GUEST EDITORIAL

The Biopharmaceutical Industry in Massachusetts—The Triple Helix in Action

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ABSTRACT

In 1980, Massachusetts was home to defense contractors and computer manufacturers and what Governor Michael Dukakis later called "The Massachusetts Miracle" did not bring to mind the life sciences. What economic activity there was in life sciences consisted of a largely invisible medical device industry, while the future biotechnology industry was just starting to spin-out of the laboratories of Harvard, MIT and Boston University. Yet in the space of just 25 years Massachusetts has become a leading center, worldwide, of first biotechnology research, then pharmaceutical research and most recently for the production of biopharmaceuticals. A number of its home grown biotechnology companies have developed into fully integrated biopharmaceutical and pharmaceutical companies, with substantial marketing, sales and other corporate functions The term "Triple Helix" was coined by Henry Etzkowitz in 1993 to describe the intertwining of academia, industry and government to create research driven high technology clusters.

Nowhere is this paradigm more vividly seen in action than in the emergence of the Massachusetts biopharmaceutical mega-cluster. The Triple Helix has undergone at least four full turns in Massachusetts. This article explores some of the actions that catalyzed this phenomenon.

INTRODUCTION

In 1980, Massachusetts was home to defense contractors and computer manufacturers and what Governor Michael Dukakis later called "The Massachusetts Miracle" did not bring to mind the life sciences. What economic activity there was in life sciences consisted of a largely invisible medical device industry, while the future biotechnology industry was just starting to spin-out of the laboratories of Harvard, MIT and Boston University.

The only traditional pharmaceutical company established in the state was the US headquarters of an obscure Swedish company which had just moved to a spectacular building inexplicably hidden and insulated from the burgeoning academic community in the center of the state.

Yet in the space of just 25 years Massachusetts has become the leading center, worldwide, of first biotechnology research, then pharmaceutical research and most recently for the production of biopharmaceuticals. A number of its home grown biotechnology companies have developed into fully integrated biopharmaceutical and pharmaceutical companies, with substantial marketing, sales and all the necessary corporate functions.

The term "Triple Helix" was coined by Henry Etzkowitz in 1993 to describe the intertwining binding together academia, industry and government to create research driven high technology clusters. Nowhere is this paradigm more vividly seen in action than in the emergence of the Massachusetts biopharmaceutical mega-cluster. The Triple Helix has undergone at least three full turns in Massachusetts.

TRIPLE HELIX DNA

Since 1953, the helix that comes to most people's minds is the double helix, the DNA structure discovered by Francis Crick, James Watson, Maurice Wilkins[1] and Rosalind Franklin.[2] The bonding between complementary base pairs—C to G, T to A—in the two strands of DNA is sufficiently powerful and specific to have encoded and faithfully preserved the essence of our humanity for

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Cite as: Ashley J. Stevens, *The Biopharmaceutical Industry in Massachusetts—The Triple Helix in Action*. J. BIOLAW & BUS., Vol. 10, No. 3, 2007.

hundreds of millennia, while still being sufficiently adaptable to allow for continued evolution.[3]

However, within two years of Crick-Watson's double helix, it became apparent that double stranded DNA can in fact bind a third strand of DNA to form a triple strand.[4] While the strength of the bonds is weaker, specific binding rules were eventually elucidated[5] and triple strand binding is believed to play a role in double stranded DNA repair in nature. The technology is being developed to repair the point mutation that causes sickle cell anemia.[6]

THE TRIPLE HELIX OF ECONOMIC DEVELOPMENT

During the Vietnam era, it was fashionable to talk about "the Military-Industrial Complex" that shaped government policy—a Double Helix. Certainly the academic community played little role in the defense industries, even spinning off its classified defense activities into separate non-profit research institutes, located off campus, to avoid the intrusion of security procedures onto campus and the consequent culture of secrecy and proscriptions on freedom to publish.

More recently, the term "Triple Helix" was coined by Henry Etzkowitz in 1993[7] to describe the intertwining that binds together academia, industry and government to create modern research driven high technology clusters. Etzkowitz has shown that this general model is broadly applicable to many countries, and, like DNA, adapts flexibly to different economic, political and cultural situations, with different strands of the helix being more prominent in different situations. Etzkowitz was not aware of the triple strand binding of DNA when he coined the term; however in retrospect the DNA binding paradigm is an even more apt analogy for the economic paradigm than even Etzkowitz envisioned.

> "In just 25 years, Massachusetts has gone from a non-existent position in the biopharmaceutical industry to one of the leading centers, both domestically and internationally."

Nowhere is this paradigm more vividly seen in action than in the emergence of the Massachusetts biopharmaceutical mega-cluster. In the U.S. generally, and in the case of the Massachusetts biotechnology industry specifically, government constitutes the third strand, with the weakest binding to the other two strands. However, government's role has been critical, both at the national level and then, in several quite discreet instances, at the local level, in the spectacular growth in the Massachusetts biopharmaceutical industry.

GOVERNMENT AT THE NATIONAL LEVEL

At the national level, a number of actions, taken totally independently and seemingly without any expectation of their collective power by the executive, legislative and judicial branches of government, came together in less than a decade to transform the environment for technology led economic development. In the process they transformed the U.S. economy from a manufacturing-led base that had demonstrably lost its edge to Japan and Europe, to an innovation-led base that can hold its own with such low cost economies as India and China.

In 1974, the Employee Retirement Income and Security Act (ERISA) redefined the "Prudent Man" rules that had governed fiduciaries since colonial days to allow modest levels of investment into such high risk vehicles as venture capital funds. This allowed such funds to start to attract significant capital inflows.

In 1978 the Republican Senate forced a capital gains tax cut on a reluctant Carter Administration, taking the capital tax gains rate below that on ordinary income for the first time. The resultant increase in tax revenues inspired the Reagan Administration to make a further cut in the capital gains tax rate four years later. The two cuts stimulated long term investment.

In 1980, in the dying days of a lame duck session, the Senate passed the Bayh-Dole Act, allowing academic institutions to take title to inventions that had been funded with federal grants and removing many restrictions on licensing terms. (The remaining restrictions were removed four years later.) Universities were now able to grant exclusive licenses and access to professors and their laboratories were reunited with control over their intellectual property. Universities were now both incented and empowered to grant exclusive licenses and a torrent of investment capital was unleashed to develop novel but embryonic technologies.

In 1982, the Supreme Court, in Diamond v. Chakrabarty, upheld the patentability of micro-organisms. This decision virtually coincided with the emergence of the biotechnology industry, and provided comfort to investors in biotechnology companies that patents on novel organisms created by biotechnologists would hold up, further stimulating the flow of investment capital into biotechnology.

Also in 1982, the Reagan administration established the Court of Appeal for the Federal Circuit as a single, nationwide venue for appeals of intellectual property cases from Federal District Courts. Prior to the establishment of the CAFC, there had been tremendous variability in the view of patents and the time-limited monopolies they permitted between the thirteen Circuit Courts of Appeal, and only one third of patents that were seriously challenged were upheld. With the establishment of the CAFC, led by an inspirational Chief Justice, Howard Markey, the balance was almost exactly reversed, with two thirds of challenged patents being upheld.

GOVERNMENT AT THE LOCAL LEVEL: THE CAMBRIDGE CITY COUNCIL

There were considerable concerns about biotechnology in its earliest days. Paul Berg, who won the Nobel Prize for

Chemistry in 1980 for his discovery of DNA splicing in viruses,[8] was very concerned about the potential for harm from recombinant DNA experimentation. In February 1975, in Pacific Grove, California, the Asilomar Conference took place, sponsored by the U.S. National Academy of Sciences and convened by the Academy's Committee on Recombinant DNA Molecules, of which Berg was the Chairman.[9]

These concerns quickly spread to Cambridge, Massachusetts, home to Harvard and MIT, which were in the forefront of this esoteric science.

In June 1976, the "Cambridge Experience" took place. Debate erupted whether to approve construction of a P3-laboratory at Harvard University. A P3-laboratory is the second most restrictive facility for recombinant DNA experiments. Led by Mayor Alfred Vellucci, members of the Cambridge citizenry participated actively in the decision-making process. As a result, the Cambridge Experimentation Review Board (CERB) was established to review and approve policies in connection with recombinant DNA research and application. Local ordinances to regulate recombinant DNA in Cambridge followed.[10, 11]

These ordinances turned out to be highly positive for the biotechnology industry. The ordinances established rules that were known and manageable, and provided a measure of assurance that compliance with the ordinances would allow research to proceed. Biotechnology companies like Genetics Institute, which initially considered locating in Somerville which had no ordinances but would undoubtedly feel obligated to establish some,[12] instead opted for Cambridge where the rules were already known and well defined.

GOVERNMENT AT THE STATE LEVEL: THE COMMONWEALTH OF MASSACHUSETTS

The Commonwealth of Massachusetts was relatively uninvolved in the emergence of the biotechnology industry. This changed in 1991, when Genzyme sought substantial tax concessions to induce it to build a biomanufacturing complex at Allston Landing on the Charles River in Massachusetts. Bill Weld, then Governor, and the City of Boston put together an incentive package to persuade Genzyme to locate the plant in Massachusetts rather than out of state. Task forces were put together to facilitate the permitting process, and Genzyme broke ground within four months.[13]

The next significant activity of the Commonwealth of Massachusetts came in 2003. Harvard Business School Professor Michael Porter, the leading academic analyst of high technology clusters, convened the Triple Helix in one place. He organized a high-level summit in which he brought together top politicians, academics and industry leaders from the Massachusetts biopharmaceutical cluster to assess the status of the cluster, what had led to its emergence and viability and what could be done to preserve that viability in the future. One of the key recommendations from Professor Porter's analysis was that the state should focus on securing the location of downstream biopharmaceutical manufacturing to build on the already manifest strengths of the biopharmaceutical R&D sector. One of his recommendations was that the state take action to facilitate the permitting of all new biopharmaceutical manufacturing facilities. The legislature passed the necessary legislation and the challenge was taken up by the state Office of Economic Development. The importance of this will become clear later.

THE ROLE OF ACADEMIA

Academia was at the heart of the emergence of the biopharmaceutical industry in Massachusetts. It was the leadership role played by Harvard and MIT in the development of recombinant DNA that was the driving force that led to the emergence of a biopharmaceutical industry in Massachusetts.

This leadership was reflected in the receipt of numerous Nobel Prizes by Boston area scientists:[14]

- Salvador Luria , a pioneer in viral genetics in the 1940's and 1950's, discovered how genes mutate and did important work on the genetic structure of viruses. He was a co-recipient of the Nobel Prize in Medicine and Physiology in 1969.
- H. Gobind Khorana shared the Nobel Prize in 1968 for his contribution to the elucidation of the genetic code, the "blueprint" of life. His research explained how messages inscribed in genes are translated into the structure of enzymes and proteins. Later work in Khorana's laboratory led to the first complete synthesis of a gene in a fully living cell, a signal achievement which established the foundation for the biotechnology industry.
- David Baltimore's discovery in 1970 of reverse transcriptase, an enzyme that catalyzes the conversion of RNA to DNA, advanced the means of DNA synthesis and helped form the basis of modern genetic engineering, the workhorse of biotechnology. Baltimore shared the Nobel Prize in 1975 for this discovery. Baltimore's later work in retrovirus vectors fundamentally contributed to the development of gene therapy, the "second generation" of the biotechnology revolution with great potential for treating diseases at their root, genetic level.
- Walter Gilbert developed methods to work out the structure of DNA and developed a rapid method to decode the base sequences in DNA and then apply this knowledge to induce bacteria to produce medically useful substances, such as insulin and interferon. He received the Nobel Prize in 1980.
- Baruj Benacerraf discovered that disease-fighting ability is passed on genetically, although the immune-response gene varies from person to person, helping us to understand: 1) the body's ability to repel microbial invasions, 2) the mechanism by which the body

accepts or rejects skin grafts or organ transplants, and 3) the growth of tumors, invaders that outwit or fool the body's defense system. Benacerraf received the Nobel Prize also in 1980.

- Susumu Tonegawa revolutionized our understanding of the genetic basis of the immune system. His work described how genes in cells recognize and fight off foreign invaders like bacteria, viruses and cancers. This helped scientists to control and manipulate the immune system, and laid the foundation for a whole range of therapeutic approaches in fighting disease, many of which are derived from biotechnology. Tonegawa was awarded the Nobel Prize in 1987.
- Phillip Sharp was named co-recipient of the Nobel Prize in 1993 for his work in the 1970's in understanding the basic structure and function of genes. Sharp's discovery of RNA splicing led to a radical revision in understanding how genes send instructions to cells to create proteins, the building blocks of life.

Several of these scientists went on to found biotechnology companies.

The Boston area academic institutions had been pioneers in the development of offices of technology transfer. Table 1 shows the dates that the various institutions founded their offices of technology transfer.

Most academic institutions didn't establish offices of technology transfer until well after the passage of the Bayh-Dole act in 1980. Massachusetts institutions were ahead of the curve and were therefore well-equipped to facilitate the establishment of biotechnology companies based on the technologies they had developed.

Harvard University in 1976, had established one of the first major partnerships between a university and a corporation, a $46 million deal with the Monsanto Company, a precondition to which was that Harvard would change its patent policy to allow the patenting of biomedical discoveries. This was followed in 1982 by an even larger deal between the Massachusetts General Hospital and Hoechst AG of Germany.

The Massachusetts academic institutions were therefore well positioned to participate in the development of the US's biotechnology industry.

THE ROLE OF INDUSTRY

Another reason Massachusetts was well-positioned to help create an entirely new industry was because it had been the birthplace of the organized venture capital industry.

The seeds of the venture capital industry were sown during the Great Depression. Some of the governmental responses to the role of investment banks in the Great Depression, such as the creation of the Securities and Exchange Commission; the Glass-Steagall Banking Act; introduction of a progressive income tax; and the rise of formalized investment trusts, had all served to disrupt the traditional sources of capital available to new ventures.

Table 1
Year Massachusetts Academic Institutions Established Offices of Technology Transfer

Institution	Year OTT Founded
MIT	1940
Boston Univ./Boston Medical Ctr.	1976
MGH	1976
Harvard Univ.	1977
Tufts Univ.	1978
Dana-Farber Cancer Inst.	1981
Brigham & Women's Hospital	1986
Children's Hospital Boston	1991
New England Medical Ctr.	1993
Woods Hole Oceanographic Inst.	1993
St. Elizabeth's Medical Center	1995
Univ. of Massachusetts	1995
CBR Institute	1997
Beth Israel Deaconess Medical Ctr.	1997
Brandeis Univ.	1998
Northeastern Univ.	2000

Source: Association of University Technology Managers

A diverse group of Massachusetts leaders, including Karl T. Compton the president of MIT; Ralph Flanders, a prominent New England businessperson; Lincoln Filene, owner of the Filene's department store, Merrill Griswold, the president of Massachusetts Investment Trust, the largest open-ended investment trust in New England, among others proposed developing private sector initiatives to support small businesses established to commercialize new products, processes, or seeking expansion capital.[15] Compton even had the vision that academic research could be the driving force that would lead Massachusetts out of the Great Depression.

World War II arrived before Compton's vision could be tested in practice. However he remained very involved in exploring a number of approaches to provide capital for new entrepreneurial endeavors, and when, after World War II was over and Vannevar Bush's July 1945 report *Science, The Endless Frontier* was poised to launch the major federal funding of academic research, Compton returned to this theme and helped launch American Research and Development Corporation ("ARDC"), the first organized venture capital fund, which raised its funding not from wealthy family trusts but from the investing public.[16]

The prime movers supporting ARDC were Ralph Flanders, then President of the Boston branch of the Federal Reserve and trustee at MIT (and soon thereafter elected as a U.S. senator from Vermont), Georges Doriot, a professor of industrial administration at Harvard Business School; Karl Compton; and Merrill Griswold. Doriot became President of ARDC, which was formed in 1947 and eventually succeeded in raising $3.7 million to fund its initial investment activities. ARDC's most famous investment was the $700,000 it invested in Digital Equipment Corporation, a stake which was eventually sold for $450 million.

ARDC spawned a number of other venture capital firms in Massachusetts, so the innovation economy in Massachusetts has always had a plentiful supply of financial fuel

and was therefore well poised to rise to the challenge of creating a new industry based on the biotechnology prowess of Massachusetts' academic institutions.

THE FIRST TURN OF THE TRIPLE HELIX: THE BIRTH OF THE START-UPS

The first dedicated biotechnology company to be founded in Massachusetts was Biogen, founded by two Nobel Prize winners, Wally Gilbert and Phil Sharp, in 1978. Mark Ptashne and Tom Maniatis of Harvard founded Genetics Institute in 1980. Collaborative Research Inc., which had been founded as a research reagent company in 1961 by Dr. Orrie Friedman, and which had Nobel laureates Salvatore Luria and David Baltimore as scientific advisors, transformed itself into a biotechnology company. Genzyme was founded in 1981 by key individuals who had previously worked at the New England Enzyme Center, a unit of the Tufts New England Medical Center which supplied enzymes needed for biotechnology research. Genzyme acquired two biochemical supply companies in the UK, Whatman Biosciences Ltd. and Koch Light Laboratories.[17]

The rate of start-ups accelerated after that. In general, the first group of early stage companies did not need licenses to specific intellectual property from Massachusetts academic institutions. All became licensees of the Cohen-Boyer patents owned by Stanford University and their interactions with Massachusetts institutions were at the personal level—the professors manned the scientific advisory boards and their graduate students and postdocs joined the companies. Most of the early companies sought to clone and overexpress a broad variety of important biological molecules that had been too rare to investigate using natural sources. The almost universal business model was to partner with large pharmaceutical companies to pay for the research in return for rights to the resultant products and royalties on sales. Academia was no longer driving advances in biotechnology at this time, because they could not afford the very high costs of the machines.

> "Building the Massachusetts life sciences infrastructure started with spin-out companies from the leading universities in Massachusetts, capitalizing on the new biotechnologies, followed by an influx of major pharmaceutical companies establishing R&D centers."

As the tools of biotechnology became cheaper—the machines needed to synthesize both DNA and proteins—academic laboratories could again compete technically with the well-funded biotechnology start-ups and academic laboratories started making and patenting important inventions. The second wave of biotechnology companies were more narrowly focused and licensed these inventions from academic institutions.

By the mid to late-1980's a shakeout started to develop. First the intellectual property ownership of the early highly competitive targets for biotechnology—the interferons, hepatitis B, Factor VIII, erythropoietin, etc.—started to be resolved in the patent courts. Some companies won and some lost. The losers generally stopped operating as free standing companies and started to merge with the winners. The first such major merger was of Integrated Genetics and Genzyme in 1989.

THE SECOND TURN OF THE TRIPLE HELIX: THE ARRIVAL OF THE ESTABLISHMENT

It was about this time that the pharmaceutical industry started to become interested in a presence in Massachusetts.

The first to arrive was Johnson & Johnson, who set up a small operation in Massachusetts in 1982 called Cambridge Research Laboratories. At that time the technical skills needed to perform biotechnology were hard to come by and truly were clustered round Stanford, the University of California, Harvard and MIT, so J&J felt they had to have a presence in Cambridge. However, in 1988, after biotechnology companies and skills had become more widely distributed, J&J shut down the facility and consolidated its activities in its corporate laboratories in New Jersey.

The first major pharmaceutical company to arrive in Massachusetts was the German company BASF. In an ironic twist, the Triple Helix operated in reverse. Very stringent recombinant DNA regulations in Germany insisted on by the Green Party forced all of the major German pharmaceutical companies to put their recombinant DNA research facilities overseas. Massachusetts welcomed BASF, who actually moved into the former J&J facility while their long term facility in the Massachusetts Biotechnology Research Park in Worcester was under construction. A major product to result from BASF's Worcester operations is the anti-TNF monoclonal antibody drug, Humira. In December 2000 Abbott Laboratories acquired the pharmaceutical operations of BASF, Knoll Pharmaceuticals, including the Worcester facility, for $6.9 billion, an incredible bargain (in hindsight) in view of the tremendous success of Humira, which reached $2 billion in sales in 2006, just its 4th year on the market.

In March 1991, Genetics Institute lost a herculean court battle with Amgen over the rights to sell erythropoietin in the US. In 1992, American Home Products acquired 60% of Genetics Institute for $300 million, marking the second entry of a major pharmaceutical company into Massachusetts. Four years later in 1996, AHP acquired the remaining 40% of GI for $1.25 billion. In retrospect, this was also a cheap price.

Things remained quiet for most of the 1990's, but at the

Table 2
Pharma Company Trends in Massachusetts Site Selection

Year	Company
1998	Amgen
1999	Pfizer
2000	AstraZeneca; Sanofi-Aventis[18]
2001	Schering-Plough
2002	Novartis
2003	DSM/Crucell
2004	Merck
2005	Organon; Shire Pharmaceuticals[19]

end of the decade the trickle became a flood. Table 2 shows the year that major worldwide pharmaceutical companies opened their facilities in Massachusetts.

Particularly noteworthy is Novartis, which moved its worldwide pharmaceutical research headquarters to Massachusetts in 2002, and recently announced that they would be joined by their worldwide vaccine research headquarters. Development operations continued to be distributed round the world.

THE THIRD TURN OF THE TRIPLE HELIX: THE ESTABLISHMENT OF BIOPHARMACEUTICAL MANUFACTURING

The issues surrounding biopharmaceutical manufacturing are very different from those surrounding traditional pharmaceutical manufacturing.

Traditional pharmaceutical manufacturing is simply chemical synthesis carried out under GMP conditions. Once the efficacy of the drug has been demonstrated in clinical trials and it has received FDA approval, it can be manufactured in any suitable GMP facility. The skills necessary to identify the drug and prove its efficacy are in no way relevant to its successful manufacture.

Biopharmaceutical manufacturing is completely different. Living organisms are used to produce the product and the skills necessary at the laboratory discovery stage are directly relevant to manufacturing the product. Indeed, the production processes for biopharmaceuticals are so delicate and sensitive to change that the regulatory process for biopharmaceuticals is twofold:

1. The safety and efficacy of the product is demonstrated in a Biologic License Application (BLA), analogous to the new drug application (NDA) of a traditional pharmaceutical; and
2. The safety of the manufacturing process is demonstrated in a Premises License Application.

The consequences of this are considerable synergies in having the process scale up of biopharmaceuticals located in close proximity to basic research, and second, that once a manufacturing facility has received its Premises License, both the manufacturing process is locked in place, and the manufacturing location is locked in place.

Therefore, while the location of traditional pharmaceutical manufacturing facilities has typically been driven by tax considerations, and many have been located in Puerto Rico and Republic of Ireland which have both provided substantial tax breaks for pharmaceutical manufacturing, the location of biopharmaceutical manufacturing facilities has typically been driven by proximity to the basic research laboratories.

The oldest biopharmaceutical manufacturer in Massachusetts was actually a branch of state government. The Massachusetts Biological Laboratory in Jamaica Plain was founded in the nineteenth century to make vaccines and sera. The MBL is one of only a few publicly operated, FDA-licensed vaccine manufacturing facilities in the country. Throughout its history, the labs have introduced into general statewide use vaccines to prevent diphtheria, pertussis, tetanus and other diseases.

The MBL became involved in the emerging biotechnology industry and developed and manufactured Respigam and Cytogam, which were licensed to MedImmune. The MBL became part of the University of Massachusetts in 1997.

The first phase of the biotechnology industry in Massachusetts involved partnerships with large pharmaceutical companies who funded development of biopharmaceuticals in return for marketing and manufacturing rights. Products such as Factor VIII, hepatitis B and alpha interferon were licensed to companies such as Baxter, Merck and Schering-Plough who located manufacturing in the traditional manner.

However, as the industry matured and moved into its second phase, developing products for its own account which it would manufacture and market itself, these factors worked very much to the advantage of Massachusetts, and to a lesser extent, New England states. The first biopharmaceutical product to reach marketing readiness was erythropoietin from Genetics Institute. GI built a pilot plant in Andover, Massachusetts, 25 miles from its Cambridge headquarters, and then started to build a production facility in West Greenwich, Rhode Island. As noted above, a patent suit prevented GI from entering the US market for erythropoietin, ultimately leading to the acquisition of GI by American Home Products, so the Rhode Island plant was mothballed for a number of years. It was eventually acquired by Immunex who were facing burgeoning demand for Embrel. The retrofitted plant opened in 2001 and underwent a $1.5 billion expansion in 2005.

Massachusetts has two producers of hyaluronic acid. Anika, a spin out from the Retina Foundation, has produced naturally produced hyaluronic acid from rooster combs in Woburn since 1983, while Genzyme's first significant product was hyaluronic acid produced by fermentation at their Binney Street location.

Genzyme's first major product, Ceredase, approved in 1991, was extracted from human placentas and was purchased from Pasteur Merieux in France. Genzyme received approval to sell Cerezyme, a recombinant version

of the same enzyme, in 1994. Genzyme received considerable tax concessions from the state of Massachusetts and the city of Boston to induce them to build a major fermentation facility at Alston Landing on the Charles River in Boston. This facility opened in 1996.

Biogen's first major product which they sold themselves was Avonex for treatment of multiple sclerosis, which received FDA approval in 1996. Biogen's first production facility was in Cambridge, and they built facilities in Research Triangle, North Carolina and recently opened a facility in Denmark.

BASF in Worcester, Massachusetts, developed a fully human monoclonal antibody to treat rheumatoid arthritis, Humira. Humira is produced in Worcester and received FDA approval in 2002.

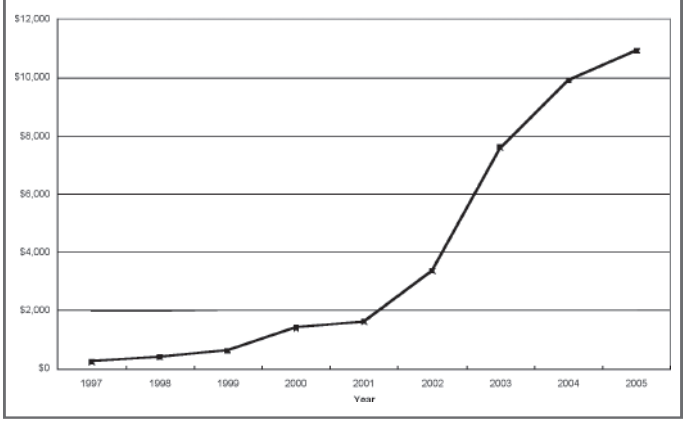
Other bioproducts that are manufactured in Massachusetts include:

Acambis	Smallpox vaccine
Organogenesis	Artificial skin
Seragen/Marathon	ONTAK
Shire Pharmaceuticals	Elapral and Replagal
ViaCell	Umbilical cord stem cells

A Swiss contract biopharmaceutical manufacturer, Lonza, has one of its major worldwide production facilities in Portsmouth, New Hampshire, just across the Massachusetts border.

Preliminary results of a study currently underway indicate that the value of biopharmaceuticals produced in the New England states of Massachusetts, Rhode Island and New Hampshire exceeded $11 billion in 2005.[20]

Figure 1
Retail Value of Biopharmaceutical Production in New England



In 2003 Professor Michael Porter of the Harvard business school, convened a summit meeting of the Massachusetts life sciences community and urged that capturing downstream manufacturing be a top priority of the State. Among several specific recommendations that were made was the need for simplified "one stop" site permitting.

The Department of Economic Development under Secretary Ranch Kimball implemented this suggestion. The first success was when a local vaccine company, Avant Immunotherapeutics, was considering locating its first production facility in Overland, Missouri. Avant was persuaded instead to build a new facility in Fall River, Massachusetts.

In 2006, the simplified permitting process was instrumental in Massachusetts winning a vigorous international competition to bring a Bristol-Myers Squibb biopharmaceutical manufacturing plant to Devens, Massachusetts. The $1.1 billion facility will open in 2009 and receive FDA approval in 2010 and will be used to produce Orencia (Abatacept, CTLA-4Ig) for a fully human recombinant fusion protein for treatment of rheumatoid arthritis. It will employ 550 people.

As of this writing, Shire Pharmaceuticals, which acquired TKT for $1.6 billion in 2005, is seeking to locate a new facility and is considering Massachusetts among other locations, while another large pharmaceutical company, codenamed Magellan but reported in the press to be Novartis, is also looking at a site for a major production facility at Devens.

THE FOURTH TURN OF THE TRIPLE HELIX – DEVELOPING MANAGEMENT DEPTH

The Baxter Boys

One of the problems the early biopharmaceutical industry faced was a lack of experienced management—because the only pharmaceutical company in Massachusetts in 1980 was Astra, there was no readily available, local source from which to draw management.

This turned out to be a national problem—pharmaceutical companies were not very entrepreneurial places in 1980. The primary source of management talent in the first phase of the biotechnology industry was not the pharmaceutical industry but some smaller but more nimble sectors of the health sector—diagnostics, specifically Abbott Laboratories, and hospital suppliers, specifically Baxter Healthcare Corporation, which had a management development program intended to develop entrepreneurial managers. One study showed that 25% of all the biotech companies with IPO's between 1979 and 1996 had someone in their management structure from Baxter.[21]

Massachusetts turned to both Abbott and Baxter for early stage management:

∑■ Biogen	James Vincent	Abbott
∑■ Genetics Institute	Gabriel Schmergel	Baxter
∑■ Genzyme	Henri Termeer	Baxter
∑■ Integrated Genetics	Robert Carpenter	Baxter

∑

So pervasive was the Baxter influence that they were known locally as "the Baxter Boys."

The early management skill set needed was business development—the ability to establish partnerships with the large companies—primarily pharmaceutical companies, but also companies from the food, beverage and some even more esoteric industries that thought they had

competencies that could provide a strategic advantage in this emerging industry.

The Emergence of FIBCO's

By the start of the 21st Century, a significant number of the early Massachusetts start-ups—including Alkermes, Biogen Idec, Genzyme, Millennium, NitroMed, Sepracor and The Medicines Company—which had successfully developed and received FDA approval for drugs to which they had retained ownership rights had developed into FIBCO's—Fully Integrated Biopharmaceutical Companies—and employ in Massachusetts a full complement of sales and marketing staffs, together with all the necessary corporate functions of human resources, legal, regulatory, etc.

SUMMARY

In just 25 years, Massachusetts has gone from a non-existent position in the biopharmaceutical industry to one of its leading centers. The process started with spin-out companies from the leading universities in Massachusetts, capitalizing on the new biotechnologies. This was followed by an influx of major pharmaceutical companies establishing R&D centers in Massachusetts. Massachusetts then became one of the leading centers for biopharmaceutical manufacturing in the world. Finally, a significant number of the start-up companies have vertically integrated from research and development all the way through to manufacturing, marketing and sales as their products have progressed through the clinical development chain.

The roots of this success are inextricably intertwined with Massachusetts' world leading universities, coupled with the availability of risk capital to fund high risk pharmaceutical discovery research and supported at key points in the process by enlightened federal, state and local government support. There are few, if any, better examples of the Triple Helix theory of economic development—cooperation between government, academia and industry—in action.

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17. http://www.genzyme.com/corp/structure/timeline_genz.asp#, accessed 2/28/07
18. Hoechst AG, a predecessor company of Sanofi-Aventis, acquired the 50% of Hoechst-ARIAD Genomics Center, LLC which it did not own on December 31, 1999 (ARIAD 10K, 1999)
19. Acquired Transkaryotic Therapies, Inc. in April 2005.
20. Parika Petaipimol, personal communication.
21. http://hbswk.hbs.edu/item/4610.html; accessed 3/27/07.