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Boston's Biotech Boom: A "New Massachusetts Miracle"

IKD Working Paper No. 36

September 2008

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May 2007

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SUMMARY

From 2000 to 2002 worldwide exports from Massachusetts declined by 18.5 percent before rising by 43.7 percent from 2002 to 2006. The European Union has been the most important destination for exports from Massachusetts, with over 43 percent of the state's worldwide exports going there in 2006, up from 39 percent in 2000. In the aggregate, these changes appear to be merely cyclical, with a trend toward more exports to Europe. When one disaggregates the export data, however, one finds that during the 2000s a significant structural change in the composition and destination of Massachusetts' exports has taken place.

Using fine-grained "six-digit" product classifications from the Harmonized Tariff Schedule of the United States dataset, we document the extraordinary growth of Massachusetts' exports to Europe since 2002. These exports are concentrated in medical manufacturing sectors in general and biopharmaceutical products in particular. In 2006 Massachusetts exported products to Europe valued at $10.4 billion, of which 478 six-digit classifications were $1 million or more. Yet the two biotech categories — antisera/blood fractions and hormones/prostaglandins — at the top of the list accounted for 24.4 percent of the state's exports to Europe in 2006. In 2000 these two categories had been only 3.1 percent of exports to Europe. When we add in exports of packaged prescription drugs, the three biopharmaceutical categories made up 30.1 percent of all Massachusetts' exports to Europe in 2006, compared with only 4.8 percent in 2000.

The Greater Boston area is the world's leading center for the development and manufacture of biopharmaceutical products. Government funding underpins Boston's biotech advantage. As a group, universities, research institutes, and hospitals in Boston have long been the premier recipients of research and training grants from the National Institutes of Health (NIH). For example, of 116 hospitals in the United States that received NIH funding in 2005, the five leading recipients are in the center of Boston, and they were awarded 52 percent of the $1.7 billion that all US hospitals received from the NIH in that year. Moreover, the same five hospitals have been the leading beneficiaries of NIH funding since at least the mid-1980s when the NIH began publishing these rankings. No other biotech center in the world can match the highly concentrated learning networks that have been built on this government-funded knowledge base.

A number of the leading biopharmaceutical companies such as Genzyme, Biogen Idec, Millennium and Vertex are based in the Boston area, while other companies such as Amgen, Merck Serono, Novartis, and Wyeth have major biotech facilities there. The central role of the government in the development of the Boston biotech industry becomes all the more apparent when we take note of the types of products that the most successful biotech companies have been producing. Among the ten leading dedicated biopharmaceutical companies in the United States in 2005, 73 percent of their $29.8 billion in product revenues came from brands that have been approved as "orphan drugs". Since 1983, under the Orphan Drug Act, biopharmaceutical companies have been receiving research subsidies and market exclusivity to develop drugs for genetic and rare diseases — drugs that, it is believed, would not have been developed without special government support. Many of these drugs have become blockbusters with sales of $1 billion or more.

Since 1983 the Food and Drug Administration (FDA) has given market approval for over 300 orphan drugs, and in recent years there has been a marked acceleration in the number of orphan drug designations filed with the FDA. The NIH claims that some 7,000 genetic and rare diseases have been identified, affecting 25 million Americans, or 1 in 12 of the nation's population. These drugs tend to be expensive — $30,000 per patient per year is not uncommon — and, as a consequence, the rich nations of Europe, along with Japan, Canada, and Australia, are the other important markets for these drugs. In 2001 the European Union passed its own Orphan Drug Act as part of an effort to catch up to the United States in biotechnology.

Besides funding the knowledge base that underpins the biotech industry and subsidizing the development and commercialization of drugs for genetic and rare diseases, the government is the source of a very significant proportion of the purchasing power for these drugs in the United States. In 2004 government expenditures as a proportion of US national health expenditures stood at over 45 percent, while national health expenditures as a proportion of gross domestic product was at almost 16 percent. Prescription drug expenditures have

been an increasing proportion of national health expenditures, reaching about 10 percent in the mid-2000s. Plan D of Medicare, introduced in 2006 to provide drug coverage to seniors, will further increase the weight of prescription drug expenditures in national health expenditures in the coming years.

Currently, Congress is debating the extent to which the government should regulate the prices of prescription drugs, which are generally far higher in the United States than in the other rich nations of the world. The biopharmaceutical companies argue that if drug prices are lowered they will have less money available to invest in R&D, with the result that fewer new drugs will become available to the public. In considering these arguments, however, policymakers should take a close look at how the successful biopharmaceutical companies are actually allocating their profits. In the cases of Amgen and Genentech, number one and number two among the independent biopharmaceutical companies, they have been allocating about as much of their profits to stock repurchases as to R&D in the 2000s.

The purpose of stock repurchases is to give a boost to a company's stock price. Prime beneficiaries of stock repurchases are none other than the high-level corporate executives who make these allocative decisions. Over the 10-year period, 1997-2006, Amgen spent $18.5 billion on R&D and did $17.9 billion in stock repurchases. The *average gains per person* from the exercise of stock options by Amgen's CEO and four other highest paid executives over this period was *$92.1 million*. It also happens that Amgen has been in the news lately for its failure to develop new products.

As Congress debates the regulation of drug prices, it is also debating, as a totally separate issue, measures to stem the continuing rise in CEO pay. As indicated by gains from the exercise of stock options at Amgen, top executive pay at US corporations is generally at a level that has long been excessive, and some might even say obscene. In the US biopharmaceutical industry, the debates over the regulation of the prices of drugs and the pay of executives should be joined.

1. The New Boom in Biotech

High-technology is important to the Massachusetts economy. In 2005 industries that the National Science Foundation classifies as "Advanced Technology" employed 211,050 people in the state. Unfortunately, these employment numbers were down significantly from 2001. While the number of Advanced Technology establishments in Massachusetts had increased from 9,382 to 9,607, Advanced Technology employment in 2005 had declined by 52,502 people, or 20 percent, from four years earlier. In 2001 employment in high-tech industry represented 9.2 percent of total employment in Massachusetts; in 2005, it had fallen to 7.7 percent.[1]

High-tech employment in Massachusetts is concentrated in the "Route 128" district that extends in a 35-mile radius to the north and west of Boston. The district developed during the post-World War II decades around the commercialization of electronics research, most of it government-funded, in the universities of the Greater Boston area, with MIT playing a central role (Dorfman 1983; Simon 1985; Roberts 1991; Rosegrant and Lampe 1992; Saxenian 1994; Etzkowitz 2002; Hsu and Kenney 2004). By the 1970s Route 128 had become the global center of the minicomputer industry, with companies such as Digital Equipment, Wang Laboratories, Data General, and Prime Computer headquartered in the region.

The expansion of the minicomputer industry in the first half of the 1980s provided the foundation for the so-called "Massachusetts Miracle", a phrase manufactured for the 1988 presidential bid of Massachusetts Governor Michael Dukakis (Moscovitch 1986; Dukakis and Kanter 1988; Lampe 1988).[2] By the late 1980s, however, the minicomputer industry was competing against ever more powerful microcomputers — a segment that had developed primarily in northern California and Texas — and by the early 1990s was in the throes of its demise. Afflicted as well by the "end of the Cold War" decline in defense spending, on which the district was also highly dependent, during the first half of the 1990s Route 128 seemed to have become a ghost of its former self.

In the last half of the 1990s, however, buoyed by the Internet revolution, the Route 128 district tapped its latent capabilities in communications technology and computer software to experience rapid growth (Best 2001, ch. 5). But then in 2001 the Internet boom turned to bust, with Massachusetts being particularly hard hit. For the period January 2001 to January 2004, as the US economy as a whole lost 1.7 percent of its jobs, Massachusetts lost 6.2 percent, by far the highest rate of job loss for any state in the nation (Glain 2004). Over this period, Massachusetts manufacturing employment declined by 20 percent, information and communication technology employment by 25 percent, and professional and business service employment by 15 percent (Glain 2004; see also Clayton-Matthews 2003). In 2002 alone, while the US economy lost 550,000, or 9.6 percent, of its high-tech jobs, Massachusetts lost almost 35,000, or 13.2 percent — the highest rate of any state.

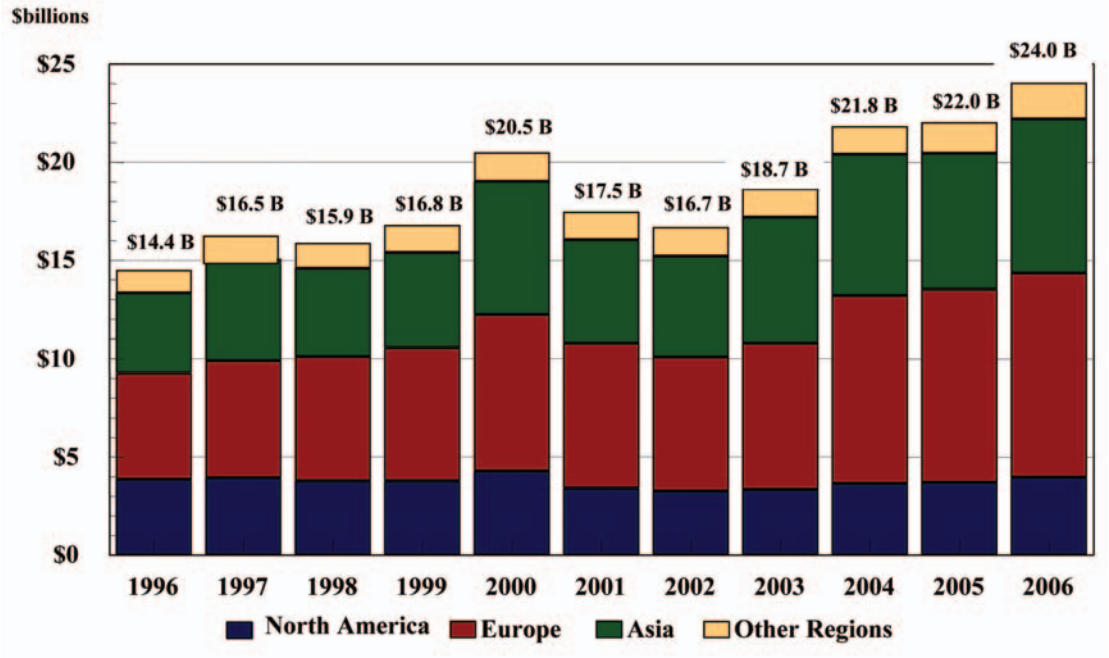
It was not until 2005 that high-tech employment in the United States as a whole and in Massachusetts began to increase. Moreover, for both the United States and Massachusetts, total employment was higher in 2005 than in 2001 in only one major high-tech sector — biotechnology and life sciences. Indeed, in both the United States and Massachusetts "biolife" employment increased in every year from 2001 to 2005.

Biolife employment accounted for 16.9 percent of high-tech employment in Massachusetts in 2001, moving up to 23.3 percent in 2005. Nevertheless, in 2005 the entire biolife sector provided less than 50,000 jobs in Massachusetts, representing just 1.8 percent of the almost 2.8 million people employed in the state in that year and under 5,000 additional biolife jobs compared with 2001. The contribution of biolife to Massachusetts' employment in 2005 was, however, significant in light of the decline during the first half of the 2000s in the proportion of the state's labor force engaged in high-tech employment.

Most of the jobs in this sector demand high levels of education and are relatively well paid. Average annual wages in the Massachusetts biolife sector were $98,614 in 2005. The 27 percent increase in Massachusetts biolife wages from 2001 to 2005 was greater than for any other Advanced Technology category in the state. While biolife wages were substantially higher in New Jersey and Connecticut than in Massachusetts in all years from 2001 through 2005, the relative position of California and Massachusetts in biolife wage levels changed from year to year.

Yet the biolife employment figures provide no hint that a "new Massachusetts miracle" has taken place. To find evidence of a "miracle" since the early 2000s one must look at changes not in employment but in exports. Measured in current dollars, worldwide exports from Massachusetts declined by 18.5 percent from 2000 to 2002 before rising by 43.7 percent from 2002 to 2006 (see Figure 1.1). As can be seen in Figures 1.1 and 1.2, over the past decade, among broad geographic areas, Europe has been the most important destination for exports from Massachusetts, and increasingly so.

Figure 1.1: Massachusetts worldwide exports, value by geographic market, 1996–2006

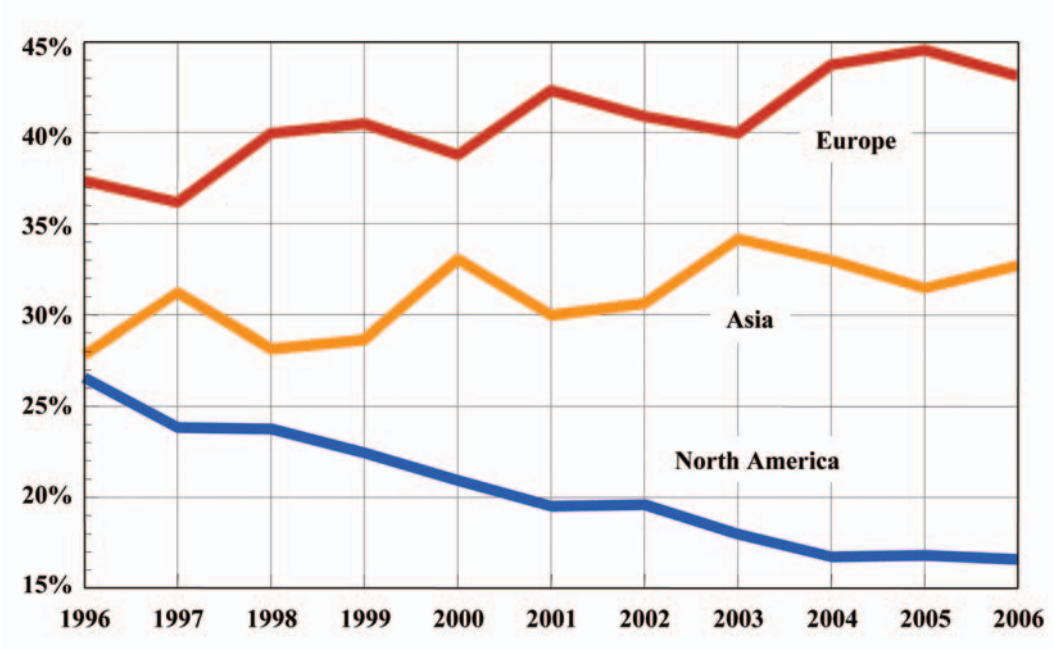


Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

In the aggregate, these changes appear to be merely cyclical, with a trend toward more exports to Europe. Indeed, measured in 2006 dollars, the value of Massachusetts' exports worldwide in 2006 was only about one-tenth of one percent higher than at the previous peak of 2000. It is only when one disaggregates the export data that one can discern that during the 2000s a significant structural change in the composition of Massachusetts' exports has taken place — one in which the increased proportion of exports going to Europe is of fundamental importance. One might even argue that a "new Massachusetts miracle" has occurred, although by definition a "miracle" is "an extraordinary event in the physical world that surpasses all known human or natural powers and is ascribed to a supernatural cause."[3] In short, a miracle cannot be explained. In this paper, we shall show that over the past few years an "extraordinary event" has occurred in Massachusetts, and more specifically in the Greater Boston area. What has happened may be surprising. It can, however, be readily explained — with important implications for government policy.

Part 2 of this paper delves into the export performance of the Massachusetts economy in the 2000s. Using fine-grained "six-digit" product classifications from the Harmonized Tariff Schedule of the United States dataset, we document the extraordinary growth of Massachusetts' exports to Europe since 2002 — growth that has been dominated by medical manufacturing sectors in general and biopharmaceutical products in particular.

Figure 1.2: Massachusetts worldwide exports, percent distribution by geographic market, 1996-2006



Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

Then in Part 3 we explain why the Greater Boston area has become the world's leading center for biopharmaceuticals. We emphasize both the role of massive government funding of the sector, primarily through the resources of the National Institutes of Health (NIH), and the dense set of knowledge networks that in biotechnology characterize the Boston area like nowhere else on the globe. We also identify the particular biopharmaceutical companies with investments in the Boston area whose products have been largely responsible for Boston's biotech boom.

In Part 4 we delve deeper into the evolution and composition of the products of these companies to reveal the extent to which "orphan drugs" represent the ultimate explanation of Boston's biotech boom. Orphan drugs are pharmaceuticals designed to treat genetic and rare diseases. Given the high cost of developing these drugs relative to the small size of the market, biopharmaceutical companies have claimed that, in the absence of financial subsidies and market exclusivity, they could not make the business case for committing resources to the drawn-out process of research and clinical trials necessary to bring these drugs to market. In the United States since 1983, the Orphan Drug Act has given the biopharmaceutical industry these subsidies and exclusivity. In 2001 the European Union passed its own Orphan Drug Act to encourage the development and support the commercialization of products to treat genetic and rare diseases.

Finally, in Part 5, we ask the inevitable question: If, as has clearly been the case, government support and subsidy have been of critical importance to the development of the biopharmaceutical industry, how can government policy capture more of the benefits of the biotech boom for the citizens who the government represents — without killing the business geese

that are laying the golden biopharmaceutical eggs? The answer to this question requires an informed analysis of the roles of technological change, product market demand, and business investment behavior in the rising costs of health care. Such an analysis must critically examine the prevalent notion that whatever the executives of biopharmaceutical companies say that they need is what they need to get. The regulation of the biopharmaceutical industry is currently a matter of national debate, with a focus on drug prices. The analysis of the Boston biotech boom that we present strongly suggests that the debate needs to delve more deeply into how and under what conditions biopharmaceutical companies allocate resources to generate higher quality, lower cost products. The debate on drug prices, we argue, needs to be joined to the debate on corporate governance.

Such an analysis is a matter of concern for Americans generally. It is of particular importance in Massachusetts, given its history as one of the most progressive states in the nation, and specifically one that is currently taking the lead in the commitment to provide affordable healthcare to all its residents. Policymakers in Massachusetts can easily become captive to the riches and euphoria of Boston's biotech boom. In the process they may ignore what it is that has made the boom possible while losing sight of how to ensure the widespread distribution of the benefits that the biotechnology revolution has the potential to offer.

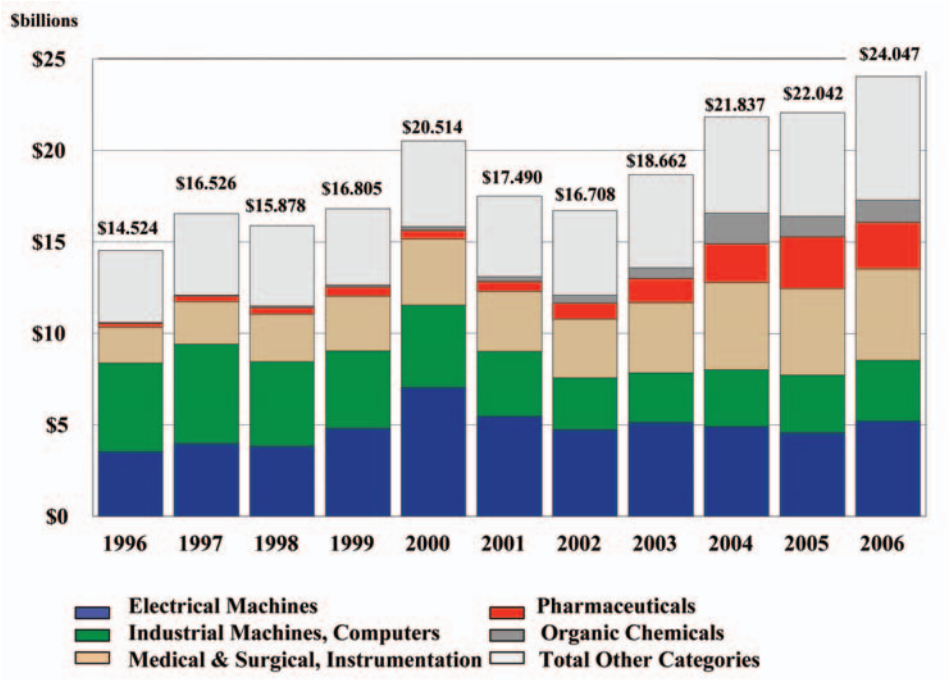
2. Massachusetts' Exports in the Biotech Boom

Using the Harmonized Tariff Schedule of the United States dataset, we can identify the specific products and geographic markets that have driven the changes in Massachusetts' export performance in the 2000s. At the "two-digit level" the five most important product categories in 2006 were, in order of most value, "Medical & Surgical Equipment, Instrumentation" (MS), "Electrical Machines" (EM), "Industrial Machines, Computers" (IC), "Pharmaceuticals" (PH), and "Organic Chemicals" (OC). Figure 2.1 shows the changing dollar value and Figure 2.2 the relative weights of these five categories for every year from 1996 through 2006. In each of these years, these five categories have been responsible for more than 70 percent of Massachusetts' exports to the world, but with changing relative proportions. In the late 1990s IC and EM constituted the two largest categories of exports, with MS also accounting for a significant and growing share, while exports of PH and OC were small. By the mid-2000s PH and OC were making far more significant contributions to the state's exports than had been the case in the late 1990s. Broadly speaking, the first half of the 2000s saw the rise of medical/chemical/pharmaceutical exports, with industrial/electrical machines remaining important export categories, but representing a declining proportion of the total.

While PH and OC are not the largest export categories in 2006, they have been *the major drivers* in the growth of the state's worldwide exports in the 2000s. The MS category has been a consistently important contributor to the total value of Massachusetts' exports. But, as seen in Figure 2.2, unlike PH and OC, MS's proportionate contribution to worldwide exports has remained relatively constant since 2001. Figure 2.3 shows that since 1996 both Europe and Asia have absorbed most of Massachusetts' MS exports, in a roughly equal amount across the two regions.

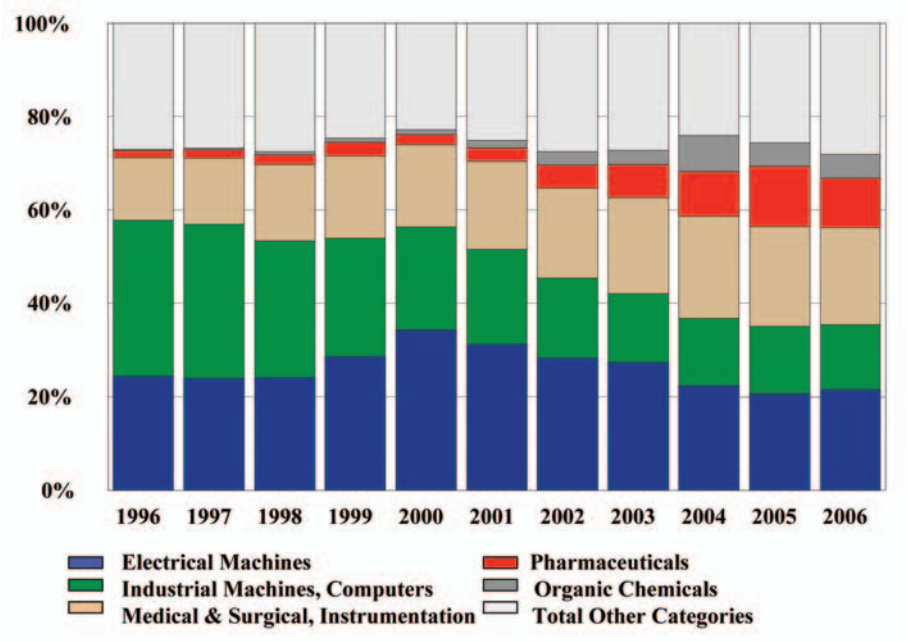
Not so, however, with PH and OC exports, as displayed in Figures 2.4 and 2.5. The value of both of these categories of exports expanded enormously in the 2000s, and especially since 2002, *with virtually all of the growth to Europe.* In 2006 81 percent of all of Massachusetts' PH exports and 95 percent of the state's OC exports went to Europe. In 2006 dollars, PH

Figure 2.1: Massachusetts worldwide exports, value of dominant two-digit categories, 1996-2006



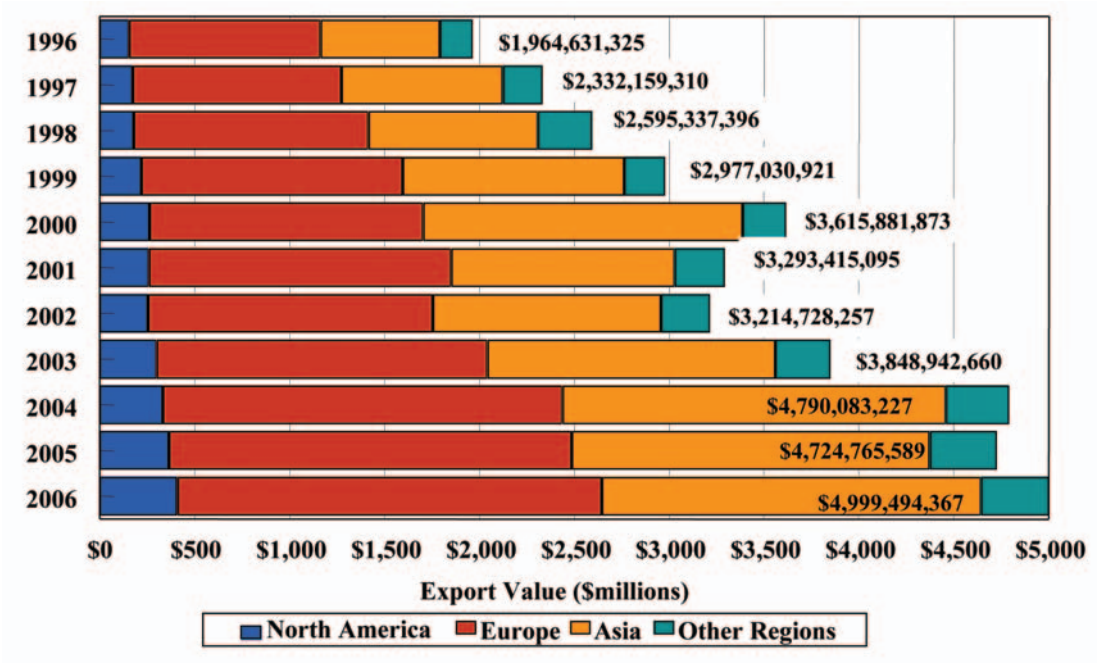
Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

Figure 2.2: Massachusetts worldwide exports, percent distribution of dominant two-digit categories, 1996-2006



Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

Figure 2.3: Massachusetts worldwide exports, value by geographic market, Medical & Surgical Equipment, Instrumentation, 1996-2006



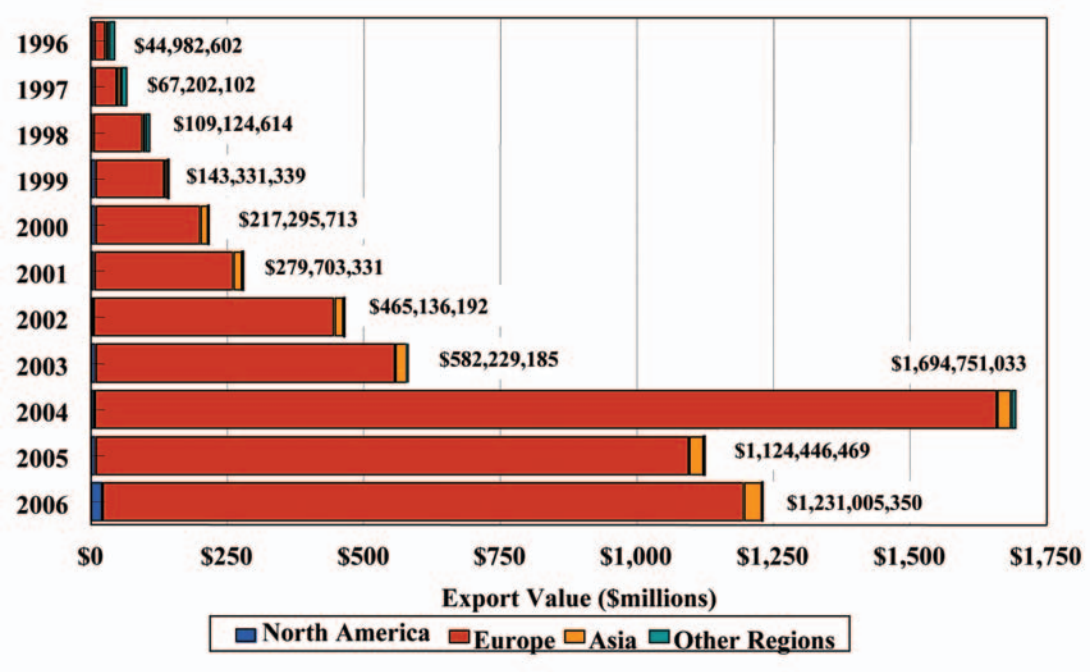
Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

exports to Europe in 2006 were 10.5 times their level in 1996 and 5.4 times in 2001, while OC exports to Europe in 2006 were 44.0 times their level in 1996 and 4.1 times in 2001. This despite the fact that, measured in 2006 dollars, the value of PH exports to Europe was 17.5 percent lower than its peak of 2005, and the value of OC exports to Europe 33.4 percent lower than its peak of 2004.

If exports are an indication of a "new Massachusetts miracle", it is necessary to explain the causes of these dramatic increases in PH and OC exports to Europe. To do so, we need to delve into the Harmonized Commodity Description and Coding System database, or the Harmonized System (HS) for short, at a more disaggregated level. HS is an international trade nomenclature for classifying exported and imported products (World Customs Organization 2007a). It is recognized and applied by more than 200 countries that account for 98 percent of world trade. The World Customs Organization maintains and periodically updates HS. The nomenclature is divided into 21 sections, each of which groups together goods produced in the same sector of the economy. Within each section, there are one or more chapters that classify products either by common basic materials or common uses. HS consists of a total of 97 chapters across the 21 sections. Within each chapter, the detailed characteristics of products are described and classified by six-digit HS codes that all HS country participants are obliged to use (World Customs Organization 2007b).

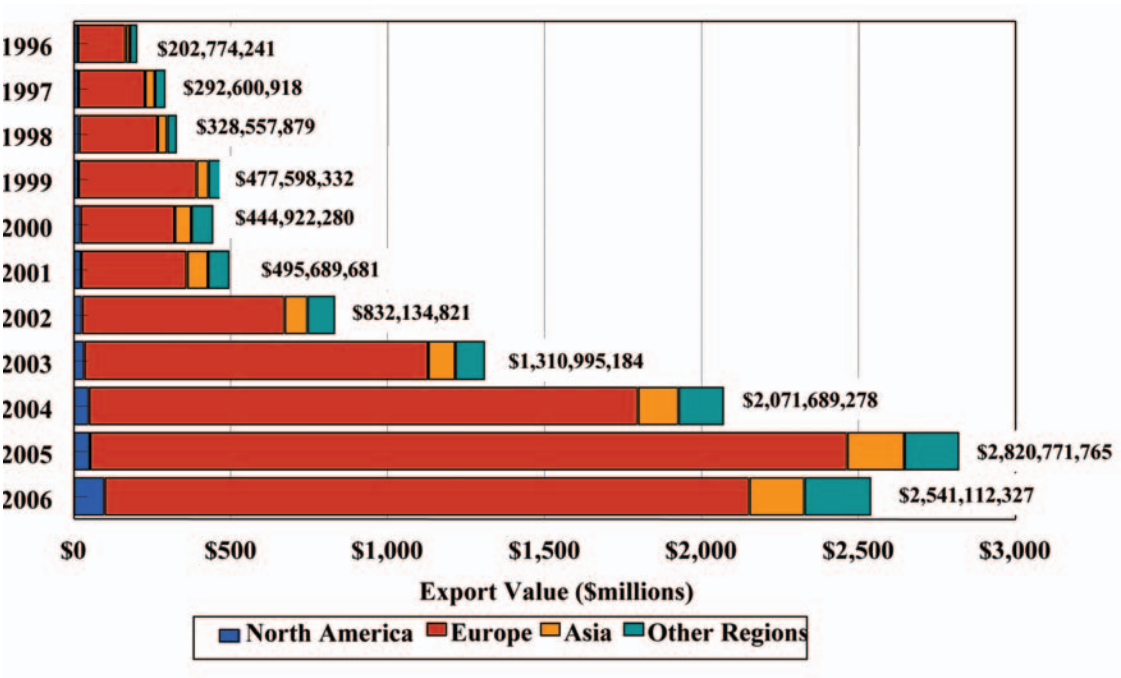
In 2006 Massachusetts' exports worldwide included 2,248 different six-digit products with a value of $100,000 or more and 1,034 products with a value of $1,000,000 or more, while the state's exports to Europe included 1,119 different six-digit products with a value of $100,000 or more and 478 products with a value of $1,000,000 or more. Yet in 2006 *the top seven*

Figure 2.4: Massachusetts worldwide exports, value by geographic market, Organic Chemicals, 1996-2006



Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

Figure 2.5: Massachusetts worldwide exports, Pharmaceutical Products, 1996–2006



Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

categories alone accounted for 28.64 percent of the value of all exports worldwide and 41.88 percent of the value for all exports to Europe (see Tables 2.1 and 2.2). These seven categories (with their six-digit HS codes in parentheses) are in order of magnitude worldwide:

1. antisera and blood fractions (300210)
2. hormones, prostaglandins (293790)
3. digital monolithic integrated circuits (854221)
4. medical needles, catheters (901839)
5. medicaments, measured dose, retail packaging (300490)
6. instruments for checking semiconductor wafers (903082)
7. medical instruments and appliances (901890)

Five of these categories — 300210, 293790, 901839, 300490, and 901890 — are related to pharmaceuticals, organic chemicals, and medical/surgical instruments, all within the broader medical field. The other two categories — 854211 and 903082 — are microelectronics products. As shown in Table 2.2, in 2006 the five six-digit medical categories represented Massachusetts' top five export categories to Europe.

Indeed, the two categories, 300210 and 293790, together accounted for 24.43 percent, or almost one-quarter, of all of Massachusetts' exports to Europe. These two categories also accounted for 10.83 percent of all Massachusetts' exports worldwide. Note that in 1996 these two categories represented only 0.63 percent of all Massachusetts' exports to Europe and 0.36 percent worldwide, and even in 2000 these proportions were only 3.09 percent to Europe and 1.39 percent worldwide. Add in 300490, which also was barely present as an export category in 1996, and in 2006 the three categories totaled 14.80 percent of Massachusetts' exports worldwide and 30.20 percent to Europe.[4]

Table 2.1: Top six-digit HS Commodity Code categories as percentage of total Massachusetts worldwide exports, 1996-2006

HS Code	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
300210	0.27	0.44	0.50	0.53	0.49	0.53	2.06	4.48	6.35	8.32	6.09
293790	0.09	0.14	0.52	0.72	0.90	1.36	2.51	2.84	7.46	4.81	4.74
854221	5.39	6.40	5.52	3.98	5.28	5.93	7.73	9.68	5.57	4.62	4.44
901839	0.87	1.34	1.97	2.17	1.99	2.96	3.05	4.38	4.80	5.00	4.33
300490	0.09	0.10	0.64	1.28	1.08	1.73	2.37	2.09	2.74	3.98	3.97
903082	0.35	0.41	0.50	0.95	2.44	1.54	2.00	2.41	3.31	2.40	2.62
901890	1.02	1.26	1.53	1.41	1.20	1.79	1.74	2.00	1.96	2.37	2.52
Seven HS categories as % of MA worldwide exports	**8.08**	**10.09**	**11.18**	**11.03**	**13.37**	**15.85**	**21.46**	**27.87**	**32.19**	**31.50**	**28.72**
MA worldwide exports, totals , $m	**14,524**	**16,526**	**15,878**	**16,805**	**20,514**	**17,490**	**16,708**	**18,663**	**21,837**	**22,043**	**24,047**

HS category product definitions:
300210: Antisera and blood fractions
293790: Hormones, prostaglandins
854221: Digital monolithic integrated circuits
901839: Medical needles, catheters
300490: Medicaments, measured dose, retail packaging
903082: Instruments for checking semiconductor wafers
901890: Medical instruments and appliances
Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

Table 2.2: Top six-digit HS Commodity Code categories worldwide* as percentage of total Massachusetts exports to Europe, 1996-2006

HS Code	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
300210	0.48	0.71	0.78	0.89	0.79	0.74	4.44	8.05	13.93	17.95	13.44
293790	0.23	0.37	1.30	1.76	2.30	3.20	6.11	5.37	17.04	10.78	10.99
901839	1.69	2.54	2.63	2.59	2.70	3.25	3.50	4.98	6.77	6.93	6.59
300490	0.09	0.12	1.23	2.32	1.69	2.84	4.10	2.57	3.94	5.95	5.77
901890	1.74	2.12	2.15	1.85	1.74	2.52	2.50	2.28	2.59	3.04	3.41
903082	0.36	0.50	0.50	1.02	1.29	1.08	0.51	0.36	0.67	0.69	1.05
854221	3.56	4.76	3.93	3.80	4.33	5.13	2.48	1.05	0.85	0.77	0.63
Seven HS categories as % of MA exports to Europe	**8.15**	**11.11**	**12.52**	**14.22**	**14.84**	**18.76**	**23.64**	**24.66**	**45.79**	**46.12**	**41.89**
MA exports to Europe, totals , $m	**5,422**	**5,974**	**6,343**	**6,805**	**7,954**	**7,403**	**6,832**	**7,455**	**9,549**	**9,819**	**10,356**

HS category product definitions: see notes to Table 2.1

* The first five categories listed in this table were among the top five six-digit HS categories both worldwide and to Europe in 2006, while 903082 ranked 13th and 854221 ranked 23rd among HS export categories to Europe in 2006. These seven categories are included in this table for comparability with the top seven HS categories of Massachusetts worldwide exports listed in Table 2.1

Source: Harmonized Tariff Schedule of the United States dataset, acquired from the World Institute for Strategic Economic Research (WISER).

What kinds of products do these categories represent? Included in HS-300210 are blood fractions and modified immunological blood products that are obtained by organic or synthetic means (except foods, beverages or bloods that are not used for therapy, diagnostic or prevention purposes) (World Customs Organization 2007b). Represented in this category are monoclonal antibodies (mAb),[5] antisense,[6] antisera,[7] and other blood-based bio-applications that are modified by antibodies or other types of proteins to treat genetic and hereditary disorders. In the HS classification system, "30" represents HS chapter 30, pharmaceutical products, with "02" representing therapeutic, preventive, or diagnostic products.

In the case of HS-293790, "29" represents HS chapter 29, organic compounds, while "37" represents hormone groups such as prostaglandins,[8] thromboxanes,[9] and leukotrienes[10] (these hormones may be natural or reproduced by synthesis from other organic chemicals). HS-293790 includes many novel hormone-based treatments and biologic applications developed by the biotechnology or pharmaceutical industries.

In the case of HS-300490 "30" represents HS chapter 30, pharmaceutical products, and "04" represents pharmaceutical medicaments packed and ready for sale. The HS-300490 category represents "other" types of mixed or unmixed therapeutic or prophylactic substances for retail sale. "Other" means that the 300490 substance does not contain penicillin, antibiotics, alkaloids, vitamins or hormones.

The exports included in HS-300210, HS-293790, and HS-300490 represent, in a word, biopharmaceuticals. The products included in these export categories manifest Boston's biotech boom.[11] In Part 3 of this paper, we explain why the boom has centered on the Greater Boston area, and then in Part 4 we explore the particular characteristics of the biopharmaceutical products on which the boom has been based.

3. Boston's Biotech Advantage

MedAdNews puts out an annual report on the top 100 biotechnology companies in the world by revenues.[12] Table 3.1 shows the distribution of these companies across the various nations in which they have their headquarters. Note the

predominance of US-based companies among the top 100 in terms of the number of companies, revenues and employees, as well as the substantial revenues of the small number of Swiss companies. Among the large European countries, France and Italy have no representation among the top 100, while smaller European countries are well-represented. In all, 20 of the 100 companies on the list are based in Europe.

The overwhelming predominance of US companies on the top 100 list is not for a lack of European competitors. According to the Ernst & Young 2006 annual report on the biotech industry, in 2005 there were 4,203 biotech companies,

Table 3.1: Top 100 biopharmaceutical companies, by 2005 revenues, with data on country of national headquarters, net income, R&D expenditures, and employees

	National Totals						National Means			
	No. of companies	Revenues US$m	R&D US$m	Net Income (Loss) US$m	Employees		Revenues US$m	R&D US$m	Net Income (Loss) US$m	Employees
Australia	7	2,616	174	418	7,524		374	25	60	1,075
Belgium	1	60	41	-14	292		60	41	-14	292
Canada	6	624	153	-360	1,235		104	26	-60	206
Denmark	3	86	121	-78	511		29	40	-26	170
Germany	3	78	100	-87	508		26	33	-29	169
Ireland	1	490	233	-384	1,899		490	233	-384	1.899
Japan	1	22	0	-12	89		22	0	-12	89
Netherlands	1	42	42	-19	282		42	42	-19	282
Sweden	2	30	9	-12	235		15	5	-6	118
Switzerland	3	3,256	801	-15	2,086		1,085	267	-5	695
UK	6	265	226	-135	953		44	38	-23	159
USA	66	35,502	9,972	3,293	31,548		538	151	50	478
All 100	**100**	**43,071**	**11,874**	**2,595**	**47,263**		**431**	**119**	**26**	**473**
	National Companies as % of All Companies						National Company Means: All Company Means			
	No. of companies	Revenues US$m	R&D US$m	Net Income (Loss) US$m	Employees		Revenues US$m	R&D US$m	Net Income (Loss) US$m	Employees
Australia	7	6.07	1.47	16.11	15.92		0.87	0.21	2.30	2.27
Belgium	1	0.14	0.35	-0.56	0.62		0.14	0.35	-0.56	0.62
Canada	6	1.45	1.29	-13.87	2.61		0.24	0.21	-2.31	0.44
Denmark	3	0.20	1.02	-3.00	1.08		0.07	0.34	-1.00	0.36
Germany	3	0.18	0.84	-3.34	1.07		0.06	0.28	-1.11	0.36
Ireland	1	1.14	1.96	-14.78	4.23		1.14	1.96	-14.78	4.23
Japan	1	0.05	0.00	-0.46	0.19		0.05	0.00	-0.46	0.19
Netherlands	1	0.10	0.36	-0.75	0.60		0.10	0.36	-0.75	0.60
Sweden	2	0.07	0.08	-0.46	0.50		0.03	0.04	-0.23	0.25
Switzerland	3	7.56	6.75	-0.59	4.41		2.52	2.25	-0.20	1.47
UK	6	0.61	1.91	-5.21	2.02		0.10	0.32	-0.87	0.34
USA	66	82.43	83.98	126.91	66.75		1.25	1.27	1.92	1.01
All 100	100	100.00	100.00	100.00	100.00		1.00	1.00	1.00	1.00

Source: "15th annual report: Top 100 biotechnology companies," Med Ad News, July 2006

both public and private, around the world, of which 1,613, or 38 percent were based in Europe compared with 1,414, or 34 percent in the United States (Ernst & Young 2006, 5). About 11 percent of these companies were based in Canada (a highly disproportionate number given Canada's population) and the other 17 percent in Asia-Pacific. Where Europe lagged was in publicly traded companies. Of the 671 public companies globally, 49 percent were based in the United States and only 18 percent in Europe. Of the global public company totals, moreover, the US-based companies generated 76 percent of the $63.2 billion in global revenues, expended 78 percent of the $16.0 billion in R&D expenditures, and absorbed 48 percent of the $4.4 billion in losses, compared with 15 percent of the revenues, 16 percent of the R&D expenditures, and 44 percent of the losses for the Europe-based public companies.

Table 3.2 lists MedAdNews' top 25 biopharmaceutical companies by sales in 2005. Eighteen of the companies are based in the United States, three in Switzerland, two in Canada, and one each in Australia and Ireland. Three of the non-US companies, Berna Biotech, CSL, and Serono (now Merck Serono), have very long histories. One of the US companies, Biogen Idec, can trace its origins to Switzerland; Biogen was founded in Geneva in 1978 before establishing its headquarters in Cambridge, Massachusetts in 1988 when it sold off its European operations. Of the 18 US-based companies on the list, seven are in California, four in Massachusetts, two each in New Jersey and New York, and one each in Maryland, Minnesota, and Pennsylvania.

Table 3.2: MedAdNews top 25 biopharmaceutical companies by revenues, 2005

	Revenues, $m		Net Income, $m		Employees		Year founded	Location of headquarters
	2005	2004	2005	2004	2005	2004		
1. Amgen	12,430	10,550	3674	2363	16,500	14,400	1980	Thousand Oaks, CA
2. Genentech	6,633	4,621	1279	785	9,500	7,646	1976	San Francisco, CA
3. Genzyme	2,735	2,201	442	87	8,200	7,100	1981	Cambridge, MA
4. Serono*	2,586	2,458	-213	471	4,826	4,740	1906	Geneva, Switzerland
5. CSL*	2,494	1,273	181	265	7,000	3792	1916	Melbourne. Australia
6. Biogen Idec	2,423	2,212	161	25	3,340	4,266	1978	Cambridge, MA
7. Gilead Sciences	2,028	1,325	814	449	1,900	1,900	1987	Foster City, CA
8. Chiron (owned by Novartis)	1,920	1,723	181	79	5,500	5,400	1989	Emeryville, CA
9. MedImmune	1,244	1,141	-17	-4	2,215	1,976	1988	Gaithersburg, MD
10. Cephalon	1,212	1,015	-175	-74	2,895	2,173	1987	Frazer, PA
11. Millennium Pharmaceuticals	558	448	-198	-252	1142	1477	1993	Cambridge, MA
12. Celgene	537	378	64	53	944	766	1986	Summit, NJ
13. Actelion	533	372	102	61	1000	854	1997	Allschwil/Basel, Switzerland
14. Elan*	490	482	-384	-395	1729	1899	1969	Dublin, Ireland
15. ImClone Systems	384	389	87	114	991	866	1984	New York, NY
16. PDL BioPharma	280	91	-167	-53	977	660	1986	Fremont, CA
17. MGI Pharma	279	196	-132	-86	575	282	1979	Bloomington, MN
18. Aeterna Zentaris	247	179	16	-2	489	350	1990	Quebec City, PQ, Canada
19. QLT	242	186	-325	-166	438	474	1981	Vancouver, BC, Canada
20. Ligand Pharmaceuticals	177	164	-36	-45	493	461	1987	San Diego, CA
21. OSI Pharmaceuticals	174	43	-157	-260	734	452	1983	Melville, NY
22. Enzon Pharmaceuticals	166	170	-90	4	306	359	1983	Bridgewater, NJ
23. Vertex Pharmaceuticals	161	103	-203	-166	813	736	1989	Cambridge, MA
24. Amylin Pharmaceuticals*	141	34	-209	-158	1150	600	1987	San Diego, CA
25. Berna Biotech* (owned by Crucell)	137	165	-11	-16	600	800	1898	Berne, Switzerland

* = originally a conventional pharma company

Source: "15th annual report: Top 100 biotechnology companies," Med Ad News, July 2006

The headquarters of all four of the Massachusetts companies in the top 25 are within city blocks of one another in the Kendall Square area of Cambridge, adjacent to the Massachusetts Institute of Technology. In contrast, the California companies are spread out geographically in a state that is 17.2 times the size of Massachusetts with 5.7 times the population. For example, the home base of Genentech is San Francisco, while that of Amgen is almost 400 miles away in Thousand Oaks, near Los Angeles and the two San Diego companies, Ligand and Amylin, another 160 miles further south. Indeed, it is in San Diego that one finds a concentration of biotech companies that rivals, but by no means matches, what one finds in Boston.

The Greater Boston area, centering on the adjacent cities of Boston and Cambridge, is the most concentrated biotech district in the world (Porter et al. 2006).[13] Critical to the emergence of Boston as what some now call "gene town" was the fact that from its origins in the mid-1970s, the biotechnology industry developed separately from the pharmaceutical industry.[14] The main center of innovative activity in pharmaceuticals was New Jersey, followed by New York, Pennsylvania and Michigan (see Audretsch and Feldman 1996, 633). Given the emergence of dedicated biotech firms, there was not a predetermined bias for them to be located in proximity to the existing pharmaceutical companies.

Dedicated biotechnology firms emerged because of a combination of the unique knowledge base that biotechnology entailed and the existence by the late 1970s of a well-developed venture capital industry that stood ready to fund biotech startups. The unique knowledge base involved recombinant DNA (rDNA), or gene splicing, a biotechnology tool invented in 1973 by Herbert Boyer of the University of California, San Francisco, and Stanley Cohen of Stanford University that permitted the laboratory reproduction of cloned genes. The Cohen-Boyer technique was one of many advances in biotechnology that resulted from projects funded by the NIH from the 1950s, subsequent to the 1953 discovery of the "double helix" structure of deoxyribonucleic acid (DNA), the molecule that carries genetic information (Kenney 1986; Orsenigo 1989; Prevezer 2001; Goozner 2004). According to Bertram Rowland, the attorney who executed the Cohen-Boyer cloning patent, "As I was informed Cohen insisted that the invention had no commercial application, was not patentable, and was really only a minor extension of what had been performed by others."[15]

In his book on the emergence of the US biotechnology industry, Martin Kenney (1986, 241) argued: "The campaigns undertaken by NIH to find cures for diseases such as cancer have also turned out to be projects that prepared commodities to the point at which they were ready for commercialization by industry." For example, from 1976 the NIH had a contract with the New England Enzyme Center of Tufts University to manufacture an enzyme, later known as Ceredase, that became the foundation of Genzyme in 1981 (Love 1993). Two decades later, the director of the Tufts project and the founder of Genzyme, Henry Blair, was quoted as saying: "Genzyme would not have existed without that NIH contract" (quoted in Kranish 2002).

At the very time that Cohen and Boyer discovered the rDNA technique, it happened that venture capital had emerged in the San Francisco Bay area as an industry devoted to new firm formation (see Kenney and Florida 2000; Lazonick 2006). Of little significance on the West Coast in the late 1950s, venture capital developed in the 1960s and early 1970s through its involvement in the growth of the microelectronics industry centered in Silicon Valley. In the mid-1970s, with the formation of new microelectronics firms in a temporary lull, venture capitalists were on the lookout for new funding opportunities. So it was that in 1975 Robert Swanson, a young partner at the Silicon Valley venture capital firm of Kleiner Perkins, sought out Boyer at UC San Francisco, and convinced him to join in the founding of Genentech, with Swanson as the CEO.

Similarly, proactive venture capitalists were responsible for the founding of Biogen, a 1978 East Coast creation to which the eminent Harvard microbiologist, Walter Gilbert, lent his name, and Amgen, formed in 1980 on the initiative of San Francisco venture capitalists who located the firm near Los Angeles to enlist the services of some well-known scientists there (Robbins-Roth 2000, ch. 2-4).

As was already the case in the microelectronics industry, the offer to scientists of stock and stock options in the inherently uncertain new ventures helped lure them away from secure positions in academia and established companies. "Big pharma" supported the emergence of independent biotech firms by funding their growth through research contracts and equity investments, with these two forms of finance often being used in combination in R&D limited partnerships (OTA 1984, 278-279; Kenney 1986, ch. 7).

The fact that in 1978 Congress had lowered the capital gains tax rate from 49 percent to 28 percent — largely in response to vigorous lobbying by the National Venture Capital Association and the American Electronics Association, and reversing a 36-year trend toward higher capital gains taxes (Pierson 1978) — made it all the more attractive for both investors and scientists (with their stock-based compensation) to allocate their resources to new biotech firms. Under the Economic Recovery Act of 1981, the capital gains tax rate for individuals was lowered to 20 percent, while it remained 28 percent for corporations (OTA 1984, 274). The magnitude of the gains that could be reaped from biotech startups became apparent when Genentech raised $36 million in its IPO in October 1980. Subsequently, there were 18 more biotech IPOs through July 1983, including what was in 1981 the largest IPO in history, the $120 million raised by Cetus, another Bay area company founded in 1971 (OTA 1984, 282).

Reinforcing the emergence of biotechnology as distinct from pharmaceuticals was the Bayh-Dole Act of 1980. By giving universities and hospitals clear property rights to new knowledge that resulted from federally funded research, Bayh-Dole facilitated the transfer of this knowledge to support the creation and growth of new technology firms (Mowery et al. 2004). The motivation for Bayh-Dole was the growing number of biotech inventions that, it was argued, would be left unexploited unless the conditions for the transfer of intellectual property were made less restrictive. The very need for the Bayh-Dole Act was testimony to the critical importance of federal funding for the accumulation of biotech knowledge.

In 1980 as well, the Supreme Court decision in Diamond v. Chakrabarty that genetically engineered life forms are patentable greatly enhanced the opportunity for the types of knowledge transfers that Bayh-Dole envisioned. The decision itself was a 5-4 ruling, and has since been the subject of debate (Lewin 1982; Eisenberg 2002; Garcia 2002). Nevertheless, it set a precedent for the patenting of genes. In the early 1990s, in the context of the Human Genome Project, launched in 1990, even the NIH began patenting partial complementary DNA sequences on the grounds that patent licenses to biotech companies would encourage product development (see Eisenberg 1992).

In 1983 the passage of the Orphan Drug Act provided another important inducement to biotech investment. Designed to encourage pharmaceutical companies to invest in the development of drugs for "rare" diseases, the Orphan Drug Act gave companies generous tax credits for research and experimentation as well as the possibility of market exclusivity for seven years from the time that a drug was approved for commercial sale by the US Food and Drug Administration (FDA). It was argued that without these financial incentives many potential medicinal drugs that could be developed for relatively small markets would remain "orphans": pharmaceutical or biotech companies would not have been willing to make

the large financial commitments required to nurture these drugs from infancy to adulthood. Through January 16, 2007, the FDA had designated 1,679 orphan drug submissions that made these companies eligible for the tax credits and had granted market exclusivity on 302 drugs that had reached the approval stage.

Nevertheless, the inducements to business investment in the US biotech industry provided by the low capital gains tax-rate, the Bayh-Dole Act, the 1980 Supreme Court decision, and the Orphan Drug Act would all have come to naught but for the massive, persistent, and fundamental investments made by the US government in scientific knowledge upon which the biotech industry has been built. Through the NIH, the US government, and by extension the US taxpayer, has long been the nation's (and the world's) most important investor in knowledge creation in the medical fields. Since its inception in 1938 through 2005, US taxpayers invested $526 billion in 2005 dollars in the work of the NIH. For the 30 years since 1976, when Genentech was founded as the first biotech company to take advantage of the new techniques of rDNA, NIH funding totaled $423 billion in 2005 dollars.

The importance of NIH funding to the willingness of venture capitalists to invest in the biotech industry —as well as a tendency for venture capitalists to "forget" this fact — is indicated in an account by two Washington Post journalists (Henderson and Schrage 1984; see also Schrage and Henderson 1984) of a meeting that took place in Silicon Valley in 1984, in the aftermath of the wave of biotech startups and IPOs of the late 1970s and early 1980s:

> During a recent visit to the United States, French President Francois Mitterrand stopped to tour California's Silicon Valley, where he hoped to learn more about the ingenuity and entrepreneurial drive that gave birth to so many companies there. Over lunch, Mitterrand listened as Thomas Perkins, a partner in the venture capital fund that started Genentech Inc., extolled the virtues of the risk-taking investors who finance the entrepreneurs. Perkins was cut off by Stanford University Professor Paul Berg, who won a Nobel Prize for work in genetic engineering. He asked, "Where were you guys in the '50s and '60s when all the funding had to be done in the basic science? Most of the discoveries that have fueled [the industry] were created back then."
>
> Berg's point was that through research grants and contracts, with thousands of its own scientists and laboratories and a budget that reached $4.5 billion in fiscal 1984, NIH created the foundation of modern biotechnology. NIH sponsored the research that yielded technical breakthroughs that are now the basic tools of the industry. NIH support also created a national wealth of highly trained biomedical scientists. "I cannot imagine that, had there not been an NIH funding research, there would have been a biotechnology industry," Berg said.

Over two decades later, government support for the biotechnology industry has not abated. In 2005 Congress appropriated $28.5 billion to fund the work of the NIH. In its 27 centers and institutes in Bethesda, Maryland, the NIH supports the medical research of 6,000 scientists and technicians. But NIH in-house research only absorbs about ten percent of the NIH budget. Of the total 2005 budget of $28.5 billion, NIH awarded $23.7 billion for research, training, fellowships, and R&D contracts in the form of "50,000 competitive grants to more than 325,000 researchers at over 3,000 universities, medical schools, and other research institutions in every state and around the world."[16]

In 2005 $10.9 billion in NIH research funds went to biotechnology, up from $9.9 billion in 2003 and $10.7 billion in 2004, with another $10.9 billion projected for 2006.[17] As one of the NIH's 27 centers, the National Human Genome Research Institute (NHGRI), created in 1989, was allocated $489 million in 2005, and since its inception its funding has totaled $4.6 billion in 2005 dollars. The most recent addition to the growing number of NIH centers and institutes is the National Institute of Biomedical Imaging and Bioengineering (NIBIB). It began receiving appropriations in 2002, and through 2005 had total funding of just over $1 billion in 2005 dollars, including $298 million in 2005. NHGRI and NIBIB are relatively small programs within NIH, together absorbing 2.8 percent of the total funds in 2005. In that year the top three centers, together accounting for 42.3 percent of the NIH's total funds, were the National Cancer Institute (NCI) with 16.9 percent of the total; the National Institute of Allergy and Infectious Diseases (NIAID) with 15.1 percent; and the National Heart, Lung, and Blood Institute (NHLBI) with 10.3 percent. These knowledge-creating programs are all highly relevant to the biotech industry.

No place in the world benefits from NIH funding more than Boston. In a very useful study published by the Brookings Institution in 2002, Joseph Cortright and Heike Mayer (2002) identified nine distinct metropolitan regions in the United States that were the major centers of the biotechnology industry. They were the areas around Boston, San Francisco, San Diego, Raleigh, Seattle, New York, Philadelphia, Los Angeles, and Washington DC (for the precise definitions of these metropolitan areas, see Table 3.3). As indicators of the relative importance of these nine biotechnology centers, Cortright and Mayer collected data on, among other things, biomedical research infrastructure (biological science PhDs, life scientists employed, NIH funding); venture capital firms, investments, and IPOs; value of biotechnology alliances; and biotechnology firms by date founded, 100 or more employees, and market capitalization. While the Boston area was not the leader in all of these categories — for example, the Washington DC area (including Bethesda, Maryland where the NIH is based) led in life scientists employed while the New York area led in biotechnology related patents and the San Francisco area in venture capital investments — it is clear from all the data taken together that around 2000 the Boston area vied with the San Francisco area for the top spot.

Table 3.3 updates the data that Cortright and Mayer (2002) presented on the distribution of NIH research funding across these metropolitan areas (in 2003 the NIH stopped providing the data on awards to the top 100 US cities on which this table is based). The Boston area is the leading recipient of NIH funding, especially in comparison with other leading biotech centers around San Francisco, San Diego, and Raleigh. Data for 2005 on NIH funding per pharmaceutical employee by state show that Massachusetts led all states with $47,112 per employee, just ahead of Maryland with $45,202 and far ahead of New York with $21,913 and California with $18,647 (Nakajima and Loveland 2007, 13).

The supremacy of the Boston area as a recipient of federal funding that supports the biotech industry as well as the critical role of this funding in underpinning the competitive advantage of Boston in biotech becomes even more readily apparent when one looks at the specific organizations — mainly universities but also a number of hospitals — that have been the recipients of the largest amounts of NIH funding. Table 3.4 shows the top 50 organizations that received funding from the NIH in 2005 as well as their rankings in 1996, 1999, and 2002. Note the stability of relative positions within the list. There are 24 states represented in the top 50 with California leading with 8 organizations, New York State with 7, and then Massachusetts with 5. Like California's biotech firms, however, the organizations that receive NIH funding in California

and New York are spread out geographically within these large states. Like Massachusetts' biotech firms, NIH-funded organizations are highly concentrated geographically in the Boston area. It is exactly four miles as a car drives from the Harvard Department of Molecular and Cellular Biology (HMCB) in Cambridge to Brigham and Women's Hospital (B&W), a teaching affiliate of Harvard Medical School, located just down the street.[18] Lying more or less in between HMCB and B&W are the other three Massachusetts organizations — Massachusetts General Hospital (MGH), Massachusetts Institute of Technology (MIT), and Boston University (BU) — in the NIH's top 50 list.

Table 3.3: NIH research awards to the top nine metropolitan areas, 2000 and 2003

Metropolitan Areas	NIH Research Awards, $ millions		NIH Research Awards, % of top hundred cities	
	2000	2003	2000	2003
Boston—Worcester—Lawrence, MA—NH—ME—CT CMSA	1,488	2,136	13.0	12.9
San Francisco—Oakland—San Jose, CA CMSA	704	1,009	6.2	6.1
San Diego, CA MSA	681	1,133	6.0	6.8
Raleigh—Durham—Chapel Hill, NC MSA	417	652	3.7	3.9
Seattle—Tacoma—Bremerton, WA CMSA	504	730	4.4	4.4
New York—north New Jersey—Long Island NY—NJ—CT—PA CMSA	1,383	1,837	12.1	11.1
Philadelphia—Wilmington—Atlantic City PA—NJ—DE—MD CMSA	560	804	4.9	4.9
Los Angeles—Riverside—Orange County, CA CMSA	595	837	5.2	5.0
Washington—Baltimore, DC—MD—VA—WV CMSA	953	1,330	8.4	8.0
Total NIH awards to top 100 cities in the United States	11,410	16,574	100.0	100.0

Source: NIH, Office of Extramural Research: http://grants1.nih.gov/grants/award/HistoricRankInfo.cfm

It is also significant that the only two hospitals among the top 50 organizations are located in the heart of Boston. In 2005 116 hospitals throughout the United States were given awards. The top five lay in close proximity to one another in the center of Boston. These five — MGH ($287 million in NIH awards), B&W ($253 million), Beth Israel Deaconess Medical Center ($123 million), Dana-Farber Cancer Institute ($117 million), and Children's Hospital ($103 million) — received $883 million, or *52 percent* of the $1,709 million given to all hospitals in the United States. Of this amount, $1,604 million was for research, as distinct from fellowships, training grants, or R&D contracts.

The other Massachusetts hospitals that received NIH funding in 2005 were (with the amount of funding and their ranking among US hospitals in parentheses): New England Medical Center Hospitals in Boston ($50 million, 10); Boston Medical Center in Boston ($39 million, 11); McLean Hospital in Belmont, next to Cambridge ($28 million, 14); Massachusetts Eye and Ear Infirmary in Boston ($16 million, 23); Hebrew Rehabilitation Center for the Aged in Roslindale, seven miles from Harvard Yard ($7.5 million, 29); Spaulding Rehabilitation Hospital in Boston ($1.6 million, 54); and Lahey Clinic affiliated with Tufts University in Burlington, 15 miles from Harvard Yard ($170,000, 104). These 12 Boston-area hospitals represented 10 percent of all hospitals that received NIH funding in 2005, but were allocated 60 percent of all the awards.

Table 3.4: Top fifty recipients in 2005 of NIH funding among organizations, and their rankings and funding levels in 1996, 1999, and 2002

	2005		2002		1999		1996		
Organization	**RANK**	**$m**	**RANK**	**$m**	**RANK**	**$m**	**RANK**	**$m**	**Location**
Johns Hopkins University	1	607	1	510	1	351	1	279	Baltimore MD
University of Pennsylvania	2	471	2	419	2	290	4	187	Philadelphia PA
University of Washington	3	462	3	406	3	279	3	212	Seattle WA
University of California San Francisco	4	452	4	365	4	256	2	213	San Francisco CA
Washington University	5	395	5	344	5	239	7	173	St. Louis MO
Duke University	6	391	11	277	13	173	11	143	Durham NC
University of Michigan	7	386	6	326	6	231	5	180	Ann Arbor MI
Univ. of California Los Angeles	8	386	7	317	10	201	9	157	Los Angeles CA
University of Pittsburgh	9	386	8	308	9	201	14	136	Pittsburgh PA
Yale University	10	337	10	290	7	229	6	175	New Haven CT
Columbia University	11	331	13	270	11	200	13	138	New York NY
SAIC-Frederick Inc.	12	328	9	294	17	158	20	114	Frederick MD
Harvard University	**13**	**321**	**12**	**273**	**8**	**217**	**8**	**167**	**Cambridge MA**
University of California San Diego	14	309	17	245	15	170	15	135	San Diego CA
Stanford University	15	306	16	248	12	191	10	153	Palo Alto CA
University of North Carolina Chapel Hill	16	297	14	264	14	171	12	140	Raleigh NC
Massachusetts General Hospital	**17**	**287**	**18**	**244**	**16**	**158**	**21**	**110**	**Boston MA**
Case Western Reserve University	18	279	23	204	18	157	17	124	Cleveland OH
Vanderbilt University	19	266	24	195	29	111	28	87	Nashville TN
University of Wisconsin Madison	20	257	19	228	22	149	18	122	Madison WI
Baylor College of Medicine	21	257	15	264	21	149	26	91	Houston TX
Brigham and Women's Hospital	**22**	**253**	**22**	**205**	**23**	**147**	**22**	**100**	**Boston MA**
University of Alabama at Birmingham	23	229	21	212	20	151	19	118	Birmingham AL
University of Minnesota	24	227	20	217	19	152	16	131	Minneapolis MN
Emory University	25	222	26	179	26	123	32	78	Atlanta GA
Scripps Research Institute	26	213	25	191	27	123	25	91	San Diego CA
Fred Hutchinson Cancer Research Center	27	209	28	167	24	135	33	78	Seattle WA
University of Chicago	28	195	35	143	25	126	27	89	Chicago IL
Cornell University	29	193	30	162	31	111	23	94	Ithaca NY
Univ. of Colorado Denver/HSC Aurora	30	182	27	168	32	107	30	83	Aurora CO
University of Southern California	31	182	32	152	30	111	24	92	Los Angeles CA
Univ. of Baltimore Maryland Prof. School	32	182	44	126	44	81	42	63	Baltimore MD
Oregon Health Sciences University	33	175	33	151	34	103	133	14	Portland OR
Mount Sinai School of Medicine of NYU	34	174	36	142	37	98	43	62	New York NY
Massachusetts Institute of Technology	**35**	**172**	**63**	**87**	**54**	**70**	**47**	**59**	**Cambridge MA**
Univ. of Texas SW Medical Center/Dallas	36	171	29	162	35	102	31	83	Dallas TX
Northwestern University	37	168	41	131	38	98	38	68	Evanston IL
University of Iowa	38	166	31	158	28	115	29	83	Iowa City IA
Mayo Clinic Rochester	39	163	40	134	45	81	45	61	Rochester NY
University of Rochester	40	162	37	136	41	87	36	71	Rochester NY
Yeshiva University	41	156	39	134	36	101	34	77	New York NY
Boston University	**42**	**155**	**34**	**147**	**33**	**104**	**37**	**70**	**Boston MA**
Univ. of Texas Anderson Cancer Center	43	153	46	112	46	77	40	64	Houston TX
University of Virginia	44	153	38	136	42	86	46	59	Charlottesville VA
New York University	45	152	43	126	39	93	35	71	New York NY
University of California Davis	46	142	47	110	48	73	49	57	Sacramento CA
Indiana University	47	137	45	122	40	92	39	67	Bloomington IN
University of Illinois at Chicago	48	134	48	109	55	68	66	44	Chicago IL
University of Utah	49	127	42	128	43	83	44	62	Salt Lake City UT
University of California Irvine	50	126	55	96	58	65	69	43	Irvine CA

Note: Boston area organizations in bold type

Source: NIH, Office of Extramural Research: http://grants1.nih.gov/grants/award/HistoricRankInfo.cfm

The dominance of Boston hospitals as recipients of NIH funding is, moreover, nothing new. The same five Boston hospitals that topped the list in 2005 have been *the top five on the NIH hospital awards list for every year since 1989* and within the top seven back to at least 1985 (the first year for which the NIH provides this ranking). In 1985 the Boston five reaped 40 percent of the total NIH funding to hospitals; in 1989 42 percent.

These hospitals are surrounded by, and interspersed among, leading research universities, research institutes, and, increasingly biotech companies. No place in the world surpasses Boston in the geographic density, scientific quality, and financial resources of a network of organizations — universities, hospitals, research institutes and firms — engaged in the generation of new biotech knowledge and its transformation into commercial products (see Owen-Smith and Powell 2004). Within a three-mile stretch between B&W and MGH in the center of Boston, one finds Harvard Medical School, Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Massachusetts Eye and Ear Infirmary, Tufts-New England Medical Center and the BU School of Medicine, all of which have played important roles in the development of Boston's biotech capabilities. About one mile from MGH across the Charles River in Cambridge is MIT, and right next to it in the Kendall Square area, the Whitehead Institute for Biomedical Research as well as the global headquarters of Genzyme and Biogen Idec.

Also in Kendall Square are the East Coast research labs of Amgen, with 135 employees in mid-2006 and a planned expansion to 200 by the end of the year. Located adjacent to MIT are the world research headquarters of the Swiss pharmaceutical company, Novartis, which in 2005 became the sole owner of Chiron, at the time the eighth largest independent biotech company. Another representative of big pharma that has an important presence in Cambridge is Wyeth. In 1996, when the company was known as American Home Products, it acquired Genetics Institute, a leading Cambridge-based biotech company. Other important Cambridge-based biomedical companies include Millennium Pharmaceuticals, Vertex Pharmaceuticals, Alkermes, ImmunoGen, and Transkaryotic Therapies (which in 2005 was acquired by the British company, Shire).

An article that appeared in the Newark Star-Ledger in August 2006, entitled "Mass. Exodus?", bemoaned the migration of biopharmaceutical jobs from New Jersey to the Boston area (May 2006). To emphasize the attraction of Boston, the article quoted a one-time migrant from New Jersey to Massachusetts, Vertex CEO, Joshua Boger: "There is an unapproachable nexus of resources on the medical and university side in the Cambridge area." Boger had been Senior Director of Basic Chemistry at Merck Sharp & Dohme in Rahway, New Jersey before founding Vertex in Cambridge in 1989.[19]

The Star-Ledger article went on to list the top 20 employers in Cambridge (population: 101,000) in 2006, as shown in Table 3.5. Along with three universities, three governments (local, state, federal), one healthcare provider and one hospital, one R&D lab that does biomedical engineering, and one medical diagnostics testing company that does clinical trials and gene-based testing, the top 20 list of employers includes six biopharmaceutical drug companies.

The Greater Boston biotech district spreads beyond the cities of Boston and Cambridge in three directions. Twenty miles to the south, in Randolph, one finds Serono Laboratories, formerly the US headquarters of Swiss-based Serono SA, which in January 2007 was acquired by the German pharmaceutical and chemical company Merck KGaA. Thirty-miles to the north, in Andover, Wyeth has a major biotech manufacturing plant that came with its 1996 acquisition of Genetics Institute and that now employs about 2,000 people. Thirty-five miles to the west along the Massachusetts Turnpike, passing the

many new biotech firms that have been springing up between Boston and Worcester, is the University of Massachusetts Medical Center, heavily involved in biomedical research; in 2005 it ranked 58th among NIH funding recipients with $115 million.

Table 3.5: Top 20 employers in Cambridge, Massachusetts, 2006

Name	Number of Employees	Organization Type
Harvard University	10,282	University
Massachusetts Institute of Technology	7,026	University
City of Cambridge	3,251	Government
Cambridge Health Alliance	1,775	Healthcare provider
Biogen Idec	1,767	Biopharmaceutical drugs
US Government	1,656	Government
Mount Auburn Hospital	1,379	Hospital
Millennium Pharmaceuticals	1,339	Biopharmaceutical drugs
Genzyme	1,231	Biopharmaceutical drugs
Draper Laboratory	1,052	R&D lab, including biomedical engineering
Novartis Institute for Biomedical Research	960	Biopharmaceutical drugs
Wyeth Research	780	Biopharmaceutical drugs
EF International	703	Language school
Commonwealth of Massachusetts	692	Government
Quest Diagnostics	649	Diagnostic testing, including biomedical
Camp, Dresser, and McKee	631	Engineering
Whole Foods	612	Supermarket
Lesley University	569	University
Vertex Pharmaceuticals	539	Biopharmaceutical drugs
Shaws Supermarkets/Star Market	510	Supermarket

Note: Biopharmaceutical drug companies in bold
Source: May 2006

Data on the value of research and development alliances in pharmaceutical/biotechnology by metropolitan region suggest the importance of these networks in the Boston area (see Table 3.6). In the period 1996-2001 the known value of R&D alliances in the nine leading biotech centers totaled $9.8 billion. Prior to 1990 the Boston area led in the value of these alliances, just ahead of the San Francisco area. In the first half of the 1990s, the San Francisco area surged ahead, while the San Diego area also became an important biotech center, and surpassed the Boston area in the value of alliances. In 1996-2001, however, the Boston area re-emerged with a vengeance as the leader in R&D alliances in biotech. With over 38 percent of the value of these alliances, the Boston area surpassed the *combined* 33 percent share of the San Francisco and San Diego areas.[20]

Boston's lead in biotech also shows up in the employment numbers. In 1997 the Boston area led the San Francisco area in the number of people employed in life sciences R&D by 11,249 to 9,674 (Cortright and Mayer 2002, 26). Updated using the 2002 census data, Boston led San Francisco by 15,863 to 14,756. By this time the surging San Diego area, which had employed 7,487 people in life sciences R&D in 1997 had, with 14,754 employed, virtually caught up with San Francisco.[21]

What does San Francisco have more of than Boston that is relevant to the growth of their respective biotech industries? The answer, as Table 3.7 shows, is venture capital. In the two six-year periods, 1995-2000 and 2001-2006, the Boston area

Table 3.6: Value of research and development alliances in pharmaceuticals/biotech by metropolitan area, prior to 1990, 1990-1995, 1996-2001

	$ millions			percent of period total*		
Metropolitan Area	Pre-1990	1990-1995	1996-2001	Pre-1990	1990-1995	1996-2001
Boston—Worcester—Lawrence, MA—NH—ME—CT CMSA	254	882	3,924	30.6	17.5	38.3
San Francisco—Oakland—San Jose, CA CMSA	230	1,357	1,205	27.7	27.0	11.8
San Diego, CA MSA	46	1,022	1,615	5.5	20.3	15.7
Raleigh—Durham—Chapel Hill, NC MSA	0	33	192	0.0	0.7	1.9
Seattle—Tacoma—Bremerton, WA CMSA	68	45	579	8.2	0.9	5.6
New York—Northern New Jersey—Long Island NY—NJ—CT—PA CMSA	149	724	1,729	18.0	14.4	16.9
Philadelphia—Wilmington—Atlantic City PA—NJ—DE—MD CMSA	5	85	127	0.6	1.7	1.2
Los Angeles—Riverside—Orange County, CA CMSA	0	73	69	0.0	1.5	0.7
Washington—Baltimore, DC—MD—VA—WV CMSA	17	260	358	2.1	5.2	3.5
Total value of R&D alliances for nine leading metropolitan centers	769	4,481	9,798	92.7	89.2	95.6

* Not all metropolitan centers in the United States with biotech R&D alliances are shown
Source: Cortright and Mayer 2002

was second to the San Francisco area, but well ahead of every other metropolitan area, in the number and value of biotech deals. In 2001-2006, the number of deals in the Boston area was 78 percent of that in the San Francisco area, and the value of investments 71 percent.

Columns A and D in Table 3.7 show the distribution of the venture-backed deals and investments across the top nine metropolitan centers of the biotech industry for 1995-2000 and 2001-2006. In both periods Boston ranked second behind San Francisco, but ahead of San Diego, in deals as well as investments. The percentages in columns A and D can be compared with those in columns B and E respectively to see the extent to which, relative to the distribution of all venture-backed deals and investments across the metropolitan areas in the two periods, biotech deals and investments were more or less concentrated in particular areas. In the San Diego, Raleigh, and Philadelphia areas deals and investments are heavily weighted toward biotech in both periods, while in the San Francisco area biotech is underrepresented in the proportion of all deals in the United States but somewhat overrepresented in the proportion of investments. In the Boston area both deals and investments are skewed toward biotech, although not to the same extent as in the San Diego and Raleigh areas.

Columns C and F in Table 3.7 show the proportions of deals and investments within specific metropolitan areas that are biotech. For the United States as a whole, the proportion of all venture-backed deals that were biotech increased from 6 percent in 1995-2000 to 10 percent in 2001-2006, while the proportion of investments that were biotech increased from 4 percent to 9 percent. All nine major metropolitan biotech centers had appreciable increases in the proportions of their venture-backed deals and investments that were biotech. In the Boston area, the leading sector for venture-backed investment in 2001-2006 was software (21.6 percent of Boston's total), followed by biotech (15.2 percent), semiconductors (8.2 percent), media and entertainment (8.1 percent), industrial/energy (6.0 percent), and medical devices and equipment (5.9 percent).

Cortright and Mayer (2002) also used market capitalization of publicly traded biotech firms as a measure of regional advantage in the industry. On this measure, as in venture capital, the San Francisco area greatly surpassed the Boston area. Cortright and Mayer (2002, 30) showed that in 2001 there were 58 publicly traded companies in the Boston CMSA with a

Table 3.7: Venture capital deals and investments in major metropolitan areas of the United States, 1995-2000 and 2001-2006

1995-2000	VC Deals				VC Investments				
Metropolitan Area	No. of biotech deals	A %	B %	C %	Biotech investment $m	D %	E %	F %	Value ($m) per biotech deal
Boston—Worcester—Lawrence, MA—NH—ME—CT CMSA	314	17.5	11.1	9.8	2,135	16.5	8.5	7.7	6.8
San Francisco—Oakland—San Jose, CA CMSA	369	20.6	27.9	4.6	3,277	25.4	24.0	4.2	8.9
San Diego, CA MSA	238	13.3	3.4	24.6	1,605	12.4	2.2	22.8	6.7
Raleigh—Durham—Chapel Hill, NC MSA	76	4.2	1.5	17.1	549	4.3	1.1	15.9	7.2
Seattle—Tacoma—Bremerton, WA CMSA	70	3.9	3.2	7.7	740	5.7	2.6	8.8	10.6
New York—Northern New Jersey—Long Island NY—NJ—CT—PA CMSA	154	8.6	10.4	5.2	1,356	10.5	12.0	3.5	8.8
Philadelphia—Wilmington—Atlantic City PA—NJ—DE—MD CMSA	150	8.4	2.7	19.5	835	6.5	2.3	11.3	5.6
Los Angeles—Riverside—Orange County, CA CMSA	70	3.9	6.5	3.7	476	3.7	6.6	2.2	6.8
Washington—Baltimore, DC—MD—VA—WV CMSA	63	3.5	4.6	4.7	347	2.7	5.9	1.8	5.5
Nine major research centers	1,504	83.9	71.2	7.3	11,322	87.7	65.1	5.4	7.5
US totals	1,792	100.0	100.0	6.2	12,910	100.0	100.0	4.0	7.2
2001-2006	VC Deals				VC Investments				
Metropolitan Area	No. of biotech deals	A %	B %	C %	Biotech investment $m	D %	E %	F %	Value ($m) per biotech deal
Boston—Worcester—Lawrence, MA—NH—ME—CT CMSA	409	16.2	12.7	12.5	4,855	17.6	10.0	15.2	11.9
San Francisco—Oakland—San Jose, CA CMSA	522	20.7	26.5	7.7	6,855	24.8	18.7	11.5	13.1
San Diego, CA MSA	312	12.4	3.8	31.9	3,534	12.8	2.9	38.3	11.3
Raleigh—Durham—Chapel Hill, NC MSA	119	4.7	1.7	27.5	1,103	4.0	1.1	33.0	9.3
Seattle—Tacoma—Bremerton, WA CMSA	90	3.6	3.4	10.4	861	3.1	1.9	14.1	9.6
New York—Northern New Jersey—Long Island NY—NJ—CT—PA CMSA	245	9.7	9.7	9.9	3,413	12.4	13.4	8.0	13.9
Philadelphia—Wilmington—Atlantic City PA—NJ—DE—MD CMSA	136	5.4	2.4	21.9	1,444	5.2	3.6	12.5	10.6
Los Angeles—Riverside—Orange County, CA CMSA	78	3.1	6.0	5.1	861	3.1	5.5	4.9	11.0
Washington—Baltimore, DC—MD—VA—WV CMSA	195	7.7	5.8	13.1	1,769	6.4	4.5	12.4	9.1
Nine major research centers	2,106	83.6	72.0	11.4	24,696	89.4	61.7	12.6	11.7
US totals	2,520	100.0	100.0	9.8	27,621	100.0	100.0	8.9	11.0

Column A =Venture-based biotech deals in a CMSA/MSA as a percent of all venture-backed biotech deals in the United States
Column B = Venture-based deals in all sectors in a CMSA/MSA as a percent of venture-backed deals in all sectors in the United States
Column C = Venture-backed biotech deals in a CMSA/MSA as a percent of all venture-backed deals in all sectors in that CMSA/MSA
Column D = Venture-based biotech investment in a CMSA/MSA as a percent of all venture-backed biotech investment in the United States
Column E = Venture-based investment in all sectors in a CMSA/MSA as a percent of venture-backed investment in all sectors in the United States
Column F = Venture-backed biotech investment in a CMSA/MSA as a percent of all venture-backed investment in all sectors in that CMSA/MSA
Note: Share is a percentage of the total value of venture capital investments made in the United States during the time period
This table updates and expands upon Table 11 in Cortright and Mayer 2002, 22.
Source: Price Waterhouse MoneyTree

total market capitalization of $52.8 billion, 90 companies in the San Francisco CMSA with a market capitalization of $82.7 billion, and 33 companies in the Los Angeles area with a market capitalization of $83.0 billion. The other metro areas were far behind these three; for example, San Diego had 33 publicly traded companies, the same as Los Angeles, but they had a combined market capitalization of only $24.7 billion. On a per company basis, there was virtually no difference in market capitalization between Boston and San Francisco. There was, however, a very big difference between these two on the one hand and the Los Angeles area on the other. Los Angeles had only 30 percent of the number of companies as San Francisco, but the average market capitalization of these companies was $2.5 billion; that is, more than 2.7 times that of Boston and San Francisco.

As can be seen in Table 3.8, these results stem from the fact that there was one company in each locale — Amgen in Los Angeles and Genentech in San Francisco — that had a market capitalization that accounted for practically the entire stock market value of biotech companies in the region! Note also the wide range of stock prices within any given year. In other

words, as a measure of regional advantage, market capitalization may not tell us much, especially when the industry concerned has a few companies that have very high market capitalizations and highly volatile stock prices. While the vast majority of companies in the biotech industry are unprofitable, in the 2000s a small number of companies have emerged as highly successful. As we have seen, some of them are based in the Boston area, and many others that are not based in Boston have important facilities and capabilities there. Let us, therefore, probe more deeply into the real foundations of Boston's biotech boom.

Table 3.8: Market capitalization* and variation in stock prices, selected biopharmaceutical companies, 2000-2006**

	2000	2001	2002	2003	2004	2005	2006
	Amgen						
High mkt. cap.	83,446	78,500	81,136	92,901	84,269	106,390	95,051
Low mkt. cap.	51,870	47,519	39,408	61,733	65,520	68,777	74,318
Stock price range	50.00-80.44	45.44-75.06	30.57-62.94	48.09-72.37	52.00-66.88	56.13-86.92	63.52-81.24
	Biogen IDEC						
High mkt. cap.	19,069	11,135	8,750	13,927	22,342	23,395	18,050
Low mkt. cap.	6,079	3,622	1,657	9,185	12,002	11,089	13,780
Stock price range	47.13-129.00	48.29-75.00	28.43-58.30	27.80-42.15	36.60-68.13	33.18-70.00	40.24-52.71
	Chiron						
High mkt. cap.	13,460	10,991	9,186	10,679	10,706	8,861	na
Low mkt. cap.	6,265	6,698	4,929	6,366	5,419	6,326	na
Stock price range	33.06-71.03	35.38-58.05	26.38-49.18	34.02-57.07	29.00-57.29	32.18-45.07	na
	Genentech						
High mkt. cap.	128,742	88,757	56,563	100,068	71,466	105,582	99,918
Low mkt. cap.	44,403	40,141	25,743	33,090	42,932	46,258	79,359
Stock price range	42.25-122.50	37.99-84.00	25.10-55.15	31.53-95.35	41.00-68.25	43.90-100.20	75.58-95.16
	Genzyme						
High mkt. cap.	19,813	13,637	12,571	11,781	14,727	20,175	19,848
Low mkt. cap.	7,579	7,318	3,358	6,390	10,128	14,298	14,395
Stock price range	39.69-103.75	34.34-64.00	15.64-58.55	25.45-52.45	40.67-59.14	55.15-77.82	54.64-75.34

* Market capitalization in millions of dollars
** Stock prices are high and low prices in dollars, adjusted for stock splits
Source: Yahoo! Finance

4. Orphan Drugs

On January 4, 1983, President Ronald Reagan signed the Orphan Drug Act. Since that time, the Orphan Drug Act has provided companies in the biomedical field with a number of incentives to invest in the development of drugs for genetic and rare diseases, and hence for markets in which ostensibly prospective revenues were too small to warrant such investment without government assistance. The Orphan Drug Act with its subsequent amendments provides drug companies with five types of services, subsidies, and protections (see Milne et al. 2002).

a. The Office of Orphan Product Development (OOPD), within the Food and Drug Administration (FDA), provides protocol assistance concerning the drug review process and information about the types of orphan drugs that might be developed.

b. OOPD awards grants "to support the clinical development of products for use in rare diseases or conditions where no current therapy exists or where the product will improve the existing therapy".[22] Through 2006 a total of 382 grants were made, resulting in the market approval of 40 drugs (13 percent of the total orphan drugs approved from 1983 through 2006). In fiscal 2007 it is estimated that, under the grant program, $10.0 million will fund noncompeting continuation awards and $4.2 million will be available for 10 to 12 new awards. The amount of a grant can be up to $200,000 (phase 1 clinical trials) or $350,000 (phase 2 and 3 clinical trials) per year for up to 3 years.

c. An orphan designation exempts a drug from FDA user fees that, as of October 2006, were $896,200 per drug requiring clinical trials plus $49,500 if and when the drug is approved.[23]

d. A company can take tax credits for up to 50 percent of the clinical development costs for an orphan drug designation. Until 1996 the credit had to be taken in the year in which the expenses were incurred, thus undermining the incentive of the tax credit for profitless companies. In 1996 Congress allowed the credit to be carried forward 15 years or backward 3 years, and in 1997 Congress made this change permanent.

e. A company that gains FDA market approval for an orphan drug has seven years of market exclusivity to reap the returns on the drug, free of competition. The main exceptions to this rule occur if another company develops what the FDA considers to be a superior drug for the same indication or if the company with market approval fails to keep up with the demand for the drug.

An orphan drug may or may not be covered by a patent. In its original formulation in 1983, the Act only covered drugs that were not patentable, but an amendment to the Act in 1985 made patented drugs potentially eligible for Orphan Drug benefits as well. While the duration of a patent is for 20 years and market exclusivity under the Orphan Drug Act is only for seven, the latter becomes effective once a drug has already been approved by the FDA for sale while, given the typically long duration of the drug development process, a patent may well be close to expiration by the time a drug is ready to be sold to the public.[24]

What makes a disease "rare"? The Act of 1983 defined a rare disease as one that "occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available…a drug…will be recovered from sales in the United States (Hogan 1995, 534). In an amendment to the Act in 1985, the definition was changed to either a disease that affects less than 200,000 people, or, if it affects more, a disease for which a drug cannot be developed profitably.[25] A company retains its right to market exclusivity even if the number of people with the disease becomes greater than 200,000 during the seven-year exclusivity period.

Moreover, a company can file for orphan drug designation for multiple indications of the same drug. For example, an orphan drug designation for "the treatment of chronic myelogenous leukemia" that Novartis obtained on January 31, 2001 was approved by the FDA, with market exclusivity, on May 10, 2001 under the tradename Gleevec. During the last five months of 2005 Novartis filed for five other orphan drug designations, and won approval for all five on October 19, 2006, each one under the tradename Gleevec. There may be long time-lags between an original orphan drug designation and subsequent ones for the same drug. For example, in 1988 the Danish pharmaceutical company, NovoNordisk, received an orphan drug designation for "the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor

VIII or Factor IX", which was approved by the FDA in 1999 and marketed under the tradename NovoSeven. In 2004 NovoNordisk filed for (fittingly) seven more indications for NovoSeven, of which three won FDA approval in 2005.[26]

In addition, a company that has received FDA approval for an orphan drug may subsequently find that it has one or more non-orphan applications. For example, Allergan filed for two orphan drug designations in 1984, one in 1986, and one in 1991 for a drug known as Botox. FDA approval for the two 1984 designations came in 1989 and for the 1986 designation in 2000. The indication approved in 2000 was for "treatment of cervical dystonia in adults to decrease the severity of abnormal head position and neck pain associated with cervical dystonia". But Allergan had also discovered that Botox could be used for "the temporary treatment of moderate to severe frown lines between the brows",[27] and had made the drug a leader in cosmetics. The company also markets Botox as a treatment for severe under arm sweating. Indeed, according to Allergan (2006 10-K, 6), Botox "is currently approved in 75 countries for up to 20 unique indications." In 2006 Botox generated $982 million in revenues (representing one-third of the company's product revenues), of which therapeutic uses were 57 percent and cosmetic uses 43 percent (Allergan 2006 10-K, 49).

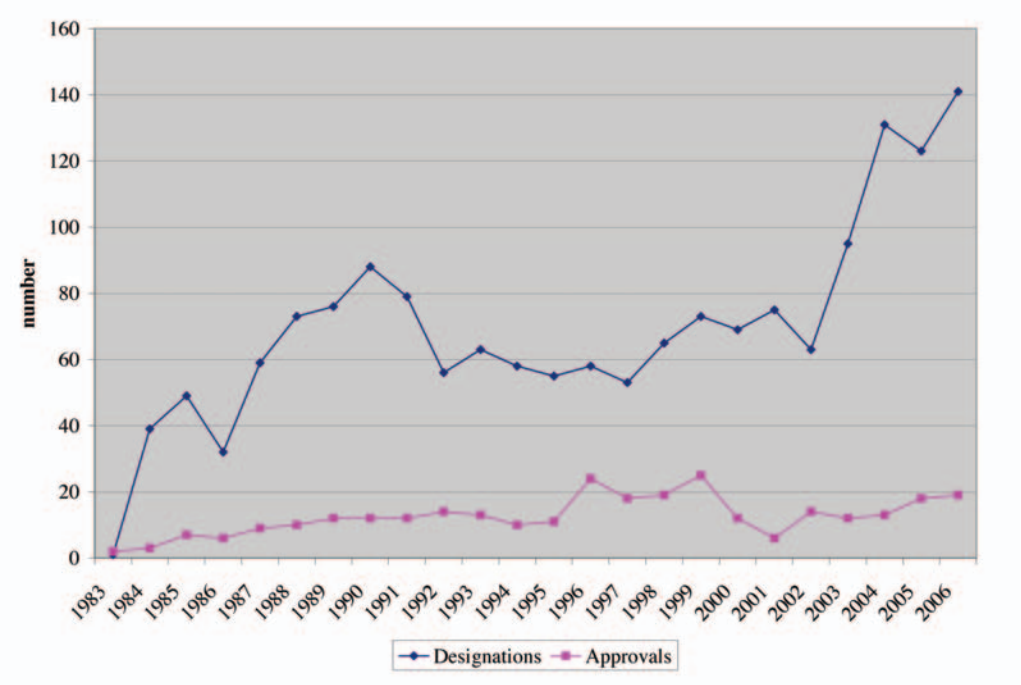
A brochure published in June 2005 by the Genetic and Rare Diseases Center of the NIH states that there are more than 7,000 rare diseases that afflict a total of 25 million Americans — or 1 in 12 of the total population and an average of about 3,600 people per rare disease (NHGRI and ORD 2005). The National Organization for Rare Disorders (NORD) rare disease database contains reports on 1,597 rare diseases.[28] Rare diseases are often genetic, and, especially given that its enactment coincided with the first wave of biotech startups, the Orphan Drug Act has been of particular importance to small biotech companies. One role that NORD has played has been to encourage large pharmaceutical companies that have been reluctant to use their proprietary knowledge to develop specific orphan drugs to license that knowledge to smaller companies (Meyers 2000).

Since the passage of the Orphan Drug Act in 1983, biotechnology and pharmaceutical companies have displayed a substantial interest in making use of it. From 1983 through 2006, there were a total of 1,694 orphan drug designations, of which 301 were approved by the FDA and, under the Orphan Drug Act, granted seven-year market exclusivity. As shown in Figure 4.1, the annual number of designations climbed in the 1980s to reach a local peak of 89 in 1990 before declining to an average of 57 per year in 1992-1997. In 1998-2002, the annual average was 69, still below the previous peak period of 1988-1991 when the annual number of designations averaged 79. In 2003-2006, however, the annual numbers of designations exploded, reaching a record 141 in 2006. The annual number of approvals has been much steadier, with a peak of 21.5 per year on average in 1996-1999. In the 2000s through 2006, the number of approvals averaged over 13 per year.

Table 4.1 shows the number of orphan drug designations and approvals of companies that as of the end of 2006 had control over at least 15 designations, including designations obtained by companies that subsequently were wholly acquired. The fifteen companies listed in Table 4.1 accounted for 25 percent of the 1,674 designations and 41 percent of the 301 approvals from 1983 through 2006. Among these companies are many of the world's largest pharmaceutical companies such as Johnson & Johnson, Novartis, GlaxoSmithKline, Bayer Schering, and Pfizer, as well as many of the leading independent biotech companies including Amgen, Genzyme, Biogen Idec, Genentech, and MedImmune.

Have orphan drugs been important to the development of the US biotech industry? The answer to this question depends on who and what you read. In surveying the literature on the biotech industry written by business academics and indus-

Figure 4.1: Number of orphan drug designations and approvals per year, 1983-2006



Source: FDA 2007

try professionals, one gets the distinct impression that the Orphan Drug Act has had little, if any, role to play in the evolution of the industry. Here are but three examples of such a perspective, all of them drawn from high-quality publications written by people who have a deep knowledge of the US biotech industry.

1. *Cynthia Robbins-Roth, From Alchemy to IPO: The Business of Biotechnology, Perseus Publishing, 2000.*

The jacket of the book describes the author as "the founder of BioVenture Consultants, which provides strategic planning and technical/business assessment to the biotech industry." The BioVenture Consultants website[29] informs the reader that she has been involved in the biotech industry since 1981, and that she "holds a Ph.D. in Biochemistry from the University of Texas Medical Branch, completed post-doctoral work in its Microbiology Department, and was a research scientist within the Immunology and Protein Biochemistry groups at Genentech, Inc. She then joined the Business Development group at California Biotechnology Inc. (now Scios/J&J)." From Alchemy to IPO, published in 2000, does not list "orphan drugs" or the Orphan Drug Act in the index. Nor is the Orphan Drug Act mentioned in a five-page "Biotech Timeline" that highlights key events in the history of the industry from 1866 to 1998. Robbins-Roth (2000: 45-46) does mention "orphan drugs" in a discussion of Genzyme's development of Ceredase and then Cerezyme to treat Gaucher's disease: "The small number of patients meant that big pharma was not interested in developing 'orphan' products to treat this fatal disease. But Genzyme, with its expertise in enzymes, was confident that it could find a way to manufacture enough replacement enzyme to treat these patients… Genzyme proved that a profitable business could be built around these so-called orphan drug indications. The company reported Ceredase/Cerezyme revenues of $126 million in 1993, which grew to $400 million in 1998."

Table 4.1: Orphan drugs designations and approvals, companies with 15 or more designations, 1983-2006, as of December 31, 2006

Company	DES	APP	Tradenames
Johnson&Johnson (including ALZA, Centocor, R. W. Johnson Pharmaceutical Research Institute, Scios, Scios Nova, Tibotec)	44	5	*Leustatin Injection, Remicade (2), Elmiron, Doxil*
Novartis (including Sandoz and Chiron)	40	17	*Cibacalcin, Lamprene, Zometa/Zabel, Gleevec (6), Simulect, Sandostatin LAR (3), Exjade, Betaseron, Proleukin (2)*
GlaxoSmithKline (including Burroughs Wellcome, Glaxo Wellcome, and SmithKline Beecham)	40	17	*Digibind, Retrovir (2), Exosurf Neonatal for Intratracheal Suspension (2,) Alkeran For Injection, Mepron (2), Flolan (2), Lamictal, Bexxar, Arranon, Triostat, Halfan, Albenza (2)*
Bayer Schering (including Berlex)	40	11	*Intron A, Rebetol, Betaseron, Fludara, Betapace, Prolastin, Thrombate III, Kogenate, Gamimune N, Trasylol, Nexavar*
Pfizer (including Pharmacia, Pharmacia & Upjohn, G. D. Searle, Sugen, Upjohn, Warner-Lambert)	39	9	*Zinecard, Genotropin (3), Aromasin, ATnativ, Ellence, Cyklokapron, Cerebyx*
Amgen (including Immunex)	28	12	*Epogen (2), Neupogen (4), Sensipar, Leucovorin calcium (2), Leukine (2), Enbrel*
Genzyme (including ILEX Oncology and Peptimmune)	27	7	*Ceredase, Cerezyme, Thyrogen, Campath, Fabrazyme, Clolar, Myozyme*
Roche (including Behringer Mannheim and Hoffmann-Laroche)	25	7	*Roferon-A (2), Lariam (2), Hivid, Vesanoid, Zenapax*
Biogen Idec	24	2	*Zevalin, Avonex*
Genentech	22	8	*Protropin, Nutropin (4), Nutropin Depot, Pulmozyme, Rituxan*
Merck Serono	20	10	*Novantrone (3), Metrodin, Serostim, Geref, Gonal-F, Zorbtive, Luveris, Saizen*
MedImmune	19	5	*Respigam, Hexalen, Neutrexin, Ethyol (2)*
Bristol-Myers-Squibb	17	8	*Sprycel (2), Ifex, Vumon for injection, Megace, Blenoxane, Taxol, Droxia*
Immunomedics	17	0	
Novo Nordisk	15	5	*Norditropin, NovoSeven (4)*

DES=designations
APP=approvals
Note: Data on designations and approval for each company are as of the end of 2006, and include designations and approvals in the name of firms that were subsequently wholly acquired by the company.
Source: FDA 2007

In a very informative book, the reader is not informed about what a "so-called orphan drug" is, or that, under the Orphan Drug Act, Genzyme was eligible for tax credits to develop the drug and received seven-year market exclusivity to generate revenues from it. Nor does Robbins-Roth indicate the proportion of orphan drugs among the 77 drugs listed in an appendix to her book as "Biotechnology Derived Products on the Market" at the end of the 1990s. Comparing her list with the FDA's list of approved orphan drugs, we found that 42 of the 77 are in fact drugs that that the FDA had approved for at least one orphan indication.

If Robbins-Roth chose to downplay the importance of orphan drugs in her 2000 book, she explicitly addressed the issues that they raise about product pricing and company profits in a May 2006 article entitled "Orphans in the storm" (Robbins-Roth 2006). Indeed, it is none other than Genzyme that is at the eye of the storm. As she writes:

> Genzyme's orphan strategy has generated jealousy among its biopharma brethren for a decade. A worldwide patient population of 4,500, some of whom get their drug through charities and other Genzyme-supported efforts, generated Cerezyme 2005 sales of $932 million — very close

> to that blockbuster $1 billion to which all aspire. Genzyme's other orphan product, aimed at 1,700 Fabry's disease patients, brought in $305 million last year. Genzyme's total 2005 revenue was $2.7 billion, with net earnings of $441.5 million, gross margins of 78 percent, and a $14 billion market cap.

Robbins-Roth quotes Henri Termeer, Genzyme's long-time CEO, in his defense of the price tags on orphan drugs:

> These therapies are expensive, and society has the right to ask questions. We explained for 15 years how the cost came about — we provide global access to these products and charge the same price worldwide, or provide it free. Genzyme has not shied away from the debate. We invited in the federal Office of Technology Assessment and journalists, and I testified at federal investigations. If you are not willing to have these open discussions, this will be a very tough business.

Robbins-Roth concludes the article with, first, the observation that "[w]ith the NIH announcement of a five-year, $71 million orphan disease clinical program, more companies may be considering following the Genzyme model", and, then, the warning: "Just be ready to weather the inevitable storm."

2. Ernst & Young, Beyond Borders: Global Biotechnology Report 2006 (20th anniversary edition), EYGM Limited, 2006.

What storm? Ernst & Young's glossy, yet fact-filled, 95-page 2006 report on the biotech industry is the twentieth such annual report that the company has issued. This latest edition sees nothing but a rosy future for the biotech industry. "As the modern biotechnology industry turns 30," writes Donn Szaro (Ernst & Young 2006, 1), Ernst & Young's Leader, Global Biotechnology Sector,

> biotech companies are leveraging resources and competitive strengths to fill critical gaps and meet strategic needs. The sector is bringing together the various worlds we inhabit — the developing world and the developed word, the worlds of research and of commercial development, the world of science and the world of finance — to give us the vibrant *global* biotechnology industry of today.

Szaro goes on to tell his readers that "[g]overnments have played a role too, through supportive public policy that helped bridge crucial gaps. Laws like the U.S. Bayh-Dole Act and Prescription Drug User Fee Act (PDUFA) unshackled biotech companies, giving them incentives to innovate and enabling them to bring drugs to the clinic more quickly." What about government funding and subsidy such as the NIH and the Orphan Drug Act provide? Reading the Ernst & Young report, one would have little idea that such resources have played a persistently important role in the evolution of the industry. There is one passing reference to the $3 billion that the NIH allocated to the Human Genome Project from 1990 (Ernst & Young 2006, 13). Later in the report the NIH appears as one of 33 US government departments, centers, and institutes in a crowded graphic entitled, "Heavy regulation: Sample of U.S. federal agencies that regulate biotechnology companies" (Ernst & Young 2006, 38). There is no mention of the Orphan Drug Act anywhere in the text of the report itself, or in the "heavy regulation" graphic just mentioned. Only those readers who take the time to look closely at the publication's four-page fold-out "commemorative poster" entitled "The Evolution of Biotechnology" will be informed that in 1983 "U.S. Orphan Drug Act enacted".

3. *Gary P. Pisano, Science Business: The Promise, the Reality, and the Future of Biotech, Harvard Business School Press, 2006.*

Gary Pisano, a professor at Harvard Business School, has been studying the biotech industry for over two decades. The main point of this recent book is that, more than three decades since Herbert Boyer and Stanley Cohen developed the techniques of recombinant DNA, the industry as a whole is not profitable. The development of biotech drugs requires the integration of diverse capabilities in a cumulative learning process that can take 10-20 years with highly uncertain prospects for success. In a Harvard Business Review article, adapted from the book, Pisano (2006a, 114-115) argues that after 30 years "biotech still looks like an emerging sector":

> Despite the commercial success of companies such as Amgen and Genentech and the stunning growth in revenues for the industry as a whole, most biotechnology companies earn no profit. Nor are they significantly more productive at drug R&D than the much maligned behemoths of the pharmaceutical industry.

Pisano (2006b, 205-209) combines data for 293 US biotech companies that were publicly held in 2004 to generate totals for revenues and operating income for these companies for 1975 through 2004. In 2004 — the only year for which Pisano's data actually reflect the combined results of all of the publicly held US companies in the biotech industry[30] — combined revenues were $35.8 billion and operating income $2.5 billion. When Amgen's results are dropped from the totals, combined revenues fall to $25.2 billion with a combined loss from operations of $2.1 billion (Pisano 2006a, 119). Moreover, as Pisano (2006a, 119) points out, one can assume that the biotech companies in existence that remained privately held in 2004 were in general less profitable than those that were publicly held.

Given these characteristics of the industry, one would think that biotech would have had difficulty securing funding from the business sector. Yet as Pisano (2006b, ch. 8) shows, biotech has received substantial funding from both venture capital firms and the public stock markets. For the period 1978 through 2004, measured in 2004 dollars, venture capital invested $38 billion and the public equity markets $168 billion in US biotechnology companies. About two-thirds of the venture capital investment (measured in 2004 dollars) occurred after 1998, with 27 percent in 2000 and 2001 alone. About two-thirds of the stock market investment occurred after 1993, with most of that money flowing into the industry in the speculative boom of 1999-2000 (Pisano 2006b, 141). Professional Wall Street speculators with inside access to new issues snapped up IPO shares of biotech companies with the intention of flipping the stock to make a fast buck (or more accurately many millions of them) in a rising stock market. The only concern of the professional speculators was whether the stock market boom might be sustained for another day, week, or perhaps a month because of the existence of "greater fools" who would take the shares off their hands. Under these circumstances, stock-market investors were not concerned whether the companies whose shares they bought had well-designed strategies with the time horizons of 10 to 20 years generally required for commercial success.

Pisano (2006b, 140-142) does not mention the possibility that such speculative investment may have been responsible for a substantial proportion of the stock market funds that flowed into the biotech industry. Yet given the overall lack of profitability of the industry that he himself demonstrates, and, as we shall discuss in the conclusion, related arguments that he makes concerning the inappropriately short time horizons of investors, Pisano does not provide any good answers for why venture capital and stock markets have provided the biotech industry with such large amounts of investment funds.

It is only in the concluding chapter of the book, where he devotes a few pages to a discussion of "the institutions of basic science" that Pisano (2006b, 186) recognizes in a general way the centrality of government funding to the biotech industry:

> The institutions of basic science include academic research laboratories, government research institutes, and government funding of science. These institutions have played an important role in advancing the underlying sciences of biotechnology. It is hard to imagine what the life sciences would look like today without the National Institutes of Health, the University of California, Stanford, MIT, Columbia, University of Washington, Harvard, the Whitehead Institute, the Institute of Genomic Research, the Human Genome Project, the MRC Laboratory of Molecular Biology, dozens of academic medical centers, countless other governmental and academic laboratories around the world and journals such as *Science* and *Nature*.

While, as we have seen, Pisano calculates the cumulative flows of venture capital and stock market funds into the biotech industry for the period 1978-2004, he attempts no such parallel calculation for government funding, notwithstanding his "hard to imagine what the life sciences would be like" statement in the paragraph just quoted. In fact, from 1978 through 2004, NIH spending on life sciences research totaled $365 billion in 2004 dollars.[31] Moreover, unlike the venture capital and stock market investments, which have fluctuated widely from year to year, NIH funding has increased in nominal terms in every single year from 1970 to the present. The rate of increase in funding in real terms was particularly large in 1999-2003 when it averaged almost 12 percent per annum. It is safe to say, as indeed Pisano implies, that without NIH funding to create the indispensable knowledge base, venture capital and public equity funds would not have flowed into the biotech industry.

When these funds have flowed in, moreover, business investment has been able to count on the government and insurance companies to provide the *demand* for the products of the biotech industry if and when they receive FDA approval. Most orphan drugs are expensive. Even when the size of the market for a drug is small, the revenues can be substantial. To take some examples of leading therapeutic drugs, the average annual cost of Amgen's Epogen and Neupogen (for anemia) is $5,000 to $20,000; Genentech's Rituxan (for rheumatoid arthritis), $15,000-$20,000; Genzyme's Cerezyme (for Gaucher's disease), $150,000-$225,000; Biogen Idec's Avonex (for multiple sclerosis), $20,000-$24,000; Merck Serono's Rebif (for multiple sclerosis), $20,000-$24,000; Gilead Sciences' AmBisone (for AIDS), over $15,000; Novartis's Gleevec (for cancer), over $40,500; and Millennium's Velcade (for cancer), over $50,000 (see Caremark 2006, 25; Stern and Reissman 2006, 737).

Business investment has also been able to count on the Orphan Drug Act to provide companies with research subsidies for drugs that qualified for "orphan" status and market protection once these drugs obtained FDA approval. Even if the diseases that orphan drugs treat are rare, the numbers of designations and approvals of orphan drugs are not. Yet in this book Pisano never once mentions the Orphan Drug Act, or the financial support and market protection that it provides. The closest that he comes to even recognizing the underlying phenomenon is when he refers to "rare genetic disorders" in the following statement of the biotech drug successes of big pharma and independent companies:

> Big pharmaceutical companies launch many drugs that are incremental improvements over existing drugs (so-called "me-too" drugs). But they have also launched true breakthrough drugs, including protease inhibitors for AIDs (Merck), selective serotonin re-uptake inhibitors for depression (Lilly), Tamofaxin for breast cancer (Bristol-Myers-Squibb), and Gleevec for leukemia (Novartis). Biotech companies have clearly introduced a number of breakthrough drugs themselves, such as erythropoietin (Amgen) for life-threatening anemia, beta interferon for multiple sclerosis (Chiron, Biogen), a number of novel cancer treatments such as Herceptin (Genentech), and treatments for rare genetic disorders (Genzyme)." (Pisano 2006b, 124-125)

Of the big pharma drugs, Gleevec is, as has already been mentioned, an orphan drug. As for the "breakthrough drugs" of the biotech companies on Pisano's list, Amgen's Epogen, Chiron's Betaseron, Biogen's Avonex, Genentech's Herceptin, and Genzyme's Ceredase/Cerezyme are all orphan drugs.

Pisano (2006b, 127) goes on to show that for the period 1985-2004 Genzyme in particular had a very low cumulative R&D cost per new drug launched when compared with companies such as Amgen, Biogen Idec, Eli Lilly, Chiron, Merck, and Genentech.

> Some of the differences across firms may have to do with strategy. Genzyme's very low cost per new drug launched may be explained largely by its focus on developing drugs for rare genetic disorders (e.g. Gauchy's [sic], Fabry's). Because the treatment populations for these diseases are extremely small, clinical trials tend to be much smaller in scale (and thus less costly) than the typical clinical development program. However, one should not discount the possibility that by focusing on a very well-defined set of diseases (rare genetic diseases that result from a missing enzyme), Genzyme has been able to also develop and exploit unique organizational capabilities and specialized technological know-how

Genzyme spent $2.4 billion (2004 dollars) on R&D from 1987 through 2004, with its R&D spending increasing (in nominal dollars) from $392 million in 2004 to $503 million in 2005 and $565 million in 2006. By 2004 its annual revenues had reached $2.2 billion, and increased to $2.7 billion in 2005 and $3.2 billion in 2006. Genzyme's most successful product, Cerezyme, accounted for $839 million in revenues in 2004, $932 million in 2005, and $1,010 million in 2006. The company began producing this product as Ceredase in 1993, and in 1999 Ceredase/Cerezyme reached a peak of 62 percent of Genzyme's total revenues. In 2001 Cerezyme's market exclusivity under the Orphan Drug Act expired, but the company will continue to benefit from patent protection on its method of manufacturing Cerezyme until 2010 and on the composition of Cerezyme made by the process until 2013 (Genzyme 2006 10-K, 19). Genzyme has four other orphan drugs: Fabrazyme (2005 sales, $305 million), Thyrogen ($78 million), Thymoglobolin/Lymphoglobuline ($128), and Campath/Clolar ($29 million). Along with Cerezyme, these orphan drugs generated $1.6 billion in revenues in 2006, or 50 percent of Genzyme's total revenues.

In 2003, Genzyme's longtime CEO Henri Termeer declared: "The orphan drug law is one of the most effective laws ever passed in the United States" (Elias 2003). Genzyme's success has been built on orphan drugs, even if in the 2000s it is much less dependent on orphan drug revenues than it was in the past. Genzyme has important non-orphan drugs, most notably Renegal (2006 sales, $515 million) for renal disease. The company is also diversified into biosurgery products ($315 million) and diagnostic products ($104 million).

Yet it would be totally wrong to say (as both Robbins-Roth and Pisano imply) that Genzyme is the only large biotech company whose success has been built on orphan drugs. Table 4.2 shows the dependence on revenues from drugs that have had orphan status of the leading independent biotech companies. Note that (similar to the case of Botox outlined above) a portion of the revenues included in the "orphan drug" revenues in Table 4.2 are from non-orphan applications of drugs that have had orphan drug status. The point is that at formative periods in their histories, several leading biotech companies have achieved significant growth through the development and marketing of drugs with orphan status. As can be seen in the row labeled TOTAL 1 in Table 4.2, in 2005 orphan drugs represented 53 percent of the total revenues and 60 percent of the product revenues of the top 10 independent biotech companies.

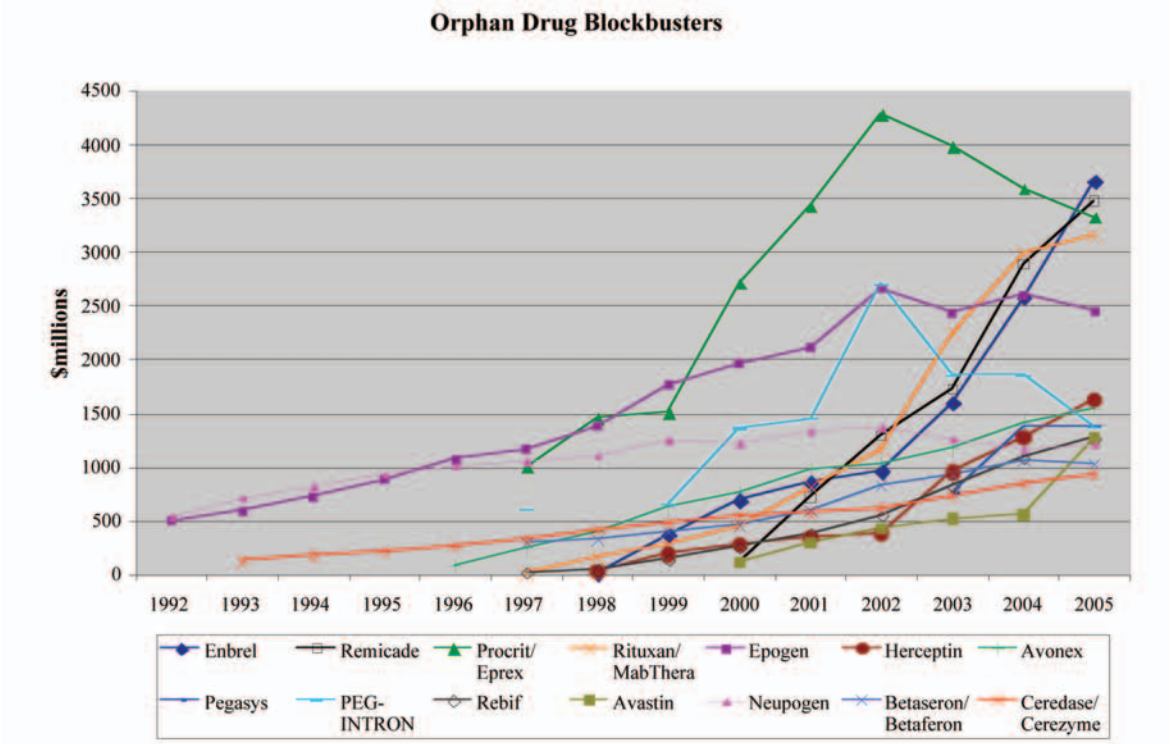
For leading companies such as Genentech, Biogen Idec, and Serono,[32] orphan drugs are more than 90 percent of their product revenues. As for Amgen, by far the leader among the independent biotech companies, it must be recognized that its two most recent blockbuster drugs, Aranesp with 2006 revenues of $4.1 billion and Neulasta with 2006 revenues of

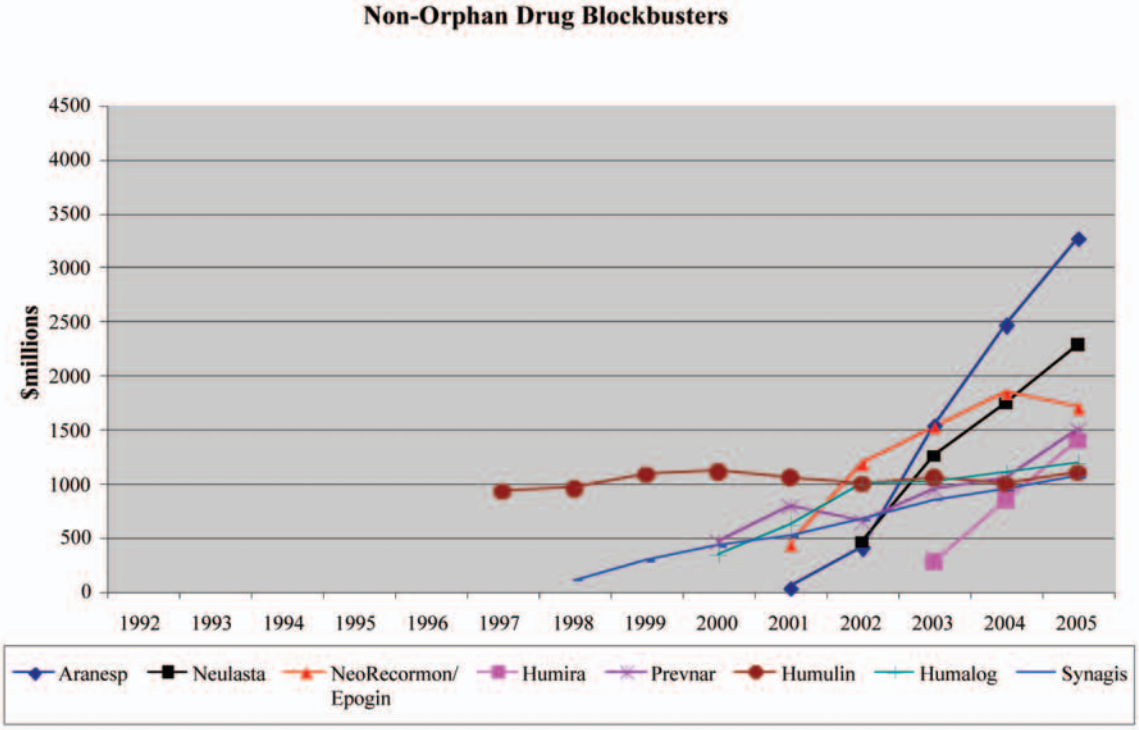
Table 4.2: Orphan drugs as a percentage of revenues of leading biotech companies, 2005 and 2006

	Total revenues, $m.		Product revenues, $m		Orphan drug revenues, $m		Orphan drug revenues as % of total revenues		Orphan drug revenues as % of product revenues	
	2006	2005	2006	2005	2006	2005	2006	2005	2006	2005
Amgen	14,268	12,430	13,858	12,022	6,603	6,244	46	50	48	52
Genentech	9,284	6,633	7,189	5,162	6,030	4,762	65	72	84	92
Genzyme	3,187	2,735	2,887	2,454	1,617	1,459	51	53	56	59
Biogen Idec	2,683	2,423	1,781	1,617	1,725	1,564	64	65	97	97
Serono		2,339		2,339		2,144		92		92
Gilead Sciences	3,026	2,028	2,588	1,809	223	221	7	11	9	12
Chiron		1,920		1,422		498		26		35
Cephalon	1,764	1,212	1,720	1,157	735	513	42	42	43	44
MedImmune	1,277	1,244		1,221		95		8		8
Millennium	487	558	469	559	221	314	45	56	47	56
TOTAL 1	35,796	33,522	31,963	29,762	17,241	17,814	48	53	54	60
TOTAL 2*	35,796	33,522	31,963	29,762	24,072	21,818	67	65	76	73

Orphan drug revenues by company and tradename (2005 and 2006 sales in $millions in parentheses, except Serono and Chiron for which data are for 2005 sales only):
Amgen: Enbrel (2,573; 2,879), Epogen (2,455; 2,511), Neupogen (1,216; 1,213)
Genentech: Rituxan (1,831; 2,071), Avastin (1,133; 1,746), Herception (747; 1,234), Nutropin (370; 378), Tarceva (275; 402), Activase (218; 243) Pulmozyne (187; 199)
Genzyme: Cerezyme (932; 1,007), Fabrazyme (305; 359), Thyrogen (78; 94), Thymoglobolin (86; 109), Campath/Clolar (58; 48)
Biogen Idec: Avonex (1,543; 1,707), Zevalin (21; 18)
Serono: Rebif (1,270), Gonal-f (547), Sazien (207), Serostim (70), Novantrone (23), Metrodin HP (15), Luveris (11), Zorbtive (1)
Gilead Sciences: AmBisome (221; 223)
Chiron: Tobi (233), Betaseron (142), Proleukin (124)
Cephalon: Provigil (513; 735)
MedImmune: Ethyol (95; 87)
Millennium: Velcade (249; 327) (includes revenues from strategic alliances and royalties)
Note: Data for 2006 not yet available for Serono (now Merck Serono)
* Total 2 treats Amgen's Aranesp (2,104; 4,121) and Neulasta (1,900; 2,710) as orphan drugs given that they are low-dose derivatives of Epogen and Neupogen respectively.
Sources: Company SEC filings and annual reports

Figure 4.2: Best-selling biotech drugs, orphan and non-orphan, 1992-2005





Source: http://www.i-s-b.org/business/rec_sales.htm

$2.7 billion, are second-generation low-dosage derivatives of Epogen and Neupogen respectively. If we treat these two drugs as products with "orphan" origins, then in 2006 orphan drugs were 94 percent of Amgen's total revenues and 97 percent of its product revenues. With Aranesp and Neulasta included, as shown in TOTAL 2 in Table 4.2, in 2005 orphan drugs represented 65 percent of the total revenues and 73 percent of the product revenues of the top 10 biopharmaceutical companies.

More generally, the importance of orphan drugs in the growth of the biotech industry can be seen by comparing the timing and growth of revenues for orphan and non-orphan blockbusters, as is done in the two panels of Figure 4.2. The first panel displays the revenue growth of the leading biotech drugs that are orphan drugs while the second panel shows the leading biotech drugs that are not orphan drugs. Comparing the two panels, orphan drugs are more numerous, their revenue growth began earlier, and many of them have greater 2005 sales than the leading non-orphan drugs. If, as was argued above, we were to transfer Amgen's Aranesp and Neulasta to the orphan drug panel, the centrality of orphan drugs in driving the development of the biotech industry would become even more apparent.

Much research and writing on the biopharmaceutical industry has focused on the independent biotech companies as if they constituted virtually all of the industry. As we discussed in Part 3, the emergence of dedicated biotech firms from the beginning of the industry some three decades ago has been its most distinctive organizational characteristic. Yet through research contracts, acquisitions of dedicated biotech firms, and, in some cases, in-house development, the big pharmaceutical companies have also become major players in the biotech industry.

We have already seen an indication of the important role of big pharma in biotech in Table 4.1 above that shows that, taking into account their wholly owned acquisitions, Johnson & Johnson, Novartis, GlaxoSmithKline (GSK), Bayer Schering, and Pfizer are the five leading companies in filing for orphan drug designations while Novartis and GSK are the leaders in approvals. Now that we have seen the importance of orphan drugs to the growth of the biotech industry as a whole, the leadership of big pharma in tapping the benefits of the Orphan Drug Act takes on a larger significance. The growing importance of big pharma to the biotech industry, and vice versa, becomes apparent when we attach company names to the blockbuster drugs displayed in Figure 4.2. Table 4.3 lists the companies for which these biotech drugs, orphan and non-orphan, generate revenues, with big pharma in italics.

From the start, big pharma has played an important role in biotech, but more through R&D partnerships than through direct control. That was also a time when dedicated biotech firms such as Genentech, Biogen, Amgen, and Genzyme were mere startups. Now these companies are big businesses that along with big pharma can reap the benefits of US government support of the biotech industry. Yet even in the 2000s, the US government still serves as an investor in knowledge creation, subsidizer of drug development, protector of drug markets, and, last but not least — as we shall discuss in the concluding section — purchaser of the drugs that the biopharmaceutical companies have to sell. The biotech industry has become big business because of big government, and remains highly dependent on big government to sustain its commercial success.

Table 4.3: Companies with blockbuster (or near-blockbuster) biotech drugs, 2005

Company (Big Pharma in italics)	Tradename	2005 revenues $m
	ORPHAN DRUGS	
Amgen & *Wyeth*	**Enbrel**	3,657
Johnson&Johnson	**Remicade**	3,477
Johnson&Johnson/Ortho Biotech	**Procrit/Eprex**	3,324
Genentech/*Roche*	**Rituxan/MabThera**	1,831
Amgen	**Epogen**	2,455
Biogen Idec	**Avonex**	1,543
Roche	**Pegasys**	1,374
Schering-Plough	**PEG-INTRON**	1,369
Serono	**Rebif**	1,270
Amgen	**Neupogen**	1,216
Genentech	**Avastin**	1,133
Schering	**Betaseron/Betaferon**	1,026
Genzyme	**Ceredase/Cerezyme**	932
Genentech/*Roche*	**Herceptin**	747
	NON-ORPHAN DRUGS	
Amgen	**Aranesp**	2,104
Amgen	**Neulasta**	1,900
Genentech/Roche/Chugai	**NeoRecormon/Epogin**	1,710
Abbott	**Humira**	1,400
Wyeth	**Prevnar**	1,508
Eli Lilly	**Humulin**	1,105
Eli Lilly	**Humalog**	1,198
Abbott/MedImmune	**Synagis**	1,063
Gilead	**Viread**	779

Source: http://www.i-s-b.org/business/rec_sales.htm

5. Is the Biotech Boom Sustainable?

How sustainable is the biotech boom in the United States in general and Massachusetts in particular? Will the conditions of supply and demand that have driven the boom thus far continue to prevail? On the supply side, the biotech boom has depended on technological innovation in the development of new drugs for the treatment of diseases, many of which were previously untreatable. In the forefront, as we have seen, have been those "genetic and rare diseases" that fall within the purview of the Orphan Drug Act. On the demand side, the biotech boom has depended on the ability of those afflicted by these diseases to acquire the new drugs. Unlike the demand for most innovative goods and services, the demand for biotech drugs is not directly dependent on personal disposable income and consumer choice. The richer households that have the money to pay both the higher taxes needed to support public insurance plans and the higher premia needed to fund private insurance plans are not necessarily the same households that are in need of the drugs. It must be recognized as well that the US biotech boom has not been solely dependent on the level of effective demand for biopharmaceuticals in the United States. As we have seen, in the biotech boom of the 2000s, the rich nations of Europe have provided important markets for the products of US biotech companies. The sustainability of Boston's biotech boom depends in part on whether firms that produce in Massachusetts can continue to capture European demand.

On the supply side, the key question is whether Boston's biotech industry can continue to lead in technological innovation. The NIH will continue to fund the creation of knowledge on a massive scale, with Boston's highly concentrated research complex continuing as a foremost recipient of grants. In 2006 dollars, the NIH budget increased from $20.8 billion in 2000 to $30.0 billion in 2004, and was at $28.5 billion in 2006. The 2007 budget is $29.2 billion, while the 2008 request is for $28.9 billion.[33]

Among the wide range of research initiatives that the NIH underwrites are projects that promise to raise dramatically the productivity of the drug discovery process itself. In June 2005 the NIH's National Human Genome Research Institute (NHGRI) announced $32 million in grants "to advance the development of innovative sequencing technologies intended to reduce the cost of DNA sequencing and expand the use of genomics in biomedical research and health care" (NIH 2005). In making the announcement, NHGRI Director Francis Collins explained the goal of the initiative:

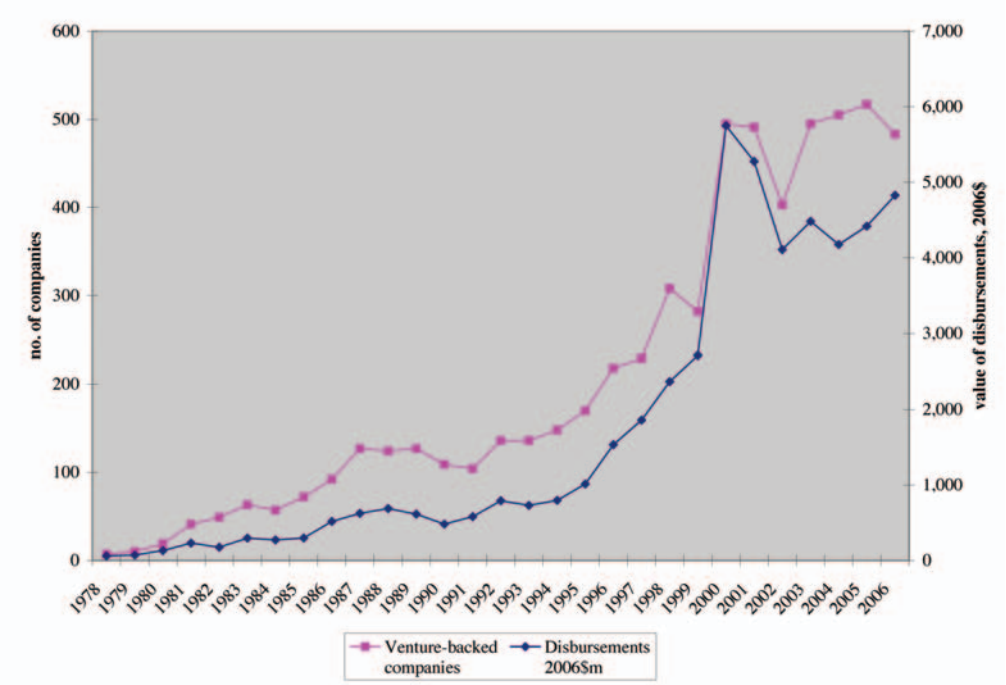
> The efforts are aimed at speeding the rate at which the next generation of sequencing technologies becomes available in the scientific lab and the medical clinic. Not only will these technologies substantially reduce the cost of sequencing a genome, but also they will provide a quantum leap in the scope and scale of research aimed at uncovering the genomic contributions to common diseases, such as cancer, heart disease and diabetes.

The announcement pointed out that, as part of the program to sequence the human genome, DNA sequencing costs had declined more than 50-fold, but that the sequencing of the three billion base pairs of DNA found in the genomes of humans and other mammals still costs about $10 million. The goals of this new round of funding are to reduce the cost of sequencing a human genome to $100,000 within five years and $1,000 over the longer term. The achievement of the $100,000 genome "would enable researchers to sequence the genomes of hundreds or even thousands of people as part of studies to identify genes that contribute to common, complex diseases." The achievement of the $1,000 genome would "enable the sequencing of individual genomes as part of routine medical care [so that] health care professionals [could] tailor diagnosis, treatment and prevention to each person's unique genetic profile."

At the same time, as shown in Figure 4.1 above, the past few years have seen a quantum increase in the number of orphan drug designations, which means that there are greater numbers of drugs for genetic and rare diseases in the pipeline. Moreover, with some 7,000 such diseases having been identified and an estimated 25 million Americans who can potentially make use of them, the need for new drugs remains far from being met. The subsidies and protection provided by the Orphan Drug Act along with the NIH-funded knowledge base and non-orphan patent protection will continue to entice the business sector, including venture capital, to invest in an industry characterized by extraordinarily long product development cycles with highly uncertain prospects for commercial success.

Indeed, since 2000 venture capital investment in the biotech industry has been at extraordinarily high levels. Figure 5.1 shows the gradual rise from the late 1970s to the late 1990s in the number of venture-backed biotech companies and the value of disbursements in 2006 dollars. After acceleration in both companies and disbursements in the last half of the 1990s, the levels of venture creation and venture funding jumped dramatically in the 2000s. Comparing 2000-2006 with 1993-1999, the average annual number of venture-backed companies more than doubled from 213 to 484, while the average annual amount of disbursements in 2006 dollars tripled from $1,572 million to $4,720 million.

Figure 5.1: Venture-backed companies and venture-capital disbursements in US biotechnology, 1978-2006



Source: Thomson Financial, Venture Xperts

One might assume that this positive attitude of venture capitalists toward the biotech industry augurs well for the contribution of startups to the innovation process. Yet, in his recent book, Pisano (2006b, 155) argues to the contrary. Technological innovation in the biotech industry depends on a process of cumulative and collective learning, whereas, Pisano argues, "[t]he high rate of firm formation means that there are many inexperienced firms in the industry."

> The typical start-up in biotech is simply going to lack the capabilities of a Genentech, which has accumulated R&D experience for more than thirty years. In addition, because newer ventures have limited financial resources, they simply cannot afford to learn from experience….[G]iven that venture capitalists are focused on a liquidity event in a three-year time frame, they have little incentive to promote learning at the organizational level. Finally, the market for know-how may also impede learning from experience. The average R&D alliance in biotechnology lasts less than four years (about one-third the expected product development cycle). Alliance partners are interested in the firm achieving its next milestone, not in building long-term capabilities. If the biotech firm cannot achieve its milestones, the partners have an easy option to terminate the relationship.

In other words, given its current organization, Pisano sees the US biotech industry as beset by "short-termism", whereas what this industry needs more than any other is "patient capital".

That still leaves unanswered the question of why such impatient capital would flow into an industry in which product development requires long-term financial commitment. We argued in Part 4 that the answer can be found in the exis-

tence of speculative stock markets in the United States that support demands by equity investors for quick exit strategies. It is not unusual for a biopharmaceutical venture to go public without a record of profitability or even a viable commercial product. Given the importance of the stock market in the US economy, there is a need for systematic research on the influence of the stock market on innovative enterprise in the biotech industry.[34]

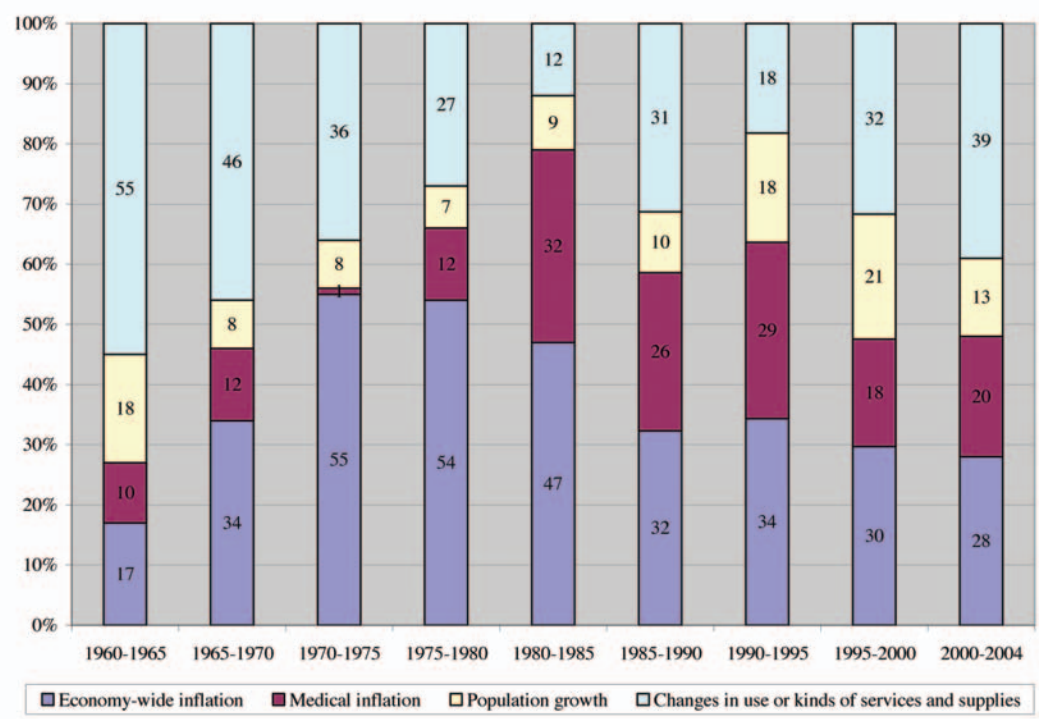
For example, we have seen in Part 3 that in the 2000s venture capital has remained a more powerful force in the San Francisco area than the Boston area (Table 3.7), reflecting the historical emergence of venture capital as an industry in its own right in Silicon Valley in the early 1970s. If Pisano is correct about the negative impact of too much venture creation on organizational learning, then it may well be, somewhat counter intuitively, that the greater involvement of venture capital in the biotech industry of the San Francisco area compared with the Boston area reflects a source of competitive *disadvantage* for San Francisco. As for Boston, its advantages in both government spending and research networks, also documented in Part 3, may be helping to offset a negative impact from excessive venture creation. Indeed, research to date — for example, the work of Walter Powell and his colleagues cited in Part 3 (see also Owen Smith et al. 2007) — suggests that the more highly concentrated *locality* rather than the more tightly organized *firm* may be the fundamental source of Boston's innovation advantage in the biopharmaceutical industry.

Innovation, however, will not in and of itself sustain the boom in biotech revenues. On the demand side, the key question is whether there will be sufficient income taxes and insurance premia in the system to absorb the industry's supply of biotech drugs, *especially* when innovations in the biotech industry have been transformed into approved drugs. In the 2000s the richest nation in the world is already straining to afford the wonders of modern medical technology. As shown in Figure 5.2, for the period, 2000-2004, of the 8.2 percent average annual percent increase in personal health expenditures, 28 percent was attributable to economy-wide inflation, another 20 percent to inflation in the price of medical goods and services, 13 percent to population growth, and a residual 39 percent to what the Centers for Medicare and Medicaid Services call "intensity"; that is, an assumed change in use or kinds of services and supplies that enter into the delivery of personal health care. In the 2000s, this technological change appears to be making a much larger proportionate contribution to increases in personal health care expenditures than in the previous two decades. Biotech drugs, particularly of the orphan variety, tend to be very expensive drugs. A proliferation of new, approved biotech drugs, even though they may address but a small fraction of the 7,000 known genetic and rare diseases, will place further strain on effective demand, given the current organization of the health care sector in the United States.

Some of the increased contribution of "technological change" in the 2000s is undoubtedly attributable to new prescription drugs. At the same time, increases in the prices of existing prescription drugs may have also contributed to the "medical inflation" category in Figure 5.2. We do know that prescription drug expenditures (PDE) have been increasing as a proportion of national health expenditures (NHE). As shown in Figure 5.3, NHE rose from 5.2 percent of GDP in 1960 to 9.1 percent in 1980 and 13.8 percent in 2000, and continued its climb to 16.0 percent in 2005. A rapidly increasing component of the rise in NHE is prescription drugs. Since 1981, when they reached a low for the whole period of 4.6 percent, PDE as a proportion of NHE have been on the rise, averaging a record 10.1 percent for the period 2003-2005.

An increasing proportion of NHE has been borne by public funds. Government expenditure as a proportion of NHE was 24.8 percent in 1960 but had jumped to 37.7 percent in 1970 as a result of the introduction of Medicare and Medicaid in 1965 as policy pillars in the "War on Poverty" (NCHS 2006, 374). This proportion stood at 42.1 percent in 1980, 40.4 percent in 1990, and 44.3 percent in 2000. In 2004 the government share of NEH was 45.1 percent.

Figure 5.2: Percentage contributions of different factors to growth in personal health expenditures, United States, 1960-2004



Average annual percent increase in personal health care expenditures

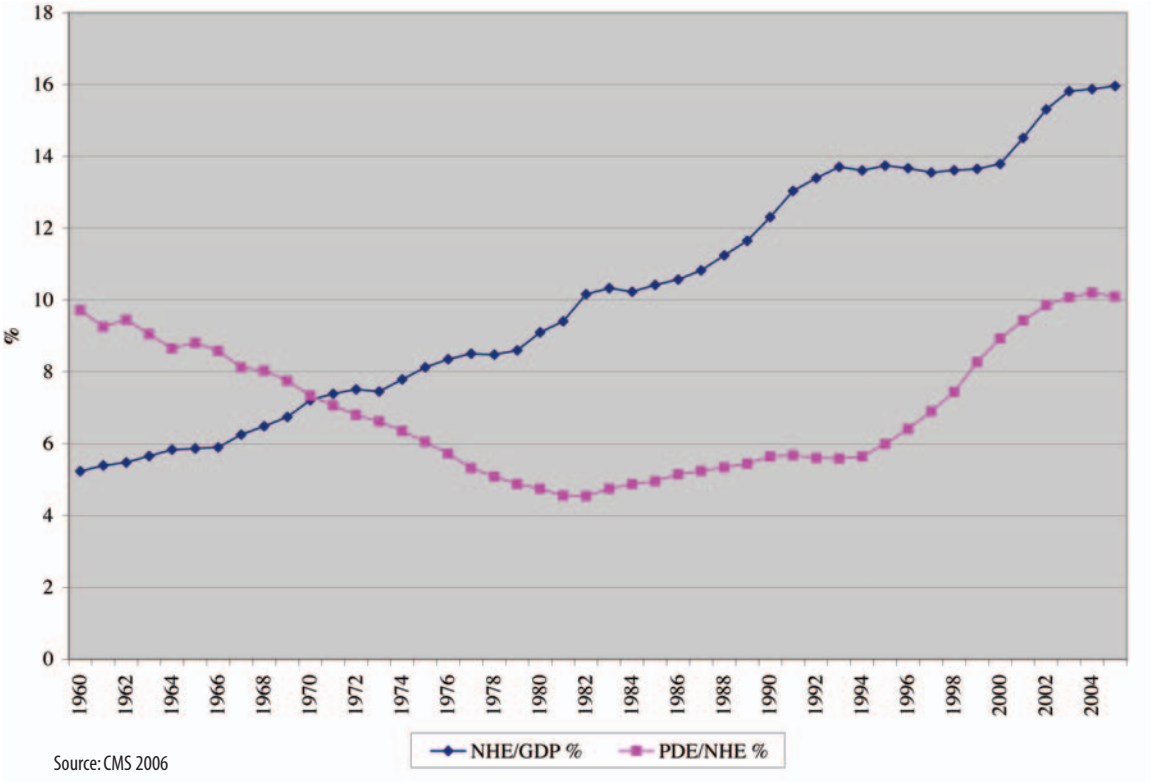
1960-1965	1965-1970	1970-1975	1975-1980	1980-1985	1985-1990	1990-1995	1995-2000	2000-2004
8.3	12.7	12.3	13.8	11.6	10.3	7.3	5.7	8.2

Note: "Changes in use or kinds of services and supplies" is a residual category.
Source: NCHS 2006, 378.

Indeed, the time series depicted in Figure 5.3 come to an end just prior to the introduction of Plan D of Medicare on January 1, 2006. Plan D implements the Medicare Prescription Drug, Improvement and Modernization Act of 2003 that will further increase PDE as a proportion of NHE as well as the government share of NHE. In total, at the beginning of January 2007, 39 million people received comprehensive prescription drug coverage under Medicare, including 24 million under Plan D, of which over 9 million were low-income beneficiaries who receive the drugs at little if any cost (CMS 2007; see also Montgomery and Lee 2006).

As depicted in Figure 5.4, a study by the Congressional Budget Office (CBO) released in January 2007 sees the cost of Medicare and Medicaid as the fastest growing component of mandatory government spending over the next decade. A key element of the growth of Medicare and Medicaid expenditures will be the cost of prescription drugs under Plan D. In 2006 the net cost of Plan D was $28 billion, and the CBO estimates that the cost will rise to $42 billion in 2007 and $142 billion by 2017 (CBO 2007, 58).

Figure 5.3: Changes in national health expenditures (NHE) and prescription drug expenditures (PDE) in the United States, 1960-2005



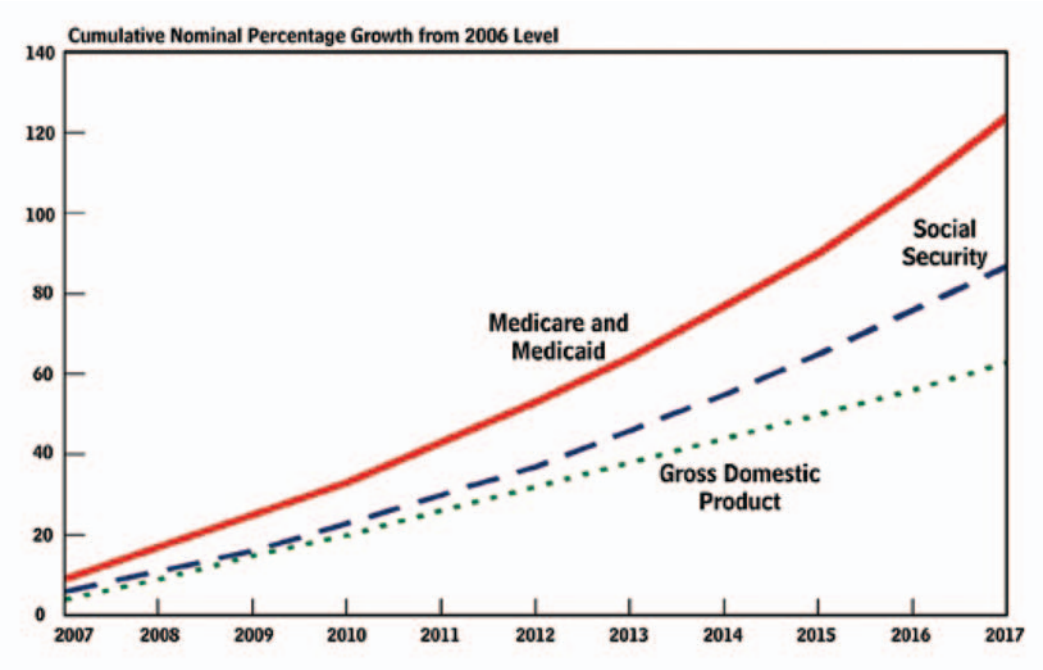
Source: CMS 2006

The US government, therefore, will continue to play a major role in bolstering effective demand for prescription drugs over the next decade. In doing so, it will help to sustain the biotech boom in Boston and other biopharmaceutical centers. Whether the Massachusetts-based biotech industry can continue to capture a large share of the European market is another question. While in 2006 compared with 2005 Massachusetts' exports of HS-293790 (hormones and prostaglandins) rose by $80 million and of HS-300490 (medicaments, measured dose, retail packaging) by $13 million, the state's exports of HS-300210 (antisera and blood fractions) fell by $371 million (see Table 2.2).

US-based biopharmaceutical companies already sell their drugs at much lower prices in Europe than in the United States (see for example Kelly 2003; Frank 2004). Meanwhile the European Union is intent on increasing the amount of funding to biotech research. In 2001, moreover, the EU passed it own Orphan Drug Act. Although initially US-based companies and the US-based operations of Europe-based companies were well-positioned to take advantage of the expansion of the European market for drugs for genetic and rare diseases, the EU is intent on building a biotech industry capable of capturing its own home demand (Ernst & Young 2006).

One way in which biopharmaceutical companies hope to sustain the boom in the United States is by keeping the government out of the business of regulating drug prices. Back in 1990 President George H. W. Bush vetoed a Congressional bill to modify the Orphan Drug Act in order to create more competition and keep down drug prices (Gibbons 1990).

Figure 5.4: Projected growth in US Medicare/Medicaid expenditures and Social Security expenditures compared with projected GDP growth, 2007-2017



Source: CBO 2007

Currently Congress is debating whether, under Plan D of Medicare, the government should use its purchasing power to step in and negotiate prices with the drug companies. Then, as now, the biopharmaceutical industry has argued that any attempt to regulate drug prices will cut into company profits, which will in turn diminish the amount of resources that companies have available to invest in R&D and, thereby, generate a flow of innovative products.

That is the supply-side business investor talking. On the demand side, regulated drug prices would help stem the rise (or at least the rate of increase) of insurance premia and help avoid the need for more taxes to help the government shoulder its considerable share of drug demand. Bringing rising health care costs under control is obviously a major challenge for US policy makers, and is especially an issue in Massachusetts as the state in the nation that has taken the lead in seeking to provide universal health coverage at an affordable cost.

In assessing the arguments of the relation between drug prices and biopharmaceutical investments in R&D, government policy makers should take seriously two salient issues that business proponents of a "free market" economy prefer to ignore. The first issue is the fact that government investment in research is more important than business investment for supporting innovation in the biopharmaceutical industry. The second issue is that when US biopharmaceutical companies get high profits from high prices they do not necessarily invest those high profits in R&D.

These two issues are intertwined. Given the role of government in funding the biotech industry, the government should take an active role in the governance of companies that make use of this support. Since the 1980s the US business community, the biopharmaceutical industry included, has embraced the ideology that the performance of their companies and the economy are best served by the "maximization of shareholder value" (see Lazonick and O'Sullivan 2000; Lazonick 2007). It is an ideology that, among other things, says that any attempt by the government to interfere in the allocation of resources can only undermine economic performance. In practice, what shareholder ideology has meant for corporate resource allocation is that when companies reap more profits they spend a substantial proportion of them on stock repurchases in an effort to boost their stock prices.

Table 5.1 charts the stock repurchase activity over the past decade for leading biotech companies that have done substantial buybacks. Not all profitable biotech companies engage in this practice; for example, Genzyme has never done repurchases. But as can be seen in Table 5.1 Amgen has done them with a vengeance; the company has repurchased stock in every year since 1992, for a total of $19.3 billion through 2006. Note that in many years the cost of Amgen's stock buybacks has surpassed the company's R&D expenditures, which totaled $19.6 billion — just slightly more than repurchases — for the period 1992-2006. Genentech only began to do repurchases in 2001. From 2001 through 2006, the company allocated $5.9 billion to R&D and $5.7 billion to stock buybacks.

Table 5.1: Stock repurchase activity by leading biopharmaceutical companies and ratios of repurchases to R&D expenditures, 1997-2006

	Amgen		Genentech		Biogen Idec		Chiron		MedImmune	
	REP $m	REP/ R&D	REP $m	REP/ R&D	REP $m	REP/ R&D	REP $m	REP/ R&D	REP $m	REP/ R&D
1997	738	**1.00**	0	0.00	7	0.02	0	0.00	0	0.00
1998	912	**1.16**	0	0.00	66	0.21	0	0.00	0	0.00
1999	1,025	**1.08**	0	0.00	198	0.65	141	0.56	0	0.00
2000	800	0.77	0	0.00	300	**1.36**	314	**1.07**	0	0.00
2001	738	0.69	40	0.08	88	0.50	201	0.58	0	0.00
2002	1,420	0.35	693	**1.16**	8	0.06	155	0.42	0	0.00
2003	1,801	**1.09**	201	0.32	0	0.00	208	0.46	230	**1.47**
2004	4,072	**1.58**	1,352	**1.43**	734	**1.07**	135	0.31	30	0.08
2005	4,430	**1.91**	2,016	**1.60**	323	0.43	0	0.00	106	0.24
2006	2,000	0.60	996	0.56	320	0.31			319	0.71
1997-2005	15,936	**1.05**	4,301	0.78	1,724	0.43	1,154	0.37	366	0.14
1997-2006	17,936	0.97	5,297	0.73	2,044	0.40			685	0.23

REP=stock repurchases
Notes: Biogen Idec includes only Biogen repurchases and R&D before the 2003 merger of the two companies
In 2005 Chiron was acquired by Novartis, and therefore data are not available for Chiron for 2006
Source: Compustat database

Why do companies do stock buybacks? Their purpose is to raise stock prices. Of course, prime beneficiaries of stock repurchases, and the consequent boosting of stock prices, are none other than the high-level corporate executives who make these allocative decisions. Table 5.2 shows the average gains per person from the exercise of stock options over the past decade by the CEO and other four highest paid executives of six leading independent biotech companies, including Amgen and Genentech. It also happens that Amgen has been in the news lately for its failure to develop new products (Pollack 2007).

The debate over the regulation of drug prices must take into account the ways in which drug companies actually allocate their profits. Currently, as Congress debates the regulation of drug prices, it is also debating measures to stem the continuing rise in CEO pay. As indicated by gains from the exercise of stock options at Amgen, top executive pay at US corporations is generally at a level that has long been excessive, and some might even say obscene. In the US biopharmaceutical industry, the debates over the regulation of the prices of drugs and the pay of CEOs should be joined. Those public policy-makers who think that the sustainability of the biotech boom might require some intelligent government regulation should take note. Next time an executive of one of these companies tells you that the innovation machine depends upon the government minding its own business, you might want to respond that the government *is* minding its own business.

Table 5.2: Gains from the exercise of stock options, average for CEO and other four highest paid executives, 1995-2006

	Amgen	Genentech	Genzyme	Biogen Idec	Gilead Sciences	MedImmune
1995	$6,817,627	$825,701	$465,309	$2,464,961	na	0
1996	5,279,364	325,679	721,100	298,066	$411,250	$500,657
1997	3,010,156	0	44,373	4,293,557	832,369	973,564
1998	11,307,884	592,149	1,471,548	615,541	491,235	6,524,812
1999	13,330,697	10,763,997	4,652,625	8,132,058	633,146	14,865,652
2000	42,131,827	23,414,861	1,846,424	9,070,194	2,227,746	27,239,986
2001	4,321,772	371,803	5,344,364	1,841,877	4,747,643	4,734,428
2002	2,951,349	0	0	736,089	2,530,736	0
2003	2,787,683	14,253,173	4,897,291	1,848,609	6,437,089	1,476,951
2004	1,729,808	24,175,200	2,116,807	14,221,925	7,563,908	315,829
2005	9,444,582	31,149,362	10,662,508	2,378,898	9,535,369	553,890
2006	1,036,550	4,445,274	0		13,967,766	
1995-2006*	**$104,149,298**	**$110,317,199**	**$32,222,349**	**$45,901,776**	**$49,378,259**	**$57,185,769**

Na=not available
* Biogen Idec and MedImmune 1995-2005 (2006 data not yet available); Gilead Sciences, 1996-2006.
Source: SEC filings and Compustat database

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Zucker, Lynne B., and Michael R. Darby, 1997, "Present at the Biotechnological Revolution: Transformation of Technological Identity for a Large Incumbent Pharmaceutical Firm," Research Policy, 26, 4&5: 429-446.

Endnotes:

[1] http://www.bls.gov/cew/home.htm

[2] Edward Moscovitch was serving on Governor Michael Dukakis' advisory panel on innovation when his op-ed piece, "The Massachusetts Miracle", was published in the Wall Street Journal in July 1986.

[3] "miracle", Dictionary.com Unabridged (v 1.0.1). Random House, Inc. 16 Dec. 2006. <Dictionary.com *http://dictionary.reference.com/browse/miracle*>

[4] The two HS categories, 901839 and 901890, are medical instruments and devices, products that are closely allied with the biopharmaceutical industry. For the analysis of the Massachusetts medical devices industry by the UMass Lowell Center for Industrial Competitiveness, see Best 2005 and 2006.

[5] antibody: "Any of a large number of proteins of high molecular weight that are produced normally by specialized B cells after stimulation by an antigen and act specifically against the antigen in an immune response, that are produced abnormally by some cancer cells, and that typically consist of four subunits including two heavy chains and two light chains — called also immunoglobulin"; mAb: "An antibody derived from a single cell in large quantities for use against a specific antigen (as a cancer cell)". (Definitions in this note and the following five notes are from the Merriam-Webster medical dictionary, accessible online at *http://www.nlm.nih.gov/medlineplus/mplusdictionary.html.)*

[6] antisense: "Having a sequence complementary to a segment of genetic material; specifically: of, being, relating to, or possessing a sequence of DNA or RNA that is complementary to and pairs with a specific messenger RNA blocking it from being translated into protein and serving to inhibit gene function".

[7] antisera: "A serum containing antibodies — called also *immune serum*".

[8] prostaglandins: "Any of various oxygenated unsaturated cyclic fatty acids of animals that are formed as cyclooxygenase metabolites especially from unsaturated fatty acids (as arachidonic acid) composed of a chain of 20 carbon atoms and that perform a variety of hormone-like actions (as in controlling blood pressure or smooth muscle contraction)".

[9] thromboxanes: "Any of several substances that are produced especially by platelets, are formed from endoperoxides, cause constriction of vascular and bronchial smooth muscle, and promote blood clotting".

[10] leukotrienes: "Any of several substances that are produced especially by platelets, are formed from endoperoxides, cause constriction of vascular and bronchial smooth muscle, and promote blood clotting".

[11] To locate the biopharmaceutical exports within the US economy, and ultimately identify the companies that produce them, we must translate the HS codes into NAICS (North American Industry Classification System) codes. The translation: 1) HS-300210, blood fractions and immunological products: NAICS-325414, "Biological Products (except Diagnostic) Manufacturing"; 2) HS-293790, hormone-based products: NAICS-325411, "Medicinal and Botanical Manufacturing"; 3) HS-300490, other medicaments for retail sale: NAICS-3254.12 "Pharmaceutical Preparation Manufacturing".

[12] Some would disagree with the selection of companies for the list. For example, Gary Pisano (2006b, 116) lists Biovail, based in Canada, and Kos, based in New Jersey, as being among the small number of profitable biotech firms in 2004. Neither is included in the MedAdNews top 100 list. Yet in 1995 Biovail's revenues of $936 million would have placed it 11th on that list, while Kos's revenues of $752 million would have placed it 12th. In addition, as we discuss in Part 4, through acquisitions and internal growth, many of the "big pharma" companies have biotech divisions that, if treated as distinct biotech companies, would be very high up on the top 100 list. The line between big pharma and the independent biotech companies is becoming increasingly blurred. For example, MedAdNews chose to leave Chiron on its 2005 list despite the fact that during 2005 it became wholly-owned by the Swiss-based pharmaceutical company, Novartis.

[13] For the emergence of Boston as a center of biotech and its geographic concentration, size, and impact relative to other biotech centers, see Cortright and Mayer 2002, Feldman 2003, Owen-Smith and Powell 2004.

[14] There is an extensive academic literature on the emergence of biotechnology as a distinct segment of the medicinal drug industry and the interaction of the biotech segment with "big pharma" in the ongoing evolution of biotechnology. See, for example, Zucker and Darby 1997, Galambos and Sturchio 1998, Zucker et al. 1998, Lacetera 2001, and Owen-Smith and Powell 2004.

[15] "Bertram Rowland and the Cohen/Boyer Cloning Patent," available at *http://www.law.gwu.edu/Academics/Academic+Focus+Areas/IP+and+Technology+Law/Alumni+Patents/Bertram+Rowland+and+the+Cohen+Boyer+Cloning+Patent.htm*

[16] *http://www.nih.gov/about/NIHoverview.html.*

[17] http://www.nih.gov/news/fundingresearchareas.htm.

[18] The geographic locations of these organizations can be observed on Google Earth.

[19] On Boger and the Vertex startup, see Werth 1994.

[20] We are currently updating these data for the period since 2001. For more recent information on R&D alliances in the Boston area, see Nakajima and Loveland 2007.

[21] *http://www.bls.gov/cew/home.htm.*

[22] *http://www.fda.gov/orphan/grants/2007RFA.html*

[23] *http://www.fda.gov/ohrms/dockets/98fr/E6-12397.htm.* The Prescription Drug User Fee Act, passed in 1992, authorizes the FDA to levy user fees on drug companies seeking FDA approval to market their products as well as to collect annual fees from drug companies based on manufacturing establishments and marketed products, "in exchange for FDA agreement to meet drug-review performance goals, which emphasize timeliness." *http://www.fda.gov/oc/pdufa/overview.html.*

[24] Some have argued that given that given the existence of patent protection for biotech drugs, the market exclusivity provision of the Orphan Drug Act may be redundant (see, for example, Rogoyski 2006). In historical perspective, however, the two forms of protection have been complementary, giving biopharmaceutical companies the possibility of two different forms of market protection. As we have seen, the right to patent a living form was only established in 1980 with the Supreme Court ruling in Diamond v. Chakrabarty. When the Orphan Drug Act was passed in 1983, it was intended for drugs that were not patentable. With the Act on the books, however, the Act was amended in 1985 to cover patentable drugs as well. The term of a patent begins at the time it is filed, which typically is early in the development stage of the intended product or process. In contrast, the seven-year period of market exclusivity under the Orphan Drug Act begins when the FDA grants marketing approval. If Company A holds market exclusivity under the Orphan Drug Act and Company B holds a patent on which the orphan drug is based, then Company A will have to negotiate licensing terms with Company B in order to market the drug. Despite holding a patent, Company B will be excluded from marketing the drug for the orphan indication until the seven-year period of market exclusivity expires. While market exclusivity under the Orphan Drug Act is only for the particular indication for which the drug has been approved, the company does not need to demonstrate, as in the case of a patent, a unique innovation in order to gain protection under the Orphan Drug Act. Until 1995 the term of a patent was 17 years, at which time it was changed to 20 years. The new law also created the possibility of a five-year extension to a new maximum of 14 years in cases in which, as is typical in biotech, the company can show long development periods that have significantly reduced the time period over which the company will be able to benefit from patent protection when the drug is finally marketable.

[25] *http://www.fda.gov/orphan/oda.htm*

[26] The three indications for NovoSeven approved in 2005 were 1) "prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX"; 2) "prevention of bleeding in surgical interventions or invasive procedures in patients with congenital F VII deficiency"; and 3) "treatment of bleeding episodes in patients with Factor VII deficiency" (FDA 2007).

[27] *www.botoxcosmetic.com*

[28] *http://www.rarediseases.org*

[29] *http://www.bioventureconsultants.com/cindy_bio.html.*

[30] Although Pisano (2006b, 5) claims to have documented "the total revenues and profitability [measured by operating income] of all publicly held biotechnology companies (in aggregate) from 1975 through 2004", in fact, as our replication of his analysis revealed, he neglected to include in the series those companies that had been publicly held prior to 2004 but had either ceased operations or had been acquired by another company. Data from Thomson Financial Venture Xperts on venture-backed IPOs of biotech companies between 1987 and 2003 reveal 136 publicly held companies that are not on Pisano's 2004 list. Three prominent examples of acquired companies that do not appear on Pisano's 2004 list are: a) Centocor (IPO, 1992), acquired by Johnson & Johnson in 1999, after reporting $338 million in revenues and $102 million in operating losses in 1998; b) Immunex (IPO, 1983), acquired by Amgen in 2002, after reporting $987 million in revenues and $97 million in operating income in 2001; and c) Idec (IPO, 1991), merged with Biogen in 2003, after reporting $404 million in revenues and $214 million in operating income in 2002. Prior to 2004, therefore, Pisano's data underestimate the combined revenues of publicly held biotech companies and misrepresent actual combined operating results.

[31] NIH, Office of Extramural Research: *http://grants1.nih.gov/grants/award/HistoricRankInfo.cfm*. For a thorough analysis of the role of the US government in supporting the pharmaceutical industry through tax credits and NIH grants, see OTA 1993, chs. 8-9.

[32] Serono (now Merck Serono) has a history that dates back to 1906 in Italy and 1961 in the United States. Yet Serono's almost complete focus on and success in orphan drugs, as shown in Table 4.3, have transformed it into a biotech company.

[33] National Institutes of Health, Office of the Budget, *http://officeofbudget.od.nih.gov/ui/HomePage.htm*.

[34] For an analysis of the relation between the stock market and innovative enterprise, including the concept of "financial commitment", in the ICT industries, see Lazonick 2007. On the historical role of the stock market in financing new industries in the United States, see O'Sullivan 2006.