a major initiative of the FDA and has been embraced by the industry. As discussed earlier, PAT helps take some of the uncertainty and thus the risk out of the biomanufacturing process by introducing ways to measure what is going on at each stage of development and creating expectations that then help explain what's gone wrong when those expectations are not met. "Root cause analysis" helps pinpoint problems in real time, and saves time in resolving them. Real-time PAT analysis "provides the basis for continuous feedback and results[s] in improved process robustness."[49]Quality by Design (QbD) is a concept that is helping implement PAT goals. QbD "promotes industry's understanding of the product and manufacturing process starting with process development, ...building quality in, not testing it" (Ibid). Using QbD, a company defines the desired product performance and identifies "CQAs", critical quality attributes. This leads to a process that is designed to deliver a consistent product that meets quality attributes. Because of the better understanding of the process, QbD also enhances the ability of companies to make changes during the development process. "Design space", referred to in the quote below, is a tool that companies are using to implement QbD. Design space refers to all of the interactions that take place among multiple input variables used in the development process, and the process parameters that a company defines that collectively have demonstrated to provide the assurance of quality. Once a company has defined its design space, it can make changes within the design space that do not have to be reported to the FDA for approval. Design space is proposed by the company to the FDA and is subject to regulatory approval. This allows companies to innovate while reducing the regulatory burden on making changes to the

[49] This discussion draws heavily from Anurag Rathore and Helen Winkle, "Quality by design for biopharmaceuticals," in *Nature Biotechnology* 27, no. 1, (January 2009).

development process. One executive explains below how QbD and design space have changed the way they operate:

> "We were the first to basically sit there and figure out how to use design space. So, now that we have the design space, it's very easy to move into the clinic, and scale up. Because we know what controls the compound that's coming out of the reactor. In the *old* days, the issue used to be one of the process was the product. That doesn't hold any more. The process isn't the product. You have to have a firm understanding of the controls within your system that affect the quality attributes of that product. And while you may not be able to measure everything. . . what *can* you measure? And what *does* have a clinical correlate? You build that in all the way along this whole manufacturing continuum. So, now, I've got an analytical group that knows what we want to do, and wants to set up processes that say, "We know what's critical to measure. Can we do it on-line? Can we start looking at new technologies?" where before, we'd have to take a sample out, and we'd learn three days later whether or not it was any good . . .if you walked into our facility 18 months ago, you'd see reactors and see some very crude measurements of how things were performing in the reactors. You walk in there now, I can show you on my computer how a process is running in a given reactor."

With better measurement systems, and an ability to detect and interpret problems in real time, companies gain greater knowledge and confidence in their biomanufacturing processes. While this does not mean a particular process is "codified" because it still has an element of uncertainty to it, it is well understood and information can be provided about the process that does not rely solely on empirical analysis. This allows a company's biomanufacturing experts located in different parts of the world to confer, looking at real-time data about a problem, and to collectively problem solve without necessarily having to be physically present when issues arise. Thus PAT and QbD represent technological innovations that make the geographic location of facilities less relevant.

These four technological innovations within the industry are having and will continue to have dramatic effects on the cost and timeline of biologics manufacturing, as well as where they are made and in what kind of facilities. Given these trends, and those that are external to the industry, the following outlines some potential scenarios for how the industry will evolve in the coming years.

6.2. Innovation within the Biomanufacturing Value Chain

The most critical innovation period in biomanufacturing is the early stage pilot and clinical manufacturing where the process development team works with manufacturing (the "manufacturing sciences" team or "technical operations" team) to scale up a compound and produce an adequate amount of material for clinical trials. This time between when process development receives a promising molecule from research and discovery, to the time the molecule has been scaled up and is ready for commercial production at the beginning of Phase III clinical trials (up to three years) represents a highly innovative, integrated period. Process development is where "the real innovation takes place." This is why over 80% of clinical facilities are located near company R&D centers. Once Phase III trials begin, for reasons of FDA approval among others, companies hope to have the biomanufacturing process "locked down." (Pisano 1997, 98). This is not to say that there aren't changes or improvements made after Phase III clinical trials begin, but these usually are incremental in nature and revolve around "continuous improvement" efforts – yield, quality, process control, process robustness, and process safety. Teams at all commercial facilities are engaged in these types of improvements.

Interviews with companies suggest that any "disruptive technologies" or new technologies that have been tried to some extent, will be experimented with within process development. These types of new technologies may not be ready to be introduced into commercial production yet and so start at a clinical level. Whether new technologies will be introduced into a commercial facility depends on a number of factors. These can include:

1) The class of product: is it a large or small molecule, vaccine?
2) What are the analytic capabilities for tracking changes?
3) What is the nature of the change? What are the inherent risks involved?
4) What impact is there on regulation?
5) What is the state of the facility? If it is older and mostly depreciated, then with 90% margin rates, the changes may not be worth it.

6) How critical is the product in the market? If it is not a highly competitive market, the company may not get much attention from regulatory authorities if it makes big changes
7) How much supply of the drug does the company have? Will introducing these changes adversely affect production?
8) What are the risks and costs of failure?

After weighing all of these considerations, if the risk to benefit ratio is favorable as well as the cost to benefit ratio, then a new technology may be introduced into commercial production. Because of the mobility and fluidity of the manufacturing science or "tech ops" teams, the introduction of these technologies could happen at any of a company's commercial sites. But companies are still concerned about potential glitches until a product is successfully launched and most likely will introduce the new technologies in the commercial facility closest to the process development team. After a product is launched successfully, "companies become agnostic as to where it is made – the competency is out there."

Up to this point, I have reviewed the importance of innovation in the biomanufacturing industry, some of the major new technologies and innovations in the field, as well as where within the biomanufacturing value chain innovation occurs and what determines whether a company will incorporate new technologies broadly into their operation. I now turn to how all of these factors will influence the location of biomanufacturing going forward.

6.3 The Future Location of Biomanufacturing

While it is always risky to try and predict what will happen in an industry, there are some clear trends in biomanufacturing that suggest a future scenario with respect to the geography of the industry. The previous section outlined how technology is influencing biomanufacturing. These innovations are affecting the industry in a number of ways, leading to lower costs, shorter timelines, excess capacity, new facility footprints and importantly, greater ease and flexibility in the separation of manufacturing activities, ie,

the ability to move the different stages – pilot, clinical and commercial – away from R&D and each other. This greater ease of separability across geography does not necessarily translate into ease of separability across organizations, however. There is little indication that companies are more willing than before to outsource their biomanufacturing needs. And if process development is "where the real innovation takes place," PD teams are firmly rooted near R&D teams and not following manufacturing facilities farther a field. Nevertheless, the changes that are occurring within and outside of the industry are leading to some significant shifts in production location in the short and long term.

Internal and External Influences on the Industry

As highlighted above, productivity is increasing, which will lead to smaller bioreactor tanks and a smaller number of new facilities being built[50]. In fact, excess capacity in the industry is predicted for the near future, which will lead to the closing or retrofitting of existing facilities, and possibly the sharing of facilities in the future. The improved processes and knowledge of scaling up biologics materials, particularly monoclonal antibodies, has also given companies greater comfort in manufacturing farther a field. In terms of facilities, multi-product facilities are now the norm, along with the use of disposable technologies. Both of these provide greater flexibility in terms of where drugs are made, and can lead to shorter timelines and lower operating costs. Finally, PAT and QbD innovations are increasing the ability to monitor and evaluate what is happening at every moment of the biomanufacturing process. These improvements in analytical capacity lessen the reliance on empirical analysis and thus, globalize the real-time analysis so that problem-solving can take place across distances. While all of these innovations facilitate the ease with which biomanufacturing can take place at a distance,

[50] Experts in the field predict that there should be sufficient capacity through the end 2010 and that utilization rates should increase from 52% currently to 73% by 2013. Predictions in the early 2000s of a shortage of capacity in the industry have turned out to be unfounded. But as highlighted throughout this research, the industry is characterized by high uncertainty. If the top five potential volume driver drugs that are in the pipeline succeed by 2010, then utilization rates will exceed 90%. If that is the case, then we can assume there will be more commercial facilities built.(Levine, 2009).

they do not, in and of themselves, make that option preferable to keeping production close to R&D. These changes, much like the changes in communication and transportation, have made biomanufacturing at a distance easier. They have also made it more accessible to smaller companies by lowering the risks and costs involved.

Other external forces, however, have a much more dramatic influence on the future location of biomanufacturing. First and foremost, the "globalization of innovative talent" (Lewin et al. 2008) has expanded the possibilities of where a company can find biomanufacturing talent. One of the impacts of globalization is better access to knowledge, and while companies that are biomanufacturing retain trade secrets and specialized know-how, the training of a skilled workforce in the industry is more feasible, and a number of regions and countries are developing the workforce and expertise required in the industry. Places such as Ireland and Puerto Rico, and more recently Singapore, have a strong base in pharmaceutical manufacturing, and now have moved up the value chain to a more advanced type of manufacturing of biologics.

A second emerging influence on biomanufacturing is a growing sensitivity to cost. Unlike pharmaceuticals, biotech drugs have not, until very recently, been subject to an attack on their margins by generics or "biosimilars". This, plus the more complicated nature of the process, has made biomanufacturers less pressured to seek out the cheapest location possible. However, this is changing as biosimilars start to make their way into the market, and big pharma, which now owns many of the large biotech firms, feels financial pressures because of drugs running off patent, the impact of generics, and the growing pressure in the US market for tighter control of drug costs. In addition, if personalized medicine grows as it is projected to do, companies will be making less of each drug for fewer patients with higher rates of success. All of these factors have made biotech companies more sensitive to overall costs, and to opportunities to reduce costs in the biomanufacturing process. Tax rates and tax policy in developing and developed countries are becoming a driving force behind location decisions for commercial manufacturing.

Third, integrity of the supply chain is becoming more important as the industry matures and becomes more global. Given some of the problems that have arisen with contamination of the supply chain (Baxter in China, for example), it is unlikely companies will risk locating biomanufacturing in regions that do not meet certain manufacturing standards, or have a highly trained workforce. Genzyme's recent troubles with meeting FDA standards for cleanliness in its manufacturing facility in Allston, MA highlights the challenges that exist in maintaining standards[51].

Finally, a growing market outside of the US, Europe and Japan, primarily in Asia, will draw companies to eventually locate production in Asia. While biosimilars will dominate for a number of years, over time demand will grow for innovator drugs and companies will eventually set up manufacturing facilities to distribute product to the market.

What does all of this mean for the future of the location of biomanufacturing? As one walks through the biomanufacturing process, the critical factors for determining location are those that were outlined in Chapter Six. A skilled workforce will continue to be critical to location, as will the stage of biomanufacturing (clinical or commercial), the number of approved products a company has, and overall biologics drug demand. The following outlines a possible scenario as it relates to biomanufacturing in the US.

Early Stage Manufacturing: Early stage pilot and clinical manufacturing will continue to locate close to R&D to benefit from the interdependencies that exist between those two parts of the value chain. Tax credits provided to companies for the R&D remain important to retaining this in a place like the US (though they are a third or a quarter of the size of commercial income tax breaks provided in TALs). The relatively small amounts of material made for pilot, Phase I and Phase II clinical trials can often be accommodated in a large pilot facility or small clinical facility, depending on the size of the company and its pipeline.

[51] See In-Pharmatechnolgist.com, March 11, 2009.

Commercial Manufacturing: In terms of initial commercial manufacturing (including for Phase III clinical trials), the location of facilities will depend to a great extent on the scale of demand for biomanufacturing capacity for the company, and scale and scope of the company's biopharma activities. If, as outlined in Chapter Six, a company is developing its first approved product and it is building their first facility, then there is a good chance itwill locate its first facility closer to R&D (if it doesn't choose to use a CMO at this stage). This has historically been the case, with most biopharma companies locating their first, and sometimes second facility onshore. This has held true for companies of all sizes, as well as for drugs with a range of sales, from minimal to blockbuster. Very likely, these facilities will accommodate pilot, clinical and commercial manufacturing as the footprint for all of this is diminished.

However, locating first commercial facilities in proximity of R&D is already becoming less critical to companies. As is evident with Lilly and Pfizer, companies of scale with (after acquisitions) a number of approved drugs, are now moving Phase III and the commercial launch of their products directly offshore, without building a first facility in the US. These companies have the significant resources required to do this, and also come from a pharmaceutical background, an industry that is accustomed to manufacturing abroad. For companies with the resources, and particularly if they believe their drug will generate significant sales, first commercial facilities are more likely to be built offshore in a TAL. This will also depend to a lesser extent on what kind of drug the company is making. Monoclonal antibodies are now the fastest growing segment of the biopharma industry and represent 85-90% of the biologics product pipeline (Levine, 2009). They are also the material with which biomanufacturing is achieving some of the highest titers. As a result, companies that are making an antibody-based drug will potentially have greater confidence and comfort in making it at a distance. While some new drugs may be more challenging to scale up and benefit from proximity to R&D during the Phase III and commercial launch phase, if the drug promises to be a blockbuster, then the "inconveniences" that arise from manufacturing offshore in a TAL can be overcome, according to one executive, in order to save the millions of dollars in tax savings.

It is unlikely given the rapid changes in technology that companies with a first facility built in the US will use the facility until it is completely depreciated (30 to 40 years). More likely, it will retrofit the facility over time to keep up with technological advancements. Unlike in Europe, where having production facilities on the continent might help with negotiating a higher price for a new drug, such benefits do not exist in the US so there is no explicit or implicit penalty for locating all commercial manufacturing offshore. Commercial manufacturing for a product that has been launched for several years will most likely be located in a TAL. Enough companies, albeit large biopharma firms, as opposed to biotech companies, said this was a "no-brainer", that it is hard to imagine a scenario in which later stage commercial manufacturing facilities get built in the US without significant change to the tax policy. Genzyme and Biogen, interestingly, are exceptions to this rule. Both are medium-size biotech companies, with a vastly different culture and history to big pharma. Biomanufacturing has also been seen as one of their core competencies. But if Genentech and Amgen, larger biotech companies, are any indication of where biomanufacturing might head, it is likely that if Genzyme and Biogen are in need of significant new capacity, they will most likely build in a tax-advantaged location. This challenge, however, may be one that will arise in the distant future given the likely excess capacity that exists. New commercial facilities will be fewer and farther between as companies use new technologies (disposables) and possibly CMOs to accommodate their short-and medium-term capacity needs.

The Location of Offshore Biomanufacturing

To date, two primary drivers have explained the move of biomanufacturing offshore: first, the expansion into new markets, such as Europe or, to a lesser extent, Asia, and second, lower costs due to tax advantages provided by certain governments. Will the four countries listed as the most prominent TALs – Ireland, Puerto Rico, Singapore and Switzerland – attract all future commercial manufacturing facilities, or can we expect to see expansions into other countries? Despite the view that some day biomanufacturing will act more like a commodity, that day is not yet in sight. The industry still has significant requirements regarding skilled labor as well as good infrastructure (including

property rights) before it is willing to make investments abroad. Ireland and Singapore in particular have invested millions of dollars to develop their labor force as well as a solid infrastructure to accommodate the industry. Switzerland already had a presence in the industry and has built upon this. Puerto Rico, while beginning to attract some biomanufacturers (two to date) still has challenges with providing the skilled labor companies need and as such, is often passed over for Europe. Finding talent in these TALs is already a challenge because of the tight labor markets.[52] Ultimately, lower costs are important, but not at the expense of quality, which suggests that the industry will continue to seek out TAL locations within the "Triad" (North America, Europe and Japan). Lower costs will most likely be derived from tax breaks, more so than in the cost of doing business. Experts in biomanufacturing suggest that the cost of doing business in India, for example, will catch up to the cost of doing business in the US by 2013, particularly since cheap labor is such a small input to the industry (Rosin, 2007). Finally, with excess capacity in the market for the near future, there will be little incentive to build new commercial facilities for a while.

Expansion in the industry to new regions in the world is most likely going to be driven by the demand generated from growing markets than from lower costs. The likely growth of the Asian market for biosimilars and innovator biotech drugs will no doubt expand the investments in that part of the world. While it is mostly CMOs operating there now, as product companies attempt to penetrate the market, they will no doubt look to set up operations. Beyond their requirements for a skilled workforce and solid infrastructure, another public policy factor may play into where expansion in Asia takes place. Many Asian countries have developed policies around the biotechnology industry as they try and develop indigenous firms and capabilities. Some of the policies support the growth of domestic biotech firms by requiring multi-national firms to create joint ventures with indigenous companies. Countries such as China, India, South Korea and Taiwan have employed such policies (Pereira, 2006). Given the control most companies want over

[52] Part of Biogen's argument for locating their first offshore facility in Denmark (where they thought they would benefit from tax breaks that were subsequently changed), was that the labor market in Ireland was very tight and they thought there were "first mover" advantages to being one of the first foreign biotech companies to locate in the country.

their biomanufacturing facilities, this may be a hindrance to the growth of the industry in those countries. Singapore is one of the few locations in Asia in which multi-national companies may operate wholly foreign-owned entities, which, along with the other strategies it has pursued, helps account for the fact that it has received some of the first multi-national biomanufacturing investments in Asia.

Uncertain Factors

A few variables introduce potential uncertainty to aspects of the trajectory of the industry outlined above. First, if the US government were to engage in the price regulation of drugs, which some believe is a possibility, companies might pay more attention to keeping some commercial production in the country to help their negotiation position. Second, while the Obama administration is going after tax havens for the offshoring of company profits and individual assets, there has been no indication that there will be an attempt to alter the transfer pricing regime that exists worldwide. While the former is seen as an attack on quasi-fraudulent behavior, the latter is a well-established practice codified in treaties within the OECD. However, if there was an attempt to change the rules of transfer pricing, this would affect where companies manufacture. Finally, as mentioned earlier, while existing biomanufacturing capacity is expected to meet demand for the next several years through 2013, if many of the potential high-volume drugs in the pipeline succeed, there may be a scramble for more capacity and the building of new facilities. Depending on the size and scale of the companies developing these products, it is most likely these new facilities will be built offshore in TALs.

6.4 Biomanufacturing Compared to the Pharmaceutical Manufacturing

Many wonder whether the future geography of biomanufacturing can already be seen in the evolution of the pharmaceutical manufacturing industry. Of course, large biopharma companies are often engaged in both types of manufacturing and as pointed out earlier, in places like Ireland and Puerto Rico, experience with the latter can help facilitate the location of the former to the same location.

However, there are important differences between biomanufacturing and pharmaceutical manufacturing that may make their paths somewhat divergent. As outlined in Chapter 2, pharmaceuticals are made from small molecules that are chemically based and can be taken orally. They are easily characterized by chemical methods and tested for "interchangeability" with similar drugs, thus the emergence of generic drugs. Biologics, on the other hand, are derived from large molecules, based in biological processes that must be grown from cell cultures, and are also delivered through more complicated means, usually by injections. They are not easily characterized and "their safety and efficacy depend more strongly on the manufacturing process." (Pore, et al, 2008). Companies can run into challenges manufacturing a biologic 10 years into making the drug. The fact that there is no clear path for the introduction of biosimilars into the US market after 30 years of introducing biotech drugs speaks to the complexity of the process and to the lack of "commoditization" of biotech drugs. Other differences include the greater fixed costs of biomanufacturing, namely for capital expenditures and operating costs. These costs, due to the expense of building facilities to meet FDA approval, as well as ensuring process approval, can be 100 times higher for biologics manufacturing than for pharmaceuticals (Grabowski et al. 2007). Finally, biotech R&D and manufacturing are more tightly linked in the early stages than in pharmaceutical drug development, which can alter location choices.

While all of this is true, it is clear biomanufacturing has matured enough that companies are beginning to offshore facilities,,, and all companies are engaging in some amount of outsourcing to CMOs. The question remains, given the differences, whether biomanufacturing will follow the same route as pharmaceutical manufacturing, which has been described as a "commodity-driven, cost-centered business ripe for outsourcing" (Finnegan and Pinto, 2006). The following is a brief summary of the evolution of pharmaceutical manufacturing to date.

6.4.1 The Location of Pharmaceutical Manufacturing

The pharmaceutical industry has undergone significant structural changes in the past couple of decades based on a number of factors including the emergence of

biotechnology, the expiration of patents, the changing demographics that have increased demand for drugs globally, and the rise in generic competition, which represent 59% of drug prescriptions by volume in the US (Cockburn 2008; Kadonaga et al. 2007). At the same time, the number of drugs receiving FDA approval has declined in this decade, even while R&D expenditures have increased, indicating declining productivity. All of these factors have put enormous pressure on firms to cut costs and develop new business models for how to compete in the pharmaceutical industry.

Pharmaceutical commercial manufacturing of drug substance or active pharmaceutical ingredient (API) was largely conducted onshore by US pharma companies from 1938, when a new system of drug regulation was put in place in the US that required inspection of manufacturing plants, until the late 1950s and early 1960s, when the first generics were being introduced (albeit with difficulty) [53]. As stated before, pharma manufacturing exhibits all of the characteristics of a commodity – codified knowledge, standardized procedures, and modular in nature. This allowed firms to set up facilities in lower-cost locations for the production of their APIs since the early 1960s. This first wave of low-cost locations included Puerto Rico and Ireland. Eli-Lilly set up its first offshore manufacturing facility in Puerto Rico in 1957, and Squibb set up the first manufacturing facility in Ireland in 1964. These locations offered a skilled workforce (more reliance on workers with a high school degree than in biotech), easy access to primary markets, good infrastructure for FDA-approved facilities and respect for intellectual property, as well as the ability to set up wholly-owned subsidiaries. More recently, as other regions in the world have developed their infrastructure and skills base, pharma manufacturing investments outside of "the Triad" – the US, Western Europe, and Japan - have increased and locations like Singapore, which in 2000 began heavily recruiting biopharma

[53] For a discussion on the introduction of generic drugs into the US market, see *Marketing to Pharmacists*, by B. F. Ganahan. State antisubstitution laws passed in the 1950s to stop counterfeiting kept generics out of the market. In 1962, Congress passed the Kefauver-Harris Drug Amendment which allowed for generic drugs, but only if they went through the expensive process of filing an NDA, which was a significant hurdle at the time. In 1970, generics were largely ushered into the market when the FDA created the abbreviated new drug applications (ANDA), which greatly reduced the time and costs of filing for generic drugs on any drugs approved between 1938 and 1962 (this was amended in 1984 to include all drugs approved after 1962). The cause of generic drugs was helped in 1975 when the Dept of Health and Human Services capped Medicaid reimbursements for drugs with a "maximum allowable costs", which brought about the end of state antisubstitution laws and increased the use of generics.

manufacturing with tax incentives and subsidies, have attracted more investments from big pharma. Companies in these TALs manufacture drugs that are still on patent. The small molecule pharma manufacturing that stays in North America and Europe primarily involves new drugs that have complex technologies or involve high potency drugs, controlled substances, complex delivery systems, and/or niche products. Pilot and clinical manufacturing, like biomanufacturing, is typically performed in partnership with the R&D organization.

Pharmaceutical firms have historically been vertically integrated, engaged in all of the activities of the value chain, from R&D to sales and marketing. At the same time, these activities have been relatively easily "de-coupled", with R&D facilities set up in multiple locations (mainly within the "Triad"), and manufacturing and marketing activities set up in separate locations. In the last decade or more, big pharma has begun to outsource many of the downstream activities such as development and manufacturing to clinical research organizations (CROs) and contract manufacturers (CMOs) as they try to reduce costs in the face of mounting pressure on their profit margins. At the end of 2007, a number of big pharma companies announced plans to significantly cut costs through outsourcing: BMS announced outsourcing was part of its cost-cutting plan which included closing or selling half of its 27 manufacturing plants; Pfizer announced it would double the outsourcing of its manufacturing from 15% to 30%, reducing its number of manufacturing plants from 93 to 48; and GSK increased its manufacturing by other companies from 9% in 2001 to 41% in 2007 (Steyer 2008). Both Pfizer and Shering-Plough are closing manufacturing facilities in Ireland in 2009 as they downsize and outsource, seeking cheaper locations in places like Eastern Europe and Asia. As the skills and drug demand in these emerging markets increase, they have become more attractive as locations for a wider range of pharmaceutical activities, primarily in development and manufacturing (Cockburn 2008).

The enormous growth of the global generics market fostered the development of the pharmaceutical manufacturing industry in both China and India, which represent the first and third largest global manufacturers of APIs (Italy is second). The APIs manufactured

offshore are almost all generics, which lowers the bar on intellectual property issues and allows places like China to compete. Costs are dramatically lower in China and India, with one tenth the labor costs and 40-90% lower capital expenditures than in the West (Pore et al, 2008). India now has the second highest number of FDA-approved manufacturing facilities in the world after the US and supplies over 20% of the world's generics drugs (PWC, 2005). The majority of this work is contract manufacturing work. Clearly, the current shift for small molecule pharmaceutical manufacturing, at least for generics, is toward Asia, specifically China and India. The talent pools, evolving IP regime and lower costs have all facilitated this move. But what about newer drugs? The evolution of the India pharma manufacturing industry, particularly in the last few years, is potentially illustrative of what is to come. The "India advantage" refers to India's strength in reverse engineering, efficient process development and scale-up capabilities and low-cost manufacturing (ECN, 2005). Historically, India has produced APIs later in the life cycle in the "intermediates" market. For the last four to five years, however, Indian companies have been acquiring companies in North America and Europe to move up the value chain to produce more high value, high tech APIs. A number of Indian companies have made acquisitions to create a "near-shore/offshore" option for customers who are more comfortable with working with a company in their same time zone, a similar culture, with sensitivity to FDA requirements (Ibid). While fears over regulatory compliance and IP have kept many pharma companies from contracting out the manufacturing of new drugs to India, this seems to be changing, with the first contract ever awarded to an Indian company in 2006 for the manufacturing of a new API (Pore, et al 2008). Thus, India and China have become the primary manufacturers of generic APIs, and at least in the case of India, are on their way to becoming locations for the manufacturing of newer APIs. Indian pharmaceutical manufacturers have developed the talent and the capacity, and now have bridged the geographic distance, to make a very good case for manufacturing in India. While cost is clearly the driver (particularly construction costs), many observers note that costs in both India and China are rising.

In addition, the large, emerging markets in both India and China are also becoming an attractive factor for pharma companies as they look for ways to access the growing

consumer base and develop relationships in these countries. By 2015, India's pharmaceutical market is expected to rise to approximately $16 billion, while China's is expected to be valued at $37 billion, the fifth largest drug market in the world (Ibid). As one pharma manufacturing executive expressed it, " We want to market our drugs more aggressively overseas (China and India) so to do so, we need to establish better working relationships within these countries. We've outsourced some activities [no manufacturing to date]... there are labor savings, but the real objective is to access the growing consumer base."

In summary, since approximately 1960, the majority of commercial pharmaceutical manufacturing has been largely conducted offshore in low-cost locations, primarily in TALs within North America and Western Europe. As generic drugs gained approval in the US in the early 1970s and more explicitly in 1984 with the passage of Hatch-Waxman[54], these moved "further" offshore, to low-wage locations in Asia, primarily in India and later in China A full fifty years after pharma companies moved production offshore, we are just beginning to see a shift toward the manufacturing of new, innovator drugs in India, a low-wage, low-cost location outside the Triad. Even with a commodity such as commercial pharma manufacturing, it has been a relatively long period of time before pharmaceutical companies were comfortable moving the manufacturing of innovator drugs to a country outside of the major markets and higher-wage countries.

6.4.2 Pharma's Influence on Biomanufacturing

One can assume that this route of 1) moving commercial production to countries within the Triad that have the skills but also provide tax advantages, 2) making generics or biosimilars in low-wage countries, and 3) eventually moving the manufacturing of "innovator drugs" to low-wage countries, is a route that biomanufacturing may well follow. Biomanufacturing is already exhibiting some parallels with pharma

[54] The Drug Price Competition and Patent Term Restoration Act of 1984, usually referred to as the Hatch-Waxman Act, was designed to promote generics while leaving in tact a financial incentive for research and development. It allows generics to win FDA marketing approval by submitting bioequivalence studies (as opposed to clinical data, which is costlier to compile). It also grants a period of additional marketing exclusivity to make up for the time a patented pipeline drug remains in development. This extension cannot exceed five years, and it is in addition to the 20 years exclusivity granted by the issuance of a patent (http://www.cptech.org/ip/health/generic/hw.html).

manufacturing in two ways. First, in the last five years, commercial manufacturing has begun to move offshore to TALs that have the talent and can ensure quality and the respect of IP. Second, the first wave of manufacturing of biosimilars, like generic pharma drugs, is happening in Asia in countries such as India, China and Singapore, which are making them for both the European market and emerging markets in Asia, and potentially for the US market soon. Both of these trends will continue and most likely grow over time. However, there are a number of factors that continue to differentiate biomanufacturing from pharma manufacturing. First, the complexity of the manufacturing process, and the fact that the "the process is the product" mentality still holds true for many companies, suggests that companies will still keep commercial manufacturing in centers of excellence where they can find talent and experience, and be close to their primary markets. Cost will continue to be a key factor in moving production offshore to tax-advantaged locations, but only if the talent and quality can be assured. Second, biopharma companies derive a competitive advantage from maintaining a core competency in manufacturing. As a result, the industry is less likely to shift its production to CMOs (except in the case of biosimilars) and thus will not be seeking the cost savings that some CMOs offer in low-cost locations in Asia. Finally, the emerging markets of India and China will need to mature further to afford many of the biotech drugs currently on the market. As such, biotech companies feel less of a pull toward locating facilities in Asia compared to big pharma companies.

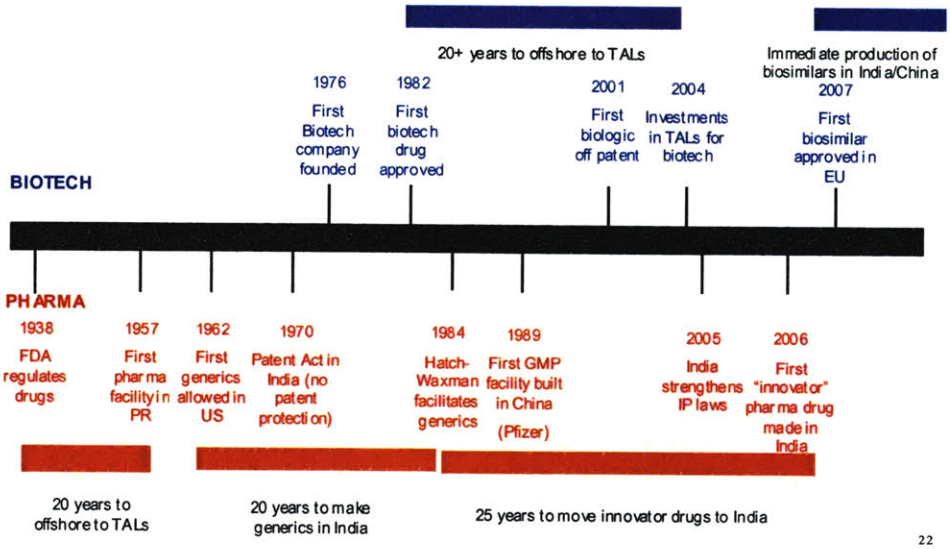
All of this suggests that biomanufacturing will follow pharma to TALs, but perhaps be slower to follow them to low-wage countries for the manufacturing of innovator drugs. Given that pharma companies are just beginning to experiment with this in this decade, it will most likely be a number of decades before new biotech drugs are manufactured in India or China (particularly since they have little to no mammalian-based production capacity today). More mature products that come off patent and receive approval as biosimilars are most likely to be manufactured in these countries first (human growth hormone, insulin, biosimilars such as EPO).

However, one of the key dimensions that has changed dramatically since the 1960s, when big pharma began offshoring, is "the compression of development time" (Whittaker, et al 2008). While it used to take decades if not a century to industrialize (as in the case of the UK), it now takes perhaps a third of the time, as countries both industrialize and enter the post-industrial era simultaneously. In addition, industrial organization has changed so that industries that once were dominated by large, vertically integrated companies and required vast amounts of capital to enter, are now vertically dis-integrated and production systems are spatially dispersed, allowing people, companies and countries to participate in a global industry at a smaller scale. This is due to a variety of factors including: new technology and the pace of technological change, global access to new knowledge, information and technology (open-source IT), new business models in which companies offshore and outsource, the rise of global value chains, and the global flow of capital. The spread of knowledge, technology and talent is now global, and the ability of regions to combine the three to develop centers of excellence has increased. On top of this process of compressed development, is the impact of increasing returns to economic growth. Places that generate knowledge and talent, beget more knowledge and talent leading to a spiraling effect.

All of this suggests that the process of offshoring innovator pharma drug manufacturing to low cost locations (which took approximately 50 years), will now take much less time for biotech drugs. An interesting parallel can be drawn between pharma and biomanufacturing. Moving pharma manufacturing offshore to TALs took approximately 20 years. As soon as the threat of generics was apparent in the 1960s, companies began offshoring to TALs. A similar situation arose in the case of biomanufacturing: 20 years after FDA approval of the first biologics, as biosimilars start to look more real and patents on the first approved drugs run out, companies are beginning to set up biomanufacturing offshore in TALs (Amgen just moved its production of EPO, approved in 1985, to Puerto Rico in 2009). For drugs approved today, the 20 years of production in the US has been shortened to approximately 4-5 years, or the time it takes to build a new facility in a TAL (for example, Abbott's experience with Humira). This shortening of the product lead time for offshoring reflects both confidence with biomanufacturing

processes, and the ability to move product at an earlier stage in the lifecycle given the talent and quality control that exists at the offshore location. This same shortening will no doubt happen with the offshoring of innovator drugs. It took India approximately 30 years to begin moving up the pharma manufacturing value chain to finally begin manufacturing new APIs. One can assume, given the increased knowledge, established industry within the country, growing global companies, and growing talent, that they will be moving up the biologics value chain at a quicker pace. Interviews with experts have put the number at 20 years.

Figure 6.1 Signs of Compressed Development in the Biopharma Market



6.5 Discussion

This chapter highlights the important role innovation plays in the biomanufacturing industry, the types of innovation that are occurring, where they occur in the value chain, and what impact, if any, they might have on the location of the industry going forward. In part due to FDA reforms, a "revolution" is taking place in biomanufacturing in which companies are pushing forward technological innovations that are translating into higher productivity, smarter facilities and greater flexibility and mobility across distances.

Overall, biomanufacturing at a distance has become easier. At the same time, the truly innovative aspects of the industry still occur at the early stages within process development and close interactions with pilot and clinical manufacturing. Given these trends, one can attempt to predict a future for the industry in which early stage and even first commercial facilities will stay close to a company's home base, including R&D. But beyond this, commercial manufacturing will most likely end up in lower-cost locations, i.e., tax-advantaged locations, until biosimilars are on the market, at which point some amount of production will head to Asia. With almost 90% of the biotech pipeline in monoclonal antibodies, we will see commercial production head to TALs earlier, perhaps as early as Phase III trials. In terms of parallels with pharmaceutical manufacturing, clearly that industry has paved the way for biomanufacturing by creating centers of excellence (such as Puerto Rico and Ireland) that have acquired the skills for biomanufacturing. Path dependency has led many biopharma companies to repeat the cycle of offshoring to these TALs. However, the significantly more complex process in biomanufacturing suggests that the transition to developing world production will not occur in a significantly shorter time frame that what transpired for pharmaceuticals. If it took 25 years for India to move from manufacturing generics to manufacturing new APIs, experts predict it will take 20 years for biologics, if that. Given the importance of innovation to economic development in countries like the US, and regions like Massachusetts, the next chapter asks what economic development opportunities biomanufacturing might provide and how a high-tech region like Massachusetts can compete in this industry.

Chapter 7

Biomanufacturing as an Economic Development Opportunity

"The US is becoming the rust belt for biomanufacturing production.
This used to be ours and we're going to lose it".

Senior Biopharma Executive

The current recession in the US and the loss of more than two million factory jobs since December 2007 have raised alarms around the country about the country's manufacturing base. President Obama has declared that "the fight for American manufacturing is the fight for America's future" and the new administration has taken a number of steps to support manufacturers, through the bailout of the auto industry, the Buy America clause in the 2009 stimulus package, and more loan guarantees for companies. Manufacturers are calling for tariffs on Chinese imports because of their undervalued currency, and looking for a "manufacturing policy" from the government[55].

This is a continuation of the debate about the role of manufacturing in the US economy that began in the 1970s, as the US went through its first phase of deindustrialization (Harrison and Bluestone 1982). How important manufacturing is to the economy, and what the government should do to retain manufacturing jobs is a subject of discussion in every economic downturn in which thousands of manufacturing jobs are lost. The loss of lower-wage, low-tech, high volume manufacturing to cheaper locations is well understood and perhaps even accepted in the public's eye. But it is the loss of more advanced, higher wage manufacturing that engenders the public's ire and leads to calls for a "manufacturing policy," in effect, an industrial policy that encourages and protects manufacturing in the US. The battle between countries for the most advanced types of manufacturing has become more intense. It is not low-cost labor or cheaper materials or better production processes that attract manufacturing offshore. In advanced manufacturing, companies can now find the talent and skills abroad. These, combined

[55] See Louis Uchitelle for a summary of recent steps taken by the Obama administration. New York Times, July 20, 2009

with emerging new markets and aggressive public policy (either in the form of a devalued currency as in China, or tax havens as in Ireland and Singapore) create a new challenge for US manufacturing. In this new world, the US has little leverage with the first two realities – growing talent and growing markets – and is reluctant to engage in the third, which puts the US in the uncomfortable position of formulating an industrial policy for manufacturing. A rise in neo-mercantilist practices, in which state and business interests are intertwined[56], is happening in countries at every stage of development, from older European countries to emerging Asian tigers. In light of this, the US may need to reexamine its policies regarding how best to promote and retain industries in which it has a competitive advantage.

Biomanufacturing presents an excellent case study for understanding how the US can and should compete in a highly advanced manufacturing industry. While biopharmaceutical manufacturing employs only about a third of the workers of the auto industry (300,000), it produces exactly the kinds of jobs that business and political leaders are trying to create and hold on to. These are highly paid, with an average salary of $96,000, and highly skilled, requiring a BA or more for 60% of the jobs. The industry exhibits some "sticky" qualities: a complex process and the need for highly skilled workers, the benefits of proximity to R&D, significant capital investments such that facilities are used for decades, strict regulatory requirements and finally, the high cost of failure, both in monetary and public health terms. It is also in an industry that is projected to grow at double-digit rates (16%; Levine, 2009). All of these factors suggest an industry in which the US should be competitive, and that is attractive from an economic development perspective, creating highly skilled, well-paying jobs that are not easily moved once a facility is built. But as talent and standards increase around the world, as well as aggressive strategies to attract the industry, commercial facilities and the jobs that go with them are moving offshore. What does this imply about growing and retaining advanced manufacturing jobs in this country? As traditional US industries like the auto industry become shadows of their former selves, the question arises, what, if any, kinds

[56] For a discussion of this trend, see Professor Dani Rodrick, *Mercantilism Reconsidered* http://www.hks.harvard.edu/news-events/news/commentary/oped-rodrik-jul09.

of manufacturing will the US compete in and what are the consequences of losing manufacturing capabilities? The federal government is going to extraordinary lengths to rescue US automotive companies, whose employment numbers will no doubt shrink from the close to one million workers in the industry in 2007[57]. Yet "niche" manufacturing industries such as biomanufacturing and semiconductors that employ fewer workers and require a higher skilled workforce may be the types of manufacturing industries that the US and regions like New England are more likely to be able to compete in and hold on to, at least for a while. Google CEO Eric Schmidt argues that advanced manufacturing is one of the most important sciences (along with biotech and "clean tech") that the US should be pursuing. Advanced manufacturing is the "manufacturing of new things that are being produced in very small volumes – nanotech, batteries, material sciences."[58] Is it possible for the US to compete in this world of "flexible specialization" without resorting to government buyouts or Buy America campaigns? The biopharmaceutical manufacturing industry presents an interesting case for exploring alternative strategies for the country.

This chapter examines biomanufacturing from an economic development perspective. First, how important is biomanufacturing to the overall success of biotech clusters? We've seen that biotech R&D "pulls" manufacturing nearby to facilitate close interactions, but if manufacturing moves to a more distant location, will it in turn "pull" R&D? Second, as has become clear just this decade, biomanufacturing operations are moving offshore in significant numbers either to enter new markets or to take advantage of tax breaks, or both. What is at risk if the US loses its biomanufacturing capacity? What effect if any will this have beyond the loss of good paying manufacturing jobs? Finally, this chapter examines the economic development opportunity in biomanufacturing for the state of Massachusetts and to what extent the industry should be a priority for state economic development efforts.

7.1 The Economic Development Impact of Biomanufacturing

[57] The auto industry employed 992, 600 workers in 2007 according to the Bureau of Labor Statistics (NAICS 3361, 3362, 3363).
[58] Speech at the Google Boston office, reported in MIT's "The Tech," November 6, 2009, p.1..

The conditions under which economic development occurs have undergone a dramatic change in the past few decades. As outlined by Paul Romer in his new growth theory twenty-five years ago, the drivers of economic growth are linked to knowledge creation and innovation. As the terms of competition have shifted from "low cost to high quality to flexibility to innovativeness", companies that can innovate in products, processes and business models are most likely to succeed (Hayes and Pisano 1994, 324). A number of factors shape this new competitive era. First, timing is critical. Particularly with knowledge-based products and services that exhibit increasing returns, companies that get into a market first can hold onto temporary monopoly profits. "You're either first or you're nowhere," as one biomanufacturing executive said. Second, place matters. The ability of companies to innovate and more broadly, compete, is not only a function of their internal capabilities but is also in part linked to their environment, as the geography of innovation literature underscores. "Much of competitive advantage lies outside a given company or even outside its industry, residing instead in the locations of its business units" (Porter 2000, p254). This understanding of the link between innovation, company competitiveness, and regional growth has led to a new "paradigm shift" in economic development that focuses on endogenous growth through innovation, human capital and the competitiveness of indigenous business.[59] Every country and region is trying to create "regional innovation systems" and "cluster initiatives" that enhance regional competitiveness and overall economic growth. Third, economic development is not a zero sum game. Knowledge-based growth can create a self-reinforcing cycle in which knowledge begets new knowledge, and faster growth triggers more knowledge and more growth. For example, the biotech industry, while expanding into new geographies, also is highly concentrated in nine locations in the US (Cortwright and Mayer, 2002). Rather than a "flat" world, we live in a "spiky" world in which certain locations can rapidly become centers of economic activity (Florida, 2005). Finally, the dynamics of "compressed development" have changed the competitive landscape such that no industry is immovable from a particular country or region (Whittaker et al, 2008). As the authors write:

[59] For a review of the "paradigm shift" in regional economic development strategies and current practices, see *Building Competitive Regions: Strategies and Governance*, OECD, 2005.

> On the one hand, would-be developers seeking to play "catch-up" are chasing a moving target. Science and technology-based innovation in now-developed countries has undergone "intensification"...Product cycle times have been drastically shortened...Global value chains facilitate these processes, but through co-evolution now-developed countries themselves are forced to run as developing countries jockey for position in the lowest segments of global value chains, and seek to claim a more significant stake over time...when we hear policy makers in the US and other now-developed countries bemoaning the loss of manufacturing jobs to China, and service and even R&D work to India, it appears that *we are all compressed developers now.*

This new era has resulted in more economic development opportunities for more places around the world as they build internal capacity, and production systems become disintegrated and spatially dispersed. It also creates a wide variety of economic development strategies from regions and countries depending on where they stand on the spectrum of development. At one end of the spectrum is the US, which has been a leader in many industries because of its cutting- edge technology, and has invested heavily in education and R&D. At another part of the spectrum are Singapore and Ireland, which, alongside significant investments in training and R&D, use aggressive tax policy to "seed" industries such as biomanufacturing.

Biomanufacturing clearly exemplifies the kind of industry that these economic development efforts are trying to grow and retain – innovative, value-added manufacturing that pays good wages and employs higher skilled workers in a time-sensitive, growth industry. But given the competition globally for the industry, what are its prospects in the US? What is at risk in losing biomanufacturing capacity in the country? The following sections address the three primary economic development impacts of biomanufacturing in the country. First, there is the creation of skilled, well-paying jobs. There is also the indirect effect of the accumulated knowledge and skills that are developed that lead to the emergence of new industries related to biotech. Second, there is the impact of innovation capacity, more specifically regional innovation capacity, both in product and process innovation. Finally, there is the revenue generated from local, state and federal taxes. I take each of these in turn.

7.2 Employment and Skills

In terms of job creation, biomanufacturing does not create huge numbers of jobs. The largest plants in the country employ a few thousand people, which, compared to the tens of thousands employed at auto plants, might seem insignificant. However, it is the quality as well as the quantity of jobs that matter today. Biopharmaceutical manufacturing, including small and large molecule and fill/finish, employ approximately 295,000 people in the US (2007), with an additional 24,000 in Puerto Rico (see Table 7.1). California, the largest region in the world for mammalian-based biomanufacturing, employs 44,000 in biopharmaceutical manufacturing while New England (primarily Massachusetts), the second largest, employs approximately 12,000 (including 2,500 jobs in NH and RI). The significant difference in employment numbers is explained by the other types of biopharmaceutical manufacturing included: all small molecule manufacturing and microbial-based, including vaccines, and fill/finish.[60] They do not include jobs created through a multiplier effect – either in services (both high and low-wage) as well as in construction jobs related to building facilities. Experts put at a 2 to 1 ratio (BCG, 2002) on the biomanufacturing multiplier, which would bring the total job generation number to close to 600,000. Job growth over the past seven years has been relatively flat, not a surprise given the increases in productivity that the industry is experiencing. Massachusetts and California, the top two locations for mammalian-based production, are the only regions exhibiting some job growth (one to three percent).

[60] These employment numbers come from the Bureau of Labor Statistics 2008 (provisional as of August, 2009) NAICS analysis of the four six-digit NAICS codes that make up Pharmaceutical Manufacturing (325411 Medicinal and Botanical Manufacturing; 325412 Pharmaceutical Preparation Manufacturing, 325413 In-vitro diagnostic substance manufacturing and 325414 Other Biological Product Manufacturing). It is impossible to separate from among these codes the manufacturing of biotech drugs from pharmaceutical drugs. But given the offshoring trends of pharmaceutical manufacturing, it is reasonable to assume that the facilities that are in the US for small molecule manufacturing represent the more complex types of manufacturing for such things as controlled substances. These number also include all herbal medicine manufacturing.

Table 7.1 Top States for Drug and Pharmaceutical Manufacturing by Employment and Establishments

State	Employment			Establishments			Ave. Size
	2001	2008	CAGR	2001	2008	CAGR	Firm '08
CA	39,199	43,037	*1%*	432	395	*-1%*	109
NJ	37,872	37,956	*0%*	203	255	*3%*	149
PR	24,646	22,663	*-1%*	81	75	*-1%*	302
PA	25,780	22,288	*-2%*	123	118	*-1%*	189
NC	18,782	18,787	*0%*	81	80	*0%*	235
IN	18,536	18,822	*0%*	41	43	*1%*	438
IL	20,275	18,534	*-1%*	125	116	*-1%*	160
MA	7,794	9,580	*3%*	85	91	*1%*	105
USA	*280,665*	*289,641*	*0%*	*2,522*	*2,623*	*1%*	110

More important perhaps than the absolute number of jobs, is the kind of jobs and the skill sets that they require. First, roughly 20 percent of the jobs require post-bachelor degrees primarily in the sciences[61]. Roughly 80 percent of the jobs go to college-educated and high school or two-year associates degree holders (divided roughly evenly between college-educated and the rest). This last point is important because, while only approximately 40% of workers may have less than a college degree, there are very few industries in which these workers can earn solid middle class wages of $40,000 to $60,000 a year. Employees with a BA usually hold their degree in the sciences (chemistry, biology, engineering). As stated before, these are on average very well paying jobs (on average $96K across the industry). These are exactly the types of jobs the National Research Council, the Council on Competitiveness, and the Congress through the America COMPETES Act of 2007, argue the country needs to create more of to compete globally. As the National Research Council wrote in 2006, " the committee is deeply concerned that the scientific and technological building blocks critical to our [the US's] economic leadership are eroding at a time when many other nations are gathering strength."

[61] This number is higher by approximately 10% than analysis conducted on biopharma manufacturing in North Carolina (see Lowe 2007). In that study, BA and less educated workers are thought to comprise at least 90% of all biopharma manufacturing jobs. However, the analysis for North Carolina includes significant amount of small molecule manufacturing as well as medical device manufacturing both of which hire more high school graduates.

Part of what explains the rise and decline and rise again of regional economies is how regions exploit the specialized skills and technologies that are developed overtime within the region. A region's "heritage of technological capabilities and skills" (Best 2001,118) can help firms, entrepreneurs and workers diversify into new products and technologies as one industry declines and another rises. Massachusetts' decline in the mid-1980s and rise in the early 1990s provides a number of examples of companies building upon the region's cumulative technological capacity to diversify into new industries: minicomputer companies into software, plastics manufacturing into medical devices, precision machining in electronics and nanotechnology. " A region's technological capabilities are an outcome of a cumulative history of technological advances embedded in entrepreneurial firms and internalized in the skill formation systems." (*Ibid*). To advance into new industries with new technologies, a region must draw from its existing base of firms and workers and build upon technological advances made by the previous generation of firms. If the previous generation of firms and workers disappears, so too does the technological capabilities and the skill set. This presents an important potential cost to the loss of biomanufacturing capacity in the US, given the growth of related new branches of industries within the life sciences. The manufacturing of therapeutics developed from stem cells will require a similar level of knowledge, expertise and safety. Likewise, the merging of medical device technology with therapeutics is creating new opportunities in "hybrid operations" that manufacture FDA-approved specialty medical devices[62]. If manufacturing jobs in these emerging industries are to stay in the US, it will require companies with the technological know-how and a specialized labor force that are currently working in biomanufacturing.

7.3 Innovation

After several decades in the 1970s and 1980s in which US manufacturing fell behind international competition, excellence in manufacturing is now understood to be critical to overall firm strategy, providing companies with a source of real competitive advantage (Hayes and Pisano, 1994). A strong manufacturing base is also thought to be critical for

[62] While the FDA has already approved 80+ specialty medical devices (Lowe, 2007), embryonic stem cell therapies are thought to be 10-20 years away from widespread commercial application (Clive Cookson, "An Industry to Grow," Financial Times, June, 25, 2009.

the economic health of the country overall. Researchers have warned of a number of risks and challenges of losing manufacturing capacity in the country and becoming just a service economy[63]. First, the country loses not only good paying manufacturing jobs for lower skilled workers but also tied with them a number of high-wage (and low-wage) service jobs that are complements to manufacturing such as product and process engineering, repair and maintenance, and testing. Lose the manufacturing and eventually these service-oriented jobs will be lost as well. Second, losing the ability to manufacture goods will leave the country with a large trade imbalance, given the amount of manufactured goods the US imports, compared to the services the country exports (three and a half times the volume of trade in goods versus services, Baker, 2009[64]). Third, manufacturing industries exhibit high productivity gains. These gains generate higher wages and ultimately higher standards of living, outcomes that are important to the US.

This last point speaks manufacturing's role in innovation. The US's advanced manufacturing is highly innovative, as is evident from its rates of productivity growth and the significant amount of funding that manufacturing, particularly high-tech manufacturing, puts toward R&D (Nordhaus 2005; Dertouzos 1989)."The decisive corporate asset required to realize technology is likely to be production skills" wrote Cohen and Zysman in 1987. Their argument, which pointed to the loss of steel and electronics manufacturing in the US in the 1970s and '80s, emphasized manufacturing's role in keeping a technological edge in an industry because of the incremental innovation that comes from having R&D tightly tied to the manufacturing of the product. Those making a product, the argument goes, will ultimately drive the innovative aspects of it and ultimately become the technology leaders.

Twenty years later, the evidence supporting this argument is mixed. Recent work supported by the National Research Council (2008) examines the increasingly global value chains of ten knowledge-intensive industries, most of which involve high-tech

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[63] These arguments draw from Cohen and Zysman, 1987, Dertouzos et al, 1989, Madrick, et al in Dissent Magazine, www.dissentmagazine.org, March, 2009.
[64] Dean Baker "Should We Still Make Things?" Center for Economic and Policy Research, www.cepr.net

manufacturing. The research finds that, since 1990, global production capacities have changed significantly. There has been a growth of innovative capabilities in a number of countries that 30 years ago were considered "developing economies." This would include India, China and Taiwan. Complementing this growing capacity is an increase in the growth and sophistication of the manufacturing activities in these economies, including South Korea and Singapore. Manufacturing expertise has also moved upstream to include more process innovation. In addition, growing consumer demand in foreign markets (namely Asia) is leading to the emergence of R&D activities in certain industries, like software and PCs, in countries with growing consumer markets. Finally, there has been an increase in vertical specialization within many industries, as firms specialize in one or a number of specific activities within an industry and provide that service to other firms (foundries in semiconductors, clinical research organizations in biopharma, for example).

A summary review of six of the ten industries[65] examined that involve manufacturing (personal computers, software, semiconductors, flat planel displays, pharmaceuticals and biotech) suggests it is not at all clear that the loss of manufacturing capacity in the US necessarily leads to a loss of the innovative activities of the industry within the country. Table 7.2 shows a stylized summary of the primary R&D and manufacturing locations of five industries compared to biotechnology (a brief summary of the industries is in Appendix A). A listing of the US as the primary location for an industry does not mean other locations do not exist, only that the US dominates the global market.

In only two of the five industries, personal computers and flat panel displays, is there evidence of manufacturing "pulling" significant R&D investments. This pull comes largely from two sources: a growing consumer market, and a vertically integrated industry. A growing consumer market for PCs in Asia (driven in part by price declines) is leading to the location of design jobs closer to the manufacturing (particularly for notebooks, which are more complex to make) and to the end users. In the case of flat panel displays, manufacturing has been based in Asia (primarily Japan, more recently Korea and Taiwan) for decades. The complexity of the manufacturing process and the

[65] The industries not included were service industries.

Table 7.2 Comparison of R&D and Production Location of Six Advanced Manufacturing Industries[66]

Industry	Location of R&D	Location of Manufacturing		Manufacturing "Pulling" R&D?	Explanation
		Process Innov.	*Production*		
PC	US/Japan	Japan/Taiwan	China	Yes	Growing Asian market; US companies setting up design centers in Taiwan for notebooks
Software	US	US	US	No	Software developed near end-user; US is the largest market (over 50%); software services growing in India and Ireland
Semiconductors	US	US	Japan/US/Europe/Taiwan/ Singapore/China/Korea	No	Vertical specialization in the industry ("fabless" firms, foundries) has led to greater segmentation of industry.
Flat Panels	US/Europe/Japan	Japan/Korea/Taiwan	Korea/Taiwan	Yes	Complex, risky and expensive manufacturing; proximity to manufacturer critical; little vertical disintegration
Pharmaceuticals	US/Europe/Japan	US/Ireland/PR	Ireland/PR; Israel/India(Generics)	No	High barriers to entry for R&D activities
Biotechnology	US/Europe/Japan	US/Europe/Japan	US/Europe Asia (Biosimilars)	No	High barriers to entry for R&D activities;

Notes:

Software: "Production" refers to design and development

Semiconductors: US represents over 60% of value of orders for semiconductors; R&D capacity spreading in Israel, Canada, Taiwan, UK and Korea.

Flat Panel Displays: Design of new products historically by suppliers in US/Europe/Japan, while process innovations in Asia.

Pharmaceuticals: Manufacturing refers to APIs and not finished products.

enormous expense (each facility can cost up to $2 billion) is such that there has been little vertical disintegration in the industry. As a result, product and process innovation take place at or near the manufacturing facility and non-Asian firms involved in product innovation locate within close proximity to the manufacturing.

In the case of the three other industries, there are different explanations for why manufacturing has not "pulled" R&D, but generally speaking, it is fair to say that in each of the three industries – software, semiconductors and pharmaceuticals – the non-standardized, innovative nature of the R&D activities have kept these activities close to sophisticated end users (software), a critical mass of R&D assets (pharmaceuticals) and large, fragmented markets (semiconductors). In the last two industries in particular, vertical specialization has allowed for specialized firms to collaborate with offshore manufacturers. Process development, however, is still kept close to R&D activities. Process development is directly linked to product innovation and overall competitive performance in both pharmaceuticals and semiconductors (Pisano 1997; Hatch and Mowery 1998). Interestingly, the parallel to biomanufacturing may be more with semiconductors than with pharmaceuticals. The following description of semiconductor manufacturing could possibly be written for biomanufacturing:

[66] This table is based on an analysis of industry trends as presented in Macher and Mowery, 2008.

> "The development …is based on art and know-how rather than science; they [the steps in the production process] are not well understood or easily replicated on different equipment or in different facilities; and they impose demanding requirements for a particle-free manufacturing environment… Imperfect scientific understanding of semiconductor manufacturing means that changes in process technologies demand a great deal of experimentation." (Hatch and Mowery 1998, 1,462).

The semiconductor industry has experienced significant vertical specialization such that an industry of contract manufacturers has emerged (foundries), as well as those that only do design (fabless firms). Will this be the way of biomanufacturing? While there is growing use of CMOs in biomanufacturing, it is hard to imagine successful companies with the resources to do their own manufacturing giving that up entirely. The strict regulatory requirements, the public health issues at risk, and the innovative gains that can be realized are more likely to lead to more in-house manufacturing than what is found in the semiconductor industry. This is confirmed by the fact that only 20% of the business of one of the leading CMOs is for later stage commercial manufacturing. Thus, while many companies will use a CMO in the early stages of production, they ultimately bring production in-house if it is successful.

This assessment of the push and pull of global innovative activities is a snap shot in time, and the situation will certainly have changed in another decade. We will no doubt see more R&D activities "offshore". But it is unclear that manufacturing will be the pull. More likely it is growing consumer markets combined with rising talent that will be the driving factors.

7.3.1 Biomanufacturing Innovation and Biotech R&D

What about the case of biomanufacturing? Like the pharmaceutical industry, there is little sign that the offshoring of biomanufacturing is "pulling" biotech R&D investments with it. As outlined in a previous chapter, the pull is largely the reverse -- that is biotech R&D pulls biomanufacturing. Most early stage and at least half of commercial manufacturing facilities are located within 100 miles of company R&D centers. The connection between the two is evident, as outlined in Chapter 5, when one compares the top eight countries

for biotech R&D by employment (countries with over 4,000 workers) with the top eight locations for biomanufacturing by volume. At a national level, all but one country, Canada, are in the top eight rankings for both R&D and biomanufacturing (Ireland, which ranks 15th in R&D, is combined with the UK, which ranks second, because of the countries' close proximity). There is only one outlier country, Singapore, which is a top biomanufacturing location (prospectively) but as of 2003 was not a top-ranked R&D center. This speaks to the clear "pull" R&D has with manufacturing. Places like Ireland and Singapore are investing heavily in developing R&D capacity by developing indigenous capacity at university research centers and labs. However, there is no sign that multinational biopharma companies are setting up new biologics R&D centers in countries with strong biomanufacturing. That is not to say that R&D won't follow eventually. In the case of one US biotech company, they chose their first location abroad in Europe in part because the country offered the potential for growing R&D capacity if desired. At this stage, however, like pharma R&D, biotech R&D is largely concentrated in a few locations within the "Triad", and also spreading into new locations within the Triad. Research into the location of biotech R&D centers in the US confirms both the concentration of the industry (only 28% of all biotech firms are located outside nine primary regional clusters) and a "branching effect" in which biotech firms emerge in new locations such as Boulder, Colorado and Salt Lake City[67]. R&D centers may lead to more biomanufacturing locations, but given the evidence at this point in time, the reverse cannot be said to be true.

A similar pattern to the country level data also emerges at the regional level in the US. Of the top eight states in life sciences research in 2006, two are not biomanufacturing centers (Florida and Texas). This reflects the fact that while Florida and Texas have significant R&D activities in basic life sciences research, they have not been centers for the commercialization of biotech. The lack of venture capital in the regions is one possible explanation (Powell et al, 2002) since venture capital firms often require companies they are funding to relocate to one of the biotech centers elsewhere in the country. Without

[67] The nine regional clusters include Boston, San Diego, Bay Area, NY/NJ/CT, DC/MD, Seattle, NC Research Triangle See Cortright and Mayer, 2002 and Powell et al., 2002.

emerging biotech companies, there is no demand for manufacturing. As the number of companies increases, however, there may be more demand down the road (Scripps Florida announced its first biotech spin-off in 2007).

In the US case, as in the global case, there is one significant outlier that is not an R&D center, but does have biomanufacturing capacity – Puerto Rico. In both of the outlier cases at the country and US regional level (Singapore and Puerto Rico, Ireland secondarily), these islands have attracted biomanufacturing investments with a reasonably skilled workforce and significant tax breaks and other incentives, but R&D has not followed. In sum, there is little risk that the loss of biomanufacturing overseas will lead to the loss of biotech R&D jobs. Building biomanufacturing capacity in places like Ireland and Singapore has happened almost simultaneously with an effort by these countries to build their R&D capacity. Whether those efforts will pay off remains to be seen.

7.3.2 Innovation Within Biomanufacturing

While there is little risk of losing R&D biotech activities to biomanufacturing centers offshore, there is the important question of losing innovative capacity within biomanufacturing itself, which affects both process and product innovation. As highlighted earlier, biomanufacturing is highly innovative and is a critical part of drug development, not only because it can lower costs, but also because improvements in biomanufacturing can lead to faster development times and enhanced product innovation. Innovations in process development have led to extraordinary gains in productivity, which are changing the shape of the industry, or at the very least, the size of bioreactors. Biomanufacturing also can affect product innovation. As one executive emphasized, "one can only innovate with a product if you know it well, and this include making it". The fact that all biopharma companies that have significant sales in biotech drugs are ultimately manufacturing these drugs themselves speaks to the advantages these firms derive from keeping manufacturing in-house. Excellence not only provides the benefits listed above, but also establishes companies as "serious" about biotech.

The bigger threat to innovation in the US is the risk of losing process development and early stage clinical manufacturing to offshore locations. Those teams are located along side drug discovery teams. Given the strong links with R&D, and the tax breaks that come with clinical manufacturing in the US, it is hard to imagine a wholesale shift of early stage manufacturing to cheaper locations abroad. All of the executives interviewed said it is preferable, though not essential, to have early stage manufacturing near R&D. While the technology transfer is possible, the benefits of proximity would seem to outweigh possible cost. Places like Ireland and Singapore are working hard to attract these investments through aggressive tax breaks that increase with greater "at risk" investments. Companies receive increased tax benefits the more proprietary information or intellectual property is located or developed in the country[68]. But, currently there is only one example of a company building clinical along with commercial manufacturing facilities in TALs. As one company executive explained, "Countries are bound by their cultures...many of these places aren't necessarily good at out of the box thinking. Ireland and Singapore don't have the innovative capacity yet." As outlined in the previous chapters, companies test new technologies primarily in process development. If a new technology meets the hurdles required to introduce it into commercial manufacturing, this most likely will happen in the facility closest to the PD team. Once a new technology has been tested and approved, it may be introduced into a company's other commercial facilities. While continuous innovation and improvement is the standard across all of a company's facilities, it is unlikely that anything but incremental innovations will arise from commercial facilities, since these facilities are most concerned with consistency and high utilization rates. Thus, innovative work is mostly likely to stay close to research within process development.

All of this suggests that the loss of commercial biomanufacturing capacity in the US does not pose an imminent threat to the innovative capacity of companies whose research is based in the US. It does, however, directly affect the regional "system of innovation" in

[68] Each commercial biomanufacturing facility is unique. They are built for the express purpose of making particular drugs, require specialized skills to operate them, and involve company trade secrets to make the drugs. As a result, companies are able to claim that any facility built represents an "at risk" investment. If, in addition, they develop new intellectual property, they will subsequently receive greater tax breaks.

biomanufacturing regions through the loss of the knowledge and expertise in the industry and hundreds of jobs for skilled workers. If commercial biomanufacturing moves offshore, the generation that built the industry and is training the next generation moves with it. While the knowledge is not necessarily lost outside the company, it is lost to the region, along with the jobs, knowledge spillovers and other benefits that come from having a critical mass of companies and specialized workers. The regional innovation system is weakened. If commercial biomanufacturing leaves Massachusetts, for example, the region loses significant talent in a technological specialization that generates skills, know-how and knowledge spillovers that contribute to the region's strength in the cluster. Still, early stage manufacturing is the engine of innovation in the industry and though it does not produce the same number of jobs, it does generate the skills, know-how and knowledge spillovers that hopefully generate new technological innovations. These, in turn, continue to attract companies to the region who want to be at the cutting edge of the research and new technologies.

7.4 Tax Revenues

Apart from employment, skills and innovation, biomanufacturing's other primary impact on economic development is through the tax system. At the federal and state levels, corporate and personal income tax revenue represent the largest sources of tax revenue generated by industry. At the risk of presenting data that has a wide margin of error, I attempt to calculate a "back-of-the-envelope" estimate of the tax revenues generated by the biopharma industry at the national and state level.

At the state level, I use a hypothetical "representative" biomanufacturing company, (analyzed across seven states by the Pioneer Institute, 2006), with annual revenues of $76.6 million and approximately $13.9 million in net income (pre-state and federal corporate tax), and 81 employees. The average size of biopharma manufacturing firms in Massachusetts is 105, thus not far from the average presented in this analysis. Assuming the 91 firms in Massachusetts (as of 2008), total state and local taxes would amount to

approximately $250 million in tax revenue.[69] In terms of personal income tax, assuming the average annual salary nationally of $96K, employment of 9,580 in 2008, and a personal income tax rate of 5.3%, personal income tax revenue amounts to $48.7 million. However, one must presume that if there were no biomanufacturing in the state, a certain portion of these workers would still be working in the state but in a different industry at a different salary. Given the relatively tight labor market for higher skilled workers in the industry, one could make the assumption that approximately 15 percent of the high skilled workers would find work outside of the state, and that the average salaries, given this exodus, would drop equally by 15%. That would result in personal income tax revenue for the state of $35 million. Thus, for the state of Massachusetts, biomanufacturing brings in approximately $285 million in revenue. Given some of the major companies manufacturing in the state (Abbott, Biogen, Genzyme, Wyeth) this may significantly underestimate the industry's impact from a tax perspective.

At the federal level, the analysis becomes much more dubious, given that few companies pay the actual corporate tax rate (35%) due to many types of deductions, credits and the like that they can apply to their corporate tax bill. My research did not yield an average "effective" tax rate, though recent research by the GAO (2008) found an average of 25.2% for multinational companies (with variation ranging from 10 to 50 percent). Using this rate as an average effective tax rate for biomanufacturing would yield corporate income tax of approximately $10 billion. In terms of personal income tax revenue, with employment of 290,000, an average salary of $95.8 K, and a federal personal income tax rate of 28%, $7.8 billion in tax revenue is generated on $27.7 billion of personal income. One can presume that if biomanufacturing employment did not exist in the country, these workers would be able to find employment someplace in the country with comparable income. Overall, tax revenue at the federal level would amount to close to $18 billion under the scenario presented here.

[69] This includes municipal property taxes (3%), Sales tax (5%), Net Worth Tax (.26%), and Corporate Tax (9.5%). All rates from 2006 (Pioneer Institute).

These numbers are useful only in that they provide a sense of magnitude of the possible revenue generated by the industry and its potential impact on local, state and federal budgets. Without any direct comparisons to other industries, it is hard to gauge whether these numbers represent a lot or a little, relative to the industry size. At the very least, it is safe to say that the state revenue number of $285 million is probably a significant number, particularly given the fiscal crisis the state of Massachusetts is currently in.

The federal corporate tax rate is the subject of some debate and worthy of a brief mention here[70]. In the mid 1980s, Britain and the US led the way within OECD nations in cutting the corporate income tax rate substantially – from 52 percent to 35 percent in Britain, and from 46% to 34% in 1986/7 in the US. Since then, there has been a wave of tax rate cuts from countries across the OECD. The average corporate tax rate for the 30 OECD countries fell from 38% in 1996 to 27% by 2008 (Edwards and Mitchell, 2008, 45). Today, the US has one of the highest statutory corporate income tax rates (39.1 percent with state and federal combined). However, many point out that it has one of the lowest effective tax rates due to all the deductions and credits that companies can use. A recent study by the US Treasure found that US corporations pay a smaller percentage of their taxes (13.4%) than the average of 19 OECD countries (16.1%). And the effective tax rate is estimated to be as low as five percent for some companies.

Regardless of where the exact truth lies about corporate tax rates, it is clear that tax policy has become a more important tool in many countries' economic development toolbox. As competition increases for internationally mobile investments, particularly those that are higher-value added and provide high wage jobs, the US risks losing a higher percentage of jobs that it can compete for on every dimension but for tax. While some see the tax competition globally as a race to the bottom, "nations cannot effectively pull out of the tax competition "game" without negative consequences for their own economic competitiveness, as the US has seen over the last 15 years with its growing

[70] This section draws from three recent publications: *Global Tax Revolution* by Chris Edwards and Daniel Mitchell (Cato Institute: Washington, DC), 2008; *Effective Corporate Tax Reform in the Global Innovation Economy* by Rob Atkinson, published by the Information and Technology Foundation, July 2009 and Putting US Corporate Taxes in Perspective, Chye-Ching Huang and Chad Stone, The Center for Budget and Policy Priorities, October 27, 2008, http://www.cbpp.org/cms/?fa=view&id=784.

trade deficit." (Atkinson 2009, 6). The answer, according to some, is to look for ways to lower the effective tax rate for companies by providing incentives that encourage investment in innovation and productivity, for example in R&D, workforce training and education and new capital equipment. This debate, particularly as it relates to biomanufacturing, merits further analysis. In the following section, I outline what other regions or countries are doing to attract biomanufacturing investments and grow the industry in their part of the world.

7.5 Economic Development Strategies in Biomanufacturing

If biomanufacturing is an industry that is worth retaining and growing, what strategies should be pursued to increase the chances of this happening? Countries and regions around the world are focused on developing biomanufacturing capacity for all of the reasons discussed to this point: The following reviews some of the primary strategies governments and public/private agencies are pursuing.

The four regions or countries reviewed here have to various degrees targeted the life sciences as part of their economic development strategy. In the cases where there was relatively little biotech R&D capacity, biomanufacturing has been a central part of building the industry (Ireland, North Carolina). Where the R&D already exists, as in the UK, biomanufacturing has been a secondary strategy. And in the case of Singapore, which had virtually no foundation in the life sciences, biomanufacturing and biotech R&D have been targeted simultaneously. Some of these initiatives began over 25 years ago, as in the case of North Carolina, which created the North Carolina Biotechnology Center in 1984. Singapore set up the Institute of Molecular and Cell Biology in 1987, and followed with the Bioprocessing Technology Center in 1990. Britain and Ireland have more recently invested in state-sponsored biomanufacturing centers just in the last five years. While these four examples do not capture all that governments are doing to build the industry, they capture some of the most aggressive efforts and give an indication of the types of strategies and scale of effort that governments are engaging in to become global biomanufacturing centers. What is striking about these approaches is how far they go beyond the classic incentive packages and "smoke-stack chasing" that has

traditionally been used (and still is) by many states in the US as well as countries. Today, incentives involve much more training, education and R&D investment, creating greater interdependencies and linkages between firms and other regional institutions such as universities, community colleges, and non-profits. The deepening of these relationships can ultimately create more value to companies and the region than initial incentive packages.

Strategies for growing the biomanufacturing industry fall into four main categories, which I discuss in turn:

1. ***Workforce development*** programs for both lower-skilled and higher-skilled workers
2. ***Research and development*** in biomanufacturing and,
3. ***Biomanufacturing production facilities*** that assist companies in early stage manufacturing
4. ***Incentives*** to companies in the form of lower tax rates, tax breaks, credits and subsidies to locate facilities in the region or country

Workforce Development: Companies in Massachusetts cite a shortage of workers both at the entry-level and at the managerial/supervisor level. This is no different in places like North Carolina or Ireland. In regions with a critical mass of companies, there is a shortage of operators and technicians, significant churn of college-degreed workers, and poaching of supervisors and managers. In an effort to increase the supply of skilled biomanufacturing workers, and also meet goals of social inclusion (in the case of NC), governments have developed specific curricula for entry-level workers, as well as higher educated workers, and also created training centers with state-of-the art biomanufacturing facilities. Some of the efforts include:

- *Network of specialized community colleges*: Community colleges, working in conjunction with industry, have created specific training programs that address skills gaps and training needs. In North Carolina, this includes BioWork, a 128-hour course that provides entry-level training for biopharma manufacturing.

- *Creation of biomanufacturing training facilities*: Three of the four locations (excluding the UK) have created state-of-the art facilities that can provide training to undergraduate and graduate students. The costs of the expensive and specialized equipment used in biomanufacturing are often covered with industry/government partnerships. Singapore's Bioprocessing Technology Institute (1990), Ireland's National Institute for Bioprocessing Research and Training (NIBRT, 2006) and North Carolina's Biomanufacturing Training and Education Center (2007) at North Carolina State University all partner with industry to train the next generation of workers.
- *Training Funds*: In North Carolina, companies within one county agreed to contribute 8 cents per $100 in property value to a training fund that helped build the county's workforce development center. The center provides companies with off-site training space. The quid pro quo for this agreement was the creation of a special economic zone that prevented companies within the county from being annexed or taxed by any town.

Research and Development: Every location that is a biomanufacturing center hopes to develop its biotech R&D capacity. By moving up the value chain, the region generates higher skilled, higher paying jobs, intellectual property, commercial opportunities, and an overall increase in the standard of living. Ireland ratchets its tax rates based on how much R&D or "at risk" investment is involved in biomanufacturing investments. In an effort to make this transition from just manufacturing to more process development and R&D, Ireland and Singapore have created bioprocessing centers that are affiliated with local universities (Ireland) or house their own proper principal researchers (Singapore). By creating a center with the facilities and the know-how for biomanufacturing research, the countries are encouraging industry/academic partnerships, which they hope will lead to the generation of intellectual property and new commercial ventures. In Ireland's NIBRT, industrial partners can either collaborate with the principal researchers at the Institute, or engage the researchers on a contract or consultancy basis. Both centers are funded by the national government. In Singapore's case, they announced this year a research partnership with GSK in which the company will invest $2 million. For places that

already have some R&D infrastructure, governments are providing investments in R&D, such as the $7 million provided in 2008 ($5 million in 2007) to North Carolina State University Bioengineering Department.

Biomanufacturing Production Facilities: Given the expense of biomanufacturing facilities, small, emerging biotech companies most likely will outsource their early stage manufacturing. This is often not ideal for a company because they lose control not only of the process, but also of the timing, which can be crucial at the early stages of a drug's development. Both Ireland's NIBRT and Britain's National Biomanufacturing Centre (NBC, opened in 2006) provide facilities for companies to use to conduct early stage manufacturing. In the case of the NBC, a contract manufacturing company runs the facility. The government also provides grants to companies (a total fund of $5 million) that want to contract with the center. The facilities can also be used as a showcase by biomanufacturing suppliers who want to demonstrate new technologies. Given the relatively newness of the facilities in Ireland and the UK, it is unclear whether this "gap" manufacturing strategy will be successful.

Incentives: The use of taxes, grants and subsidies as part of incentive packages is standard economic development practice. The extent to which these are used depends upon the degree to which biomanufacturing is core to the government's economic development strategy, and the resources made available. Tax breaks, which are significant in Ireland and Singapore, are part of the incentives. But in addition, companies often receive "grants" for buildings, land, and subsidized training for workers. North Carolina has used incentive packages aggressively, having provided $102 million in direct company incentives over the past 10 years. The following example illustrates how incentive packages work. North Carolina gave $36 million to Merck in 2004 to build a new vaccine manufacturing facility. As part of the Job Growth and Infrastructure Act (JGIA) passed in 2003, a Site Infrastructure and Development Fund was created which buys and develops industrial sites for major biopharma manufacturing facilities. Merck received $24 million to buy and prepare a 256-acre site. To tap the "restricted reserve fund," projects must involve a capital investment of at least $100 million and create at

least 100 new jobs. In addition, the JGIA fund provides pharmaceutical and bio-processing projects with sales-tax rebates on construction materials used to build facilities that have a value of $100 million or more. That provided Merck with an estimated $4.7-million rebate. The rest of Merck's incentives came from a $3.7-million, 10-year state cash grant and from various existing tax breaks.

While Singapore's Economic Development Board, which negotiates incentive packages with companies, won't allow details of the packages to be released, professionals in the field say that beyond the highly favorable tax rates, the country provides grants to build facilities, as well as subsidies to train the Singaporean workforce, including training the workers abroad. Lonza's new $200 million facility was, in the words of one biomanufacturing expert, "paid for" by the Singaporean government. In addition, the state's venture capital arm, Bio*One, is a shareholder in the Lonza operation.

Evaluating the effectiveness of these strategies is challenging. Each has different timelines and performance metrics. It is easier to measure the number of graduates from a training program than to measure the impact of R&D investments. But each of the strategies has one thing in common: significant expenditures by the state. In each of these cases, the government is spending millions of dollars either in training, infrastructure, or incentives to attract biomanufacturing investments. Some of these expenditures have a clear "public good" aspect to them, such as new training facilities. Others, such as direct grants to companies, are private investments that the state hopes will generate social benefits. Whether the economic development benefits generated to date or in the future are justified by these investments is difficult to discern at this relatively early stage. In the case of tax incentives many suggest they are just the "icing on the cake" when it comes to a company's decision to locate someplace and work at best on the margin. In surveys of business location decisions, taxes enter the decision-making process at the very last stage, if at all (Buss, 2001). Hundreds of studies have attempted to determine whether tax incentives have an impact on business location and economic growth and the consensus seems to be, it is unclear. Tax incentives are "neither good nor bad from the standpoint of efficiency in the economy." (Ibid, 101.). There is little impact on the national economy,

but potentially a waste of local resources. Anecdotally, it seems that tax incentives come into discussion once a company has a short list of locations it is interested in. Then neighboring states, for example, Rhode Island and Massachusetts, may have a bidding war using incentives and subsidies.[71]

Based on investments to date, it is fair to say that, given the role sunk costs and economies of scale play in this industry, strategies which help establish a country's foothold in the industry have a good chance of leading to future investment.

7.6 Discussion

In summary, as the U.S. struggles with defining what a "manufacturing policy" might look like, advanced manufacturing industries such as biomanufacturing offer a window into how the U.S. leads in an industry internationally, and what threatens that lead. The US continues to be strong in the most innovative aspects of biomanufacturing's product life cycle, but loses jobs to locations that, while equally or more expensive to manufacture in than the U.S., are willing to use aggressive public policy to seed the industry in their country or region. Biomanufacturing, while not a large employer nationally, and experiencing flat job growth, potentially represents the kind of manufacturing the US can expect to compete in going forward. While some might say there is little economic development opportunity, in fact, given the new emphasis in economic development on timing, location, and knowledge creation as a self-reinforcing cycle, maintaining critical mass and excellence in a particular industry, no matter how small, can still lead to important economic development outcomes. Biomanufacturing contributes to economic development primarily through highly skilled, well paying jobs and highly innovative product and process development, which leads to the retention and growth of existing companies, but also leads to entrepreneurial endeavors in new technologies and new drug therapies. To the extent that a regional innovation system exists within the industry in places like Massachusetts, it helps embed skills and technology that help usher in the next wave of technologies and new industries that will

[71] As discussed in the next chapter, this played out in a bidding war for the expansion of Shire, a Massachusetts-based company. The company ultimately chose to expand in Massachusetts, once the state topped Rhode Island's offer of $40 million in tax incentives. Massachusetts offered $47 million.

follow. Finally, there are tax implications that are not insignificant. As the theory of compressed development suggests, the economic development window is always changing and is not open forever. Many other competitors are trying to climb through the window, using many of the economic development strategies outlined in this chapter. The US must stay at the cutting edge of innovation in the industry, while enhancing the benefits that come from agglomeration economies. Clearly, companies continue to locate commercial facilities and add capacity within the US for reasons highlighted elsewhere in this research. Supporting these investments and finding ways to offer competitive effective tax rates will help retain and grow the industry in the country.

Chapter 8

The Biomanufacturing Opportunity in Massachusetts

8.1 The Massachusetts Economy

The history of the Massachusetts economy offers a window into the history of the growth of the US economy as a whole. Since the industrial revolution, the region has been the birthplace of American industry, both in machine tools and textiles. Today it is the birthplace of some of the most advanced technological innovations in twenty-first century industries such as biotechnology and nanotechnology, and provides an interesting case study of how a highly innovative region competes globally. With each successive economic cycle as well as increased global competition, the region must find a way to stem the decline and regenerate itself. Massachusetts has suffered a number of downturns, but unlike some regions, has repeatedly managed to recover and come back, often diversifying into new, emerging industries[72]. Few could have predicted in the 1950s as the region lost jobs in traditional industries like textiles and shoes, that in the 1980s, the "Massachusetts Miracle" would be touted for the creation of America's first high-tech industrial district around Route 128. In the 1980s, the state came close to matching the 20% growth rate in payroll employment that the country was experiencing. The resilience of the region is explained in part by its world class research universities and government-supported research labs, entrepreneurial culture, new business models and the skills and know-how that are embedded in the region. In 1989, the state went into a deep recession for three years, losing 10% of the state's job base, only to come back in the next decade with significant growth in jobs and productivity growth, as the economy moved more into services and knowledge-driven industries such as information technology, health care and life sciences. Manufacturing jobs as a percentage of total employment declined from 24% in 1983 to 13% in 2000 to 9% in 2006, which has been a significant blow to the economy. Manufacturing has made up a key part of the state's export base, which in turn

[72] The following summary of the Massachusetts economy draws from a number of sources: Best (2001); Center for Labor Market Studies, *The State of the American Dream in MA, 2002*, MassInc, 2002; Sum et.al, *Mass Jobs: Meeting the Challenges of a Shifting Economy,* MassInc, 2007; Barry Bluestone: *Sustaining the Mass Economy: Housing Costs, Population Dynamics and Employment*, Boston Federal Reserve, 2006.

generates jobs in other sectors of the economy. The national recession of 2001 hit the region particularly hard because of the bust of the "high-tech" bubble, and to this day the region is still trying to recover the 200,000 jobs that were lost as of 2004, half of which were in manufacturing. Part of the jobless recovery of this decade is explained by the state's high labor productivity rates, which rank 7th in the country and have outpaced the nation.

The Massachusetts economy has evolved into what some call a "boutique economy" (Sum, et.al 2007) in which knowledge-driven clusters are highly specialized and employ higher skilled workers (MA has the highest share of working-age population with a BA or higher – 33% - in the country). The state ranks first in the country in indices measuring "the new economy" including the number of "knowledge jobs", global exports, economic dynamism and technological innovation (New Economy Index, 2008). However, there are a number of challenges. For those without higher education, the loss of manufacturing jobs, flat wages during the decade in most industries, and the high cost of living in the region, makes it difficult to succeed. The high cost of living (primarily driven by housing prices) is also leading to outmigration of many working-age college-educated workers who want a more affordable location to raise a family. In short, the Massachusetts economy contains all the right ingredients for long-term growth in an innovation-driven economy, but also all the potential downside of not making that growth more inclusive for the whole population and state.

8.2 Biotechnology in the Commonwealth

Biotechnology, and the life sciences more broadly, is a critical part of Massachusetts' "boutique economy." The industry was pioneered in the state and is home to some of the largest and most successful biotech companies, including Biogen and Genzyme. A critical mass of companies (close to 300 in 2002), many of them spin-offs from university research, have located in the area, creating a fertile area for biotech research and entrepreneurship. In addition, big pharma companies such as Merck and Novartis have established research teams in the region. The state continually ranks as one of the top, if

not the top location in the country in a wide variety of performance metrics[73]. It ranks in the top three locations in the country by employment in biopharma research as well as medical devices. It is also eighth for drug and pharmaceutical manufacturing. In all, the biopharma industry employs approximately 56,000 people (2006) and if one applies a multiplier effect of 2 to 1, the industry employs well over 100,000 in the state. With regard to some of the key inputs that determine success in the industry, such as research funding, venture capital investment, educational attainment and patents, the state scores very high. Massachusetts ranks first on a per capita basis for NIH funding (second overall), venture capital funding (second overall) and life sciences higher education degrees awarded (ninth). It is second only to California in terms of total patents awarded in the life sciences between 2002 to 2007.

In order to maintain this position of excellence, significant public and private efforts have focused on retaining and growing the life sciences in the region. In 2002, the Mass Biotech Council, in conjunction with the Boston Consulting Group, published the Mass Biotech 2010 report that outlined the key challenges facing the industry in the state:

1) Responding to growing competition from other regions
2) Maintaining the state's legacy of world-class research and innovation and becoming the best at convering research into commercial innovation
3) Extending the industry further down the value chain into development and manufacturing, and
4) Leveraging the resources and networks of the broader life sciences economic cluster beyond biotech

[73] This section draws primarily from two reports: *MassBiotech 2010*, by the Boston Consulting Firm and the Mass Biotech Council, 2002, and *Technology, Talent and Capital: State Bioscience Initiatives, 2008,* by Battelle. As explained in an earlier chapter, a strict definition of biotechnology would focus on Drugs and Pharmaceutical Manufacturing, and Research, Testing and Medical Laboratories (NAICS 3254 and 541380, 541710, 621511, and 621512). Broader definitions, like those employed by Battelle, include Medical Devices and Equipment and Agricultural Feedstock and Chemicals. For purposes of analysis of Massachusetts, Medical Devices and Agricultural Feedstock and Chemicals are not included in the definition of biotechnology, and Agricultural Feedstock and Chemicals is excluded from the definition of life sciences.

The state moved to support this agenda institutionally, creating the Life Sciences Collaborative (LSC) in 2007, a privately-led consortium of universities, teaching hospitals and companies from the life sciences as well as supporting industries such as venture capital (the Massachusetts Technology Collaborative manages the LSC). The LSC has outlined a broad agenda to address competitiveness issues focusing on a range of issues (early stage funding, talent, NIH funding, transportation, manufacturing, the business environment and the cost of living)[74]. In addition, in the spring of 2007, following the lead of other states such as California and North Carolina, the Governor pledged $1 billion to support the growth of the life sciences and created the Massachusetts Life Sciences Center, a state agency.

8.3 Biomanufacturing in the Massachusetts Region

Capturing more of the downstream manufacturing in biopharma has been established as an economic development priority for Massachusetts. But what is the economic development opportunity? This section outlines the opportunity, the region's competitive advantages and disadvantages, and potential strategies to pursue.

An often-heard phrase in biomanufacturing is "the process is the product." This refers to the fact that biotechnology is essentially the production of genetic material for human consumption. Thus, the pioneering of the biotech industry is the pioneering of biomanufacturing in Massachusetts, which occurred with some early discoveries about bioprocessing at MIT. Beginning in the early 1990s, the first large-scale biomanufacturing facilities were built in the region. The first commercial facility was built in Rhode Island by WellGen in 1991, followed by Genetics Institute in North Andover in 1992, BASF in Worcester in 1993 and Genzyme's facility in Allston in 1995. In all, there are approximately 90 biopharmaceutical manufacturing establishments in the state employing 9,600 people in 2008, up from 7,800 in 2001[75]. Only 10 of these companies are engaged in mammalian-based production. The other are presumably engaged in small molecule and microbial, including vaccine production, as well as

[74] See http://www.masslsc.com.
[75] Numbers from the BLS; 2008 numbers are provisional.

supplying equipment and services to the industry. There are approximately 2,800 additional jobs in New Hampshire and RI, which share the same regional labor pool. "As soon as Amgen opened up their facility in Rhode Island [online in 2006], I had to increase the pay of my supervisors by 20%", said one Cambridge-based biomanufacturing executive.

As has been pointed out elsewhere, these jobs are well-paid and employ a high percentage of highly skilled workers. Interviews with companies suggest that roughly 18-25% of these jobs require an advanced degree (Master's or PhD), an additional 40% require a BA, and the remaining 40% or so require a two-year associates degree or high school diploma. This latter category is of particular interest if one of the goals for the state's economic development is employing lower skilled workers.

Unlike biotech R&D, where Massachusetts is one of the top locations in the country and the world, in biopharmaceutical manufacturing, Massachusetts is ranked eighth by state. (see Table 8.1, repeated from the last chapter).

Table 8.1 Top States for Drug and Pharmaceutical Manufacturing by Employment and Establishments

State	Employment			Establishments			Ave. Size
	2001	2008	CAGR	2001	2008	CAGR	Firm '08
CA	39,199	43,037	*1%*	432	395	*-1%*	109
NJ	37,872	37,956	*0%*	203	255	*3%*	149
PR	24,646	22,663	*-1%*	81	75	*-1%*	302
PA	25,780	22,288	*-2%*	123	118	*-1%*	189
NC	18,782	18,787	*0%*	81	80	*0%*	235
IN	18,536	18,822	*0%*	41	43	*1%*	438
IL	20,275	18,534	*-1%*	125	116	*-1%*	160
MA	7,794	9,580	*3%*	85	91	*1%*	105
USA	*280,665*	*289,641*	*0%*	*2,522*	*2,623*	*1%*	110

Most of these states have a significant biopharma manufacturing presence because of the headquarters or major R&D centers of large companies. The leading states by a

significant margin are California and New Jersey, both homes to major biotech and pharma companies that keep large molecule and complicated small molecule production nearby. The same can be said for Pennsylvania, Indiana and Illinois (California – Amgen, Genentech, Baxter; New Jersey – Imclone, Roche; PA – Johnson & Johnson, GSK; Illinois – Abbott, Takeda; Indiana - Lilly). These states have a long history in the pharmaceutical industry. Puerto Rico, because of its significant tax breaks, has become home to primarily standardized small molecule production as well as fill/finish operations. North Carolina is the relative newcomer to the industry, without a long legacy in biotech or pharma. The state has become a center for manufacturing, primarily in vaccines and microbial production, which are less complex and require a lesser skilled workforce than mammalian production.

The fact that California and New Jersey (and specifically the NY-Northern New Jersey-Long Island MSA and the San Francisco-Oakland-Fremont MSA) are the top locations for biopharma manufacturing suggest that the cost of doing business is not a driving factor in the location of some portion of the industry. These regions are just as expensive as Massachusetts. While Massachusetts may not compete with Puerto Rico or North Carolina for less complex types of manufacturing, it should be able to compete in the more complex mammalian-based production, which is the growth area within biotech. Interestingly, the only states to show some significant employment growth in manufacturing since 2001 are California and Massachusetts, the two centers of mammalian-based production.

The Opportunity

The opportunity for Massachusetts is thus in specialized aspects of biopharmaceutical manufacturing – mammalian-based production and possibly complex small molecule production. It is also in the highly innovative stages of production – pilot and clinical manufacturing as well as companies' first commercial production facility. This draws on a host of supporting services such as analytics, instrumentation and bioinformatics, which also has growth potential in the state. Because of the state's entrepreneurial base in biotech and the strong link between R&D and early stage manufacturing, Massachusetts

can potentially be home to early stage manufacturing for emerging and growing biotech companies, which may become the next Biogen or Genzyme. In addition, for the few established companies that are building their first commercial facilities of scale, such as BMS, the state offers the experience, know-how and R&D support that a company may want. The location of BMS' first commercial facility of scale at Fort Devens in 2006 was a huge boon to the industry in the state but many biomanufacturing experts in the region say that those kinds of investments will be few and far between going forward. In addition to the early stage manufacturing and first commercial facilities, one of the key areas for growth in the region comes from existing, established companies who have created a critical mass in the state. The recent expansions by Genzyme and Shire speak to the power of sunk costs in people and infrastructure and economies of scale. Finally, changes in technology that will decrease the cost of manufacturing may lead companies to build continuous production facilities, that is, facilities that can go from pilot through commercial at the same location. This would be most likely for companies that are producing relatively small volumes (Neurotech, a new company located in Rhode Island that makes hybrid devices for retinal work, is using this model).

While job growth was three percent between 2001-8 on a compounded annual basis, the highest in the country, there may not be significant job growth in the short term given increased productivity rates and excess capacity. But with industry growth projected at 16% per annum, there is certainly potential. As highlighted earlier, the importance of the industry to skills development, innovation and competing in the next frontier industry make this an important industry to retain and grow. In the words of one biomanufacturing executive in the state, "there is no reason the state can't compete in this industry." Biomanufacturing is perhaps indicative of the kinds of industries that the region will likely compete in going forward – a niche industry for a boutique economy.

8.4 A Biomanufacturing Strategy for Massachusetts

By the mid-1990s, biomanufacturing as an economic development opportunity for Massachusetts was on the state's radar screen. When, in the early 1990s, the state lost several commercial facility investment opportunities, the then Secretary of Economic

Development, Ranch Kimball commissioned a study to understand why Massachusetts was not successfully competing against other states in the US, such as North Carolina. The study found that Massachusetts was not perceived as "business friendly" compared to other states that were "rolling out the red carpet," in the words of one biotech executive. As a result of this and other efforts in the state, a number of steps were taken to make the state more competitive for manufacturing within the US. This included the passage of expedited permitting (which helped with the BMS deal in 2006), and research and investment tax credits for new manufacturing sites. The expansions by Genzyme and Shire show that in fact the state is an attractive location for some companies. However, its niche may be narrow, and the state will have trouble competing with cheaper locations like Georgia and North Carolina for the less complicated types of biomanufacturing. Comments by the President of the Mass Biotech Council that in effect suggest the state cannot compete for biomanufacturing facility investments is short-sighted and does not take into account the state's "sweet spot" as well as changes in technology that may make it more affordable to build facilities in the US, and in Massachusetts.

A decade after the state's big efforts around biomanufacturing, several discussions with biomanufacturing leaders in 2008-2009 highlight what are currently perceived as the competitive advantages and disadvantages of the region compared to other domestic and international locations. In terms of competitive advantages, the region has great talent (in part from the universities and the critical mass of the industry that is located here), a strong entrepreneurial base of companies, highly innovative research from excellent universities and research institutions, and a good education system. In terms of competitive disadvantages, the industry finds a shortage of workers, both entry level and at the managerial level, the high cost of living, challenges with physical infrastructure and the ability to compete on taxes and incentives with other places within and outside the US. These are discussed below.

8.4.1 Competitive Advantages of the State

Talent: The primary competitive advantage the state has in the industry is talent. As outlined in Chapter 4, finding a highly skilled workforce is a prerequisite for the

establishment of biomanufacturing. Many of the pioneers of the industry who built the first facilities and produced some of the first biomaterial like Factor 8 and human growth hormone live in the region and have spent their professional careers working for one or more companies improving biomanufacturing processes through "learning by doing." Many of them are now in their fifties and are training the next generation of workers, of whom they say there are too few. Biochemical engineers graduating with Masters or PhDs today are often interested in going into cutting edge work, which biomanufacturing can provide. The demand for top talent is significant. Many companies complain of too much poaching among companies for senior managers and supervisors.

Strong Entrepreneurial Base: Massachusetts is one of the most significant centers for biotech R&D in the world. It also has an entrepreneurial culture, and a strong base of small and medium size biotech companies. The ability of the region not just to develop new concepts and compounds, but also to commercialize them is a continual source of demand for biomanufacturing talent and facilities as emerging companies engage in manufacturing their drugs. While most small firms will initially have their product made by CMOs, they still need an in-house team that can interact with and monitor the CMOs. Once these companies have a viable product, there is a good chance they will seek to make the product themselves. A general industry benchmark is that companies should have at least one approved drug and four additional products well along in the pipeline before they decide to invest in biomanufacturing capacity. If this is the case, they will want to have a pilot and clinical facility close by to scale up the product. This research and entrepreneurial base continually feeds demand for biomanufacturing capacity.

Research, Universities, and Innovation

The rich research environment in biotechnology and biomanufacturing is a draw to many companies that want to be near cutting edge technology, either for access to new products and processes, or because it attracts the best talent. There are no less than eight universities that specialize in one or another aspect of biopharmaceutical manufacturing (MIT, Northeastern, Tufts, U Mass Dartmouth, U Mass Lowell, U Mass Worcester, U Mass BioLabs, Worcester Polytechnic Institute), one of which, MIT, is consistently

ranked one of the top two engineering schools in the country, for both undergraduates and graduates. The research as well as training that these universities generate is the engine behind innovation in the industry. The innovative culture creates a virtuous cycle that keeps talent and companies in the region.

Education System: As discussed below, one of the competitive disadvantages of the region that is often cited is the high cost of living, particularly housing costs. One of the factors that offsets this negative is the strong education system. While families pay more for housing and other expenses such as utilities, the public and private education systems are perceived as quite strong, which is attractive to workers with families.

8.4.2 Competitive Disadvantages of the State

Of course there are a number of challenges in the region that hinder further growth in biomanufacturing, some of which are within the region's control, some of which are not. These include:

Shortage of Trained Workers: While a talented workforce is one of the region's primary strengths, there is still a challenge to find workers at both the entry level and the supervisor level. First, in terms of operators and technicians, companies say there is a shortage of workers with either the training or experience. Companies prefer workers either with an associate degree or with a high school diploma and some work experience. While there are a few community colleges that have introduced biomanufacturing degrees, these are few and far between and do not graduate a high number of workers. Second, companies complain of constant "poaching" of manufacturing supervisors, those with at least a BA or more who oversee the production process. With many companies to work for in the region, people with the skills and experience are in high demand. In addition to these shortages, senior executives raise a national-level issue around access to visas for foreign workers. The restrictions on H-1B visas for skilled foreign workers (a cap of 65,000 for the country) have hindered companies' ability to hire freely and have made competition for the visas fierce.

Physical Infrastructure: The Massachusetts region is densely populated and as a result does not have the significant tracts of open land sometimes desired for new facilities. Companies often are looking for 80 to 100 acres to develop for a new commercial facility. While Massachusetts was able to accommodate BMS with 88 acres at the Fort Devens industrial park (35 miles from Boston), there are few sizeable tracts of land of that scale that can accommodate new development. In addition, locations need sufficient access to water and adequate utilities infrastructure to meet the demands of large bioreactors. The state government provided the city of Framingham approximately $13 million for water and sewer upgrades to accommodate Genzyme's expansion in 2008. Older, industrial cities often are ill equipped for the demands placed on their older physical infrastructure. This contrasts with places like North Carolina, Ireland and Singapore that can build on greenfields and provide modern physical infrastructure.

Cost of Living: One of Massachusetts' major challenges in competing with places like North Carolina, is the cost of living. On one cost of living index[76], Boston is over twice as expensive as Raleigh. The cost of living drops dramatically once one moves outside the 495 ring road (Worcester is half as expensive as Boston). A number of recent studies have pointed to the high cost of housing in particular as a real deterrent, not only to people considering moving to the area, but also to younger professionals who are trying to buy a house and raise a family[77]. In fact, the state is losing population between the ages of 25 and 34, an important cohort for developing the next wave of professionals. The cost of housing is considered a factor in the decline in population and employment within the state. While housing costs are high (median home in 2004 cost $376,000 and Boston rents are second only to New York), other costs also enter into the equation such as child care, health care and federal and state taxes Overall, Boston's Metropolitan Statistical Area (MSA) ranks as the most expensive in the country for a family of four. Interviews suggest that companies looking for a location for their facility need to draw both from communities that are home to hourly workers (operators, technicians) and also

[76] A cost of living index can be found at the Council for Community and Economic Research website, http://c2er.org/store.asp.

[77] A summary of recent statistics on how Massachusetts ranks can be found in *Sustaining the Mass Economy: Housing Costs, Population Dynamics and Employment*, by Professor Barry Bluestone. Presentation to the Boston Federal Reserve, May, 2006.

communities where the higher educated workers live. North Andover, Devens and Lexington (locations for Wyeth, BMS and Shire) all meet this requirement. But in order to benefit from the knowledge spillovers that arise from proximity, companies often want to be closer to Boston and Cambridge.

Cost of Doing Business: While few companies cited the cost of doing business within Massachusetts as a major factor (the far bigger challenge are lower tax rates outside the US), it is useful to look at a recent study by the Pioneer Institute (2006) that looked at a "representative" biomanufacturing company based in the Boston MSA and compared its business costs to a similar business in six other US states (NH, NJ, NY, NC, RI, TX) (see Table 8.2).

Table 8.2

Comparison of Cost of Doing Business In MA with Six US States, 2006
Representative Biotech Manufacturing Company with 81 employees, annual sales of $76m, and sq. ft of 50,000

Rates	MA	NH	NJ	NY	NC	RI	TX
Labor Costs							
Unemployment Ins.	5.48	2.70	4.30	4.60	3.24	4.80	3.50
Worker's Comp.	1.70	3.19	2.38	2.97	2.32	3.01	3.08
Other Costs							
Industrial Electricity	1.59	2.09	1.78	1.37	0.92	1.80	1.28
Industrial Gas	1.62	1.43	1.32	1.34	1.24	1.36	0.91
Rental Costs - Industrial	7.76	5.35	5.52	9.09	6.08	6.42	3.57
Municipal Taxes - Indust.	1.63	0.55	0.95	2.32	0.84	2.04	3.07
Sales and Use Tax	5.00	0.00	7.00	8.38	7.00	7.00	6.25
Net Worth Taxes	0.26	0.00	0.00	0.00	0.15	0.03	0.25
Cost Differential w/MA	-	***-22.50***	***2.50***	***6.20***	***-22.20***	***-2.70***	***-25.30***
Corporate Income Tax*	9.50	8.50	9.00	7.10	6.90	9.00	0.00

* Rates as of July, 2009.

Pioneer Institute, 2006.

Table 8.2 presents average rates in percentage terms across the major business expenses (excluding health care premiums) in seven states. Because of the higher cost of living, wages are assumed to be higher in Massachusetts, leading to higher labor costs (unemployment insurance, worker's compensation, health care premiums). While Massachusetts is generally competitive with three of the six competitor states in utilities (electricity), sales and municipal taxes, it is less competitive in industrial rents and property/net worth taxes. After calculating these costs before state corporate taxes on

income, Massachusetts is found to be roughly equal to or cheaper than NJ, NY and RI, but 20+ percent more expensive than NH, NC or Texas. However, this analysis is highly generalized and interviews with companies suggest that labor costs, which are not a large part of total costs, are similar across US locations (and higher in Europe). In addition, while the study uses the Boston MSA as its reference, there are significant differences in costs, in particular rents, within the MSA. For example, Cambridge office space averages approximately $60 a square foot, compared to $40 or less just 12 miles or more outside of the Boston/Cambridge area[78].

Tax Breaks and Subsidies: While every state, region and country use tax breaks and subsidies to attract investment, these often can play a minimal role in the final determination of where a company locates (Buss, 2001).However, as has been made clear through the actions of a number of biopharma companies in recent years, tax breaks can play a deciding factor once a short list has been drawn up as to where a company locates a new commercial facility. The US federal tax rate of 34% is a significant barrier to investment compared to 12, two or zero percent available in some places. While Massachusetts cannot compete on tax policy at the federal level, its tax breaks at the state level are considered relatively competitive with other states. Table 8.3 provides the details on two deals completed in Massachusetts recently in which the state provided significant tax incentives.

Table 8.3 Recent Biomanufacturing Investments in MA Using State Tax Incentives

Year	Company	Company Investment	Jobs	State Incentives	Details
2008	Shire	$394m	680	$48m	No local tax for 20 yrs
2006	BMS	$750m	800	$33m	Additional $34m bond

In the case of the Shire deal, the state was competing with three other locations that offered competitive tax incentives – Rhode Island ($40m), North Carolina ($42m) and South Carolina ($50m). The latter would not be a strong competitor given the type of

[78] Biogen Idec announced in December, 2008 that it would move its corporate headquarters out of Cambridge to Weston, MA and reduce costs per square ft by approximately $20. http://boston.bizjournals.com/boston/stories/2008/12/01/daily15.html

biomanufacturing Shire engages in. Rhode Island, however, is a significant competitor and ultimately the state had to top that state's incentive package.

A very simplistic calculation of dollars spent by the state per job yields $70,600 for Shire and $41,000 for BMS ($96,000 if you include the bond). While these numbers seem high, given an average salary of $96,000, the number appear more reasonable. However, this calculation ignores the value of the investment by the company. In Shire's case, the company's investment is eight times that of the state's, and in BMS's case it is 10 times. In addition, the bond provided by the state to invest in an upgrade in infrastructure for BMS is technically an investment in a public good. In the case of these substantial investments, there is a smaller amount of risk that these companies will move these investments any time soon because of the nature of the work and the size and scale of the investment. In cases where companies are working in the state's "sweet spot" and the investments are significant, a strong case can be made for the use of incentives.

While the state is clearly competitive in terms of tax incentives with other states in the US, Massachusetts may be less competitive with respect to direct subsidies or grants to a company. The state has resisted in most cases giving grants with no strings attached, but instead will provide subsidies that represent some element of a public good, for example, physical infrastructure. In the case of the BMS investment, the state provided the largest investment ever to a company, providing $34 million in physical infrastructure improvements. Workforce training support is another valuable contribution the state can make. This can come in the form of worker training programs organized at the community college level, such as BioWork organized in North Carolina, or more significant support, such as that provided by Singapore, in which the country offers in addition to the training to pay for the on-the-job training of workers, both in Singapore or in the home country. While Massachusetts' community colleges have a couple of biomanufacturing programs that receive high praise, the system is fractured and not as well coordinated as what one finds in North Carolina. The limits that the state places on the incentives and subsidies it is willing to provide are justified, particularly when competing with lower cost locations like North Carolina, South Carolina, Texas or

Georgia. The state is better positioned to compete in its "sweet spot" and invest in things that provide a public good such as education, R&D and physical infrastructure.

Clearly what makes Massachusetts competitive with other locations in the US and around the world is the talent and innovation within the region. While it might be cheaper to manufacture in North Carolina or Texas, companies that are looking for the knowledge that is "in the air", to use Alfred Marshall's phrase, are willing to pay the difference to be located in the state. However, given the aggressive strategies employed around the world to build the biomanufacturing industry, Massachusetts will have to actively pursue the industry to keep the foothold it has today. The following outlines a biomanufacturing strategy for the state.

8.4.3 A Biomanufacturing Strategy for Massachusetts.

As outlined previously, the "sweet spot" for biomanufacturing investments in the Massachusetts region has several components. First, it involves innovative work, which means early stage manufacturing (pilot and clinical) as well as companies' first commercial manufacturing investments. Second, it involves emerging and growing companies that are most concerned with time to market and overseeing their production process. Third, given the critical mass of large biomanufacturers in the state, it involves retaining and growing the existing companies in the region.

Developing the biomanufacturing cluster in the Massachusetts region entails many of the key elements of any cluster development strategy that one would find in the US today. It must focus on talent, innovation, and supportive public policy and institutions. Many reports and case studies have been written about cluster initiatives, and key principles that are important to success.[79]To keep Massachusetts as a center of excellence for biopharma manufacturing, the region needs to organize around some core guiding principles and

[79] For a summary of cluster development strategies, see Mills et al, *Clusters and Competitiveness: A New Federal Role for Stimulating Regional Economies*, The Brookings Institute, 2008; *Competitive Regional Clusters: National Policy Approaches,* OECD, 2007; and *The European Cluster Memorandum*, Center for Strategy and Competitiveness, Stockholm School of Economics, 2007.

four action agenda areas. These principles and the action agenda have evolved out of a number of roundtable discussions with industry leaders in the region.

The guiding principles are the following:

- Develop a strategy for biomanufacturing in the state that is inclusive, engaging firms, academic institutions and non-profits across the range of the product life cycle, products and services
- Support and promote innovation within and across companies and academic institutions to create a "regional system of innovation" for biomanufacturing
- Promote collaboration and dialogue among stakeholders
- Engage companies, educational institutions and non-profits from across New England and beyond
- Base work on fact-based analysis and a global perspective on the industry

With these guiding principles in mind, the following outlines four areas that form an action agenda for the state. A strategy for prioritizing them follows this discussion.

1. Develop Skills and Talent

Companies are drawn to the region largely because of the talent found here. Highly skilled biochemists and engineers are trained in some of the top universities in the region, and innovative research is conducted here. In addition, the pioneers of the industry are located here and are training the next generation of workers in state-of-the-art facilities. To maintain and grow this talent, a multi-pronged approach should be followed that addresses developing talent at both the entry-level and the managerial level. Strategies should include:

- Develop a coordinated network of community college training curricula developed with industry; gain better understanding of the capacity and output of community colleges

- Create more co-ops/internships based on the Northeastern University model that connects students and companies for a six-month period

- Create an inventory of relevant higher education degrees and courses across the Commonwealth; develop continuing education courses in partnership with industry to grow the next generation of supervisors and managers

2. *Spur and Support Innovation*

   How innovation occurs within and across firms is a subject of enormous interest with a significant literature (Lazonick, 2005). The internal organization of firms and their ability to "integrate, build, and reconfigure internal and external competences to address rapidly changing environments" (Teece et al, 1997) is essential to the development of the innovative firm. As many have noted, innovation is in many respects a social and collective enterprise, which involves collaboration within firms, but also across them. This applies not only to firms, but also other institutions such as universities.

While it is difficult, if not impossible, to affect or change the culture within a firm, there are ways in which innovation can be supported across firms and other institutions. "Regional systems of innovation" attempt to do just this. Creating such an innovative system for biomanufacturing could involve the following steps:

- Create "interpretive space" (Lester and Piore, 2004) for biopharma manufacturers to convene and discuss research and cutting-edge technologies, as well as operational excellence and market developments. Promote conferences and workshops as well as roundtables around specific types of new technologies. Build upon existing efforts by MIT, Northeastern and others.

- Identify and catalog existing areas of innovative work among university researchers and companies in the region. Develop a priority list among

industry and academia of research areas to pursue in industry/academic partnerships or consortia. Develop potential sources of funding.

- Compile a list of existing consortia and collaborations among industry and academia here, as well as elsewhere (such as MIT's Center for Biomedical Innovation's Biomanufacturing Center, or the Center for Biopharmaceutical Operations at UC Berkeley).

- Develop strategies for helping smaller, emerging biopharma companies interested in manufacturing locally; explore ways to use U Mass pilot manufacturing facility at Dartmouth (to be built in 2010) to advance innovative technologies

3. Ensure Competitive Public Policies

While talent and innovation are two of the most important driving forces behind the location of biomanufacturing, public policy clearly can be a tipping factor for companies, depending on what kind of investments they are making. For companies that are looking for talent, but are less concerned with an innovative environment, there are a number of possible locations in the US and Europe, and public policy, namely tax policy and subsidies, can be differentiating factors. On the whole, public policy in the state should strive to be competitive with other US locations, but should refrain from providing subsidies that do not have any positive spillover effects for the public good. A public policy strategy should include the following:

- Assess key competitive strengths and weaknesses of the region relative to other locations in the US with a focus on the cost of doing business; determine key differences in public policy at the state and local levels

- Develop more detailed understanding of the interplay between tax policy, transfer pricing and intellectual property to determine, how, if at all, the US can compete with tax-advantaged locations in other countries. Determine whether there is any action item in this area.

- Develop a database of available sites in MA that meet land, utilities and permitting requirements for companies interested in setting up biomanufacturing facilities (build upon Mass Biotech efforts).

- Enhance the state's economic development efforts for biopharma manufacturing through the creation of a specialized team focused on retention, growth and attraction of biopharma manufacturing companies. Compile data and marketing materials that emphasize the competitive advantages of the region. Approach companies that have R&D capacity but no manufacturing in the region.

4. Enhance Institutions and Knowledge that Support the Cluster

Institutions have been recognized by many social scientists as critical to promoting economic growth (North, 1990). They have also been recognized in cluster and regional innovation literature as the differentiating factor between having an agglomeration of companies in a related industry, and having a working *cluster*, in which companies and other institutions are actively engaged in networking and promoting business and regional growth in the industry. A range of institutions play a role in cluster development – trade associations, chambers of commerce, colleges and universities. As it stands, Massachusetts has a number of entities that are directly or indirectly involved in promoting biomanufacturing (the Massachusetts Biotech Council, the Massachusetts Life Sciences Council, the Massachusetts Life Sciences Center, the International Society of Physical Engineers). The state would benefit from the creation of a steering committee of biomanufacturers that could provide strategic vision and guidance to the work of the many institutions that are involved with the industry. Strategic steps include:

- As part of the Life Sciences Council, create an industry-led steering committee that meets regularly to develop and implement a biopharma

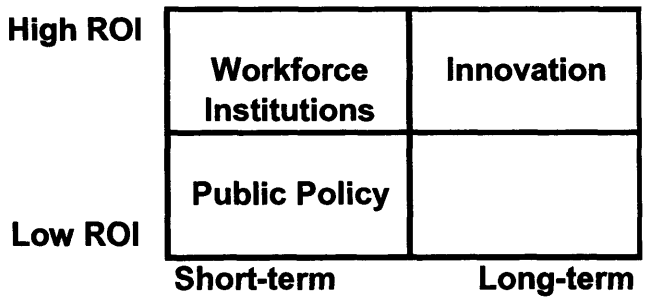
manufacturing strategy for helping the region and its companies compete globally.

- Expand analysis of the regional cluster with further research on microbial-based manufacturers, small molecule manufacturers, suppliers, and fill-finish providers.

This strategy focuses on three key inputs that differentiate one place from another and help build competitive advantage in the face of increasing globalization: talent, innovation and institutions. The fourth factor, public policy, is a tool that all places have at their disposal and can be used to varying degrees, from creating a competitive business environment, to actively attracting and seeding an industry to a location. Ultimately, to build a healthy economy, public policy needs to by guided by core principles and should not create negative externalities. By investing in the first three factors, and using the fourth to support and promote biomanufacturing, Massachusetts should be able to not only keep a foothold in the industry but successfully compete for the best talent, innovations and companies going forward.

In terms of prioritizing these four areas, two basic criteria should be used: the return on investment and timeline for implementation. I use a two-by-two matrix to provide a rough guide for how efforts should be prioritized.

Figure 8.1 Prioritizing Strategic Initiatives for Massachusetts Biomanufacturing



Given that it is always useful to have some immediate success in implementing a strategy, biomanufacturing efforts should focus on those initiatives that have the highest

ROI and can be accomplished in the shortest time frame. Both the workforce development efforts and building institutional capacity fit these criteria. The innovation agenda, while the most complex and the most timely to implement, will no doubt have the greatest return on investment. It is a long-term priority that should be focused upon once the first two agenda items are in motion. Finally, the public policy agenda, while relatively quick to implement, is not a major driver of growth of the industry in the region and should be considered low priority.

8.5 Discussion

This chapter provides a brief overview of the Massachusetts economy and how the region has continually "reinvented" itself through technological innovation. Ranked the top "high-tech" region in the US, Massachusetts provides an excellent case study for understanding how a region competes in a highly innovative, globalizing industry such as biomanufacturing. The region is one of the top centers in the world for biotechnology R&D and as a result, is also one of the top locations for biomanufacturing. Biotechnology and biomanufacturing aptly fit into Massachusett's "boutique" economy because of the highly specialized nature of the industries.

Massachusetts has a significant cluster in biomanufacturing. The state has approximately 90 companies in biopharma manufacturing, and employment of 9,600 (12,000 in the region). It also is one of two states in the country (the other being California) that experienced job growth between 2001 and 2008. These are highly skilled, high paying jobs that are rooted in STEM education. Beyond the critical mass of investments already made in the state, the significant biotech R&D, along with the entrepreneurial culture, create a demand for biomanufacturing, particularly among small and emerging biotech companies. In addition, tremendous innovation in the field comes out of the state's academic institutions as well as many of the companies located here. Finally, biomanufacturing was pioneered in the state and there is thus a wealth of talent that is training the next generation of leaders in the industry.

In terms of the opportunity for the state, it lies in innovative work, which means early stage manufacturing (pilot and clinical) as well as companies' first commercial

manufacturing investments; emerging and growing companies that are most concerned with time to market and overseeing their production process; and retaining and growing the existing companies in the region. A strategy for the state will focus first on workforce development strategies and building supportive institutions to develop and implement an action agenda for the cluster, second, on seeding innovative work in the industry and finally, on a public policy agenda.

Chapter 9

Conclusion

9.1 Findings

In today's global economy, many argue that to succeed, companies need to "break free of geography." Overly invested in their home base, "blinded" by the power of clusters and the old product life cycle strategy of projecting products into new markets, companies need to shake these chains and seek out new sources of technologies and market intelligence from every corner of the world (Doz et al. 2001). While this strategy would seem to be attractive to any company that must continually innovate to differentiate itself, it underestimates the lingering importance of geography, even in a global economy.

In this dissertation, I examine the geographic evolution of a highly complex advanced manufacturing industry to understand where a high value-added, high-skilled industry such as biomanufacturing is located and what factors explain its location. I find that, while the globalization of talent has provided more opportunities for locating and seeding the industry in more places, and modular production networks have given companies more opportunities for segmenting and off shoring manufacturing, the location of biomanufacturing is nevertheless driven by factors that are geographically determined. Agglomeration economies explain the original location of the industry because of the importance of a specialized labor pool and the high value of shortening time-to-market. Product life cycle theory explains the evolution of the industry as the complexity of developing biological drug substances keeps the production close to R&D through early stage manufacturing and in many cases, in the first launch of commercial production as well.

With respect to product life cycle theory, I find that biomanufacturing provides some twists to the classic theory that add to the "richness" of the model. As an R&D intensive, complex "competitive oligopoly," regulatory institutions (the first twist) help slow the product life cycle down by providing intellectual property patents and also by ensuring that production is limited only to those places that respect intellectual property laws. While companies have expanded their R&D locations, they still, for the most part, are

developing new products in the Triad (U.S., Europe, Japan), and keep early stage pilot and clinical manufacturing close by. As Vernon predicted, first commercial facilities are also almost always within close proximity to the R&D centers. Once commercial manufacturing is up and running, if a product is successful and a company needs to expand, production is potentially moved off shore to a low-cost location that may also serve a new market. Tax-advantaged locations (TALs – the second twist) have created a new version of a low-cost location for high-skilled, high-wage advanced manufacturing industries, a kind of "middle station" where companies can both serve important markets (such as Europe) and reap the benefits of low-cost production without the risks associated with moving production to a developing country. In the TALs in North America and Europe (Puerto Rico, Ireland, Switzerland) there is a long history of pharmaceutical manufacturing and a skilled labor pool that is moving up the skills ladder to work on the higher value added biomanufacturing. Once a product is off patent and a biosimilar exists (which is just beginning to take place in this industry), production is moved to lower cost locations, both in terms of labor and infrastructure. Currently, biosimilars are being made in Asia, particularly in India, but also in Israel and Eastern Europe.

As the ability to make biologics has improved, and the regulatory process has become less of a hindrance, the product life cycle has speeded up significantly. Whereas the first approved biotech drugs stayed onshore for 20 years before production was moved to a low-cost location, today's approved drug might be moved within four to five years.

In such a complex field, there will undoubtedly be segmentation within the market, such that some of the drugs with more standardized production processes may be manufactured immediately at a middle station location. While this is the case for big pharma companies such as Pfizer and Lilly, this does not constitute a trend. A number of companies are still manufacturing in first and second facilities that are not in TALs. Given the formidable challenges a company like Genzyme has had recently at its Alston, MA facility (involving contamination by both a virus and glass particles), it is clear that the high cost of failure in this industry still puts a premium on locating some manufacturing near the home base.

Apart from the theoretical frameworks that help explain the drivers of location for this industry, my data analysis underscores a number of patterns and trends within the industry that will affect the geography of the industry going forward. My analysis of actual and projected biomanufacturing facility investments from 2002 and 2013 confirm the US's predominance in the industry (measured by volume of capacity). But the data also reflect some of the important changes that are taking place in the industry that challenge this predominance – technological innovations that are increasing productivity and utilization rates and reducing demand for more capacity, and the rise of Asia in biomanufacturing, specifically contract manufacturing. While half of the top ten locations for biomanufacturing in the world are in the US, two of them will be in Asia by 2013. The data also support the theory that countries and regions that have strong biotech R&D also are strong in biomanufacturing, which highlights again the importance of skilled labor in the industry as well as the value of proximity between research and manufacturing. To the latter point, I present data on the distance between company R&D centers and biomanufacturing facilities and find that almost without exception, clinical manufacturing facilities are located close to R&D centers, as are approximately half of the commercial facilities. Finally, I show how drug sales, company growth and a company's overall drug portfolio can influence where commercial manufacturing facilities are located. Companies with drug sales less than $500 million tend to have only one commercial facility that is located near their R&D, while the majority of companies (thought not all) with drug sales greater than $1 billion tend to have a facility (second, third or fourth) in a tax-advantaged locations (TALs). Since 2004, 11 product companies and one CMO have built or arein the process of building commercial facilities in TALs. This constitutes one of the major emerging trends in the industry, and provides insight into how countries and regions are using public policy to compete for advanced manufacturing investments.

One of the broader trends I look at in detail is the way in which technological innovations are changing the industry and affecting both the facility of the future, and potentially the geography of biomanufacturing investments. I find that these new technological

advancements (higher titers, disposable technology, multi-product facilities, and better monitoring and evaluation data through PAT and Quality by Design initiatives) are having a significant effect on the industry's productivity, facility design, flexibility in terms of size, number and location of facilities, as well as dramatically reducing costs, timelines and risk. While these innovations may reduce the number and character of facilities in the future, they are not necessarily changing where innovation in the industry takes place. It is within process development and early stage manufacturing that the real innovation in the industry occurs. While continual innovation is becoming the mantra across the industry and something that is encouraged at commercial facilities, companies want consistency and reliability at the commercial production level, not real innovation and risk taking. This suggests that while the U.S. might lose commercial manufacturing facilities to offshore locations, it does not risk losing the innovative aspects of the industry. In terms of following the route of pharmaceutical manufacturing, I find that biomanufacturing has followed the product life cycle of pharma manufacturing in two important ways: first in moving production of "innovator" drugs offshore to TALs, and second with the location of biosimilars production in Asia. The question becomes, what about the production of innovator drugs in low-cost locations in Asia? This took approximately 50 years to occur in pharmaceuticals (production of the first innovator drug made in India began in 2007). While biotech drugs are much more complex, we also have the effects of "compressed development", which are speeding up the learning curve of offshore locations around the world. Many predict innovator biologics will be made in Asia within 20 years.

After reviewing the drivers of location of biomanufacturing and trends in the industry that may change its current geography, I turn to the economic development impact and opportunity presented by the industry. The industry impacts economic development at the national and state levels in three main ways: jobs and skills, innovation, and tax revenue. While biomanufacturing generates only a third of the jobs that the auto industry generates, it nevertheless represents the kind of high skilled, high wage, innovative industry that policy makers and business leaders are most interested in producing and keeping in the country. With approximately 300,000 jobs at an average salary of $96,000,

it is one of the highest average salaries in the country, and for all the reasons explained earlier on in this research, factors such as sunk costs, economies of scale, and deep pools of specialized labor, it is an industry that is stickier than many. The industry was pioneered in the U.S. and the skills developed today will help usher in future emerging industries in related biomanufacturing fields such as stem cells, tissue and hybrid devices.

Importantly, the country's "sweet spot", similar to the sweet spot for Massachusetts, is in the innovative aspects of the industry - the early stage and commercial launching of products. Demand is generated by strong biotech R&D, which the US continues to lead in. Given that innovation in the industry occurs largely at these early stages, there is at little risk that commercial manufacturing abroad will pull process development with it, or that new R&D centers will pull the manufacturing with it. More likely, other countries will develop innovative capacity and process development expertise over time on their own soil. This is not surprising as the biotech pie grows. The goal for the U.S. should be to hold on to a portion of that expanding pie. Companies often like to have two facilities for back-up purposes. The U.S. could still be well positioned to retain some portion of commercial manufacturing, though growth in commercial manufacturing, which in the short term will be limited globally, will clearly happen elsewhere.

Finally, on the tax front, while it is impossible to estimate with any degree of confidence what the industry generates in terms of tax revenue, I find that at the federal level, the industry may generate approximately $18 billion annually, including personal income tax ($8 billion at 28%) and corporate income tax revenues ($10 billion at an effective tax rate of 25.5%). At the state level, I estimate that Massachusetts generates approximately $35 million in personal income tax revenue (at 5.3%) and $250 million in corporate state and local tax revenue across a number of different taxes.

In terms of the economic development opportunity for the state of Massachusetts, this is in fact an advanced manufacturing industry that the state is poised to compete in for decades to come. As outlined earlier the state's opportunity lies in three areas. First, it involves innovative work, which means early stage manufacturing (pilot and clinical) as

well as companies' first commercial manufacturing investments. Second, it involves emerging and growing companies that are most concerned with time to market and overseeing their production process. Third, given the critical mass of large biomanufacturers in the state, it involves retaining and growing the existing companies in the region.

The state's competitive advantages in the industry are the essential elements for retaining and growing the industry – talent, significant R&D and innovation from academia and industry, a strong entrepreneurial base of biotech companies, and a good education system. The competitive disadvantages – a shortage of trained workers, physical infrastructure, and the cost of living and cost of doing business – while all significant challenges, are actually more easily addressed than if the state had to build any of its competitive advantages from the bottom up. I outline a four-point strategy that involves human capital development, promoting innovation, building strong institutions to support the industry, and a public policy agenda. The public, private and non-profit sectors all have a role to play in implementing this agenda. I prioritize the human capital and institution-building agenda first because they have a high return on investment and can be addressed in the short-to-medium term. Developing an innovation agenda that supports the "regional system of innovation" will take time both to articulate and implement, but it is the critical component to the entire endeavor.

9.2 Implications

The implications of this work are three-fold. First, in terms of a future for manufacturing in the U.S. and in high-tech regions like Massachusetts, the case of the biomanufacturing industry suggests that there is a future, albeit proscribed and potentially limited in terms of the number of jobs it generates. Unable to compete on pure costs, high-skilled, high wage regions like Massachusetts must compete on the talent and innovation that resides in the region. An obvious question that this research raises is how unique this industry is and whether it provides insights into other industries. Clearly, unlike other manufacturing processes, biomanufacturing involves life and death consequences. In this respect it is unique as is its regulatory framework. But in other ways, the industry's highly specialized

processes that are becoming more customized, are similar to other industries such as semiconductors. The US's ability to compete in this arena depends, like in any industry, on its innovative capacity and its talent.

Second, while some would like to break free of geography, it still plays a critical role in terms of industry emergence and evolution. In industries with unique attributes, such as substantial regulation in the biopharma industry, product life cycle theory does an excellent job of modeling the growth and evolution of the industry. It is still the case, in a complex and risky business like biomanufacturing, that early stage clinical and commercial manufacturing benefits from proximity to R&D. The cost structure of the industry, along with the public safety issues, slow down the product life cycle such that a "middle station" low-cost location has emerged in which countries and regions with similar cost structures as those in the U.S. offer tremendous tax breaks to move the production off shore. This suggests that the U.S. may find that its ability to compete in advanced manufacturing industries depends on having some of these unique attributes associated with the industry, such as a regulatory regime. It also underscores the important role tax policy is playing in global competition. As factor inputs such as talent and capital become equal across more locations, tax policy may become a bigger differentiator among countries. While the product life cycle model still holds, it is undoubtedly the case that it has accelerated such that products invented 20 years ago that were not off shored until a few years ago, could today be off shored within four to five years. There is no turning back when it comes to the speed of the product life cycle. As stated earlier, we are all "compressed developers" now.

Finally, related to the previous point about the importance of geography, this research shows the limits to arguments that suggest, lose the manufacturing, lose the innovation. In this case, the locating of manufacturing offshore has not pulled either biopharmaceutical R&D or the innovative aspects of biomanufacturing. These have remained fairly centralized around companies' R&D centers. While more R&D teams are being located in emerging markets, that is a result of growing markets and not a result of any push or pull vis-a-vis manufacturing. In a world in which increasing returns explain

much of the economic growth, increasing knowledge and innovation is not a zero-sum game, but results in greater knowledge that is accessible to all.

9.4 Future Research

This topic is ripe for a range of future research projects. For a more refined analysis than I was able to do in this work, one would take the work down to the product level and analyse the manufacturing life cycle for each particular drug. While I obtained the broad outlines of this through my research, analysis at a more detail level would take into account the complexity of the drug (as measured, for example, by its molecular weight) and whether that has an impact on where the drug is made. Another important development in the biopharma industry is the emergence of biosimilars. It is unclear how the economics of biosimilars will affect their growth. Some suggest there will be high-grade and low-grade biosimilars, the latter made largely for local home markets. The political economy of biosimilars will have an enormous impact on the industry and on its geography.

From an organizational behavior perspective, I believe this topic is rich for understanding the role of culture in organizations. The industry teeters between trying to be risk-averse and trying to be innovative. Understanding how companies and teams walk this fine line would be extremely interesting to research. In addition, a more in-depth understanding of how tacit knowledge is transmitted between different teams with the biomanufacturing process would potentially shed more light on the integrality and modularity of the industry. There are different degrees of tacit knowledge conveyed within each stage of the process that challenge the idea that proximity is critical in the exchange of tacit knowledge.

From the perspective of cluster research, there is much more to learn about how biomanufacturing clusters emerge and grow in locations that do not have roots in biotech R&D. Locations like Ireland, Puerto Rico and Singapore, that are starting "downstream" with manufacturing and hoping to head "upstream" toward R&D, will be very interesting case studies to examine in the future. If places like Ireland and Singapore that are

investing in both ends of the value chain are successful, it will challenge the presumed wisdom that clusters cannot arise out of nothing. Given the global access to talent, knowledge and know-how, it is not clear that this assumption will hold.

Overall, this topic provides a number of potential research directions that could be pursued which delve into the changing landscape in both industrial organization and economic geography, particularly the geography of innovation.

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Appendix A

Summary of Industry Location Dynamics Between R&D and Manufacturing

Software: R&D and manufacturing are largely one in the same. The "production" process refers primarily to the design and development activities in the software value chain. Because of the customized nature of the product, software activities tend to locate in close proximity to the end user. The US is the largest market for software and also the largest exporter of software products.

Semiconductors: Since the 1980s, the industry has become more vertically specialized, creating segmentation within the industry between companies that only manufacture (foundries), those that design and manufacture (integrated device manufacturers) and those that design and market ("fabless" firms). The increased capital requirements for semiconductor manufacturing has been a contributing factor to separating those who manufacture (and can spread the risk across a wide product mix) and those that don't. A growing, fragmented market that has expanded beyond PCs into wireless communications and other non PC consumer products has created more non-standardized products for a wide range of system providers. As a result, product design for these new applications is locating closer to system customers, many of whom are located in Southeast Asia because of that growing market. On the whole, however, there is little evidence of R&D activities moving offshore to follow manufacturing.

Pharmaceuticals: The industry shows little sign of moving R&D outside of the "Triad." While some vertical specialization is occurring, with the creation of clinical research organizations (CROs) and contract manufacturers (CMOs), and these activities are heading offshore, pharmaceutical companies are not moving significant portions of their R&D to some of the low-cost locations where they are manufacturing.

Personal Computers: In the 1990s, the entire PC value chain was made in the US and Japan, from design concept through to mass production. By 2000 however, all of the development activities post-design moved to Asia: component level R&D and concept design stayed in Japan while applied R&D moved to Taiwan; product development for mature products as well as all production moved to China by 2006. Only the design activities of concept development and product planning are left in the US. This relatively rapid shift of all development and production work to Asia is attributed to the significant price declines that the PC industry has experienced in the last 15 years, and the growing market in Asia, such that product development is moving closer to the end users.

Flat Panel Displays: The flat panel displays industry involves a highly sophisticated, complex and expensive manufacturing process that is only economical for high-volume production. Innovations in the industry require close interactions with the manufacturers such that US supplier firms that still compete in this industry have been successful

because they have partnered with the Asian manufacturers, who entered and dominated the market early on.