This report was sponsored by the Pharmaceutical Research and Manufacturers of America (PhRMA), and executed with the support of the Economic Research & Analysis Unit of The Donahue Institute, University of Massachusetts. The Rasky/Baerlein Group provided industry liaison for the project.

© 1999 Anurag Sharma and University of Massachusetts.
EXECUTIVE SUMMARY

Based on a study of the pharmaceutical industry by the University of Massachusetts Economic Project, the following two key generalizations can be made:

1. The pharmaceutical industry has significant and growing presence in Massachusetts.
2. Massachusetts has among the highest concentration of medical research in the country. Such research supports a thriving local bio-pharmaceutical industry and it attracts substantial investments into the local economy from the traditional companies worldwide.
3. Massachusetts is a breeding ground for future drug ideas and for new pharmaceutical companies for the next millenium.

These findings emerge from a detailed analysis of data about research and manufacture of drugs in the state. Key elements of the supporting data are discussed below:

Summary of Key Observations

The data suggest that Massachusetts attracts a significant amounts of public and private monies for medical research, and that the pharmaceutical industry also has noticeable presence in the state in terms of manufacturing value added. The industry directly provides over twenty five thousand benefited jobs in Massachusetts, and conceivably tens of thousands more indirect jobs contiguous business activities that support the discovery, manufacture, and distribution of pharmaceuticals in the state.

Below is a summary listing of key data gathered regarding the presence of pharmaceutical industry in Massachusetts. Note that while the study relied mostly on archival data, it also used information from a mail survey sent to over two hundred firms with operations in the state. See Appendix 1 for a discussion of the survey.

Research

- During the period 1994-1998, medical research institutions and organizations in Massachusetts have attracted over $5 billion in research monies from the National Institutes of Health. The annual receipts grew 30% from $901 million in 1994 to $1.2 billion in 1998.

- During each year in the period 1994-1998, Boston was #1 city in the nation in terms of attracting research monies from the National Institutes of Health. The annual receipts grew 34% from $630 million in 1994 to $847 million in 1998.

- Five cities in the Commonwealth are among the top 100 cities receiving funds from the National Institutes of Health. These cities (Boston, Cambridge, Worcester, Waltham, and Watertown) accounted for over 90% of all NIH monies coming into the state.

- With regards to biological, biotechnical, and medical research in 1998, 7.37% of all establishments and 16.26% of all employment in United States were located in Massachusetts.
During the period 1995-1997, a sample of 15 pharmaceutical and 17 bio-pharmaceutical companies reported to have invested over $1 billion in drug research and related activities in the state. Survey

During the period 1998-2000, the 32 pharmaceutical and bio-pharmaceutical companies project that they will invest more than $1.36 billion in research and related activities in the state. Survey

More than half of respondents to the UMass Survey indicated that they expect to significantly expand their research activities in the state during the period 1998-2000. Survey

In 1999, the thirty-two responding pharmaceutical and bio-pharmaceutical companies reported as having a total of 397 separate ties with research institutions and organizations in the state. The ties were distributed as follows: clinical research (148), licensing patent (73), basic research (133), and technology transfer (43). Survey

In 1999, the thirty-two survey respondents had a total of 121 explicit links with universities in Massachusetts. Of these 69 (57%) involved pharmaceutical companies and the remaining 52 (43%) involved bio-pharmaceutical companies. Survey

Bio-Pharmaceutical companies responding to the UMass Survey indicated that 75% of their monies for research come from traditional pharmaceutical companies. Survey

The above statistics indicate that Massachusetts has a highly developed infrastructure for biological and medical research that is necessary for drug discovery and development. The dense network of world-renowned universities, hospitals, and research foundations makes the Commonwealth – particularly the eastern seaboard – a magnet for substantial monies from both the public and the private sectors.

It is important to note that the various elements of the research infrastructure in the state are mutually reinforcing and strongly needed complements to each other. The work of talented professionals at universities and hospitals attracts the public monies for basic research from federal agencies such as the National Institutes of Health. Yet, private monies from pharmaceutical companies play a crucial role in supplementing basic research dollars and in supporting applied research aimed at developing specific drugs for specific drug targets. Because of the top quality of research universities and the culture of medical research in the area, therefore, it is likely that Massachusetts receives a disproportionate share of the estimated $17 billion the pharmaceutical companies spent on research and clinical trials in the United states in 1998.

In addition, the strength of medical research in Massachusetts is also reflected in the investment capital that small start-ups in the state attract from private investors. According to PricewaterhouseCooper-Boston Globe survey, for example, biotechnology and pharmaceutical start-ups in Massachusetts raised about $450 million in venture capital funding during the 1997-1998 period. Hence, the research infrastructure in the state contributes to and, equally importantly, sustained by the triad of NIH, pharmaceutical companies, and private investors.
Manufacturing

- During the period 1995-1997, the manufacturing sector of the drug industry is estimated to have invested a total of $358 million in new capital expenditures in the state.

- In 1998, the manufacturing sector of the drug industry is estimated to have invested $128 million in new capital expenditures in the state.

- During the period 1995-1997, drug industry is estimated to have contributed a total of $3.3 billion in manufacturing value added to the economy of the Commonwealth.

- In 1998, pharmaceutical industry is estimated to have contributed $1.2 billion in manufacturing value added to the economy of the Commonwealth.

- With regards to drug manufacturing in 1998, 3.07% of all establishments and 1.99% of all employment in United States were located in Massachusetts.

- Two of 15 pharmaceutical companies and 5 of 17 bio-pharmaceutical companies responding to the UMass Survey indicated that they expect to significantly expand their manufacturing activities in the state during the period 1998-2000. Survey

- Respondents to the UMass Survey indicated that they expect to spend $198 million on manufacturing activity and $226 million on sales and marketing in Massachusetts during the 1998-2000 period. Survey

- Respondents to the UMass Survey indicated that they expect to spend $277 million on construction activity in Massachusetts during the 1998-2000 period – a 377% increase over the $73 million these companies reported for 1995-1997. Survey

Although Massachusetts is not one of the big drug manufacturing states in the Union, it does participate in that sector at a non-trivial level. The above statistics are estimated from the data provided by the Annual Survey of Manufactures compiled annually by The Census Bureau. As the statistics show, the new capital expenditures made by the industry ran into hundreds of millions of dollars over a span of the most recent five year period. Similarly, the value added by drug manufacturing in the state averaged over $1 billion in each of the last five years. The total economic impact on the state of the manufacturing sector, in other words, is non-trivial.

Places to Work

- In 1998, there were 329 research, manufacturing, and the wholesale establishments in the drug industry in Massachusetts – up 21% from 271 in 1995.

- The drug industry is highly concentrated both by the size of establishment and by geography.
• In 1998, 67% of drug manufacturing establishments employed less than 50 people. Yet, 80% of manufacturing employment was concentrated in 13 establishments employing 100 or more people.

• Similarly, in 1998, 75% of drug research establishments employed less than 50 people. Yet, 71% of manufacturing employment was concentrated in 15 establishments employing 100 or more people.

• In 1998, over 85% of manufacturing establishments were concentrated in five Counties with 10 or more establishments each. Similarly, over 88% of drug-related research establishments were concentrated in four Counties with 10 establishments or more. [Middlesex County had 51 manufacturing and 61 research establishments].

• In 1998, almost 90% of manufacturing employment in the state was concentrated in five Counties [32% in Middlesex County]. Similarly, over 95% of drug-related research employment were concentrated in five Counties [39% in Suffolk County and 36% in Middlesex County].

In effect, data show that both research and manufacturing sectors of the drug industry are highly concentrated. Most of the employment is in few large research and manufacturing establishments. In addition, most of the establishments and employment are concentrated in five Counties, all of which are in the densely populated eastern part of the state.

**Employment & Wages**

• During the first quarter of 1998, research, manufacturing, and the wholesale sectors for the drug industry provided an estimated 25,788 “covered” or benefited jobs in Massachusetts.

• The “covered” employment in the commercial medical, biological, and biotechnical research sector of the industry grew about 59% from an average of 5,872 in the fourth quarter of 1993 to an average of 9,319 in the same period of 1997. Average monthly employment in the research sector was estimated to be 12,538 in the first quarter of 1998.

• The number of covered employees in the drug wholesale sector grew 39% from an average of 4,328 in the fourth quarter of 1993 to an average of 6,028 in same period of 1997. Employment in the drug wholesale trade was estimated to be 5,885 in the first quarter of 1998.

• The combined wages in research, manufacturing, and wholesale trade of drug industry in the state increased 63% from $1.05 billion in 1995 to an estimated $1.71 billion in 1998.

In effect, then, the chief conclusion of the research is that the pharmaceutical industry has significant and growing presence in the state. The research, manufacturing, and wholesale segments of the drug industry provided over 25,000 benefited jobs in Massachusetts during the first quarter of 1998 – up 40% since the last quarter of 1995. Reflecting the geographic concentration of the industry, however, most of these jobs are located in the densely populated eastern seaboard – particularly in the Greater Boston area.
It is estimated, moreover, that in 1998 the drug industry in Massachusetts shipped over $1.6 billion worth of goods and it provided almost $1.2 billion in manufacturing value added. Although non-trivial, however, the contribution of drug manufacturing is arguably of lesser import to the local economy than is the collective impact of drug-related research in the state. In 1998, for example, while about 3% of all drug manufacturing establishments in the United States were in Massachusetts, over 7% of commercial research establishments in the nation were located in the Commonwealth. Similarly, while just 2% of all drug manufacturing employment in the country were in Massachusetts, over 16% of commercial research employment in the nation were located in the Commonwealth.

In fact, the report shows that Massachusetts is on the leading edge of biological, biotechnical, and medical research in the Union. The commonwealth is second only to California, for instance, in obtaining research monies from the National Institutes of Health – getting almost $1.2 billion (or 10.5%) of the $11.2 billion in intramural research funds distributed by NIH in 1998. Public support for medical research attests to the fact that the state has a rich and highly effective network of superb research universities and teaching hospitals. It is no surprise, therefore, that the pharmaceutical industry complements the public investment by itself aggressively supporting medical research in the institutions in the state. In so doing, the industry both benefits from and contributes to the building a competitive research infrastructure in Massachusetts.

According to the survey administered for this study, thirty-two companies (that responded to a questionnaire) plan to invest over $1.36 billion in research and clinical trials in Massachusetts during the 1998-2000 period. This represent an increase of 30% over what these same companies indicated they spent on research in the state during the preceding three years. In a similar vein, the survey indicated that these thirty-two companies are deeply embedded in the local research institutions – nurturing almost 400 linkages (for clinical trials, licensing, basic research, and technology transfer) with academic and non-academic institutions/organizations in the Commonwealth.

An Assessment

Massachusetts, home to world-class research universities and medical institutions, is the most research intensive state in the Union. The pharmaceutical enterprise, driven by science-based discovery and development of new therapies, is the most research intensive of all industries in the economy. It is no surprise, therefore, that the state of Massachusetts both contributes to and benefits from the presence of the pharmaceutical industry in its towns, communities, and in research institutions.

In fact, given the momentum of developments in the last few decades, the drug industry is poised to enter what some analysts call the Golden Age of medicine in the next century. Consequently, it is likely that the industry’s already high commitment to medical research ($17 billion in 1998) will intensify even further in coming years. Given, therefore, that eastern Massachusetts has evolved into perhaps the most prominent center in the world for biological and medical research, the state is poised to play an important role in the pharmaceutical industry of the future – and to attract investments and the industry’s growing pool of research monies.
The industry no doubt is attracted to and benefits from several unique infrastructure assets in the Commonwealth – excellent institutions of higher education, world-renowned medical schools and teaching hospitals, and a deep-rooted culture of serious research. In addition, the culture of medical research in Massachusetts is complemented by an equally strong culture of business and services in the area. The Commonwealth of Massachusetts is one of the leading states in the country for the business communication and computer software industries – both skills critical for increasingly information-intensive drug research. Similarly, the state is among the top two in the nation with respect to attracting venture capital funds for new business ideas – monies that, along with those from pharmaceutical industry and from the National Institutes of Health, play an important complementary role in encouraging drug research. Finally, the Commonwealth has a high density of professional service firms supplying first-rate auxiliary services such as patent law and accounting – services that critically lubricate the business end of commercial biological and medical research.

At the same time, unsurprisingly, the state benefits in both tangible and intangible ways from the presence of the pharmaceutical industry. The decision of drug companies to locate research or manufacturing in Massachusetts brings in investment dollars and jobs that directly impact the economies of local communities. Moreover, because the entire pharmaceutical enterprise is driven by discovery and development of sophisticated new therapies, many drug companies are deeply embedded in rich networks of alliances, research grants, and joint projects with both public and private research organizations in the state. In so doing, the drug companies help create pathways for basic biological and medical research to find applications into concrete revenue-generating products. As important as direct economic impact, therefore, the industry’s strong presence in the state validates and strengthens the research infrastructure already in place.

It is no surprise, therefore, that employment in drug-related commercial research more than doubled from 6,137 in 1995 to 12,538 in 1998, and that the state’s share of total nationwide employment in commercial research organizations increased from 10.4% in 1995 to 16.2% in 1998. Consistent with trends in employment, Massachusetts continues to be a leading state in terms of getting research monies from the National Institutes of Health – growing 26% from $932 million in 1995 to almost $1.2 billion in 1998. Similarly, in a survey conducted for this study, thirty-two pharmaceutical and bio-pharmaceutical firms indicated that they intend to spend $1.36 billion on research and clinical trials during the 1998-2000 period – approximately 30% more than the preceding three-year period. The same survey respondents reported that between 1998 and 2000, they plan to spend over $277 million in construction activities – up 377% from the $74 million they spent on such activities in the 1995-1997 period. In effect, then, there appears to be in process a natural market-driven alignment between institutions in the Commonwealth and the pharmaceutical industry.

Such state of affairs should not be taken for granted, however. Notwithstanding enviable strengths, Massachusetts is only one of the many locations worldwide where pharmaceutical companies can invest their substantial, yet finite, funds for drug discovery, development, and manufacture. California, New York, Pennsylvania, and Maryland also offer some of the same benefits as attracting public (NIH) monies for research, proximity to formidable research and teaching institutions, and access to private capital. In fact, some executives in the industry consider quite attractive even a relative late comer such as North Carolina.
This is at least in part because of aggressiveness of the state officials in promoting the Research Triangle Park – which is served by an international airport, is proximate to three large universities, and which now houses an increasingly dense network of like-minded companies. Ironically, even such small neighboring states as Rhode Island and Connecticut have considerable attraction to firms that may want to locate in the Northeast but for whatever reason, would prefer to stay out of Massachusetts.

Hence, it is imperative that instead of taking the industry for granted the Commonwealth explores ways in which to strengthen the important and evolving presence of the pharmaceutical industry. Perhaps it would be prudent for the state to conduct a vigorous needs assessment with the industry to understand what kind of, if any, public policies or investments might be effective in assuring the commitment for continued investment by pharmaceutical firms into the institutions and infrastructure within the Commonwealth.

It should be noted that the market forces already appear to be nurturing and strengthening an implicit partnerships between the industry and select institutions in Massachusetts. It is no secret that the industry continues to find productive use for its capital in the universities and hospitals of the state. After all, as one industry executive noted, what makes Massachusetts such a viable place for the pharmaceutical industry is the long history that has produced strong teaching institutions and research universities, and a thriving financial community. The rest is done by a community of interests that efficiently connects available capital to viable research ideas and capabilities. There is little that the state government has done or can do to directly forge business ties between the pharmaceutical industry and medical research institutions. What the state can do, of course, is to focus on fundamentals that encourage and give momentum to the favorable developments currently under way.

**Considerations for the Future**

While adequately addressing such issues would require a study in its own right, I submit some questions that future researchers might deem worthy of exploration.

One of the most pressing challenges, for instance, is that virtually all infrastructure and assets needed to sustain the high intensity of drug research are concentrated in the Greater Boston and Cambridge area. While the high density of institutions, people, and ideas have worked well to attract high levels of investments into the state, industry executives appear to be uneasy about the increasing congestion in the area. According to one industry executive who participated in a focus group, competition for scarce geographical space is strong and the talent pool of skilled personnel in the Boston and Cambridge area is stretched almost to a breaking point. Consequently, the cost of doing business continues to spiral upward.

Of course, congestion is the other blade of a double-edged sword: as economic theory would suggest, there are obvious economic and strategic benefits from industry clusters. In spite of annoyance with occasional traffic jams and in spite of a feeling of helplessness at the spiraling costs of real estate, the Greater Boston area continues to provide very good reasons for industry to locate there. Such is clearly evident in recent newspaper reports and in the UMass survey results which suggest that the next few years will bring substantial investment into the already congested eastern part of the Commonwealth.
Even so, and despite the dogma of industry clusters, it may be useful for future researchers to explore the implications of the narrow geographic presence of the pharmaceutical industry in the state. It would be helpful, for instance, for future research to try to estimate the carrying capacity of Greater Boston area. At what point do costs begin to outweigh the benefits of locating in the current hot spots in the state? When might pharmaceutical companies (and those in other industries, for that matter) decide that the Boston area is just too much trouble and that they would rather go to Providence, RI or Groton, CT or to another region altogether. These questions must be carefully explored to understand the long-run potential of the pharmaceutical industry in the state.

In a similar vein, future researchers should explore ways in which the pharmaceutical industry may be able to (and, if need be, offered incentives to) more broadly participate in the state. In fact, as this study has shown, while the Eastern part of the state is being weighed down by the numerous demands on its infrastructure, the rest of the state has virtually no participation in the evolving (implicit) partnership with the industry. Certainly such is because of the concentration in the area of universities, hospitals, and other organizations that complement drug research and manufacture. Yet, the vast stretches of almost barren land outside Route 495 could be utilized to accomplish the dual objectives of relieving pressure on Boston and Cambridge, and of developing opportunities in the rest of the state for both the industry and the residents.

It is, no doubt, outside the scope of this project to recommend specific alternate sites for developing infrastructure that is conducive to drug research and manufacture. Yet, it is incumbent upon the state to seriously explore Western regions that may have such potential. In the spirit of initiating thinking in this regard, one possibility to explore might be better connections (e.g., fast rail link) between Boston/Cambridge area with Worcester, which in recent years has been successfully developing a biotechnology park around the University of Massachusetts Medical School. Another possibility that should be explored is the Greater Springfield area in Western Massachusetts. With a superb location at the intersection of prominent highways going East-West and North South, the city of Springfield connects important regions in the Eastern United States. In addition, Springfield not only has several technical schools that may serve as sources of a skilled workforce, the city also is geographically proximate to the University of Massachusetts and several liberal arts colleges in the Amherst-Hadley-Northampton region.

Another challenge confronting in the evolving participation of the pharmaceutical industry in the state is the wide variance in zoning laws and other regulations across different towns and cities. While some communities such as Worcester have made concerted efforts to shape local regulations to attract pharmaceutical manufacturing and R&D, industry executives note that many others continue to be uninformed about the industry’s potential to contribute. Many towns across the state remain skeptical, therefore, about drug research or manufacturing facilities locating inside their jurisdiction. Consequently, while a few communities are open to investments by the industry, others knowingly or unknowingly put forth impediments that get in the way of a wider participation of the industry in the state. It may be useful, therefore, for future researchers to explore ways in which the state might be able to present a common front to the pharmaceutical industry (and others as well), while simultaneously preserving the time-honored tradition of home rule so valued by local communities.
Additionally, in the course of doing business with the various state government agencies, pharmaceutical companies (like other businesses) often encounter challenges they are ill-equipped or poorly prepared to handle. While the oversight of the state is important in such legitimate matters as industrial zoning, employee safety, and environmental permitting, there are numerous knotty practical issues around coordinating with the many departments at the state and local levels. In order to realize the full potential from the implicit partnership between Massachusetts and the pharmaceutical industry, therefore, mechanisms need to be put in place to help the industry navigate through regulations and requirements at the various levels of the government. Hence, future researchers should explore the feasibility of and potential value from identifying experienced individuals (ombudsmen of sorts) – who would be dedicated to represent the development of the industry in the state and whose explicit job it would be to assist the pharmaceutical companies in getting through the red tape.

Along with focusing on the above fundamentals to explore ways to consolidate favorable developments already underway, future researchers should explore other indirect influences that may help enhance the attractiveness of the state to the industry. Some of the issues to consider are as follows:

- **Technology Licensing and Transfer** – The breakthrough biological and medical work in the academic research institutions in the state often finds its way into the real world of products and solutions to real problems. Some of these institutions have improved their ability to transfer out their technology by partnering with pharmaceutical and bio-pharmaceutical companies. Such partnerships not only bring in private monies to complement the limited funds for basic research; they also create pathways via which basic research can help improve the quality of life for the state’s residents. While some academic institutions have over time created an art form of transferring out the technology coming out of their laboratories, many other academic centers do not have the ability or the experience to participate in the commercial markets for research. Hence, future research should explore the feasibility of and the ways in which a larger set of academic institutions could participate in technology licensing and transfer in an organized, concerted fashion.

- **Clinical Trials** – Pursuant to the mandate by the FDA, the pharmaceutical industry routinely engages in clinical trials for new drugs under development, investing an estimated $5 billion on such activities nationwide last year. In addition to satisfying the FDA mandate, such trials are often previews of research-based solutions to existing medical problems that lack satisfactory cure. As such, they benefit the patients in search for cures and the medical professionals in search of remedies for costly recurring illnesses. Hence, there are significant benefits – both economic and health related – for hospitals from actively participating in clinical trials for new drugs. While some hospitals in the state have in the last several years organized themselves to attract clinical trials, many others have neither the knowledge nor the ability to reorganize their operations so as to benefit by participating in such practical medical research. Hence, future research should explore the feasibility of and the ways in which a larger set of hospitals could participate in industry-sponsored clinical trials in an organized, concerted fashion.

- **Early Stage Manufacturing** – Although traditional pharmaceutical manufacturing has a non-trivial presence in Massachusetts, it is unlikely that the state can in the long run effectively compete for
investments in manufacturing with many other low-cost locations around the world (such as Ireland and Puerto Rico). In contrast, manufacturing of bio-pharmaceuticals is a relatively recent phenomenon and many factors other than labor cost (e.g., proximity and control) play an important role in location decisions – particularly in the early stages of manufacture when the production methods have not been adequately stabilized and standardized. Given that Massachusetts has a high density of bio-pharmaceutical companies and most of these are in the product development stage, it is likely that the next several years will bring many of these companies the opportunity to build manufacturing plants for their first products. Rather than simply let such investments go elsewhere, consideration should be given to keep the early stage manufacturing of bio-pharmaceuticals within the state – perhaps in regions other than the congested eastern seaboard. Although it is not clear whether Massachusetts can be a viable location for bio-manufacturing in the long run, the importance of biotechnology industry in the state virtually mandates that a careful study of this issue should be undertaken.

In summary, the role that Massachusetts will play in the pharmaceutical industry of the next millenium will be driven by the strength of research in its universities and institutions, and by the ability of the general economic infrastructure to support investments. Conversely, the economic impact of the pharmaceutical industry on the Commonwealth will be greatly influenced by the perception about how attractive it is to make investments in the state and local economies. Ultimately, the strength of industry ties in the state will be influenced by the perceived productivity of investments made by individual companies.
PREFACE

Man’s search for cure is almost as old as antiquity itself; yet, the pharmaceutical enterprise today is as “high-tech” and sophisticated as it gets – and, ironically, highly controversial too. In fact, the modern pharmaceutical industry is so rich in paradoxes that it is worthwhile to outline some salient issues briefly here at the beginning of the report.

• The industry is considered one of the most profitable in the U.S. economy; yet, it is also one of the most intensely competitive, with even the blockbuster drugs under pressure from new generation products, from imminent generic copies, and from emergent institutions wrestling to control the escalating costs of healthcare. Interestingly, competition in the industry is driven by innovation, as companies try to escape pricing pressure by developing innovative therapies. This in turn encourages expensive investments in state-of-the-art research facilities and sophisticated marketing operations.

• The industry is granted patent protection in the hope of preserving incentives for private firms to innovate; yet, it is one of the most highly regulated to ensure that the products the industry research puts out are safe and effective against target diseases. Regulation shortens effective patent life, but also protects the industry’s reputation and the market for drugs from potential fly-by-night operators.

• The industry is praised for the breakthrough research that results in products that alleviate pain and suffering, and that save lives; yet, it is criticized for spending too much money on marketing deemed necessary by the trade for disseminating information about the products and their correct uses. The scientific research in the labs is invisible (perhaps irrelevant) to a patient paying up at the pharmacy, unlike the obviously expensive advertising and education materials aimed at consumers/professionals.

• The industry’s products are typically less expensive and less intrusive than healthcare alternatives such as recurrent doctor visits, hospital stays, and surgery; yet, the industry is constantly taken to task for the seemingly high inflation in prices that patients pay at their local pharmacy.

• Pharmaceutical products are the first line of defense against most illnesses; yet they are among the least visible of all means for improving health available in the healthcare system. The details about the manner in which a drug interacts with and relieves the body of an illness are out of sight and beyond the comprehension of typical patients – unlike, say, the tangible signs of recovery from surgery.

• In physical appearance, the drugs that people consume seem very simple products, almost commodity-like (no different than placebo); yet, the discovery, development, and manufacture (lately, also distribution and marketing) activities are some of the most sophisticated across all economic sectors.

Perhaps the most important reason that the pharmaceutical industry is sometimes highly controversial in the public arena is that, as one executive noted, drugs are intricately related to the quality of life issues of virtually everyone. Unlike other products such as, say, computers or cars or dining out, drugs are necessary for
relief from bodily discomfort when people are ill. One can be without a computer or even avoid eating out if money is tight, but not being able to afford medicine to contain pain from arthritis, to use one example, is simply not acceptable to most Americans. When combined, therefore, with the fact that investments in discovery, development, and manufacture of drugs are dispersed throughout the globe – such that consumers cannot identify with the challenges of supplying a cure – the expenditures on drugs become highly charged local issues.

The paradoxes raised above are immensely deep, however, and the limited resources available put an elaborate discussion beyond the scope of this project. While a broad understanding of issues is important to put things in perspective, therefore, the focus here is on understanding – and documenting to the extent possible – the role that the pharmaceutical industry plays within the boundaries of the Commonwealth of Massachusetts. For those who might be interested in obtaining a general understanding of the industry, I have included an appendix that comprises some relevant materials about history, competition, manufacturing, and research in the pharmaceutical industry at large. In the body of the report, however, the focus is maintained on understanding the nature of the presence of the pharmaceutical industry in the Commonwealth of Massachusetts.

Acknowledgements

To anyone who has been involved in economic impact studies, it should be clear that it takes several committed individuals to produce a product as this one. To borrow the famous words of a popular public figure of our times, “it takes a village” to raise an idea from abstraction to tangible product. So let me take a few lines to acknowledge the confederation of high quality people who have made this project possible.

One name that immediately comes to mind is Craig Moore, who recruited me to research and write about the pharmaceutical industry in Massachusetts. Craig has been for some time trying to assemble a team of University of Massachusetts faculty who would make the investment to learn about and over time become experts in particular spheres of economic activity in the Commonwealth. After listening to his presentation on the telecommunications industry some years ago, I had mentioned to Craig that I would be interested in working on the pharmaceutical industry – my interest driven largely by the perception that the industry is issue-rich and, therefore, a researcher’s delight. So, when Craig brought this project to me last fall, I was easily persuaded to explore and invest and learn about the industry. Ever since, he has been an important presence in this project, and he has been very generous with advice, both technical and inspirational.

I want to thank Steve Landau of The Donahue Institute and Jennifer Peck of The Rasky/Baerlein Group. Steve and Jennifer have been absolutely instrumental in getting this project done, and it is no exaggeration to say that the project just could not have been done without their numerous contributions. In spite of being new in the job, Steve has skillfully protected me from numerous administrative and contractual issues that are integral to working on such projects in a university setting. His ready availability and keen insights were invaluable throughout the project. Jennifer has been instrumental in keeping open the lines of communication with the Pharmaceutical Research and Manufacturers of America (PhRMA) and member companies. Her genuine eagerness to help with industry information were beyond the call of duty, and her patience and persistence were key to bringing this project to fruition.
I am grateful to Bob Nakosteen, Executive Editor of Massachusetts Benchmarks, for his friendly encouragement. His experience and wisdom were invaluable during challenging times. I want to thank Tom O’Brien, Dean of Isenberg School of Management, for his generous support during this assignment, and Tom Chmura, Vice President for Economic Development at the University for all his efforts in making this project possible. I thank Janice Bourque, Executive Director of Massachusetts Biotechnology Council, for help with the mail survey and for hosting a focus group with industry executives. I am also grateful, of course, for the many industry executives who participated in this project in various ways.

In addition, I much appreciate Mr. Chad Cook, Mr. Chou Lu, and Ms. Rebecca Lovelace for their superb help with the collection and organization of data. I also thank Ms. Sue Bridge for writing the first drafts of the three sidebars included in the report.

I would like to especially thank members of the panel of reviewers who provided constructive critique and suggestions for improvement to the penultimate draft of the report.

Of course, the views expressed in this report remain my own and interpretations of industry executives I met during the course of the project. The report does not necessarily reflect the positions of other individuals and institutions involved in the project. I have taken care to accurately represent what I have learned about the pharmaceutical industry in the Commonwealth. Even so, I take full responsibility for any unintentional errors of commission or omission.

Anurag Sharma
Amherst, MA
May, 1999
Economic Impact Of The Pharmaceutical Industry
Massachusetts

TABLE OF CONTENTS

Executive Summary
Preface
Table of Contents
List of Charts & Tables
Chapter 1: Introduction
Chapter 2: Definitions and Sources of Data
Chapter 3: Pharmaceutical Industry in Massachusetts
Chapter 4: Medical Research in Massachusetts
Chapter 5: Summary of Impact on the State
Chapter 6: Future of the Industry in the State
Chapter 7: Conclusion

SIDEBARS

Box 1: Meeting the Challenge of AIDS
Box 2: Innovation is Strength
Box 3: Risky Business of Innovation

APPENDIX

Appendix 1: Results of the UMass Mail Survey
Appendix 2: Note On The Pharmaceutical Industry
Appendix 3: Note on Drug Discovery & Development
Appendix 4: Note on Drug Manufacturing
LIST OF CHARTS & TABLES

Map 1 Distribution of Drug Manufacturing In Massachusetts
Map 2 Distribution of Biological, Biotechnical, & Medical Research Massachusetts

Figure A2.1 Drug Discovery & Development

Table 2.1 Description of Standard Industrial Classification Codes
Table 3.1 Establishments in Massachusetts, 1995-1998
Table 3.2 Employment in Massachusetts, 1995-1998
Table 3.3 Distribution of Manufacturing Establishments by Size, Massachusetts 1995 & 1998
Table 3.4 Distribution of Research Establishments by Size, Massachusetts 1995 & 1998
Table 3.5 Industry Presence by County, 1998
Table 3.6 Quarterly Wages & Payroll in Massachusetts, 1995-1998
Table 3.7 Other Economic Variables
Table 3.8 Shift Share Analysis For Establishments
Table 3.9 Shift Share Analysis For Employment
Table 4.1 Top Five States Receiving Support From NIH, 1994-1998
Table 4.2 Top Five Cities Receiving Support From NIH, 1994-1998
Table 4.3 Ranked Cities In Massachusetts Receiving Support From NIH, 1994-1998
Table 4.4 NIH Support For Institutions In Massachusetts
Table 4.5 NIH Funds To Massachusetts By District
Table 5.1 Diseases and Conditions Targeted by Firms in Massachusetts: Bio-Pharmaceutical Companies
Table 5.2 Diseases and Conditions Targeted by Firms in Massachusetts: Pharmaceutical Companies
Table 5.3 Sources of Research Support for Bio-Pharmaceutical Companies
Table 5.4 Expenditures on Research & Clinical Trials in Massachusetts, 1995-1997
Table 5.5 Industry Network in Massachusetts
Table 5.6 Industry-University Partnerships in Massachusetts
Table 5.7 Summary of Industry-University Partnerships
Table 5.8 Employment & Payroll in Massachusetts, 1997 & 1998 (Estimated)
Table 5.9 Expected Increase in Employment, 1998-2000
Table 5.10 Taxes to the Commonwealth, 1996-1998
Table 5.11 Expansion in the State, 1998-2000
Table 5.12 Projected Investments, 1998-2000
Table A3.1 Economic Sectors Providing Inputs into Drug Manufacturing
Table A3.2 Economic Sectors Consuming Outputs of Drug Manufacturing
Table A3.3 Occupations Employed by Drug Manufacturing Sector
Table A3.4 Selected Ratios for Drug Manufacturing
Chapter 1

INTRODUCTION

The research reported in this document is focused on the economic impact of pharmaceutical industry on Massachusetts. Its particular objective is to quantify to the extent possible the employment and investment effects of drug discovery, development, and manufacture in the state. To this end, the report is based on observations made from at least three different sources: (1) archival data collected by the various government and private organizations, (2) mail surveys conducted by the University of Massachusetts and (3) focus groups involving industry executives.

The chief conclusion of the research reported here is that the pharmaceutical industry has significant and growing presence in the state. The research, manufacturing, and wholesale segments of the drug industry provided over 25,000 jobs in Massachusetts during the first quarter of 1998 – up 40% since the last quarter of 1995. Reflecting the geographic concentration of the industry, however, most of these jobs are located in the densely populated eastern seaboard – particularly in the Greater Boston area.

It is estimated, moreover, that in 1998 the drug industry in Massachusetts shipped over $1.6 billion worth of goods and it provided almost $1.2 billion in manufacturing value added. Although non-trivial, however, the contribution of drug manufacturing is arguably of lesser import to the local economy than is the collective impact of drug-related research in the state. In 1998, for example, while about 3% of all drug manufacturing establishments in the United States were in Massachusetts, over 7% of commercial research establishments in the nation were located in the Commonwealth. Similarly, while just 2% of all drug manufacturing employment in the country were in Massachusetts, over 16% of commercial research employment in the nation were located in the Commonwealth.

In fact, the report shows that Massachusetts is on the leading edge of biological, biotechnical, and medical research in the Union. The commonwealth is second only to California, for instance, in obtaining research monies from the National Institutes of Health – getting almost $1.2 billion (or 10.5%) of the $11.2 billion in intramural research funds distributed by NIH in 1998. Public support for medical research attests to the fact that the state has a rich and highly effective network of superb research universities and teaching hospitals. It is no surprise, therefore, that the pharmaceutical industry complements the public investment by itself aggressively supporting medical research in the institutions in the state. In so doing, the industry both benefits from and contributes to the building a competitive research infrastructure in Massachusetts.

According to a survey administered for this study, thirty-two companies (that responded to a questionnaire) plan to invest over $1.36 billion in research and clinical trials in Massachusetts during the 1998-2000 period. This represent an increase of 30% over what these same companies indicated they spent on research in the state during the preceding three years. In a similar vein, the survey indicated that these thirty-two companies are deeply embedded in the local research institutions – nurturing almost 400 linkages (for clinical trials, licensing, basic research, and technology transfer) with academic and non-academic institutions/organizations in the Commonwealth.
While the quantifiable impact on the state economy is impressive, however, it pales in comparison to the strategic role that the pharmaceutical industry can play (arguably it already does) in sustaining and promoting medical research in Massachusetts. This is because the industry's fundamental need for breakthrough (or blockbuster) drugs can be eminently fed with the extremely robust network of research institutions and teaching hospitals – particularly those in and around the Greater Boston area. Through the private actions of intensely competitive member companies, therefore, the industry invests hundreds of millions of dollars annually in the research institutions located in the Commonwealth. In so doing, the pharmaceutical industry effectively participates as a (yet unnoticed) private partner in the (as yet unrecognized) bid of the state to strengthen its persistently evolving strength in biological, biotechnical, and medical research. There is, in other words, a natural alignment between the interests of the pharmaceutical industry and those of the research institutions in Massachusetts.

Following this introduction is Chapter 2 where the pharmaceutical industry is defined along the lines of standard industrial classification (SIC) system used by federal government’s Office of Management and Budget. Also discussed in the same section are the chief sources of archival data used in the study to estimate the values of several economic variables as they relate to the industry in the commonwealth.

Chapter 3 is devoted to presenting the data on several economic variables for the pharmaceutical industry in the state. Employment, establishments, wages and payroll, value added of manufacture, and other variables are reported by SIC codes for research, manufacture, and wholesale of drugs. In addition, also discussed are the relative shares of pharmaceuticals-related employment and establishments in Massachusetts as compared to the rest of the country.

In Chapter 4, the larger picture of medical research in Massachusetts is discussed – particularly with respect to the role the National Institutes of Health in funding basic research and the role of pharmaceutical industry in creating pathways for basic science to mature into practical applications.

Based on the analyses reported in preceding parts of the report, Chapter 5 is a short summary of the pharmaceutical industry’s economic impact on Massachusetts. This is followed by some comments in Chapter 6 on the future of the industry in the state. Concluding comments are presented in Chapter 7.

The report also includes four appendices. In Appendix 1, the methods and results of a mail survey are discussed. In spite of the best efforts of many people and the good work of some companies that took the time to cooperate, the response rate to the survey was lukewarm at best. Hence, it is not possible to report statistically generalizable results – those that apply to non-respondents as well. A decision was made, therefore, to report aggregate numbers for the entire, rather small, group of companies that did fill out the survey. As such, the survey data captures the lower bound of values for items in the survey.

Appendices 2 through 4 provide a background materials for readers who may not be familiar with the history. Appendix 2 is a note on the history of and competitive dynamics within the pharmaceutical industry. Appendix 3 is a note on the process of drug discovery and development in the industry. Appendix 4 is a note on the nature of drug manufacturing vis-à-vis the manufacturing sector at large.
Chapter 2

DEFINITIONS & DATA SOURCES

The pharmaceutical industry defies simple definition. Both geographic and product boundaries of the industry are elusive. It is a truly global industry in which the member companies have substantial operations in many different countries. The small size of product units makes transportation relatively small part of the total delivered cost, and, as a result, drugs conceived and produced in one location can be easily made available in virtually any other part of the world. Because the discovery, development, and manufacturing operations of pharmaceutical companies are typically dispersed across many locations worldwide, it is often difficult if not impossible to determine where particular drugs originated. It is, therefore, perhaps meaningless to put geographical bounds on the pharmaceutical industry as a whole.

Moreover, the products that the industry produces range from ordinary vitamins to very sophisticated life-saving drugs developed by highly talented scientists working in state-of-the-art research laboratories. Defining where the industry begins and where it ends in terms of the products is, therefore, at least partly a matter of taste – and, in the end, a bit arbitrary. While some of the core drug products can be classified as clearly having medicinal value, many others evade easy classification because of their appearance as drugs, for instance, but serving cosmetic ends, or vice versa.

In addition, the definition of what a drug is and what it is not is further complicated by the fundamental changes currently under way in the pharmaceutical industry. The emergence of biotechnology as a major force in the discovery and development of drugs blurs the boundaries between products that have medicinal value for people and that have, say, productivity enhancing value in such diverse areas as environmental pollution, agriculture, food quality, or fine chemicals. Similarly, rapid developments in medical diagnostics, drug delivery, and medical devices blur the boundaries between a “pure” drug that has therapeutic value and a pharmaceutical product that is integral to a form of delivery or to a medical device.

Finally, drugs are part of the total healthcare system. People, to paraphrase a famous marketing insight, are not looking to buy drugs; what they want is to get better (or to not get ill at all). And while drugs do play an important role – often as the first line of defense against illness but also in other ways as diseases progress – they are but a part of a larger system of healthcare that includes such things as nutrition, doctor visits, surgery, physical therapy, and rehabilitation. In fact, according to a report by the Congressional Budget Office, spending on prescription drugs in the United States accounted for less than 6.5% of the national health expenditures in 1990. Even so, because the inflation in the retail price of drugs is believed to be high, the pricing of pharmaceuticals has been a controversial and much debated issue.

Notwithstanding the difficulties with defining the pharmaceutical industry, attempts have been made to classify the producers of pharmaceuticals under the Standard Industrial Classification system by the federal government’s Office of Management and Budget. For the purpose of this report, therefore, the SIC codes were used to locate organizations and entities that were engaged in pharmaceutical-related activities.
Traditionally, the manufacturing sector of the pharmaceutical industry has been classified as being part of the Chemical and Allied Products Group (SIC 28). The group entitled “Drugs” (or SIC 283) includes establishments primarily engaged in manufacturing, fabricating, or processing medicinal chemicals and pharmaceuticals. These are:¹

1. **SIC 2833, Medicinal Chemical and Botanical Products**

This classification covers establishments primarily engaged in manufacturing bulk organic and inorganic medicinal chemicals and their derivatives and processing – grading, grinding, milling – bulk botanical drugs and herbs. Included in this industry are establishments primarily engaged in manufacturing agar-agar and similar products of natural origin, endocrine products, manufacturing or isolating basic vitamins, and isolating active medicinal principals from botanical drugs and herbs.

2. **SIC 2834, Pharmaceutical Preparations**

This industry includes establishments primarily engaged in manufacturing, fabricating, or processing drugs in pharmaceutical preparations for human or veterinary use. The greater part of the products of these establishments are finished in the form intended for final consumption, such as ampoules, tablets, capsules, vials, ointments, medicinal powders, solutions, and suspensions. Products of this industry consist of two important lines, namely: pharmaceutical preparations, promoted primarily to the dental, medical, or veterinary profession; and pharmaceutical preparations promoted to the public.

3. **SIC 2835, In Vitro and In Vivo Diagnostic Substances**

This category covers establishments primarily engaged in manufacturing in vitro (“in glass,” such as a test tube) and in vivo (“in the body”) diagnostic substances, whether or not packaged for retail sale. These materials are chemical, biological, or radioactive substances used in diagnosing or monitoring the state of human or veterinary health by identifying and measuring normal or abnormal constituents of body fluids or tissues.

4. **SIC 2836, Biological Products, Except Diagnostic Substances**

This category covers establishments primarily engaged in the production of bacterial and virus vaccines, toxoids, and analogous products (such as allergenic extracts), serums, plasmas, and other blood derivatives for human or veterinary use, other than in vitro and in vivo diagnostic substances. Included in this industry are establishments primarily engaged in the production of microbiological products for other uses.

¹ Encyclopedia of American Industries, Second Edition. Text verbatim from pages (1) 546, (2) 551, (3) 561, and (4) 562, respectively.
The wholesale sector of the pharmaceutical industry is designated SIC 5122, and it is defined as:

1. **SIC 5122, Drugs, Drug Proprietaries, and Druggists’ Sundries**

   Establishments primarily engaged in the wholesale distribution of prescription drugs, proprietary drugs, druggists’ sundries, and toiletries.

The research activities and outputs of the pharmaceutical industry are subsumed in the larger category SIC 8731 within the service sector of the economy, which is defined as follows:

1. **SIC 8731, Commercial Physical and Biological Research**

   Establishments primarily engaged in commercial physical and biological research and development on a contract or fee basis. [Within this larger category, however, finer distinctions are available through a commercial database so that it is possible to locate those establishments engaged in biological research (SIC 8731-0100), biotechnical research (SIC 8731-0102), and medical research (SIC 8731-9902).]

The above three groups of establishments cover the research, manufacture, and distribution of pharmaceutical products, and they were, therefore, the primary focus of this study. In addition, an attempt was also made to locate those establishments that were engaged in the retail trade. Such were defined as follows:

1. **SIC 5912, Drug Stores and Proprietary Stores**

   Establishments engaged in the retail sale of prescription drugs, proprietary drugs, and nonprescription medicines, and which may also carry a number of related lines such as cosmetics, toiletries, tobacco, and novelty merchandise. These stores are included on the basis of their usual trade designation rather than on the stricter interpretation of commodities handled. This industry includes stores which also operate a soda fountain or lunch counter.

In summary, the industry classifications used for this study are as follows:

<table>
<thead>
<tr>
<th>SIC</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>283</td>
<td>Drugs</td>
</tr>
<tr>
<td>2833</td>
<td>Medicinals and Botanicals</td>
</tr>
<tr>
<td>2834</td>
<td>Pharmaceutical Preparations</td>
</tr>
<tr>
<td>2835</td>
<td>Diagnostic Substances</td>
</tr>
<tr>
<td>2836</td>
<td>Biological Products Except Diagnostics</td>
</tr>
<tr>
<td>5122</td>
<td>Pharmaceutical Wholesale</td>
</tr>
<tr>
<td>8731</td>
<td>Commercial Physical and Biological Research</td>
</tr>
<tr>
<td>8731-0100</td>
<td>Biological Research</td>
</tr>
<tr>
<td>8731-0102</td>
<td>Biotechnical Research</td>
</tr>
<tr>
<td>8731-9902</td>
<td>Medical Research</td>
</tr>
<tr>
<td>5912</td>
<td>Drug Stores and Proprietary Stores</td>
</tr>
</tbody>
</table>
Archival Sources of the Data

Using the above definitions, three archival sources of economic data were used to estimate the impact of pharmaceutical manufacturing on select economic variables in the state. The first source is the employment and wages data from the Division of Employment and Training (DET) of Massachusetts. The data reported by DET have a special characteristic in that they include only those employees that are covered by State Unemployment Insurance (UI) laws and, in the case of federal civilian workers, by the Unemployment Compensation For Federal Employees (UCFE) program. In what is known as the Covered Employment and Wages, or ES-202, program, the data are derived from quarterly tax reports submitted to State employment security agencies by employers subjected to UI and UCFE laws.

Note that, depending on the industry, DET probably under-reports employment data for the industry because it does not include employees that are not covered under the unemployment insurance laws. The figures typically would not include contract workers supplied into the pharmaceutical industry, for instance. Similarly, the DET data do not include employment numbers associated with auxiliary units (such as off-site administrative offices, warehouses, research & development laboratories) that may be assigned an industrial classification different from the manufacturing establishments they serve in the state or elsewhere. It is likely, therefore, that these data deflates the employment numbers by as much as 15 percent.

The second data source considered for analysis here is the Annual Survey of Manufactures (ASM) reported as Official Statistics of the Census Bureau. Unlike DET, ASM reports not only total employment and payroll but also several other economic variables such as cost of materials, value added by manufacture, value of shipments, and capital expenditures. These data are collected at the national level, however, and numbers for each state are allocated based on mailing address on the returned surveys. Consequently, ASM is less reliable for state level data -- except for those years when the survey numbers are expressly reconciled with other reporting services such as County Business Patterns and DET. The last year when such reconciliation took place was 1992. Unfortunately, therefore, it was not possible to use ASM figures and a decision was made to use only relevant ratios derived from 1992 ASM data tables. The ratios so obtained were then applied to more recent data from DET to obtain estimates about a range of variables for Massachusetts.

Notwithstanding such limitations, DET and ASM data complement each other because together they provide a sense of the overall economic activity associated with a manufacturing industry in the state.

Finally, to complement DET and ASM, data on number of establishments are obtained from Dun & Bradstreet (D&B) Information Services. Unlike the government sources, D&B are a private enterprise and its data gathering activities are targeted at the business rather than research community. In addition, D&B do not have the power of the state to force compliance in reporting. Yet, D&B are very meticulous about identifying each business site and reporting the name and address of each business unit included in the database. Unlike DET and ASM, moreover, D&B include business establishments of all sizes, including those that have very low employment. Hence, in addition to obtaining the count of establishments in the drug manufacturing and research sector, the data from D&B are also used to obtain appropriate ratios that could then be applied to the data obtained or estimated from DET.
Chapter 3

DRUG INDUSTRY IN MASSACHUSETTS

In order to quantify the presence of the drug industry in Massachusetts, estimates are made for values of several economic variables for which data were publicly available. Hence, discussed below are numbers for industry-related establishments in the state, employment, distribution of industry presence in the state by size, wages and payroll, as well as several other aggregate economic variables. Finally, the presence of the drug industry in Massachusetts is evaluated vis-à-vis some nationwide aggregate numbers.

Establishments

The data on the number of establishments in the drug sector in Massachusetts are shown in Table 3.1. As reported by Dun & Bradstreet, the number of separate locations involved in the manufacture of pharmaceuticals grew 35% from 86 in 1995 to 116 in 1998 (t-stat=7.35, p=0.18). Most of the establishments were involved in manufacturing traditional pharmaceutical products. In 1998, 66 of 116 establishments were involved in pharmaceutical preparations (SIC 2834) and 22 establishments were involved in the manufacture of diagnostic substances (SIC 2835). The remaining 28 establishments in 1998 were evenly divided between medicinal/chemical/botanical (SIC 2833) and biological products (2836).

The number of separate locations involved in commercial research in biological, biotechnical, and medical sciences grew 24% from 89 in the last quarter of 1995 to 110 in the last quarter of 1998 (t-stat =3.05, p=0.09). There was more or less even distribution of these establishments. In 1998, 34 establishments were devoted to biological research, 37 establishments were involved in commercial biotechnical research, and 39 establishments were classified as commercial medical research units.

Note also that the number of separate locations involved in the wholesale sector of the drug industry grew 7% from 96 in 1995 to 103 in 1998 (not a trend). Yet, the trend across the three sectors of the pharmaceutical industry was positive and marginally statistically significant (t-stat =3.84, p=0.06).

### TABLE 3.1

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture</td>
<td>283</td>
<td>116</td>
<td>101</td>
<td>93</td>
<td>86</td>
</tr>
<tr>
<td>Wholesale</td>
<td>5122</td>
<td>103</td>
<td>100</td>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>Research</td>
<td>8731</td>
<td>110</td>
<td>102</td>
<td>86</td>
<td>89</td>
</tr>
<tr>
<td>TOTAL</td>
<td>All</td>
<td>329</td>
<td>303</td>
<td>269</td>
<td>271</td>
</tr>
</tbody>
</table>

Analysis of trends: α – p<.01, β – p<.05, γ – p<.10

Source: Division of Employment and Training, Massachusetts
Employment

The data on employment in the drug manufacturing sector (SIC 283) in Massachusetts are shown in Table 3.2. As reported by DET, the number of covered employees grew 43% from an average of 5,255 in the fourth quarter of 1993 to an average of 7,499 in same period of 1997—and then, in the first quarter of 1998, DET reported manufacturing employment as 7,365 \((t=3.14, p=0.09)\). Note that most (over 85 percent) of the employment was in the manufacture of traditional products – that is pharmaceutical preparations and diagnostic substances (SIC Codes 2834 and 2835).

Other than the manufacturing sector, drug industry also provides employment in other sectors of the Massachusetts economy. Research and development, for instance, is an important element in the entire drug enterprise. Unlike manufacturing, however, clear numbers for employment in drug research are not available. So, the starting point for making an assessment about employment in the drug research are the data available for SIC code 8731, which refers to commercial physical and biological research establishments.

Unfortunately, since DET does not desegregate the industry data beyond 4-digit SIC code, it is not possible to know the proportion of such employment in SIC 8731 that is attributable to the pharmaceutical industry. Hence, using employment numbers from 8-digit SIC data obtained from D&B, estimates were made of the proportion of 1998 total employment in SIC 8731 was in the areas of biological, biotechnical, chemical, and medical research. It was assumed that this proportion reflects employment in commercial research that is related to drug discovery and development. It was estimated, therefore, that the number of covered employees in the research sector of the industry grew about 59% from an average of 5,872 in the fourth quarter of 1993 to an average of 9,319 in the same period of 1997. In the first quarter of 1998, DET numbers yielded an estimated the average monthly employment as 12,538 for biological, biotechnical, chemical, and medical research organizations \((t=6.50, p=0.02)\).

Finally, the drug wholesale sector also provided nontrivial employment in Massachusetts during the period under consideration. As reported by DET, the number of covered employees in drug wholesale (SIC 5122) grew 39% from an average of 4,328 in the fourth quarter of 1993 to an average of 6,028 in same period of 1997. In the first quarter of 1998, DET reported the total “covered” employment of 5,885 in the drug wholesale sector in the Commonwealth (statistically non-significant trend).

Based on estimates made from DET data, then, the combined average monthly “covered” employment in drug research, manufacturing, and wholesale trade is estimated as an average of 25,778 during the first quarter of 1998 (a positive upward trend since 1995 – \(t\)-statistic 14.3, \(p=0.004\)). Seventy-seven percent of this total was in the research and manufacturing sector. Note also that, with over 200% employment growth between 1995 and 1998, the research sector of the drug industry (SIC 8731) appears to gaining the most ground in the state.

*Pharmaceuticals/Massachusetts*
*Anurag Sharma, May 1999*
TABLE 3.2

Employment in Massachusetts, 1995-1998

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture</td>
<td>283γ</td>
<td>7,365</td>
<td>7,499</td>
<td>6,801</td>
<td>6,292</td>
</tr>
<tr>
<td>Wholesale</td>
<td>5122</td>
<td>5,885</td>
<td>6,028</td>
<td>6,210</td>
<td>6,016</td>
</tr>
<tr>
<td>Research</td>
<td>8731β</td>
<td>12,538</td>
<td>9,319</td>
<td>7,297</td>
<td>6,137</td>
</tr>
<tr>
<td>TOTAL</td>
<td>Allα</td>
<td>25,788</td>
<td>22,846</td>
<td>20,308</td>
<td>18,445</td>
</tr>
</tbody>
</table>

Analysis of trends: α – p<.01, β – p<.05, γ – p<.10

Source: Division of Employment and Training, Massachusetts

Total indirect employment attributable to the pharmaceutical industry is more difficult to estimate. This is because a wide range of sundry product and services consumed by the research, manufacturing, and wholesale activities in the state are just too numerous and, undoubtedly, deeply diffused in the larger economy. It is not practical, therefore, to estimate accurately and exhaustively the extent to which the pharmaceutical industry supports of employment in these other sectors of the state economy.

Even so, it should be noted that employment generated by the retail sector is larger than the combined employment in research, manufacturing, or wholesale sectors. According to DET data, average monthly employment in drug retail (SIC 5912) grew almost 20% from 17,066 in the fourth quarter of 1993 to 20,396 in the fourth quarter of 1997. This represents a compounded growth rate of 4.6% per year, which when applied to the following year gives an estimated employment of 21,334 in the fourth quarter of 1998.

Note that the above statistics indicate only “direct” employment in the drug research, manufacture, and wholesale activities in the state, as measured by conventional yardsticks. Indirect employment and wages provided by the industry are more difficult to estimate. Yet, it is clear that the actual numbers of jobs that could be related to the pharmaceutical industry is much larger than what the above statistics show. And that is because of several reasons.

First, the numbers above do not include employment and wages in the retail sector of the pharmaceutical industry – partly under the assumption that independent and chain pharmacies can exist in a state even if the research, manufacturing, and wholesale segments are absent. Even so, broadly conceived, pharmaceutical industry should arguably include retail pharmacies in its definition. According to DET, the average monthly employment (with employment insurance) in the drug retail sector in the state grew 20% from 17,066 in the fourth quarter of 1993 to 20,396 in the fourth quarter of 1997. In the first quarter of 1998, DET reports that the average monthly employment in drug retail establishments was 20,378.
Second, the employment and wage information is obtained from the Massachusetts Division of Employment and Training. Since only jobs with unemployment insurance are included in the DET count, however, the numbers are lower than actual industry employment in the state. All contract employees who are not correctly assigned to a particular industry do not show up in the employment and wages figures. It is likely that this characteristic of the data deflates the employment numbers by as much as 15 percent.

Third, the DET numbers for the drug manufacturing or research sectors do not include employment in such activities as sales and marketing, which are important and labor intensive functions in the overall drug enterprise. Pharmaceutical companies that do not have manufacturing or research presence in Massachusetts do still have sales and marketing presence that is not accounted for in the numbers above. They show up elsewhere.

Fourth, it is particularly difficult to estimate the employment provided by other business sectors that supply business services to the pharmaceutical industry in the state. The routine business needs of firms in the industry require and sustain at least partly employment in such diverse areas as professional services like insurance, law, and management consulting. The industry also supports employment in building and construction companies that specialize in manufacturing pharmaceutical equipment or in setting up pharmaceutical related research, manufacturing, and distribution facilities. In addition, employment in other areas of healthcare such as hospitals may be partly supported by clinical trials initiated by the pharmaceutical companies.

Hence, the employment statistics are likely to underestimate the total employment impact of the pharmaceutical industry on the state. The actual employment is very difficult to find, however, and it can only be guestimated based on some very rough assumptions about certain ratios. Given the large extent to which the pharmaceutical industry is interconnected with other sectors of the economy, it may be that for every job in the research, manufacturing, and wholesale sectors of the drug industry there is at least one indirect job in the state.

**Distribution of the Drug Industry by Size and Geography**

As shown in Table 3.3, there is a great deal of variation in the size of drug manufacturing establishments in Massachusetts. According to Dun & Bradstreet data, for instance, 69% of establishments in 1995 and 67% of those in 1998 employed less than 50 employees. On the flip side, 13% of establishments in 1995 and 11% of those in 1998 employed 100 or more people. In contrast, most of the employment in drug manufacturing was concentrated in a few large establishments. In 1995, for instance, 78% of the known employment was in the 11 establishments employing 100 or more people – in 1998, 13 establishments accounted for 80% of the known employment. Note that employment figures were not available for 11 establishments in 1995 and for 21 establishments in 1998. Hence, the overall employment in drug manufacturing in the state is lower that that reported in the DET data for corresponding periods. The accuracy of distribution of employment by size of the establishment is, therefore, limited by the limitations of the Dun & Bradstreet data used.
TABLE 3.3

Distribution of Manufacturing Establishments by Size, Massachusetts 1995 & 1998
(Drug Manufacturing, SIC 283)

<table>
<thead>
<tr>
<th>Size of Establishment (Employees)</th>
<th>Establishments</th>
<th>Total Employment</th>
<th>Average Employment Per Establishment</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>3</td>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>2 to 4</td>
<td>17</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>5 to 9</td>
<td>13</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>10 to 24</td>
<td>18</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>25 to 49</td>
<td>9</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>50 to 99</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>100 to 249</td>
<td>6</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>250 to 499</td>
<td>4</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>500 &amp; Above</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Total/Average</td>
<td>86</td>
<td>116</td>
<td>4,214</td>
</tr>
</tbody>
</table>

Note: The employment numbers reported by above are lower than those reported by the Massachusetts Division of Employment and Training (DET). Yet, D&B numbers are used here to obtain the detail not supplied by DET.

Source: Dun & Bradstreet

For drug-related research establishments in Massachusetts, Table 3.4 shows that the distribution of establishments by size is even more skewed than that for manufacturing establishments. In 1995, for instance, 74% of establishments in 1995 and 75% of those in 1998 had less than 50 employees. On the flip side, 13% of establishments in 1995 and 14% of those in 1998 employed 100 or more people. In contrast, however, most of the employment in drug-related research was concentrated in a few large establishments – although to a lesser extent than in manufacturing. In 1995, for instance, 55% of the known employment was in the 12 establishments employing 100 or more people. This proportion had grown to 71% by 15 establishments in 1998. Note that while there was no establishment employing more than 250 people in 1995, 3 establishments fell in this size range in 1998. Note also that, as in the case of numbers for drug manufacturing, employment figures were not available for 3 research establishments in 1995 and for 2 establishments in 1998. Hence, the overall employment in drug-related research in the state is likely to be slightly lower that that reported in the DET data for corresponding periods.
### TABLE 3.4

**Distribution of Research Establishments by Size, Massachusetts 1995 & 1998**

*Biological, Biotechnical, and Medical Research, SICs 8731-0100, 8731-0102, 8731-9902*

<table>
<thead>
<tr>
<th>Size of Establishment (Employees)</th>
<th>Establishments</th>
<th>Total Employment</th>
<th>Average Employment</th>
</tr>
</thead>
<tbody>
<tr>
<td>One</td>
<td>4</td>
<td>4</td>
<td>33%</td>
</tr>
<tr>
<td>2 to 4</td>
<td>25</td>
<td>28</td>
<td>26%</td>
</tr>
<tr>
<td>5 to 9</td>
<td>19</td>
<td>21</td>
<td>20%</td>
</tr>
<tr>
<td>10 to 24</td>
<td>10</td>
<td>11</td>
<td>16%</td>
</tr>
<tr>
<td>25 to 49</td>
<td>8</td>
<td>9</td>
<td>17%</td>
</tr>
<tr>
<td>50 to 99</td>
<td>8</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td>100 to 249</td>
<td>12</td>
<td>13</td>
<td>12%</td>
</tr>
<tr>
<td>250 to 499</td>
<td>0</td>
<td>-----</td>
<td>2%</td>
</tr>
<tr>
<td>500 &amp; Above</td>
<td>0</td>
<td>-----</td>
<td>1%</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>3</td>
<td>2%</td>
</tr>
<tr>
<td>Total/Average</td>
<td>89</td>
<td>110</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The employment numbers reported above are lower than those reported by the Massachusetts Division of Employment and Training (DET). Yet, D&B numbers are used here to obtain the detail not supplied by DET.

**Source:** Dun & Bradstreet

As with distribution by size, the drug industry is also concentrated geographically in Massachusetts. In 1998, as reflected in Table 3.5 below, a large proportion of manufacturing establishments (51 of 116) was concentrated in the Middlesex County. Essex, Norfolk, Suffolk, and Worcester counties also had ten or more manufacturing establishments each. Correspondingly, the employment in the drug-manufacturing sector in the state was also concentrated in these counties as follows: Middlesex (32%), Essex (9%), Norfolk (21%), Suffolk (10%), and Worcester (17%).

Finally, commercial biological, biotechnical, and medical research in the state was concentrated as follows: Middlesex (61 establishments and 36% employment), Suffolk (15 establishments and 39%
employment), Norfolk (11 establishments and 10% employment), and Worcester (10 establishments and 6% employment).

**TABLE 3.5**

<table>
<thead>
<tr>
<th>County</th>
<th>Number of Establishments</th>
<th>Percent of Total Employment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIC</td>
<td>SIC</td>
</tr>
<tr>
<td>Barnstable</td>
<td>3 8731</td>
<td>0.54% 2.72%</td>
</tr>
<tr>
<td>Berkshire</td>
<td>1 --</td>
<td>0.04% --</td>
</tr>
<tr>
<td>Bristol</td>
<td>6 --</td>
<td>6.71% --</td>
</tr>
<tr>
<td>Essex</td>
<td>12 5</td>
<td>8.94% 1.83%</td>
</tr>
<tr>
<td>Franklin</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td>Hampden</td>
<td>2 --</td>
<td>0.52% --</td>
</tr>
<tr>
<td>Hampshire</td>
<td>-- --</td>
<td>-- --</td>
</tr>
<tr>
<td>Middlesex</td>
<td>51 61</td>
<td>32.05% 36.20%</td>
</tr>
<tr>
<td>Nantucket</td>
<td>-- 1</td>
<td>-- --</td>
</tr>
<tr>
<td>Norfolk</td>
<td>14 11</td>
<td>21.24% 9.54%</td>
</tr>
<tr>
<td>Plymouth</td>
<td>2 4</td>
<td>2.79% 4.70%</td>
</tr>
<tr>
<td>Suffolk</td>
<td>15 15</td>
<td>10.29% 39.04%</td>
</tr>
<tr>
<td>Worcester</td>
<td>10 10</td>
<td>16.89% 5.97%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>116 110</td>
<td></td>
</tr>
</tbody>
</table>

*Source: Dun & Bradstreet*

**Wages & Payroll**

A summary of data on wages and payroll in the drug manufacturing sector (SIC 283) in Massachusetts are shown in Table 3.6. As reported by DET, total wages paid to covered employees grew 47% from $339 million or ($12,303 per employee) in 1995 to an estimated $498 million ($15,565 per employee) in 1998. The increase is statistically significant (t=3.50, p=0.07), implying a growth trend in wages paid in Massachusetts in the drug manufacturing sector.

With respect to research, Dun & Bradstreet employment ratios are used to estimated the proportion of total employment in 8731 that was attributable to commercial biological, biotechnical, and medical research. Also assumed for simplicity, moreover, was that the average wages for researchers were
the same regardless of the kind of research they did. The DET data then show that the total wages paid to covered employees grew by more than a factor of two from $406 million ($14,413 per employee) in 1995 to an estimated $872 million ($17,784 per employee) in 1998. Once again, the increase is statistically significant (t=10.19, p=0.009), implying a growth trend in wages paid in Massachusetts in the drug research sector.

Finally, wages and payroll in the drug wholesale sector are estimated as follows. The DET data show that the total wages paid to covered employees grew 42% from $301 million ($12,880 per employee) in 1995 to an estimated $336 million ($13,356 per employee) in 1998. Statistical test did not reveal a growth trend, however.

In sum, the combined wages in research, manufacturing, and wholesale trade of pharmaceutical products grew 63% from 1.05 billion in 1995 to an estimate $1.7 billion in 1998, signifying a growth trend during this period (t=18.23, p=0.003).

TABLE 3.6

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacture</td>
<td>283</td>
<td>498</td>
<td>467</td>
<td>336</td>
<td>339</td>
</tr>
<tr>
<td>Wholesale</td>
<td>5122</td>
<td>336</td>
<td>322</td>
<td>367</td>
<td>301</td>
</tr>
<tr>
<td>Research</td>
<td>8731</td>
<td>872</td>
<td>663</td>
<td>521</td>
<td>406</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1,706</td>
<td>1,452</td>
<td>1,224</td>
<td>1,046</td>
</tr>
</tbody>
</table>

Analysis of trends: α -- p<.01, β -- p<.05, γ -- p<.10
Annual numbers derived from quarterly data, and, based on a conversation with DET personnel, they assume no seasonality.

Source: Division of Employment and Training, Massachusetts

Other Economic Variables

The Annual Survey of Manufactures also provides data for several additional economic variables in the SIC 283 group of industries (see Table 3.7). For instance, the value of shipments attributed to the industry were $419.7 million in 1990, and this figure had grown to $1.09 billion in 1992. Based on the 1992 average shipments per employee figure of $221,878 and the first quarter 1998 employment of 7,365, the 1998 industry shipments from establishments in Massachusetts are estimated to be $1.63 billion.

Similarly, according to ASM, value-added by manufacturing establishments in Massachusetts was $336.9 million in 1990, and it had grown to $779.5 million in 1992. Again, based on the 1992 average value-added per employee figure of $159,082 and the average first quarter 1998 employment of 7,365, the 1998 value added by drug manufacturing in Massachusetts is estimated to be about $1.2 billion.
With respect to capital investment, ASM notes that new capital expenditures by industry in Massachusetts amounted to $14.6 million in 1990 and had grown to $85.3 million in 1992. Once again, based on the 1992 average new capital expenditure per employee figure of $17,408 and the estimated 1998 employment of 7,365, the 1998 new capital expenditures by the drug industry in Massachusetts are estimated to be $128.2 million.

**TABLE 3.7**

**Other Economic Variables**
Drug Manufacturing in Massachusetts, SIC 283
(Dollars in Thousands)

<table>
<thead>
<tr>
<th>Variable</th>
<th>1992</th>
<th>1998*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Value Added</td>
<td>779,500</td>
<td>1,171,636</td>
</tr>
<tr>
<td>Value Of Shipments</td>
<td>1,087,200</td>
<td>1,634,128</td>
</tr>
<tr>
<td>New Capital Expenditures</td>
<td>85,300</td>
<td>128,211</td>
</tr>
</tbody>
</table>

* Author's estimates. In making 1998 estimates of these variables, it is assumed that values per employee have remained unchanged. This is a conservative assumption because it does not account for possible productivity improvements in years between 1992 and 1998.

**Source: Annual Survey of Manufacturers, The Census Bureau**

**Massachusetts in Context**

In order to put drug manufacturing in Massachusetts in context, the economic variables were compared across all states in the country. In addition, a shift share analysis was also performed on the relative share of employment in drug research and manufacturing in the state.

The latest reliable data (reconciled at the state level) compiled by the Annual Survey of Manufactures reveals that, in 1992, Massachusetts was ranked among the top fifteen in the country for all the variables considered. With the 1992 total drug manufacturing employment of 4,900 and payroll of $194.9 million, the Commonwealth of Massachusetts was ranked eleventh in the nation. The state was ranked fourteenth in terms of total value added by manufacturing ($779.5 million), fourteenth in terms of value of shipments (1.09 billion), and eighth in terms of new capital expenditures ($85.3 million). Because of lack of availability of credible data, it is not clear how the relative standing of Massachusetts has changed since 1992. Because of the growing importance of bio-pharmaceutical during the 1990s, however, and because of the increasingly strong presence of biotechnology firms in the state, it is likely that the
Commonwealth has maintained, if not improved its ranking in the drug-manufacturing sector relative to the other states in the Union.

Table 3.8 below shows how national unit share of Massachusetts in terms of establishments has changed during the period 1995-1998. For the drug manufacturing sector (SIC 283), the state had a 2.99% share in 1995, which after a peak of 3.08% in 1996 dropped to 3.03% and 3.07% in the subsequent two years. For commercial biological, biotechnical, and medical research – segments within the SIC 8731 classification, the national share of Massachusetts was 8.39% in 1995, 7.58% in 1996, 8.33% in 1997, and 7.37% in 1998. Upon regressing the market shares against time, however, there was no statistically significant trend found regarding the national share of commercial biological, biotechnical, and medical research establishments in Massachusetts. Similarly, there was no statistically significant trend with respect the state’s share of all manufacturing establishments.

Note also that the share of Massachusetts for all manufacturing establishments in the United States was 2.74% in 1995, 2.86% in 1996, 2.77% in 1997, and 2.70% in 1998. Similarly, the share of Massachusetts for all research establishments falling under SIC 8731 was 5.21% in 1995, 5.23% in 1996, 5.50% in 1997, and 4.93% in 1998. Upon regressing the market shares against time, however, none of the trends was found to be statistically significant. Again, upon regressing the market shares against time, there was no statistically significant trend found regarding the national share of drug manufacturing establishments in Massachusetts. Similarly, there was no statistically significant trend with respect the state’s share of all commercial research establishments.

| TABLE 3.8 |
| Shift Share Analysis For Establishments |
| Establishments in Massachusetts as Percent of Total Establishments in the United States |

<table>
<thead>
<tr>
<th>Manufacture</th>
<th>Research</th>
<th>Manufacture</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIC 283</td>
<td>SIC sub-8731</td>
<td>All</td>
<td>All SIC 8731</td>
</tr>
<tr>
<td>1995</td>
<td>2.99%</td>
<td>8.39%</td>
<td>2.74%</td>
</tr>
<tr>
<td>1996</td>
<td>3.08%</td>
<td>7.58%</td>
<td>2.86%</td>
</tr>
<tr>
<td>1997</td>
<td>3.03%</td>
<td>8.33%</td>
<td>2.77%</td>
</tr>
<tr>
<td>1998</td>
<td>3.07%</td>
<td>7.37%</td>
<td>2.70%</td>
</tr>
</tbody>
</table>

Source: Dun & Bradstreet
Table 3.9 below shows how national unit share in terms of establishments in Massachusetts has changed during the period 1995-1998. For the drug manufacturing sector (SIC 283), the state had a 1.73% share in 1995, which after a peak of 2.08% in 1997 dropped to 1.99% in 1998. For commercial biological, biotechnical, and medical research, the national share of Massachusetts was 10.39% in 1995, 10.74% in 1996, 12.16% in 1997, and 16.26% in 1998. Upon regressing the market shares against time, a marginally significant increasing trend (t-stat=3.15, p=0.087) was found with respect to the state’s share of the total national employment in the commercial biological, biotechnical, and medical research establishments. In contrast, there was no statistically significant trend with respect the state’s share of all employment in commercial research establishments.

Note also that the share of Massachusetts for all manufacturing establishments in the United States was 3.14% in 1995, 2.58% in 1996, 2.59% in 1997, and 2.57% in 1998. Similarly, the share of Massachusetts for all research establishments falling under SIC 8731 was 5.35% in 1995, 5.18% in 1996, 5.13% in 1997, and 4.73% in 1998. Upon regressing the market shares against time, however, none of the trends was found to be statistically significant. Again, upon regressing the market shares against time, there was no statistically significant trend found regarding the national share of drug manufacturing employment in Massachusetts. Similarly, there was no statistically significant trend with respect the state’s share of employment in all manufacturing establishments.

| Table 3.9 |
| Shift Share Analysis For Employment |

Employment in Massachusetts as Percent of Total Employment in the United States

<table>
<thead>
<tr>
<th>Manufacture</th>
<th>Research</th>
<th>Manufacture</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIC 283</td>
<td>SIC sub-8731†</td>
<td>All</td>
<td>All SIC 8731</td>
</tr>
<tr>
<td>1995</td>
<td>1.73%</td>
<td>10.39%</td>
<td>3.14%</td>
</tr>
<tr>
<td>1996</td>
<td>1.77%</td>
<td>10.74%</td>
<td>2.58%</td>
</tr>
<tr>
<td>1997</td>
<td>2.08%</td>
<td>12.16%</td>
<td>2.59%</td>
</tr>
<tr>
<td>1998</td>
<td>1.99%</td>
<td>16.26%</td>
<td>2.57%</td>
</tr>
</tbody>
</table>

Analysis of trends:  α = p<.01,  β = p<.05,  γ = p<.10

Source: Dun & Bradstreet

*Pharmaceuticals/Massachusetts*

*Anurag Sharma, May 1999*
The above numbers suggest that, in terms of share of establishments and employment on a national scale, Massachusetts is more of a research rather than manufacturing state. In 1998, for instance, 2.70% of all manufacturing establishments and 4.93% of all commercial research establishments in the country were located in Massachusetts. Similarly, in 1998, 2.57% of all manufacturing employment and 4.73% of all employment in commercial research establishments in the country were in Massachusetts. Yet, the emphasis on research is particularly strong in the state when it comes to the drug industry. In terms of the relative number of establishments, for instance, the Commonwealth plays an almost two-and-a-half times larger role (7.37% versus 3.07%) in drug-related research than in drug manufacture. Similarly, in terms of relative total employment, Massachusetts plays an almost eight times larger role in drug-related research (16.26% versus 1.99%) than in drug manufacture. In addition, the analysis also shows that there is a marginally upward trend with respect to employment in the commercial research sector in the state.
Chapter 4

MEDICAL RESEARCH IN MASSACHUSETTS

The pharmaceutical industry is driven by scientific research and innovative drugs that result from it. The long term financial health of firms in the industry is, in fact, tightly coupled with the rate at which they discover and develop new therapeutic solutions. The culture of research is, therefore, of primary importance to the industry. It is not only the research that pharmaceutical firms do in-house, moreover, but also the research done at hospitals, universities, and non-profit foundations that make up the larger culture conducive to innovation in the industry. The research done by pharmaceutical companies is symbiotic with the medical research, both basic and applied, done at locations outside the industry.

Massachusetts is one of the most research intensive states in the country. There is strong culture of scientific and medical research at the several leading hospitals, universities, private firms, and non-profit research foundations located in the state. While it is difficult to estimate the private monies that flow into research activities in the state, some indication of the strength of the research culture is evident in the inflow of funds from the National Institutes of Health (NIH).

During the last five years, almost 350 institutions and organizations in 11 congressional districts Massachusetts have received a total of over $5 billion in support from NIH (see Table 4.1). Preliminary data from NIH show that the state received almost $1.2 billion of these funds in 1998. Representing 10.51% of the total NIH budget for extramural support, this level of support placed Massachusetts second only to California – a state almost five times the size in terms of population. Moreover, the inflow of funds has grown over 30% since 1994 when the state received about $900 million from the National Institutes of Health.

TABLE 4.1

Top Five States Receiving Support From NIH, 1994-1998
(Dollars in Thousands)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CALIFORNIA</td>
<td>1,662,297</td>
<td>1,582,040</td>
<td>1,474,131</td>
<td>1,410,722</td>
<td>1,256,148</td>
</tr>
<tr>
<td>MASSACHUSETTS</td>
<td>1,174,887</td>
<td>1,084,821</td>
<td>1,017,073</td>
<td>932,490</td>
<td>900,865</td>
</tr>
<tr>
<td>NEW YORK</td>
<td>1,130,365</td>
<td>1,045,184</td>
<td>985,034</td>
<td>955,722</td>
<td>961,562</td>
</tr>
<tr>
<td>PENNSYLVANIA</td>
<td>735,132</td>
<td>681,452</td>
<td>617,197</td>
<td>590,246</td>
<td>543,225</td>
</tr>
<tr>
<td>MARYLAND</td>
<td>681,948</td>
<td>637,748</td>
<td>650,372</td>
<td>596,447</td>
<td>624,704</td>
</tr>
<tr>
<td>TOTAL U.S.</td>
<td>11,177,960</td>
<td>10,456,031</td>
<td>9,834,722</td>
<td>9,371,896</td>
<td>9,070,833</td>
</tr>
</tbody>
</table>

Source: National Institutes of Health
Most of the NIH monies are concentrated in the eastern part of the state. Boston, for instance, received $846 million in 1998 and, for the last five years it has been ranked as the top ranked city recipient of funds from the NIH (see Table 4.2).

**TABLE 4.2**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BOSTON</td>
<td>846,540</td>
<td>760,355</td>
<td>704,234</td>
<td>650,705</td>
<td>630,110</td>
</tr>
<tr>
<td>NEW YORK</td>
<td>765,486</td>
<td>697,225</td>
<td>649,720</td>
<td>628,821</td>
<td>627,885</td>
</tr>
<tr>
<td>SAN DIEGO</td>
<td>467,701</td>
<td>473,297</td>
<td>428,239</td>
<td>411,176</td>
<td>279,454</td>
</tr>
<tr>
<td>PHILADELPHIA</td>
<td>455,565</td>
<td>412,303</td>
<td>369,617</td>
<td>359,723</td>
<td>336,120</td>
</tr>
<tr>
<td>BALTIMORE</td>
<td>426,058</td>
<td>391,141</td>
<td>374,111</td>
<td>342,665</td>
<td>354,159</td>
</tr>
</tbody>
</table>

*Source: National Institutes of Health*

Four other cities in the Commonwealth are consistently ranked among the top 100 cities receiving monies from the NIH. As shown in Table 4.3, in 1998 these cities were: Cambridge ($152 million), Worcester ($53 million), Waltham ($27 million), and Watertown ($17 million).

**TABLE 4.3**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BOSTON</td>
<td>846,540</td>
<td>760,355</td>
<td>704,234</td>
<td>650,705</td>
<td>630,110</td>
</tr>
<tr>
<td>CAMBRIDGE</td>
<td>152,025</td>
<td>149,715</td>
<td>133,821</td>
<td>130,734</td>
<td>133,264</td>
</tr>
<tr>
<td>WORCESTER</td>
<td>53,048</td>
<td>53,685</td>
<td>52,212</td>
<td>45,447</td>
<td>47,720</td>
</tr>
<tr>
<td>WALTHAM</td>
<td>27,429</td>
<td>29,382</td>
<td>29,818</td>
<td>24,576</td>
<td>24,887</td>
</tr>
<tr>
<td>WATERTOWN</td>
<td>17,020</td>
<td>17,129</td>
<td>18,101</td>
<td>16,605</td>
<td>15,161</td>
</tr>
</tbody>
</table>

*Source: National Institutes of Health*
Funding from NIH is also concentrated in terms of the recipient institutions. The share of funds received by the four largest recipients increased from 42% in 1994 to 44% in 1998. Similarly, the share of the eight largest recipients increased from 64% in 1994 to 65% in 1998. Top 25 recipients accounted for just over 90% of total NIH funds coming into the state in both 1994 and in 1998.

| TABLE 4.4 |

| NIH Support For Institutions In Massachusetts |
| (Dollars in Thousands) |
|------|------|------|------|------|
| Research Universities |
| Harvard University | 188,616 | 180,022 | 166,727 | 152,509 | 151,177 |
| Boston University | 89,234 | 73,596 | 69,919 | 65,825 | 58,651 |
| Massachusetts Institute Of Technology | 62,578 | 61,612 | 59,167 | 57,871 | 65,829 |
| Tufts University | 36,878 | 37,061 | 32,262 | 29,621 | 29,934 |
| Brandeis University | 18,350 | 19,774 | 16,755 | 13,974 | 13,001 |
| University Of Massachusetts Non-Medical | 11,535 | 10,483 | 11,136 | 8,859 | 8,241 |

| Top Five Medical Institutions |
| Massachusetts General Hospital | 136,733 | 119,831 | 109,956 | 103,484 | 98,191 |
| Brigham And Women's Hospital | 131,178 | 113,716 | 99,967 | 103,065 | 92,460 |
| Beth Israel Deaconess Medical Center | 64,520 | 54,976 | 44,227 | 36,669 | 37,543 |
| Dana-Farber Cancer Institute | 62,578 | 54,797 | 56,620 | 46,827 | 52,894 |
| University Of Massachusetts Medical School | 51,085 | 50,843 | 50,400 | 42,882 | 44,524 |

| Other Medical Research Institutions |
| Children's Hospital (Boston) | 43,993 | 40,945 | 42,877 | 38,179 | 38,886 |
| Whitehead Institute For Biomedical Res | 26,819 | 25,058 | 21,615 | 22,881 | 17,847 |
| New England Medical Center | 22,378 | 23,957 | 23,500 | 23,481 | 23,687 |
| Center For Blood Research | 17,420 | 16,069 | 14,426 | 12,976 | 8,993 |
| Boston Medical Center | 17,090 | 16,538 | 13,455 | 12,414 | 12,231 |
| Joslin Diabetes Center | 15,079 | 10,938 | 9,232 | 10,055 | 10,439 |
| New England Research Institutes, Inc | 13,659 | 13,010 | 14,567 | 14,912 | 13,112 |
| McLean Hospital (Belmont, Ma) | 12,038 | 11,611 | 12,783 | 10,014 | 10,293 |

*Source: National Institutes of Health*
There are, of course, downsides as well upsides to the NIH funding being highly concentrated in the eastern part of the state – particularly in congressional districts 9 and 10. On the one hand, it indicates that the rest of the state is not sharing in the support for research provided by an agency of the federal government. Consequently, the return of taxpayer’s money is not evenly distributed among the residents of the state.

**TABLE 4.5**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number One</td>
<td>--</td>
<td>200</td>
<td>394</td>
<td>98</td>
<td>--</td>
</tr>
<tr>
<td>Number Two</td>
<td>9,141</td>
<td>8,776</td>
<td>9,053</td>
<td>7,111</td>
<td>6,283</td>
</tr>
<tr>
<td>Number Three</td>
<td>859</td>
<td>1,083</td>
<td>1,715</td>
<td>1,094</td>
<td>1,164</td>
</tr>
<tr>
<td>Number Four</td>
<td>54,460</td>
<td>54,790</td>
<td>52,712</td>
<td>45,887</td>
<td>48,100</td>
</tr>
<tr>
<td>Number Five</td>
<td>20,555</td>
<td>17,371</td>
<td>16,670</td>
<td>15,359</td>
<td>8,511</td>
</tr>
<tr>
<td>Number Six</td>
<td>5,670</td>
<td>6,591</td>
<td>6,080</td>
<td>4,843</td>
<td>3,128</td>
</tr>
<tr>
<td>Number Seven</td>
<td>11,192</td>
<td>9,528</td>
<td>14,363</td>
<td>10,474</td>
<td>6,286</td>
</tr>
<tr>
<td>Number Eight</td>
<td>46,921</td>
<td>48,423</td>
<td>47,151</td>
<td>40,324</td>
<td>39,937</td>
</tr>
<tr>
<td>Number Nine</td>
<td>779,148</td>
<td>705,989</td>
<td>653,674</td>
<td>608,413</td>
<td>593,695</td>
</tr>
<tr>
<td>Number Ten</td>
<td>243,439</td>
<td>228,046</td>
<td>211,342</td>
<td>195,103</td>
<td>191,421</td>
</tr>
<tr>
<td>Number Eleven</td>
<td>3,502</td>
<td>3,207</td>
<td>3,476</td>
<td>3,688</td>
<td>2,337</td>
</tr>
<tr>
<td>Total for the State</td>
<td>1,174,887</td>
<td>1,084,004</td>
<td>1,016,630</td>
<td>932,394</td>
<td>900,862</td>
</tr>
</tbody>
</table>

*Source: National Institutes of Health*

On the other hand, NIH support dollars are allocated largely on the basis of quality of research ideas, as well as the reputation of the researchers and institutions proposing them. In a way, therefore, the high dollar amounts coming mostly to a few large recipients in a concentrated geographical area reflect the results of a market at work – *scientific culture attracts research monies*. In supporting research, moreover, the NIH monies contribute to strengthening the already strong base of scientific and medical research in the eastern part of the state – *research monies strengthen scientific culture*.

Consequently, eastern Massachusetts has a high density of medical research that serves as its own engine in a self-perpetuating cycle of research-funding-research. This, in turn, has built a culture that has two important implications for the Commonwealth.
First, the high density of medical institutions, laboratories, and researchers has made Massachusetts a leading center for biotechnology. Most prominent biotechnology drugs on the market today have been developed with at least partial research support from the National Institutes of Health. For instance, Epogen by Amgen (AIDS-related anemia), Intron A by Biogen (leukemia, Kaposi’s sarcoma, hepatitis B & C), and Recombivax HB by Chiron (hepatitis-B vaccine) were developed with research funded in part by NIH. In fact, many companies in the biotechnology field are a direct result of research funded internally in NIH laboratories and externally in the laboratories of grant recipients.

According to a survey conducted by the Massachusetts Biotechnology Council, the number of biotechnology companies in Massachusetts increased from 88 in 1991 to 215 in 1998, and the total employment provided in this sector was reported to have increased from 7,682 to 16,872 during the same period. Most of these companies (123) were in the eastern part of the state – inside Route 128, a smaller number (58) were between Routes 128 and 495, and the remaining 25 were in the western part of the state.

A second implication of the strong culture of medical research is that it attracts private capital into the Commonwealth. Not only the non-profit government funding agencies, in other words, but also for-profit pharmaceutical companies use various forms of investments to take advantage of research talent and institutional infrastructure in the state. Although exact numbers are not available, it is common knowledge in the industry that large drug companies invest tens of millions of dollars in medical research in the state.

The pharmaceutical companies make investments into the state in a variety of ways. First, they support institutions of higher education by funding joint research projects, by purchasing services of key personnel in the research universities, and by licensing technology generated in the university laboratories. Second, because of their expertise in the research and marketing of medical products, pharmaceutical firms are well equipped to support research at small biotechnology firms and to then help the emerging products through the human clinical trials and downstream business functions. To this end, the large companies participate in the activities of the local companies via partnerships, strategic alliances, and direct equity investments. Finally, because of the strength of research culture, large pharmaceutical companies also often invest considerable capital to set up their own research operations in the Commonwealth.

In summary, then, the strength of medical research at the universities, hospitals, and private firms attracts considerable sums of both public and private monies into the state. The monies so attracted, in turn, strengthens the already strong culture and infrastructure for serious medical research in the state. It is this virtuous cycle of strength-investment-strength that needs to be nurtured and augmented through public policy that encourages research oriented companies to locate in the state.
The worldwide AIDS epidemic has not spared Massachusetts. Since 1979, more than 13,000 AIDS cases have been identified in the Commonwealth. Having peaked in the 1993 at more than seventeen hundred, the rate of new cases infected with the AIDS virus still hovers around 500 per year in the late 1990s. The striking decline in recent years is attributable to greater understanding about the disease, strengthened prevention efforts, and, importantly, breakthroughs in the development of new drugs. As a happy consequence, the number of deaths from AIDS have decreased correspondingly.

In spite of some semblance of control over the disease, however, the number of people infected with AIDS virus has remained high. The disease continues to confront the state with an unprecedented set of social, ethical, medical, and scientific challenges.

In a way, AIDS is the medical problem of our times. It is responsible for creating a social divide which only in recent years is being slowly undone as people come to understand the causes and consequences of the illness. It imposes tremendous emotional costs on individuals who become vulnerable to it. And, because of its devastating effects on those who get in its way, the disease inflicts a huge financial burden and psychological vulnerability on the society at large.

Yet, because it is a disease, AIDS also presents significant medical challenges for individuals and organizations in the healthcare industry. Not only does AIDS present a set of problems that are crying out for solutions, in other words, it also presents opportunities to advance the state-of-the-art in medical science.

Unfortunately, because it is a difficult disease – in fact, several diseases in one – attempts to find solutions are peppered with scientific and, consequently, economic risks. Such is evident in the experiences of two firms located in Massachusetts. The struggles of these firms – Therion Biologics Corporation (Cambridge) and Seragen Inc. (Hopkinton) – illustrate the enormous difficulties involved in creating scientific platforms that will permit the medical communities to find ways to prevent, impede, and cure this devastating disease.

Therion, founded in 1991, is on its way to developing two kinds of drugs for AIDS. One of these incorporates multiple human immunodeficiency (HIV) proteins, and the other involves live attenuated HIV vaccines. Both are intended for use by HIV-positive subjects and they are designed, in particular, to bolster an HIV-specific immune response. Therion obtained two key patents in 1997, and they initiated human clinical trials the following year. Because of apparent lack of interest in AIDS vaccines among those in the finance community (e.g., the venture capital world), however, all but $2 million of the $14 million spent in Therion’s AIDS vaccine research came from public sources, most notably the National Institute of Health. As a result, the Company has found it prudent to shift much of its efforts toward another worthy adversary: cancer.
One other Massachusetts firm involved in research on drugs for AIDS is Seragen, Inc. In the summer of 1998, an FDA advisory panel approved the use of Seragen’s genetically engineered fusion protein toxin, Interleukin-2, for use in treating lymphoma. The drug, to be marketed in improved form under the name Ontak, has shown promise in treating a disfiguring and deadly type of skin cancer, and it has long been seen as a possible treatment for AIDS. The good news about FDA approval came too late to shore up the collapsing company, however. In August, 1998, the Company – teetering on the brink of bankruptcy despite Boston University’s controversial investment in its stock – was sold to California-based Ligand Pharmaceuticals. Given the change in ownership, it is not clear whether further clinical trials to test Ontak’s effectiveness with respect to AIDS are contemplated.

In addition to illustrating of real challenges faced by real companies battling AIDS, the above two examples also show that some of the best minds in the avant-garde of modern biotechnology are residents of Massachusetts. The access to several research universities, a strong and growing culture of scientific research, and ready access to the financial community in the greater Boston area puts the Commonwealth in the vanguard of search for the cure for AIDS. In taking on the perhaps one of the most challenging scientific conundrums of our age, moreover, local firms and researchers are playing a central role the worldwide healthcare industry. Massachusetts is well positioned to contribute in any major advances in prevention, treatment, or cure for AIDS.
In an industry that is dominated by giants, a small Massachusetts company has finessed an ingeniously simple strategy to create an enviable position for itself. Located in Marlborough, the company, Sepracor, targets highly successful drugs already on the market, and then, using the latest technology and high-powered expertise in chiral chemistry and pharmacology, it develops purified formulations that have greater efficacy and fewer side effects. The Company patents these so-called improved chemical entities, or ICEs, and then negotiates favorable business arrangements with the large pharmaceutical companies behind the original formulations.

Sepracor’s most important successes to date have entailed addressing an oddity shared by a number of blockbuster drugs on the market. It is widely known that many organic molecules (and active ingredients in drugs) exist as mixtures of mirror images, or optical isomers that were originally named S (“sinister) for left and R for right. Only one of these isomers is responsible for the drug’s benefits, however. The other, or the evil twin, is sometimes innocuous, sometimes inconvenient, and, at times, highly dangerous to the patients because of severe harmful side effects it causes.

Until Sepracor came along in 1984, both isomers were left together in the drug, partly because the technology did not exist to actually separate them, but partly also because the big companies had no great incentives to do so. The Company has developed technology and equipment to just that, and a good portion of its research and development efforts are focused on separating the desirable isomer from the undesirable isomer.

In a second, more recent strategy, Sepracor has honed in on the fact that the body itself transforms drugs into a variety of related chemical forms (metabolites), not all of which are therapeutically active or useful for the patient. On again, therefore, by directly developing active metabolites in drug form, the company attempts to improve the side effect or efficacy profiles for widely prescribed drugs on the market.

Sepracor has applied its aggressive research strategy in the areas of allergy, asthma, urology, psychiatry and gastroenterology. Because the Company’s research deliberately builds on work done by other firms in developing the original drug, it typically is cost-effective, speedier, and less risky than doing original research and pushing one or more compounds though the stringent FDA approval process.

Nineteen ninety-eight was a banner year for Sepracor. During the spring of the year, Johnson & Johnson (J&J) agreed to a second very lucrative deal in which Sepracor would work on developing a safer version of J&J’s best-selling antihistimine; an earlier agreement covered improvement of a J&J product used to treat a serious form of heartburn. Similarly, in December...
of 1998, Eli Lilly agreed to pay up to $90 million plus future royalties to obtain Sepracor’s improved version of its fabulously successful antidepressant, Prozac.

Despite the fact that it had yet to turn a profit, Sepracor’s share price doubled in 1998. A number of Massachusetts-based players, including Fidelity, Putnam, John Hancock, Fleet Investment Advisors, MFS, Boston College and the Boston Museum of Fine Arts, were among the young Company’s happy shareholders.

But how did the multinational pharmaceutical giants find themselves in such a vulnerable position in the first place? How could an upstart snatch patents for some of their most valuable product from under their corporate noses? And what are they going to do about it? Sepracor’s president and CEO, Timothy Barberich, believes that part of the problem of the large companies has been cultural, and part of it has been legal. The glamour work among researchers at the big companies is in developing new drugs, not tinkering with those that someone else discovered or synthesized. And, in any case, uncovering problems with successful drugs already in wide use could create legal and ethical dilemmas the original makers would rather avoid.

Their well-earned successes to date notwithstanding, Sepracor’s nimble entrepreneurs face significant challenges in the years ahead. Not surprisingly, industry giants are moving, if belatedly, to bring the work of “cleaning up” their products in-house, and the FDA is encouraging – even requiring – them to do so. Hence, although it is well capitalized and ensured healthy revenues under existing agreements for at least the next ten years, Sepracor has already begun to respond to the changing environment by diversifying into a riskier, perhaps even more lucrative, part of the pharmaceutical business. In the future, the Company will also seek to develop, test, manufacture and market its own drugs from scratch.

Last but not least, a price-to-earnings ratio – which stands at this writing at an astronomical 154 – will require much skill and a heavy dose of luck, as well as an extra measure of patience from the investment community.
BOX 3

Risky Business of Innovation

Studying a surprising failure can sometimes be more instructive than applauding a straight-ahead success. Consider, for example, the high drama played out recently at Ergo Science Corporation, a small biopharmaceutical firm incorporated in 1990 in Delaware, but located in Charlestown, MA to take advantage of heavy concentration of medical researchers in the area.

The Company was founded to develop treatments for metabolic disorders, as well as immune disorders and some types of cancer. Using what is called Neuroendocrine Resetting Therapy (NRT), Ergo Science was developing drugs to target a vast primary market comprising 16 million Americans who suffer from Type 2 diabetes – also called adult-onset diabetes. The drug’s other market, the country’s obese, was even larger. The Company’s secondary research focus, using the same technology, was on immune disorders and breast cancer.

The Company’s founding scientists were bright and had high pedigrees. They had, in fact, spent over 30 years researching the role of neurotransmitters in regulating glucose and lipid metabolism. And, they were committed to developing a drug that operated through the central nervous system to alter how patients metabolize sugar and fat. Moreover, they would design the drug such that the patients would take orally and only one dose a day.

The drug, Ergoset, was to be a fast-release reformulation of bromocriptine, which was sold by Novartis as a treatment for Parkinson’s disease. Ergoset would compete with other drugs on the market to treat Type 2 diabetes – Warner-Lambert’s Resulin and Bristol-Myers Squibb’s Glucophase, both of which had 1997 sales running into several million dollars. Ergoset was to also be the flagship product that would be at the core of all of the Company’s other proposed drugs.

Ergo Science was considered to be very successful in developing various novel treatments. In 1997, seven years of hard work was rewarded when the company successfully completed a pivotal clinical trial for Ergoset. The potential for the drug was considered so great that, in February of 1998, the pharmaceutical giant Johnson & Johnson invested $10 million for a fraction of the company’s outstanding shares. Johnson & Johnson also agreed to pay another $10 million for an up front license to Ergoset and the underlying technology. An additional twenty million dollars were conditional upon the small company’s ability to meet certain milestone.

Then, in May, Ergo Science sustained a body blow from the Food and Drug Administration (FDA). A panel of the FDA’s outside experts concluded unanimously that to approve Ergoset they would need evidence of its long-term effects on human subjects. This was because the drug was to be marketed as lifelong medication for Type 2 diabetics. Based on an earlier understanding with the FDA, the company had clinical data for only six months. Under the new guidelines, which were still in draft form, the FDA panel wanted more data to assess the long-term effects of the
They also wanted more data to help them understand how the drug achieved its effects in the human body.

The company’s stock fell by fifty-five percent. Over the summer, the number of employees on the payroll was reduced from 65 to forty.

In late November came a second, near-fatal blow. The FDA sent Ergo Science a formal letter of non-approval for Ergoset tablets. The rejection letter cited the same reasons as its outside experts had in May: (1) It was not clear how Ergoset worked, and (2) It was not clear how the drug might affect brain chemicals and the metabolism of glucose in the long run.

In early December, Johnson & Johnson, which had recently pulled out of a diabetes deal with another company and which had announced plans to slash its 100,000-strong workforce by 4% literally the day before, terminated its relationship with Ergo Science.

The news was enough to bring about another sharp drop in the share price of Ergo Science. The company was in crisis. It cut its workforce from 40 to twenty.

The principals of the company were now faced some unpleasant choices. They knew that it would be prohibitively expensive to conclusively demonstrate Ergoset’s long-term safety and efficacy, particularly now that Ergo Science was financially quite weak. Yet, failure to prove long-term safety and efficacy to the FDA’s satisfaction would mean that a promising new drug with a range of important potential applications could not go to market.

In 1999, perhaps the Company’s only hope for the time being was some positive news from a 300-patient, double blind, placebo-controlled trial of Ergoset’s efficacy in treating obesity. Results for these trials were expected sometime during the summer.
Chapter 5

SUMMARY OF IMPACT ON MASSACHUSETTS

Based on the analyses of archival data and responses to the mail survey, it is evident that the pharmaceutical industry is deeply embedded in the economy of the Commonwealth. Far from being an accident, the industry’s substantial presence in Massachusetts is driven largely by a superb infrastructure of medical research in the Greater Boston and Cambridge areas. And while the industry benefits from the resources available in the state, it also contributes to the research infrastructure by being an active participant and by making significant investments in a wide range of scientific endeavors. In fact, if anything, the presence of the industry in the state is characterized by a thick network of collaborative arrangements between public and private research institutions.

Even so, drug manufacturing and wholesale also have notable presence in the state. And, although these two sectors are not as high profile as state of the art research for which the industry is mostly known, they provide non-trivial number of jobs and economic value in the state. The data show, for instance, that the drug-manufacturing sector not only provides thousands of jobs with unemployment insurance coverage but also an estimated annual value added of over $1 billion to the state.

Presented below is a summary of key data regarding the presence of the pharmaceutical industry in the Commonwealth of Massachusetts.

Research

- During the period 1994-1998, medical research institutions and organizations in Massachusetts have attracted over $5 billion in research monies from the National Institutes of Health. The annual receipts grew 30% from $901 million in 1994 to $1.2 billion in 1998.

- During each year in the period 1994-1998, Boston was #1 city in the nation in terms of attracting research monies from the National Institutes of Health. The annual receipts grew 34% from $630 million in 1994 to $847 million in 1998.

- Five cities in the Commonwealth are among the top 100 cities receiving funds from the National Institutes of Health. These cities (Boston, Cambridge, Worcester, Waltham, and Watertown) accounted for over 90% of all NIH monies coming into the state.

- With regards to biological, biotechnical, and medical research in 1998, 7.37% of all establishments and 16.26% of all employment in United States were located in Massachusetts.

- During the period 1995-1997, a sample of 14 pharmaceutical and 17 bio-pharmaceutical companies reported to have invested almost $1 billion in drug research and related activities in the state.
During the period 1998-2000, 31 pharmaceutical and bio-pharmaceutical companies project that they will invest more than $1.32 billion in research and related activities in the state.

More than half of respondents to the UMass Survey indicated that they expect to significantly expand their research activities in the state during the period 1998-2000.

In 1999, the thirty one responding pharmaceutical and bio-pharmaceutical companies reported as having a total of 391 separate ties with research institutions and organizations in the state. The ties were distributed as follows: clinical research (148), licensing patent (71), basic research (131), and technology transfer (41).

In 1999, the survey respondents had a total of 115 explicit links with universities in Massachusetts. Of these 63 (55%) involved pharmaceutical companies and the remaining 52 (45%) involved bio-pharmaceutical companies.

Bio-Pharmaceutical companies responding to the UMass Survey indicated that 75% of their monies for research come from traditional pharmaceutical companies.

The above statistics indicate that Massachusetts has a highly developed infrastructure for biological and medical research that is necessary for drug discovery and development. The dense network of world-renowned universities, hospitals, and research foundations makes the Commonwealth – particularly the eastern seaboard – a magnet for substantial monies from both the public and the private sectors. It is important to note, however, that the various elements of the research infrastructure in the state are mutually reinforcing and strongly needed complements to each other. In fact, it is perhaps no exaggeration to say that the research infrastructure in the state both contributes to and is sustained by the triad of NIH, pharmaceutical companies, and private investors.

**Manufacturing**

During the period 1995-1997, the manufacturing sector of the drug industry is estimated to have invested a total of $358 million in new capital expenditures in the state.

In 1998, the manufacturing sector of the drug industry is estimated to have invested $128 million in new capital expenditures in the state.

During the period 1995-1997, drug industry is estimated to have contributed a total of $3.3 billion in manufacturing value added to the economy of the Commonwealth.

In 1998, pharmaceutical industry is estimated to have contributed $1.2 billion in manufacturing value added to the economy of the Commonwealth.

With regards to drug manufacturing in 1998, 3.07% of all establishments and 1.99% of all employment in United States were located in Massachusetts.
• Two of 14 pharmaceutical companies and 5 of 17 bio-pharmaceutical companies responding to the UMass Survey indicated that they expect to significantly expand their manufacturing activities in the state during the period 1998-2000.

• Respondents to the UMass Survey indicated that they expect to spend $198 million on manufacturing activity and $194 on sales and marketing in Massachusetts during the 1998-2000 period.

• Respondents to the UMass Survey indicated that they expect to spend $277 million on construction activity in Massachusetts during the 1998-2000 period – a 377% increase over the $73 million these companies reported for 1995-1997.

Although Massachusetts is not one of the big drug manufacturing states in the Union, it does participate in that sector at a non-trivial level. The above statistics are estimated from the data provided by the Annual Survey of Manufactures compiled annually by The Census Bureau. As the statistics show, the new capital expenditures made by the industry ran into hundreds of millions of dollars over a span of the recent three year period. Similarly, the value added by drug manufacturing in the state averaged over $1 billion in each of the last five years. Using a multiplier of 2, therefore, the total economic impact on the state of drug the manufacturing sector alone amounts to over $2 billion per year.

Places to Work

• In 1998, there were 329 research, manufacturing, and the wholesale establishments in the drug industry in Massachusetts – up 21% from 271 in 1995.

• The drug industry is highly concentrated both by the size of establishment and by geography.

• In 1998, 67% of drug manufacturing establishments employed less than 50 people. Yet, 80% of manufacturing employment was concentrated in 13 establishments employing 100 or more people.

• Similarly, in 1998, 75% of drug research establishments employed less than 50 people. Yet, 71% of manufacturing employment was concentrated in 15 establishments employing 100 or more people.

• In 1998, over 85% of manufacturing establishments were concentrated in five Counties with 10 or more establishments each. Similarly, over 88% of drug-related research establishments were concentrated in four Counties with 10 establishments or more. [Middlesex County had 50 manufacturing and 61 research establishments].

• In 1998, almost 90 % of manufacturing employment were concentrated in five Counties [32% in Middlesex County]. Similarly, over 95% of drug-related research employment were concentrated in five Counties [39% in Suffolk County and 36% in Middlesex County].

Pharmaceuticals/Massachusetts
Anurag Sharma, May 1999
Note that the above statistics represent only those establishments that indicate their primary business as drug-related. The numbers do not include other establishments engaged in drug-related business but with primary concerns elsewhere.

**Employment & Wages**

- During the first quarter of 1998, research, manufacturing, and the wholesale sectors for the drug industry provided an estimated 25,788 “covered” jobs in Massachusetts.

- The “covered” employment in the commercial medical, biological, and biotechnical research sector of the industry grew about 59% from an average of 5,872 in the fourth quarter of 1993 to an average of 9,319 in the same period of 1997. Average monthly employment in the research sector was estimated to be 12,538 in the first quarter of 1998.

- The number of covered employees in the drug wholesale sector grew 39% from an average of 4,328 in the fourth quarter of 1993 to an average of 6,028 in same period of 1997. Employment in the drug wholesale trade was estimated to be 5,885 in the first quarter of 1998.

- The combined first quarter 1998 wages in research, manufacturing, and wholesale trade of drug industry in the state are estimated to be about $426 million.

Note that the above statistics indicate only “direct” employment in the drug research, manufacture, and wholesale activities in the state, as measured by conventional yardsticks. Inevitably, many other sectors of the state economy intersect with the drug industry. It is rather difficult to estimate the employment that may be attributable to the industry from its routine business interactions with the likes of professional service organizations such as law and accounting firms, building and construction companies, contract research organizations, and staff at research universities and hospitals staff, among others. Even so, it is clear that the actual numbers of jobs connected to the industry are presumably much larger than what the above statistics show.
Chapter 6

FUTURE OF THE INDUSTRY IN MASSACHUSETTS

Given the momentum of changes currently under way in the pharmaceutical industry at large, it is likely that scientific research will continue to play a critical role in the discovery and development of new drugs during the next millennium. As more and more complicated illnesses come within the fold of the ever-expanding frontiers of scientific knowledge, individuals and organizations equipped with skills in basic and applied sciences will become even more indispensable than they are today to the pharmaceutical enterprise. Hence, along with information (for locating patient needs) and logistics (for supplying drugs where needed), research (developing what is needed) will retain its fundamental importance in the decades-old formula that pharmaceutical firms use to generate revenues and profits. [For a general overview of the industry, see the attachments: Appendix 2 for history & competition, Appendix 3 for drug discovery and development, and Appendix 4 for drug manufacturing].

Unlike the previous decades, however, the pharmaceutical industry is becoming increasingly frayed in the upstream activities such as basic/applied research, clinical trials, and, to some extent, even manufacturing. With the help of fundamental breakthroughs in research technology and an unprecedented dispersion of know-how among a widening pool of technology-savvy workers, a great deal of state-of-the-art research is now happening outside the laboratories of large vertically integrated multinational pharmaceutical company of the old. Numerous research boutiques, highly focused on particular molecules or methods, have become fixtures on an industrial landscape once dominated by a few firms that had the advantages of scale and scope.

Fragmentation up the research function is visible, for instance, in the growing proportion of human gene patents obtained by academic institutions and focused biotechnology companies. Ironically, the tiny research entities seen today are often spawned by large research-intensive universities that have over the years become sophisticated at bringing technology to market. The researchers and graduates of these universities freely mingle with a thriving venture capital community to create the specialized and highly focused boutiques.

In addition, it is common knowledge that the industry is now also populated with new specialists such as Contract Research Organizations (CRO) and Contract Manufacturing Organizations (CMO) which offer functional expertise to virtually any company that has the ability and a willingness to pay. Once available almost only within vertically integrated firms, in other words, several important functions (clinical trials and manufacturing) are now increasingly for hire in the open market.

Of the fundamental changes sweeping through the pharmaceutical industry [Appendix 2], fraying of drug research in particular plays right into the natural strengths of Massachusetts. This is partly because the wide dispersion of research capabilities outside the laboratories of large firms has increased their reliance on partnerships with focused upstarts and with research programs in academic institutions. And, with a very high density of biotechnology firms, leading research universities, and academic hospitals on its Eastern
seaboard, Massachusetts offers pharmaceutical firms the opportunity to tap into highly active networks of peoples and institutions that are invested in bringing research ideas to commercial ends.

In fact, the conditions that make the state attractive for investment by the pharmaceutical companies are the same as those that have induced a thriving biotechnology industry in the area. Industry executive participating in the study acknowledged that the leading academic institutions in the state produce transferable new technology, they also develop a workforce with continually updated skills needed by the industry to maintain a steady stream of new ideas and techniques.

In addition, the culture of research in Massachusetts is complemented by an equally strong culture of business and services in the area. The Commonwealth of Massachusetts is one of the leading states in the country for the business communication and computer software industries - both skills critical for increasingly information-intensive drug research. Similarly, the state is among the top two in the nation with respect to attracting venture capital funds for new business ideas - monies that, along with those from pharmaceutical industry and from the National Institutes of Health, play an important complementary role in encouraging drug research. Finally, the Commonwealth has a high density of professional service firms supplying first-rate auxiliary services such as patent law and accounting services that critically lubricate the business end of commercial biological and medical research.

It is no surprise, therefore, that employment in drug-related commercial research more than doubled from 6,137 in 1995 to 12,538 in 1998, and that the state's share of total nationwide employment in commercial research organizations increased from 10.4% in 1995 to 16.2% in 1998. Consistent with trends in employment, Massachusetts continues to be a leading state in terms of getting research monies from the National Institutes of Health - growing 26% from $932 million in 1995 to almost $1.2 billion in 1998.

This growth in public support is matched by increasing private commitment to medical research in the state. In a survey conducted for this study, for instance, thirty-two pharmaceutical and biopharmaceutical firms indicated that they intend to spend almost $1.4 billion on research and clinical trials during the 1998-2000 period - approximately 30% more than what they spent in the state during the 19951997 period. The same companies also reported that between 1998 and 2000, they plan to spend over $277 million in construction activities - up 377% from the $74 million they spent on such activities in the 19951997 period. [See the appendix for a full reporting of the mail survey conducted by the University of Massachusetts]. In effect, then, there appears to be in process a natural market-driven alignment between institutions in the Commonwealth and the pharmaceutical industry (particularly its research arm).

Such state of affairs should not be taken for granted, however. Notwithstanding enviable strengths, Massachusetts is only one of the many locations worldwide where pharmaceutical companies can invest their substantial, yet finite, funds for drug discovery, development, and manufacture. California, New York, Pennsylvania, and Maryland also offer some of the same benefits as attracting public (NIH) monies for research, proximity to formidable research and teaching institutions, and access to private capital. In fact, some executives in the industry consider quite attractive even a relative late comer such as North Carolina. This is at least in part because of aggressiveness of the state officials in promoting the Research Triangle Park - which is served by an international airport, is surrounded by three large universities, and which now
houses an increasingly dense network of like-minded companies. Ironically, even such small neighboring states as Rhode Island and Connecticut have considerable attraction to firms that may want to locate in the Northeast but for whatever reason would prefer to stay out of Massachusetts.

As Arnold Toynbee would have said, therefore, this is no time to rest on our oars. Industrial competition is an open-ended process and the favorable current state of affairs is by no means an end game. It is imperative that instead of taking the industry for granted the Commonwealth explores ways in which to strengthen the important and evolving presence of the pharmaceutical industry. Perhaps it would be prudent for the state to conduct a vigorous needs assessment with the industry to understand what kind of, if any, public policies or investments might be effective in assuring the commitment for continued investment by pharmaceutical firms into the institutions and infrastructure within the Commonwealth. While adequately addressing such issues would require a study in its own right, I submit below a range of questions that future researchers might deem worthy of exploration.

One of the most pressing challenges, for instance, is that virtually all infrastructure and assets needed to sustain the high intensity of drug research are concentrated in the Greater Boston and Cambridge area. While the high density of institutions, people, and ideas have worked well to attract high levels of investments into the state, industry executives appear to be uneasy about the increasing congestion in the area. According to one industry executive who participated in a focus group, competition for scarce geographical space is strong and the talent pool of skilled personnel in the Boston and Cambridge area is stretched almost to a breaking point. Consequently, the costs of doing business continue to spiral upward.

Of course, congestion is the other blade of a double-edged sword: as economic theory would suggest, there are obvious economic and strategic benefits from industry clusters. In spite of annoyance with occasional traffic jams and in spite of a feeling of helplessness at the escalating costs of real estate, the Greater Boston area continues to provide very good business reasons for industry to locate there. Such is clearly evident in recent newspaper reports and in the UMass survey results which suggest that the next few years will bring substantial investment into the already congested eastern part of the Commonwealth.

Even so, and despite the obvious benefits of industry clusters, it may be useful for future researchers to explore the implications of the narrow geographic presence of the pharmaceutical industry in the state. It would be helpful, for instance, for future research to try to estimate the carrying capacity of Greater Boston area. At what point do costs begin to outweigh the benefits of locating in the current hot spots in the state? When might pharmaceutical companies, large and small, decide that the Boston area is just too much trouble and that they would rather go to Providence, RI or Groton, CT or to another region altogether. Of course, the data gathered for this study are not adequate to answer these questions. Yet, they must be addressed to understand the long-run potential of the pharmaceutical industry in the state.

In a similar vein, future researchers should explore ways in which the pharmaceutical industry may be able to (and, if need be, offered incentives to) more broadly participate in the state. In fact, as this study has shown, while the Eastern part of the state is being weighed down by the numerous demands on its infrastructure, the rest of the state has virtually no participation in the evolving (implicit) convergence of interests with the industry. Certainly such is because of the concentration in the area of universities,
hospitals, and other organizations that complement drug research and manufacture. Yet, the vast stretches of almost barren land outside Route 495 could be utilized to accomplish the dual objectives of relieving pressure on Boston and Cambridge, and of developing opportunities in the rest of the state for both the industry and the residents.

It is, no doubt, outside the scope of this project to recommend specific alternate sites for developing infrastructure that is conducive to drug research and manufacture. Yet, it is incumbent upon the state to seriously explore Western regions that may have such potential. In the spirit of initiating thinking in this regard, one possibility to explore might be better connections (e.g., fast rail link) between Boston/Cambridge area with Worcester, which in recent years has been successfully developing a biotechnology park around the University of Massachusetts Medical School. Another possibility that should be explored is the Greater Springfield area in Western Massachusetts. With a superb location at the intersection of prominent highways going East-West and North-South, the city of Springfield connects important regions in the Eastern United States. In addition, Springfield not only has several technical schools that may serve as sources of a skilled workforce, the city also is geographically proximate to the University of Massachusetts and several liberal arts colleges in the Amherst-Hadley-Northampton region.

Another challenge confronting in the evolving participation of the pharmaceutical industry in the state is the wide variance in zoning laws and other regulations across different towns and cities. While some communities such as Worcester have made concerted efforts to shape local regulations to attract pharmaceutical manufacturing and R&D, industry executives note that many others continue to be uninformed about the industry's potential to contribute. They pointed out that many towns across the state remain skeptical about drug research or manufacturing facilities locating inside their jurisdiction. Consequently, while a few communities are open to investments by the industry, others knowingly or unknowingly put forth impediments that get in the way of a wider participation of the industry in the state. It would be useful, therefore, for future researchers to explore ways in which the state might be able to present a common front to the industry, while simultaneously preserving the time-honored tradition of home rule so valued by local communities.

Additionally, in the course of doing business with the various state government agencies, pharmaceutical companies (like other businesses) often encounter challenges they are ill-equipped or poorly prepared to handle. While the oversight of the state is important in such legitimate matters as industrial zoning, employee safety, and environmental permitting, there are numerous knotty practical issues around coordinating with the many departments at the state and local levels. In order to realize the full potential from the implicit partnership between Massachusetts and the pharmaceutical therefore, mechanisms need to be put in place to help the industry navigate through regulations and requirements at the various levels of the government. Hence, future researchers should explore the feasibility of and potential value from identifying experienced individuals (ombudsmen of sorts) - who would be dedicated to represent the development of the industry in the state and whose explicit job it would be to assist the pharmaceutical companies in getting through the red tape.
Along with focusing on the above fundamentals to explore ways to consolidate favorable developments already underway, future researchers should explore other indirect influences that may help enhance the attractiveness of the state to the industry. Some of the issues to consider are as follows:

- **Technology Licensing and Transfer** - The breakthrough biological and medical work in the academic research institutions in the state often finds its way into the real world of products and solutions to real problems. Some of these institutions have improved their ability to transfer out their technology by partnering with pharmaceutical and bio-pharmaceutical companies. Such partnerships not only bring in private monies to complement the limited funds for basic research; they also create pathways via which basic research can help improve the quality of life for the state's residents. While some academic institutions have over time created an art form of transferring out the technology coming out of their laboratories, many other academic centers do not have the ability or the experience to participate in the commercial markets for research. Hence, future research should explore the feasibility of and the ways in which a larger set of academic institutions could participate in technology licensing and transfer in an organized, concerted fashion.

- **Clinical Trials** - Pursuant to the mandate by the FDA, the pharmaceutical industry routinely engages in clinical trials for new drugs under development, investing an estimated $5 billion on such activities nationwide last year. In addition to satisfying the FDA mandate, such trials are often previews of research-based solutions to existing medical problems that lack satisfactory cure. As such, they benefit the patients in search for cures and the medical professionals in search of remedies for costly recurring illnesses. Hence, there are significant benefits - both economic and health related - for hospitals from actively participating in clinical trials for new drugs. While some hospitals in the state have in the last several years organized themselves to attract clinical trials, many others have neither the knowledge nor the ability to reorganize their operations so as to benefit by participating in such practical medical research. Hence, future research should explore the feasibility of and the ways in which a larger set of hospitals could participate in industry-sponsored clinical trials in an organized, concerted fashion.

- **Early Stage Manufacturing** - Although traditional pharmaceutical manufacturing has a non-trivial presence in Massachusetts, it is unlikely that the state can in the long run effectively compete for investments in manufacturing with many other low-cost locations around the world (such as Ireland and Puerto Rico). In contrast, manufacturing of bio-pharmaceuticals is a relatively recent phenomenon and many factors other than labor cost (e.g., proximity and control) play an important role in location decisions - particularly in the early stages of manufacture when the production methods have not been adequately stabilized and standardized. Given that Massachusetts has a high density of bio-pharmaceutical companies and most of these are in the product development stage, it is likely that the next several years will bring many of these companies the opportunity to build manufacturing plants for their first products. Rather than simply let such investments go elsewhere, consideration should be given to keep the early stage manufacturing of bio-pharmaceuticals within the state - perhaps in regions other than the congested eastern seaboard. Although it is not clear whether Massachusetts can be a viable location for bio- manufacturing in the long run, the importance of biotechnology industry in the state virtually mandates that a careful study of this issue should be undertaken.
In summary, the role that Massachusetts will play in the pharmaceutical industry of the next millennium will be driven by the strength of research in its universities and institutions, and by the ability of the general economic infrastructure to support investments. Conversely, the economic impact of the pharmaceutical industry on the Commonwealth will be greatly influenced by the perception about how attractive it is to make investments in the state and local economies. Ultimately, the strength of industry ties in the state will be influenced by the perceived productivity of investments made by individual companies.
Commissioned to assess and evaluate the economic impact of the pharmaceutical industry on Massachusetts, this research was compiled from archival data, mail surveys, field interviews, and historical analyses. The data reveal an industry that, by virtue of its intense focus on scientific research, is closely aligned with the strong culture of medical research in the state. While manufacturing and wholesale sectors of the industry are certainly present in the state, it is clearly the research function that makes for a unique network of arrangements involving public and private enterprises with a common interest in biological/medical science.

The quantitative analyses show that the pharmaceutical industry has significant economic impact on the state. It provides at least 25,000 jobs that are secured with unemployment insurance. It supports a payroll of over $400 million per quarter or sufficiently over $1 billion on an annualized basis. The manufacturing value added in the state by the industry is estimate to be more than $1 billion per year. The industry, in short, spends considerable sums of money in the state, adding up to hundreds of millions of dollars, in carrying out its research, manufacturing, marketing, and wholesale functions.

In addition, and perhaps critically, the pharmaceutical industry is deeply embedded in the economy of the Commonwealth. It is clear from the data that pharmaceutical firms are engaged in rich, multi-faceted collaborative relationships with research universities and health institutions in the state. Although not quantified, it is also evident that the industry benefits from and sustains numerous other businesses and organizations in the thriving economy of the state.

While the quantifiable impact on the state economy is impressive, however, it pales in comparison to the strategic role that the pharmaceutical industry can play (arguably it already does) in sustaining and promoting medical research in Massachusetts. This is because the industry's fundamental need for breakthrough (or blockbuster) drugs can be eminently fed with the extremely robust network of research institutions and teaching hospitals – particularly those in and around the Greater Boston area. Through the private actions of intensely competitive member companies, therefore, the industry invests hundreds of millions of dollars annually in the research institutions located in the Commonwealth. In so doing, the pharmaceutical industry effectively participates as a (yet unnoticed) private partner in the (as yet unrecognized) bid of the state to strengthen its persistently evolving strength in biological, biotechnical, and medical research. There is, in other words, a natural alignment between the interests of the pharmaceutical industry and those of the research institutions in Massachusetts.

The industry no doubt is attracted to and benefits from several unique infrastructure assets in the Commonwealth: excellent institutions of higher education, world-renowned medical schools and hospitals, deep-rooted culture of serious research, a vast pool of highly educated and talented people, and an active community of private financiers. At the same time, unsurprisingly, the state benefits in both tangible and intangible ways from the presence of the pharmaceutical industry. Because the entire pharmaceutical enterprise is driven by discovery and development of sophisticated new therapies, many drug companies
are deeply embedded in rich networks of alliances, research grants, and joint projects with both public and private research organizations in the state. In so doing, the drug companies help create pathways for basic biological and medical research to find applications into concrete revenue-generating products. As important as direct economic impact, therefore, the industry's strong presence in the state validates and strengthens the research infrastructure already in place.

In essence, driven partly by intense competition within and partly by unprecedented opportunities for medical breakthroughs made possible as a result of advancements in the laboratory sciences, the industry continues to grow its multi-billion dollar annual budget for research. Cognizant, moreover, of the fast evolving capabilities outside their own research laboratories, companies in the industry are eager to partner with leading research institutions and specialized boutiques. Under such circumstances, therefore, it stands to reason that Massachusetts - home for many renowned research universities and academic hospitals, not to mention the thriving biotechnology industry - is well positioned to receive more than a proportionate share of research expenditures of the pharmaceutical companies. Such investments, already evident in the survey data, will complement the monies made available by NIH and private investors, and, in so doing, strengthen the culture of research in the state.

It is, therefore, certainly with the realm of possibility that the 21st Century will present an opportunity for Massachusetts to become the center of gravity for the global pharmaceutical industry. During the last three hundred years, the state of Massachusetts has been at the periphery of the industry, as the centers for excellence in medical research have moved from France (in 18th century) to Central Europe (in 19th century) to England (early-middle 20th century) to the Mid-Atlantic states in the United States during the last fifty years. Given the current trajectory of medical science, the pressure on research-intensive pharmaceutical to produce remedies for ever more challenging illnesses, and the strong culture and infrastructure of scientific research in Massachusetts, it is possible that the future of the pharmaceutical industry may be joined with the culture of research in the Commonwealth. Whether or not such a future is realized will depend on the will and vision of the industry and state leadership.
END-NOTES

1 Telephone conversation with DET personnel on January 18, 1999.

ii Based on a personal conversation with personnel at The Census Bureau. January 20, 1999. The main reason for suspecting ASM was a big jump in the number of all employees in SIC 283 – which increased from 6,900 in 1994 to 12,600 in 1995. It is not clear why there was this sudden change in numbers because a corresponding change is not seen in the numbers provided by the Division of Education and Training, by the County Business Patterns, or by the Dun & Bradstreet.

In a telephone conversation (January 19, 1999) with personnel at The Census Bureau, it was understood that such sudden changes could result, among other things, from reclassifying one or more large establishments from some other SIC to SIC 283 – although no specifics were given. In a conversation the following day, much doubt was expressed by another Census Bureau employee about the reliability of the state-level data.

iii Note that not all biotechnology firms responded to the survey sent out by MBC, and 11 of 215 did not provide employment figures. In addition, given the nature of this industry, one-product research-based start-ups emerge and disappear at a fairly rapid rate. Consequently, it is very difficult to get a fix on the exact number of firms and employment figures for this sector of the economy.
Appendix 1

RESULTS OF THE MAIL SURVEY

Following an emerging convention, firms engaged in this industry are broadly classified as those using the traditional means of developing and manufacturing drugs, and those using mostly the relatively recent advances in biotechnology to generate pharmaceutical products or substances. This classification is based mainly in the fact that although the served healthcare markets may be the same, the enabling technologies used to access those markets are markedly different. Hence, in spite of some overlap where traditional firms also are increasingly invested in biotechnology, respondents to the survey were classified as being pharmaceutical or biopharmaceutical companies.

In January 1999, two groups of companies were sent mail surveys that comprised a series of questions about each target company's operations in Massachusetts. The first group included 71 pharmaceutical companies that were members of the Pharmaceutical Research And Manufacturers Of America (PhRMA). The second group included 139 members of the Massachusetts Biotechnology Council. All companies that appeared in both lists had been removed such that only one survey went out to each of the 210 companies. The survey instrument sent to the two groups of companies were essentially the same, except three questions that were modified in consideration of slightly different, ownership, financing and tax issues faced by biotechnology companies. A copy of the survey instrument is available from the author.

The survey had the following five sections: A - Company Profile, B - Research in Massachusetts, C Employment Profile, D - Taxes to the State, and E - Future Investments in the State. The surveys were sent along with a confidentiality agreement signed by the principal investigator. Upon receiving only a few surveys back by the original deadline of February 8, a reminder was sent on February 23 and a new deadline was set as March 15. The last survey included in the study was received in the middle of April.

Fifteen pharmaceutical companies and seventeen biotechnology companies completed and returned the surveys. Six pharmaceutical companies indicated that they did not have resources to participate in the study. Two pharmaceutical companies wrote back that they did not have operations in Massachusetts. The low response rate was surprising in light of the fact that PhRMA had sponsored the study and they had encouraged their member companies to participate. In addition, Massachusetts Biotechnology Council had also helped first by providing the list of their member companies, and then by sending a reminder in March for them to complete the surveys.

It is not clear whether timing for the survey could have been better, as the beginning of a new year is often taxing for the companies in many different ways. It is also possible, however, that (particularly) pharmaceutical companies just do not record information on a state-by-state basis and, therefore, they found it very difficult to compile the requested information. It is also not clear how the companies that did not respond are different along the relevant variables from those that did. Hence, along with the fact of low response rate, it cannot be guaranteed that the responding companies are representative of the entire sample that received the surveys. It is meaningless, therefore, to present statistical averages from the survey.
Presented below, instead, are the total tallies and aggregate values across the thirty one companies that did respond. It should be noted that since many companies did not get to complete the survey, the numbers presented below indicate the lower bound for variables of interest. So, for instance, it is accurate to say that pharmaceutical firms invested at least $1 billion in research in the state during 1995-1997 period.

RESULTS

Section A: Company Profile

As shown in Table 5.1, the 17 biopharmaceutical companies that responded to the survey were engaged in medical research that targeted 37 different diseases or illnesses. Four of these 17 companies were involved in research on AIDS and another 5 were targeting various types of cancer. In addition, these firms also targeted breast cancer, cystic fibrosis, genetic disorder, nerve disorders, and osteoporosis.

TABLE 5.1
Diseases and Conditions Targeted by Firms in Massachusetts
Bio-Pharmaceutical Companies

<table>
<thead>
<tr>
<th></th>
<th>Disease/Medical Condition</th>
<th></th>
<th>Disease/Medical Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AIDS (4)</td>
<td>20</td>
<td>Helicobacter Pylori</td>
</tr>
<tr>
<td>2</td>
<td>Anti Inflammatories</td>
<td>21</td>
<td>Hematoposis</td>
</tr>
<tr>
<td>3</td>
<td>Arthritis</td>
<td>22</td>
<td>Infectious Disease Vaccines</td>
</tr>
<tr>
<td>4</td>
<td>Asthma</td>
<td>23</td>
<td>Japanese Enupha</td>
</tr>
<tr>
<td>5</td>
<td>Atherosclerosis</td>
<td>24</td>
<td>Kidney Damage</td>
</tr>
<tr>
<td>6</td>
<td>Bacteriological Fungal Infections</td>
<td>25</td>
<td>Leukemia</td>
</tr>
<tr>
<td>7</td>
<td>Bone Fractures</td>
<td>26</td>
<td>Male Erectile Dysfunction</td>
</tr>
<tr>
<td>8</td>
<td>Bone Marrow Transplantation</td>
<td>27</td>
<td>Malenoma</td>
</tr>
<tr>
<td>9</td>
<td>Breast Cancer (2)</td>
<td>28</td>
<td>Nerve Disorders</td>
</tr>
<tr>
<td>10</td>
<td>Cancer (5)</td>
<td>29</td>
<td>Non Hodgkins Lymphoma</td>
</tr>
<tr>
<td>11</td>
<td>Candidias</td>
<td>30</td>
<td>Organ Transplantation</td>
</tr>
<tr>
<td>12</td>
<td>Cardiovascular Disease</td>
<td>31</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>13</td>
<td>Cartilage Misplacement</td>
<td>32</td>
<td>Periodontal Disease (2)</td>
</tr>
<tr>
<td>14</td>
<td>Chronic Heart Failure</td>
<td>33</td>
<td>Prostate Cancer</td>
</tr>
<tr>
<td>15</td>
<td>Cystic Fibrosis</td>
<td>34</td>
<td>Restenosis</td>
</tr>
<tr>
<td>16</td>
<td>Dengue</td>
<td>35</td>
<td>Sexually Transmitted Diseases</td>
</tr>
<tr>
<td>17</td>
<td>Fibrotic Diseases</td>
<td>36</td>
<td>Transfusion Medicine</td>
</tr>
<tr>
<td>18</td>
<td>Gastrointestinal Diseases</td>
<td>37</td>
<td>Wound Healing</td>
</tr>
<tr>
<td>19</td>
<td>Genetic Disorder</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figures in parenthesis indicate the number of respondents indicating illness as target.

Source: University of Massachusetts Survey
Similarly, as shown in Table 5.2, the 15 pharmaceutical respondents were engaged in medical research that targeted more than 45 diseases or illnesses. Eleven of the 15 respondents were involved in research on various forms cancer, 9 firms were involved in research on illnesses related to the central nervous system, and 8 firms were targeting cardiovascular diseases. In addition, pharmaceutical companies in Massachusetts were involved in research on AIDS, Alzheimer's disease, arthritis, depression, diabetes, multiple sclerosis, obesity, and pain.

**TABLE 5.2**  
Diseases and Conditions Targeted by Firms in Massachusetts  
*Pharmaceutical Companies*

<table>
<thead>
<tr>
<th></th>
<th>Disease/Condition</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Aging</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>AIDS (4)</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Allergic Diseases</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>Alzheimer's Disease</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Anemia</td>
<td>29</td>
</tr>
<tr>
<td>6</td>
<td>Anemia not due to CRF</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>Arthritis/Inflammation</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>Asthma (2)</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>Bone &amp; Tissue Repair</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>Cancer (11)</td>
<td>34</td>
</tr>
<tr>
<td>11</td>
<td>Cardiovascular Disease (8)</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>Central Nervous system (9)</td>
<td>36</td>
</tr>
<tr>
<td>13</td>
<td>Depression</td>
<td>37</td>
</tr>
<tr>
<td>14</td>
<td>Diabetes (3)</td>
<td>38</td>
</tr>
<tr>
<td>15</td>
<td>Endocrinology (2)</td>
<td>39</td>
</tr>
<tr>
<td>16</td>
<td>Gastrointestinal Diseases</td>
<td>40</td>
</tr>
<tr>
<td>17</td>
<td>Gastroesophageal Reflux Disease</td>
<td>41</td>
</tr>
<tr>
<td>18</td>
<td>Genitourinary/Sexual Health</td>
<td>42</td>
</tr>
<tr>
<td>19</td>
<td>Growth Disorder</td>
<td>43</td>
</tr>
<tr>
<td>20</td>
<td>Hairy Cell Leukemia</td>
<td>44</td>
</tr>
<tr>
<td>21</td>
<td>Hematology (2)</td>
<td>45</td>
</tr>
<tr>
<td>22</td>
<td>Hemophilia</td>
<td>46</td>
</tr>
<tr>
<td>23</td>
<td>Hepatitis C</td>
<td>47</td>
</tr>
<tr>
<td>24</td>
<td>Immunology (2)</td>
<td>48</td>
</tr>
</tbody>
</table>

Figures in parenthesis indicate the number of respondents indicating illness as target.  
*Source: University of Massachusetts Survey*
Section B: Research in Massachusetts

As shown in Table 5.3, the National Institutes of Health and traditional Pharmaceutical Companies were the chief sources of research funding for the bio-pharmaceutical companies in Massachusetts. Respondents indicated that seventy five percent of the total funding they received for research in 1997 was supplied by the traditional pharmaceutical companies.

TABLE 5.3

Sources of Research Support for Bio-Pharmaceutical Companies
(Dollars in Thousands)

<table>
<thead>
<tr>
<th>Source</th>
<th>Amount 1997</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institutes of Health</td>
<td>2,200</td>
<td>15%</td>
</tr>
<tr>
<td>National Science Foundation</td>
<td>500</td>
<td>3%</td>
</tr>
<tr>
<td>Pharmaceutical Companies*</td>
<td>10,700</td>
<td>75%</td>
</tr>
<tr>
<td>Others</td>
<td>889</td>
<td>6%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>14,289</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: University of Massachusetts Survey

As shown in Table 5.4, the pharmaceutical and bio-pharmaceutical companies spent more than $985 million on drug related research during the 1995-1997 period. Of this, $634 million (61%) was spent

TABLE 5.4

Expenditures on Research & Clinical Trials in Massachusetts, 1995-1997
(Dollars in Thousands)

<table>
<thead>
<tr>
<th>Source</th>
<th>1997</th>
<th>1996</th>
<th>1995</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Companies</td>
<td>633,757</td>
<td>263,242</td>
<td>214,085</td>
</tr>
<tr>
<td>Bio-Pharmaceutical Companies</td>
<td>413,593</td>
<td>152,988</td>
<td>140,580</td>
</tr>
<tr>
<td>Combined</td>
<td>1,047,350</td>
<td>416,230</td>
<td>354,664</td>
</tr>
</tbody>
</table>

Source: University of Massachusetts Survey
by pharmaceutical companies and the remaining $413 million (39%) were spent by biopharmaceutical companies. Note that some of the monies indicated by bio-pharmaceutical companies may be double counted if it was supplied to them by the traditional pharmaceutical companies. The surveys did not provide information to sort out such detail.

In concert with the dollar investments in research and clinical trials in the state, pharmaceutical and bio-pharmaceutical companies also indicated extensive ties with public and private research organizations. As shown in Table 5.5, the respondents reported a total of 397 linkages with other entities in the state. Of these 277 (70%) were reported by pharmaceutical companies and 120 (30%) were reported by bio-pharmaceutical companies. Of the 397 total linkages, moreover, 148 (38%) were for clinical research and 133 (34%) were for basic research. Along the same lines, of the 397 total linkages, 152 (38%) were with academic research institutions, 116 (29%) were with non-academic health institutions, and 129 (32%) linkages were with other for-profit organizations in the Commonwealth.

**TABLE 5.5**

<table>
<thead>
<tr>
<th>Type of Linkage</th>
<th>TOTAL</th>
<th>Academic Research</th>
<th>Non-Academic Health</th>
<th>Other For Profit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Ph.</td>
<td>Bt.</td>
<td>All</td>
</tr>
<tr>
<td>Clinical Research</td>
<td>148</td>
<td>126</td>
<td>22</td>
<td>53</td>
</tr>
<tr>
<td>Licensing Patent</td>
<td>73</td>
<td>48</td>
<td>25</td>
<td>36</td>
</tr>
<tr>
<td>Basic Research</td>
<td>133</td>
<td>67</td>
<td>66</td>
<td>47</td>
</tr>
<tr>
<td>Technology Transfer</td>
<td>43</td>
<td>36</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>TOTAL</td>
<td>397</td>
<td>277</td>
<td>120</td>
<td>152</td>
</tr>
</tbody>
</table>

Ph. -- Pharmaceutical Company Respondents  
Bt. -- Bio-Pharmaceutical Company Respondents

*Source: University of Massachusetts Survey*

As shown in Table 5.6, the survey respondents reported extensive ties with several research universities in the Commonwealth. Twenty eight pharmaceutical and 20 bio-pharmaceutical ties were reported with Harvard University and affiliated teaching hospitals. Eighteen pharmaceutical and 9 biopharmaceutical ties were reported with the Massachusetts Institute of Technology. Eight pharmaceutical companies and 10 bio-pharmaceutical ties were reported with the University of Massachusetts Medical School. The other
institutions with which the respondents reported having research ties were Tufts University (13 links) Boston University (8 links).

**TABLE 5.6**

<table>
<thead>
<tr>
<th>University</th>
<th>Pharmaceutical Companies</th>
<th>Bio-Pharmaceuticals Companies</th>
<th>All Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a  b c d  Total</td>
<td>a  b c d  Total</td>
<td>Combined</td>
</tr>
<tr>
<td>Boston University</td>
<td>4  1 - -  5</td>
<td>1  1 1 -  3</td>
<td>8</td>
</tr>
<tr>
<td>Harvard University</td>
<td>12 6 4 6  28</td>
<td>3  7 6 4 20</td>
<td>48</td>
</tr>
<tr>
<td>Massachusetts Institute of Technology</td>
<td>5  5 4 4  18</td>
<td>2  2 4 1  9</td>
<td>27</td>
</tr>
<tr>
<td>Tufts University</td>
<td>3  - - -  3</td>
<td>4  4 0 2 10</td>
<td>13</td>
</tr>
<tr>
<td>University of Massachusetts</td>
<td>6  1 - 1  8</td>
<td>3  3 2 2 10</td>
<td>18</td>
</tr>
<tr>
<td>Babson College</td>
<td>- 1 - -  1</td>
<td>-  - - -  1</td>
<td></td>
</tr>
<tr>
<td>Beth Israel Hospital</td>
<td>1  - - -  1</td>
<td>-  - - -  1</td>
<td></td>
</tr>
<tr>
<td>Brandeis University</td>
<td>1  1 - -  2</td>
<td>-  - - -  2</td>
<td></td>
</tr>
<tr>
<td>Other Health Research Hospitals</td>
<td>1  1 1 -  3</td>
<td>-  - - -  3</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>33 16 9 11 69</strong></td>
<td><strong>13 17 13 9 52</strong></td>
<td><strong>121</strong></td>
</tr>
</tbody>
</table>

Legend: (a) Funded Research, (b) Joint Projects, (c) License Technology, and (d) Key Personnel

*Source: University of Massachusetts Survey*

As Table 5.7 shows, moreover, there were a total of 121 industry partnerships with research universities in the state. Of these, 69 (57%) were reported by pharmaceutical companies and 52 (43%) were reported by bio-pharmaceutical companies. With regards to the type of partnerships, respondents indicated that 46 (38%) of the partnerships involved funded research, 33 (27%) involved joint projects, 22 (18%) involved technology licenses, and 20 (18%) involved key personnel of the respondent coming from the partner research university. Note that industry-university partnerships are often multifaceted, so a single relationship may include more than one type of partnerships.
TABLE 5.7

Summary of Industry-University Partnerships

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Ph.</th>
<th>Bt.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funded Research</td>
<td>46</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Joint Projects</td>
<td>33</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Licence Technology</td>
<td>22</td>
<td>9</td>
<td>13</td>
</tr>
<tr>
<td>Supply Key Personnel</td>
<td>20</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>121</td>
<td>69</td>
<td>52</td>
</tr>
</tbody>
</table>

Source: University of Massachusetts Survey

Section C: Employment Profile

As shown in Table 5.8, the respondents employed over 5,500 people in 1998 and they had a total payroll of over $369 million. In 1998, twelve traditional pharmaceutical companies reported more than twice the employment than did the sixteen bio-pharmaceutical companies; and they reported a payroll that was 73% larger than that of the bio-pharmaceutical companies.

TABLE 5.8

Employment & Payroll in Massachusetts, 1997 & 1998 (Estimated)
(Dollars in Thousands)

<table>
<thead>
<tr>
<th></th>
<th>Employment</th>
<th>Payroll</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Companies*</td>
<td>3,962 3,685</td>
<td>$234,257 $211,819</td>
</tr>
<tr>
<td>Bio-Pharmaceutical Companies**</td>
<td>1,681 1,455</td>
<td>$135,275 $122,496</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>5,643 5,140</td>
<td>$369,532 $334,315</td>
</tr>
</tbody>
</table>

* Based on 12 useable responses
** Based on 16 responses for employment and 15 responses for payroll

Source: University of Massachusetts Survey
As shown in Table 5.9, the respondents expect to add another 1047 jobs in Massachusetts. More than half of these jobs (608) are expected to be in research and related functions. The bio-pharmaceutical companies are expected to provide 726 (69%) of these new jobs, with the remaining 321 (31%) coming from the traditional pharmaceutical companies.

### TABLE 5.9

| Total Research Mfg. Sales Other |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Pharmaceutical Companies*     | 321             | 169             | 8               | 144             | n/a             |
| Bio-Pharmaceutical Companies**| 726             | 439             | 95              | 96              | 96              |
| TOTAL                         | 1047            | 608             | 103             | 240             |

* Based on between 4 and 7 useable responses
** Based on 16 responses

*Source: University of Massachusetts Survey*

### Section D: Taxes to the State

The data for taxes paid by the respondents was rather spotty and many companies indicated that such information was not available. Even so, the few companies that did provide information indicates that we have a lower bound of how much the industry paid in taxes to the state of Massachusetts.

### TABLE 5.10

| Taxes to the Commonwealth, 1996-1998  |
|-------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Pharmaceutical Companies*           | 32,367          | 10,778          | 11,478          | 10,111          |
| Bio-Pharmaceutical Companies**      | 24,862          | 9,632           | 8,967           | 6,263           |
| TOTAL                               | 57,229          | 20,410          | 20,445          | 16,374          |

* Based on between 7 and 10 responses to the survey
** Based on about 10 responses to the survey

*Source: University of Massachusetts Survey*
As shown in Table 5.10, the state received over $54 million in taxes (net of research credits) from the industry during the period 1996-1998. Of this total amount, the share of the traditional pharmaceutical companies was $32 million (56%) and that of the bio-pharmaceutical companies was $25 million (44%).

**Section E: Future Investments in the State**

With regards to future investments by the pharmaceutical industry, Table 5.11 provides some relevant numbers. Of the 17 bio-pharmaceutical companies responding to the survey, 16 indicated that they expected to expand significantly during the next three years at least some part of their operations in the state. The areas in which the respondents expect to expand are as follows: Basic Research (8), Clinical Trials (9), Applied Research & Product Development (10), Manufacturing (5), and Sales & Marketing (2). Similarly, of the 15 pharmaceutical companies responding to the survey 10 indicated their expansion plans as follows: Basic Research (7), Clinical Trials (4), Applied Research & Product Development (6), Manufacturing (2), and Sales & Marketing (2).

<table>
<thead>
<tr>
<th>TABLE 5.11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expansion in the State, 1998-2000</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pharmaceutical Companies</td>
</tr>
<tr>
<td>Bio-Pharmaceutical Companies</td>
</tr>
<tr>
<td>TOTAL</td>
</tr>
</tbody>
</table>

BT - Basic Research; CT - Clinical Trials; AR - Applied Research & Product Development
Mfg – Manufacturing; SM - Sales & Marketing

**Source: University of Massachusetts Survey**

As shown in Table 5.12 below, the companies responding to the survey estimate that they will spend $1.36 billion in research and related operations in the state during 1998-2000 - a 30% increase over the estimated expenditures on research by these same companies during the 1995-1997 period. About $920 million (68%) of these expenditures are expected to be made by the bio-pharmaceutical companies and the remaining $441 million (32%) by the traditional pharmaceutical companies.

Also during the same period (1998-2000), the industry respondents expect to spend $198 million on manufacturing related activities and another $226 million on the sales and marketing. Once again, the bio-pharmaceutical companies expect to make the lion's share of future expenditures in both manufacturing ($145 million or 73% of total) and in marketing ($124 million or 55% of total).

| TABLE 5.12 |
Finally, as shown in Table 5.13, the survey respondents also indicated that, during 1998-2000, they expect to spend over $277 million on renovation of existing buildings or on new construction projects in the state. This represents an increase of 377% over such expenditures by these same companies during the 1995-1997 period. About $180 million or 65% of the total monies to be spent on new construction and renovation projects in the state will come from bio-pharmaceutical companies. [Note that monies to be spent on construction may overlap somewhat with those spent on functions indicated in Table 5.12.]

<table>
<thead>
<tr>
<th></th>
<th>Research &amp; Clinical Trials</th>
<th>Manufacturing</th>
<th>Sales &amp; Marketing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Companies</td>
<td>441,812</td>
<td>52,930</td>
<td>101,500</td>
</tr>
<tr>
<td>Bio-Pharmaceutical Companies</td>
<td>920,178</td>
<td>145,354</td>
<td>124,799</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1,361,990</td>
<td>198,284</td>
<td>226,299</td>
</tr>
</tbody>
</table>

Source: University of Massachusetts Survey

In closing, the low response rate to the mail survey limits the ability to make generalizable statements about the role of pharmaceutical companies in Massachusetts. Yet, it is possible to say that the numbers presented above indicate the lower bound of the investments that the industry has made and that it expects to make in the state during the next few years.

### Table 5.13

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceutical Companies</td>
<td>36,598</td>
<td>96,777</td>
<td>264%</td>
</tr>
<tr>
<td>Bio-Pharmaceutical Companies</td>
<td>36,895</td>
<td>180,361</td>
<td>489%</td>
</tr>
<tr>
<td>TOTAL</td>
<td>73,493</td>
<td>277,138</td>
<td>377%</td>
</tr>
</tbody>
</table>

Source: University of Massachusetts Survey

Summary Of Results From The Mail Survey

- During the period 1995-1997, a sample of 15 pharmaceutical and 17 bio-pharmaceutical companies reported to have invested over $1 billion in drug research and related activities in the state.
During the period 1998-2000, the respondents to the survey project that they will invest more than $1.36 billion in research and related activities in the state. The bio-pharmaceutical companies expect to make almost twice the level of investment in research than that anticipated by the traditional pharmaceutical firms that participated in the study. *Survey*

In 1998, the respondents to the survey employed 5,643 people in Massachusetts - up 9.8% from 1997. Of these, 3,962 (70%) were employed by the traditional pharmaceutical firms. *Survey*

The 32 respondents to the survey reported a payroll of $369,532 in 1998 - up 10.5% from 1997. Of this amount, the traditional pharmaceutical firms provided $234,257 (63%). *Survey*

During the period 1998-2000, the 32 pharmaceutical and bio-pharmaceutical companies expect to add another 1,047 jobs in the state - most (608) of which in the area of research and clinical trials, and a majority (726) of which to be provided by bio-pharmaceutical companies. *Survey*

More than half of respondents to the UMass Survey indicated that they expect to significantly expand their research activities in the state during the period 1998-2000. *Survey*

The thirty-two responding pharmaceutical and bio-pharmaceutical companies reported as having a total of 397 separate ties with research institutions and organizations in the state. The ties were distributed as follows: clinical research (148), licensing patent (73), basic research (133), and technology transfer (43). *Survey*

The thirty-two survey respondents had a total of 121 explicit links with universities in Massachusetts. Of these 69 (57%) involved pharmaceutical companies and the remaining 52 (43%) involved bio-pharmaceutical companies. *Survey*

Bio-Pharmaceutical companies responding to the UMass Survey indicated that 75% of their monies for research come from traditional pharmaceutical companies. *Survey*

Two of 15 pharmaceutical companies and 5 of 17 bio-pharmaceutical companies responding to the UMass Survey indicated that they expect to significantly expand their manufacturing activities in the state during the period 1998-2000. *Survey*

Respondents to the UMass Survey indicated that they expect to spend $198 million on manufacturing activity and $226 million on sales and marketing in Massachusetts during the 1998-2000 period. *Survey*

Respondents to the UMass Survey indicated that they expect to spend $277 million on construction activity in Massachusetts during the 1998-2000 period - a 377% increase over the $73 million these companies reported for 1995-1997. *Survey*
Appendix 2

NOTE ON THE PHARMACEUTICAL INDUSTRY

It is perhaps a truism to say that, through much of history, disease and illness have been the most formidable foes of mankind. It is also no exaggeration to note that, over the centuries, more people have succumbed to all varieties of diseases than the combined toll from all the internecine wars – and countless others have suffered a poor quality of life fighting hopeless battles against microbes and other causes of degenerative diseases.

And, while the search for cures is probably as old as history itself, mankind have (until this century) been pitifully ill-equipped to adequately deal with even minor microbial invasions into the body. Just about two centuries ago, for instance, and almost three decades after having led a rag-a-tag army of patriots to defeat the most powerful nation on earth, George Washington, the first president of this then new republic, succumbed to what seems to have been a bad cold.¹

Only since the beginning of the twentieth century has there been significant progress in identifying and combating the various diseases. As technology has progressed and as scientific culture has gained momentum, ever greater number of unfriendly microbes and other sources of diseases have been subdued. Many of the most notorious illnesses of even the recent past have been successfully combated with the aid of rapidly growing scientific knowledge and a concurrently evolving institutional infrastructure.

On the eve of the twenty-first century, informed observers believe, the pharmaceutical industry is entering a Golden Age, where decades of scientific breakthroughs have poised researchers to combat even the most formidable illnesses of our times. Driven mostly by science-based innovation, the industry in the late 1990s brings great value to the masses; it is very profitable; and, ironically, it is also one of the most fiercely competitive. It is, therefore, replete with issues that need elaboration.

Historical Context

When the pilgrims landed on the coast of Massachusetts in 1620, they brought with them not only a desire to establish a new home where they could practice their faith without persecution, but also the English medical wisdom accumulated through the ages in the Old World. On board the Mayflower was Rembert Dodoens’ book of botanical remedies, A Brief Epitomy Of The New Herbal Etc., First Set Forth In Ye Dutch Tongue.

Dodoens’ book reflected folk medicine which, as historians note, blurred the lines between the natural, the supernatural, and the occult. Diseases of all kinds were regarded as Divine retribution, and religion was integral to the cures. This was not surprising given that the cures then prescribed for various
illnesses were based in rather primitive theories of humors and highly speculative herbal polypharmacy
developed by the Roman physician Galen (AD 129-199). These theories, themselves derived from the
works of Hippocrates of ancient Greece, claimed that illness was a result of imbalance in the four major
fluids or humors (yellow bile, blood, phlegm, and black bile) that permeate the human body. As such, the
treatments for illnesses were based on restoring the balance by such means as bleeding, sweating, and
purging, and with the aid of herbs that presumably had desirable properties in relation to particular humors.

Embedded in authority and tradition, the Galenic theories persisted through the Dark Ages in
Europe for over twelve hundred years. It was not until the sixteenth century that they were attacked by the
Swiss physician, Paracelsus (1493-1541), who argued that there were distinct diseases, each with their own
causes and cures. He proposed the “doctrine of signatures” to explain the connection between specific
herbs and cures for specific diseases. Considered the Father of chemical treatment because of his affinity
for metals (such as arsenic, copper, lead, iron, mercury, and antimony), Paracelsus nonetheless attributed
much value to herbs. He claimed that the outward appearance of plants reflected their inner virtues which
“God hath put in them for the good of man.”

Galenic and Paracelsian theories were, therefore, well established in Europe by the time the
pilgrims set sail for the New World. Inevitably, the herb gatherers among the early settlers, mostly English
women, relied heavily on the folklore that extended back to very early times in their native lands. In fact,
as late as the eighteenth century the influence of these traditional theories could be seen in the wide use of
saffron and tumeric which, by virtue of their color, were believed to be cures for jaundice (or yellow fever).
Similarly, as George Gifford notes, “walnut meats, because of their rough resemblance to the convolutions
of the brain, would afford a natural cure for all cranial ailments” (1980, p. 265).²

The settlers relied, moreover, on the accumulated knowledge – formalized and compiled in
Dodoens’ book – that was mostly about plants indigenous to the Old World. The settlers had little, if any,
knowledge about plants in Massachusetts and, therefore, they depended for a long time on herbs brought
from across the Atlantic. Over time, through interactions with the native peoples in the New World, the
settlers learned about the medicinal value of animals and plants available in their immediate surroundings.
There was widespread belief that Providence located appropriate cures in the same geography where
corresponding diseases were found. The New World flora was, in other words, thought to be a great
potential source of cures for illnesses in the New World.

Not surprisingly, therefore, numerous plants with purported medicinal value were identified in
Massachusetts and other colonies during the subsequent decades. Tobacco, for instance, was the one of the
most famous flora of the New World and it was purported to have a great many virtues for the ills of early
Europeans in Massachusetts. Gradually, the discovery, cultivation, and sale of plant drugs became a
profitable activity in New England. Throughout the seventeenth and eighteenth centuries, large quantities
of plant derivatives were exported to England. As such local herbs provided considerable economic benefit
to the colonies.
The first records of pharmaceutical business transactions in New England are found in the Account Book of Bartholomew Browne, a “pharmaceutical-chemist” in Salem at the turn of the seventeenth century. Browne made extensive use of tartar as cure for many ills and he also dispensed many herbal preparations of local origin. Yet, the citizenry of Massachusetts still depended heavily on England for drug supplies, listed in the London *Pharmacopoeia* of 1650, that were much too complicated to be correctly compounded locally.

In spite of emergent dispensers and formalized *Pharmacopoeias*, however, the English emigrants in Massachusetts cherished advice for self-treatment and cultivation of herbs. Several books, treasured by the colonial housewife, were published in the eighteenth century. Nicholas Culpeper’s *The London Dispensary*, first published in 1649, was reprinted in Boston in 1720. William Buchan’s *Domestic Medicine* was, in fact so popular that it was reprinted more than fifteen times after its initial publication in 1669. By the turn of the seventeenth century, the self-help tradition was well-established in American.

As George Gifford writes,

“Early colonial botanic remedies were, then, composites of several distinct traditions intermixing, tempered by the American environment with its own flora. There was the ‘Kitchen physic’ that grew out of the leech and ‘good woman’ tradition; there was the Indian materia medica; there was the flood of self-help books by authors such as Culpeper, Buchanan, and Wesley; there was the ‘Angelic Conjunction’ or the physician-minister who suffused the decoction with theological endorsement; and there were the official remedies based on the English Pharmacopoeias, which were, in turn, based on the dying Galenic theories and the new theories of [English physician] Sydenham, who [like Paracelsus] advocated specific cures for specific diseases. These varying traditions were fused by a long period of empirical, largely self-administered, and, consequently, independent evaluation.”

To be sure, the available remedies did not effectively protect the residents of early Massachusetts and New England. Immigrants into the colonies brought various diseases with them and they were greeted with many other diseases well-established in the local populations. Smallpox, diptheria, scarlet fever, and measles were rampant, and so were intestinal problems and respiratory ailments such as pneumonia and pulmonary tuberculosis. Smallpox was a particularly aggressive disease that ravaged the peoples. As Eric Christianson reports,

“Originating in British Isles, the West Indies, or in Canada, smallpox epidemics ravaged Massachusetts and most of New England in 1648, 1666, 1677, 1689, 1702, 1721, 1731, 1751, 1764, and in the 1770s. During the celebrated epidemic of 1721, during which inoculation was first practiced in America, over half of Boston’s 10,670 inhabitants became infected and over 800 died” (1987, p. 116).

As an interesting aside, Dr. Samuel Fuller, a physician on the *Mayflower*, also had succumbed to smallpox in 1633, thirteen years after coming ashore the new land.
The improvement in dietary habits and housing did reduce the incidence of some diseases during the late eighteenth century. But the epidemics continued and they generated a widespread sense of vulnerability among inhabitants of the new colonies. Such is evident in the words of Dr. Stephen Williams, a physician in Franklin County in the western part of the Commonwealth. He wrote,

“In 1831, the typhus fever, according to Dr. Dorrance, prevailed extensively in Sunderland. This town, lying on the east bank of the Connecticut river, then contained about seven hundred inhabitants. The town had been unusually healthy up to this period, when, in early part of winter, the scarlet fever and whooping cough prevailed extensively there. Soon after, typhus fever commenced, and up to November, sixty cases occurred in that neighborhood. Six weeks after, the same fever again commenced and spread rapidly, until ‘one hundred, principally in the village of fifty houses and perhaps three hundred inhabitants, were the subjects of it. Of three hundred cases, nine proved fatal.’ Fevers of a typhoid character have prevailed sporadically, and in some cases almost as epidemics, in various parts of the county at different times”5 (1842, p. 18).

Pharmacy in the Nineteenth Century

Given the benefit of hindsight, it is not surprising that the medicines available in the colonial period were no match for the diseases that plagued mankind in Massachusetts and elsewhere. In spite of some spillover benefits from rapidly increasing understanding of scientific medicine in revolutionary Paris and then among the dye makers of Central Europe, most treatments remained speculative.6 Neither professionals nor lay patients had any systematic knowledge of the safety and effectiveness of medicines consumed. There was, moreover, great variation in therapeutic practice as opinions about the illnesses and their cures came from small pharmacists, large manufacturers of proprietary medicines, patent medicine makers, large chemical firms, physicians, and, of course, good neighbors.

In order to overcome the confusion from lack of standardization in drug formulations or medical practice, attempts were made to formalize whatever knowledge there was about drugs considered to be respectable therapeutics in the arsenal of doctors of the time. The United States Pharmacopoeia (UPS), published by doctors in 1820, listed the composition and techniques of manufacture for a standard list of pharmaceutical preparations. Other pharmacopoeias had been published by the middle of the century, including two simultaneously in 1935. In fact, the UPS was revised several times by the pharmacists, who, in 1888, published their own National Formulary to complement and supplement the doctors’ volume.

Yet, the pharmacopoeias were collections of empirical and traditional knowledge and their compilers made no attempt to validate the information they provided. Although some efforts were made in later part of the century to establish clinical effects of various drugs, only a handful of the drugs included in the above two compendia are considered to be effective by the yardsticks of late twentieth century.7 The two hundred or so other drugs in the pharmacopoeias were either useless or of only minor benefit. Peter Temin approvingly quotes another historian of medicine as saying, “The great lesson…of medical history is that the placebo has always been the norm of medical practice” (1980, p. 25).
No doubt that, by late nineteenth century, the residents of Massachusetts and elsewhere had begun to take advantage of medical developments occurring mostly in Europe. Deeper understanding in the arenas of nutrition and vaccines had enabled systematic control of illnesses arising from poor diet and from infections. The nineteenth century brought many levels of understanding about sources of and cures for diseases. The smallpox vaccine, for example, had been in use in the United States since 1800, when a colleague in England had sent some of it to Benjamin Waterhouse, a doctor in Boston.8

The discovery of microorganisms and acceptance of a germ theory of disease, among other things, set the stage for major breakthroughs in the twentieth century.

The beneficial effects of these developments were slow in coming, however. It was not until 1855 that Massachusetts became the first state to pass the law requiring all children to be vaccinated against smallpox before entering school.9 The disease was not eradicated from the United States and most other developed world until a hundred years later in the early 1950s. Other illnesses such as diptheria continued to plague the populations through the end of the nineteenth century. Diseases such as pulmonary tuberculosis, cholera infantum, diptheria, and measles, not to mention a whole range of other infections, were major causes of morbidity and mortality in large cities as well in rural areas of Massachusetts.

It should be noted that, for much of the first half of the nineteenth century, the manufacture of drugs was accomplished mostly by two groups of participants.10 On the one hand, a few large manufacturers of proprietary drugs – concentrated largely in Philadelphia and New York – sold their wares in bulk and who made moderately large profits for their troubles. On the other hand were numerous small pharmacists – spread throughout the land – who sold specialty preparations for the drug trade and who also operated retail businesses.

Then the war with Mexico (1846-48) and the Civil War (1861-1865) significantly increased the army’s appetite for medicines and brought in orders for large quantities that justified investments in manufacturing capacity. High volumes brought about by war conditions and good prices paid by the army encouraged manufacturers to produce on a much larger scale than pre-war years. Large scale, in turn, laid the groundwork for consolidation of production that was to follow in later years. By the turn of the century, moreover, changes in distribution technology and a rapidly proliferating number of drugs on the shelves of retailers had given rise to large wholesalers. These mass distributors provided new opportunities for consolidating distribution of drugs now being increasingly produced at a large scale by large manufacturers.

By the turn of the century, large “ethical” pharmaceutical manufacturers had – in addition to expanding the production of proprietary medicines – taken over much of the production of drug compounds previously in the domain of small pharmacists.

Breakthroughs in the Twentieth Century
The cumulative effects of centuries of search for cures and of the scientific culture sweeping Europe since the middle eighteenth century finally began to yield significant results in the twentieth century. Paul Ehrlich proposed receptor theories and discovered the anti-syphilitic properties of an already-patented drug Salvarsan during the early years of the new century. An arsenical compound, Salvarsan was considered the first “magic bullet” to selectively destroy disease-causing microbes. Ehrlich’s faith in chemical solutions to biological problems led to other experiments and, in 1935, Gerhard Domagk of I.G. Farbenindustrie announced the discovery of a new anti-infective red dye named Prontosil. The active compound in Prontosil was soon found to be sulph-nilamide and that was the basis for the sulfa drugs that revolutionized medicine at the time. The sulfa drugs were the true magic bullets because unlike the arsenicals, they killed the germ without attacking the host.

Similarly, the discovery of penicilium by Alexander Fleming at Oxford in the early 1920s propelled a line of work that spawned over time a whole range of antibiotics to combat bacteria dangerous to humans. The discovery also in the years between the wars, of solutions to the thyroid problem, of insulin, and of steroids helped significantly develop the science of endocrinology.

As historians of the industry note, it was the interruption of supplies from Germany during the First World War that gave American companies the impetus to begin scientific development and large scale production in a systematic way. The suspension of patents held by German companies provided opportunities for American manufacturers to obtain rights and produce important drugs. In 1916, for instance, the Dermatological Research Laboratories (DRL) synthesized Salvarsan which had been developed by Paul Ehrlich at Hoechst of Germany in 1909. DRL was later purchased by Abbott Laboratories in 1922, but only after showing that American firms could develop science-based drugs and challenge the German monopoly of advanced products.

In the years after the First War, the industry was caught in a larger merger wave sweeping through the country. Many small firms merged with big ones to survive the growing trend toward scale and specialization. By the 1930s, the large American drug manufacturers had significantly pared their product lines from thousands of items to concentrate on a few specialized ones. The consolidation of product lines allowed firms to enhance fewer products with laboratory science and to then vigorously sell them through advertising and other means.

The breakthroughs in research would not have brought the benefits to the masses, in fact, without concurrent and significant improvements in production methods. Although penicilin was discovered in England, for instance, its large scale production was made possible during the Second World War by American manufacturing know how in both government laboratories and in private organizations. By the late 1940s, mass production of biological and synthetic medicines was a strength that propelled American companies on to the world scene. Large scale production of many other newly discovered antibiotics followed in years after the war. More importantly, driven partly by the profit motive, breakthroughs in production technology was crucial in making medical science available to the general population on a massive scale.
Role of the Drug Companies

Interestingly, almost none of the breakthroughs up until World War II resulted from research done by or at the drug companies. Although pharmaceutical companies had established their own laboratory techniques and although they routinely consulted with university-based researchers and medical professionals, their business interests were largely in manufacturing and trading of proprietary drugs. Historians note that ties with outside researchers at the time were as much a marketing ploy to legitimize manufacturers’ products as it was a genuine effort to leverage science for medical solutions.

In fact, the drug trade had become quite large since the end of the previous century, and it enabled some of the drug companies to also develop very sophisticated sales infrastructures for marketing their products directly to physicians – who, over time, had become influential gatekeepers between drug companies and patients.

So, at the end of World War II, American companies used large-scale manufacturing facilities and extensive sales networks to make drugs available to the masses. The scale of their operations brought substantial benefits in terms of both availability and their affordability of drugs by the masses. Commercially produced penicillin, for instance, first became available in the United States in early 1942. In 1943, it was available at $200 per million units. By 1950, at least partly because of improvements in manufacturing techniques (such as deep-tank fermentation), the price had dropped to 50 cents per million units.

In spite of focus on manufacturing and sales, moreover, the large American pharmaceutical companies had remained keen on collaborating with researchers in universities to work on specific drug-related problems. The development and manufacture of insulin, for instance, came about under the umbrella of an agreement in 1922 between researchers at the University of Toronto and Eli Lilly. Within a year, the drug company was making insulin in sufficient quantities to meet the needs of diabetics.

Similarly, in 1938, Merck established a fellowship at Rutgers University for the research laboratory of Selman Waksman. By the middle of 1940s, this partnership had resulted in the development of streptomycin – an antibiotic that attacked microbes insensitive to penicillin, especially those that cause tuberculosis. Like penicillin, improvements in large-scale production reduced the cost of streptomycin about seventy-fold between 1946 and 1950.

As Temin reports, the success of streptomycin was, in fact, quite significant in other respects as well. First, in discovering streptomycin, Waksman used a technique that demonstrated the effectiveness of systematically screening soil samples to uncover germicidal substances. Waksman, therefore, opened up the potential to develop a whole range of other antibiotics by looking into the natural substances in the soil that would help in the fight against bacteria. What is more, this technique of mass screening and stepwise development of drugs extended beyond antibiotics, giving drug researchers a powerful technique to do their work. As Weatherall notes, “the pathway to discovery was established and the scale on which resources
were expended to make these discoveries represents a fantastic extravagance” (1987, p. 182) when compared with those available to researchers working with penicillin.

Second, it soon became evident that streptomycin and other specific drugs were patentable because they were not “naturally” occurring but had to be derived from substances found in nature. These two developments, the availability of a technique that could be widely used and the ability to protect a product with patents, transformed the drug industry. There was now a formula to generate revenues and make profit. Ironically, because a patent was good only for a single product, it was not an adequate defense against close substitutes. Most drug companies, now equipped with the Waksman technique, had strong incentive to invest in research and develop a whole slew of patentable drugs -- as a defense against competitors who could easily develop drugs with therapeutic effects similar to those of drugs already on the market.

Finally, Temin reports, for both political and economics reasons, companies did not license their patents but resorted, instead, to manufacturing the drugs themselves. Combined with the sales and distribution infrastructure some drug companies had begun to assemble over the years, the decision to self-manufacture gave rise to large integrated pharmaceutical firms that we see in the industry today.

So, beginning with the acceptance of Louis Pastuer’s germ theory around the turn of the century, the industry had made significant progress in chemo-therapeutics by the 1930s and 1940s. New and improved techniques in synthetic organic chemistry and soil microbiology created significant opportunities by way of solving age-old illnesses. Major products developed after the war years included tranquilizers, amphetamines, and advanced antibiotics. During the next couple of decades, significant advances were also made in such areas as virology, enzymology, and microbial biochemistry – which were to become the foundations of breakthroughs in the 1990s.

In effect, the three forces that propelled the American pharmaceutical industry during the decades after the war: (1) a research technique that could be widely used, (2) patent protection for new discoveries, and (3) the large integrated firms that brought research, manufacture, and sale of drugs under common ownership. There was, therefore, an easy logic to the industry during the post-war years. The integration of functional activities allowed control and continuity in operations necessary to produce adequate profits – which were ploughed back into the research function in the hope of developing more patentable drugs – which were then mass produced and mass marketed using the resources of the integrated firm.

So, by the middle of the twentieth century, the good news for the pharmaceutical firms was that they had an easy formula to sustain their market positions. The bad news for them, however, was that everyone else in the industry knew and used the same formula.

The Modern Era

With a few significant differences, the U.S. pharmaceutical industry in recent years has been propped and propelled by the same three basic forces that drove it in the years and decades after World War
II. Research, patents, and marketing continue to be the crucially important, perhaps even more so in recent years because of several institutional and technological changes that have been sweeping through the industry.

The incentives for firms to invest in research have remained particularly strong, perhaps even intensified. The effective life of patents for new drugs has continued to shrink because of strong competition. Even while the patents for a new drug is in place, that is, that drug is often under constant threat from functionally similar products from actual or potential competitors. Ironically, therefore, while patents have helped generate protected cash flows for innovating firms, they also seem to have started a “race” in recent years to find breakthrough new drugs.

It is, perhaps, for this reason that the pharmaceutical industry has been one of the most, if not the most, research intensive during the last several years. In 1998, for instance, American research-based pharmaceutical companies are expected to have spent over $21 billion or 20% of revenues (U.S. sales and exports) on research and development worldwide. This figure represents a sharp increase in outlay since 1990 when the research expenditures were less than $8.5 billion or 16.2% of revenues. The importance of research is also evident in the fact that, in 1997, 52,793 (25.3%) of 208,288 domestic employees in the industry were categorized to be associated with the research and development function.

Research firms in the pharmaceutical industry also invest, moreover, considerable amounts of capital into their sales and marketing operations. In 1997, for example, 65,481 (31.4%) of 208,288 domestic employees in the industry were engaged with the marketing function. What is more, like research expenditures, marketing outlays in the industry continue to spiral upwards because of intense competition between firms to get patients to use their drugs rather than those of their competitors. As such, these expenditures reflect the expendable and limited, albeit important, protection that patents provide to firms’ revenue streams both in the short and long run.

Moreover, since the average effective patent life for prescription drugs is between 9 and 13 years, it becomes imperative for producers of new drugs to gain wide acceptance in the marketplace as soon as possible after obtaining approval from the Food and Drug Administration (FDA). Doing so allows firms to maximize returns to the irrecoverable investments they have already made in developing particular drugs. Consequently, from a competitive standpoint, firms need to have in place a marketing and sales infrastructure not only to support existing products but also to quickly roll out new products generated in the research laboratories.

Intense marketing becomes necessary in this industry because of the tremendous information asymmetry that exists between producers and consumers of prescription drugs, and because of the complex gatekeeping roles played by physicians, pharmacists, and a growing number of powerful third parties. In addition, the multiple agents involved in the distribution of drugs also create significant logistic challenges that the firms attempt to overcome by investments in state-of-the-art information systems and sales operations.
Similar to practice in other industries, marketing by the pharmaceutical firms is done to inform, educate, and persuade medical professionals and lay patients to choose particular drugs for particular indications. Recognizing the important role that medical professionals play in selection of prescription drugs, firms routinely engage in resource-intensive marketing directly to physicians via such means detail sales forces, direct mailings of promotional literature, and professional symposia. In addition, direct to consumer (DTC) advertising is also increasingly used, of late, to influence ultimate consumers’ preference for advertised prescription drugs.

In a way, then, while manufacturing remains important to the private pharmaceutical enterprise, research and marketing functions are now the chief sources of value in this industry. Consistent with general business principles, search for economic rents (or profits) in the industry is the attempt to build mini-monopoly positions, however transient and vulnerable, with highly effective patent-protected remedies that are highly differentiated from those of competitors.

Capabilities of firms in the research and marketing functions complement each other, therefore, because while research creates the potential to realize profit, effective marketing converts that potential into real cash flows that, in turn, enable further investments into research. Competitive success in the industry requires, in other words, that firms make investments in a research infrastructure to generate a steady stream of patentable new products and in a marketing organization to persistently educate, inform, and persuade the influential gatekeepers. Failure to do either fractures the business logic that drives the profitability of firms this industry.

The New Competition

Even as pharmaceutical firms seek to generate profit and growth, they have to contend with several institutional and technological forces changing the face of the industry in the 1990s. After an enviable history of innovation, growth, and profits, the industry in now facing new challenges on both the cost and revenues sides of the profit-making equation. Inevitably, the accompanying changes in the larger environment also have a bearing on future investments and innovation in the industry.

Reduced Pricing Flexibility

On the revenue side of the equation, there is growing evidence that the on-going structural changes are reducing pricing flexibility that the pharmaceutical firms once enjoyed. There are three important sources of such changes. First, as indicated earlier in the report, patents for an innovative drug are, at best, imperfect defense against competition – they do not prevent introduction of functionally similar (or “me-too”) drugs that have a slightly differentiated chemical formulation but use the same basic mechanism to use treat the disease. As a result, even breakthrough drugs – those that are the first to use a particular therapeutic mechanism – are under constant threat of being dethroned by newcomers.

Such threat is particularly real because, in spite of great advances in research technology, serendipity – the basis of drug discovery through the centuries – remains very much part of the research
culture in the pharmaceutical industry. It is not uncommon for a firm in search of cures for a particular illness (e.g., cardiovascular malfunction) to accidentally hit upon a cure for another (e.g., sexual dysfunction). The research capabilities of competing firms, in other words, give them a reach into each other’s therapeutic domains either by accident or by design. It is no surprise, then, that of the 13 therapeutic that the Congressional Budget Office studied for its report, “the first me-too drug entered the market within one year in six cases and within two years in another six cases” (1998, p. 18).

Second, an increasing unit share of the market is now served by lower-price generic drugs whose manufacturers are not hampered by large sunk investments and continuing expenditures necessary to conduct original research. While generics made up only 2% of the unit market in 1980, for instance, in 1984 they had a 18.6% share, which then grew to about 43% in 1997. Given that several major drugs are expected to come off patent in the next few years, moreover, the unit share of generics is expected to further increase to over 50% of units sold by the end of the decade.

The lower prices of generics mean, however, that in spite of high unit volume their dollar market share is still relatively low – in 1997, the sales of generic drugs accounted for $12 billion (or 14.3%) of the $84 billion in total domestic sales of prescription drugs. In addition, the available evidence suggests that generics have so far not been able to reduce the prices of brand-name drugs no longer protected by patents. Even so, it is highly likely that, in combination with structural changes occurring in the industry, rapid incursions by generics do constrain prices of here-to-fore patented products.

The third reason for reduced flexibility in pricing arose from broad changes in the delivery and financing of healthcare services. In particular, the growth of managed care organizations and the emergence of pharmaceutical benefit management (PBM) companies created consolidation of buying power in an industry that historically had a highly fragmented customer base. By 1995, for instance, 61 percent of full-time employees of medium and large firms were enrolled managed care plans – up from 26 percent in 1988.

Since the managed care plans compete largely on the basis of price (mostly selling their services to large organizations), they are cost conscious customers of pharmaceutical products. Consequently, these plans use their size to negotiate better prices for their members from both manufacturers and retailers of pharmaceutical products. Similarly, the growth of pharmaceutical benefit management companies since the 1980s has created powerful wholesale buyers who negotiate lower prices in return for channeling the large numbers of their patients to particular formulations of drugs within the various therapeutic categories.

The modus operandi of managed care organizations and of PBMs is to develop their own formularies which comprise, where possible, generic copies or lower priced me-too (branded) functional substitutes of higher priced innovator drugs. Consequently, these large cost-conscious buyers exert a good deal of downward pressure on the prices of pharmaceutical products.

In short, then, both the emergence of generics and the consolidation of buyer power have increased the pressure on prices. Ironically, these market forces may also have strengthened the incentives
for research pharmaceutical companies to intensify their search for breakthrough products that would alleviate somewhat the threat to their revenue streams.

Growing Complexity and Costs

Amidst changes in the environment on the demand side, the industry has also been undergoing a fundamental transformation in its technology regimes – or in the techniques generally employed to discover and develop new drugs. Rational drug design and the biotechnology revolution begun in the 1970s have been complemented by the late 1990s with combinatorial chemistry (CCh) and high-throughput screening (HTS). Together these phenomenon have created both unprecedented opportunities and challenges for the pharmaceutical industry of today. They have also greatly influenced the economics of the industry on the cost side.

For much of the industry’s history, drugs have been developed largely through trial and error, coupled with the ability of researchers to see opportunity in accidents. Handicapped by a rather limited understanding of how diseases worked inside the human body, researchers relied on empirically testing particular chemical compounds and then using the results to incrementally modify the chemical structure of those that appeared promising. The compound that Paul Ehlrich developed to treat syphilis was Salvarsan 606, indicating the numerous trials that led to the final product. Based on clinical experiences with the drug, Ehlrich then produced a more manageable compound, numbered 914, several years later.

And sure enough, by the 1950 and 1960s, pharmaceutical firms had great success with the trial and error approach of discovering new drugs. They invested in very large libraries of chemical compounds, and, over time, greatly refined the techniques of rapidly screening very large numbers of compounds in test tubes and animals. Such libraries were very resource-intensive and, therefore, much of the success came to large, vertically integrated firms.

The base of knowledge that drove the mass-screening approach to drug discovery was mostly empirical, however. With few exceptions, it was very difficult to target particular diseases because of the lack of theoretical knowledge in relevant disciplines.

By the 1970s, years of experience with diseases, along with parallel developments in the relevant sciences, had created a critical mass of useful knowledge about the workings of diseases inside the human body. It then became possible theoretically to begin with detailed knowledge of the biochemistry of a particular disease and “design” a chemical compound that would effectively combat it. Although this approach has not matured, by late 1990s, into an exact science, the knowledge of the biochemical roots of many diseases has allowed researchers to do “guided” searches for cures. Over the years, this so called rational drug design has, in fact, led to the development of such breakthrough drugs as those that combat depression (Prozac), cholesterol (Mevacor, Pravacol), hypertension (Propranolol, Captotril), ulcer (Tagamet, Zantec), and viral infections (Retrovir, Vidax).
Partially overlapping the breakthroughs in the sciences of biochemistry and enzymology were developments in recombinant (‘r’) DNA technology and molecular genetics. At least in theory, researchers could now harness life in their search for cures -- rather than relying completely on chemical synthesize of molecules needed for drug development. The first breakthrough came in 1982 when the Food and Drug Administration approved Genentech’s genetically engineered human insulin. Over time, molecular biologists were able to produce large quantities of additional desirable proteins needed to make particularly difficult drugs for particularly difficult diseases. By the mid to late 1990s, about 30 products had reached the medical market and several hundred others were undergoing human clinical trials.

During the last several years, moreover, breakthroughs in knowledge about the inner working of diseases have been complemented by two productivity enhancing techniques – which themselves have been made possible by the ongoing computer revolution. The first is called combinatorial chemistry (CCh), and it refers to the emerging set of techniques whereby researchers can rapidly synthesize numerous variants around a single “backbone” molecular structure – enabling quick construction of a vast number of related chemical compounds. The second, referred to as high-throughput screening (HTS), entails using high speed robots for biologically testing for therapeutic properties the very large number of candidates generated by combinatorial chemistry techniques. These are basically test-tube-based screening methodologies that are amenable to automation – made practical by immense, yet relatively inexpensive, computing power now available commercially.

Ironically, while advancements in medical knowledge and laboratory techniques have contributed significantly to treatment of illnesses, they have also resulted in explosion of costs in drug discovery and development. There are several reasons for increases in such costs.

Since rational drug design requires close coordination between numerous experts from a wide range of disciplinary bases, including the basic sciences related to medicine, it is inherently more challenging than the traditional mass-screening approaches. In fact, to harness the power of both rational drug design and biotechnology, the various aspects of drug research are conducted via complex networks that include large and small for-profit firms, public and non-profit institutions, government labs and research universities. Although research has been done in this manner for much of this century, therefore, the very large and ever-growing web of contractual ties brought about by the explosion in scientific knowledge now makes drug discovery qualitatively more complex and costly.

In addition, the new medical knowledge and techniques have been enabling researchers to take up the challenge of targeting chronic illnesses – such as alzheimer’s disease, arthritis, cancer, depression, diabetes, hypertension, and AIDS, which are persistent, degenerative, and life threatening. These targets mean that the drugs being developed in the current environment are scientifically more complex than they were just a few decades ago. Some industry executive claim, in fact, that the average weight (proxy for size and complexity) of a new chemical entity (NCE) developed in the late 1990s is double than what it was in the mid 1970s.
The increasing complexity of chemical entities being synthesized appears to have raised not only the cost of discovery but also the time and expenditures related to development and manufacturing of drugs. For instance, partly because researchers are increasingly targeting complex diseases, the costs associated with obtaining FDA approval has been on the rise.\textsuperscript{44} The mandated clinical trials now require more patients and more procedures per patient to document the safety and efficacy of new drugs under development.\textsuperscript{45} As a result, perhaps, the total drug development time from synthesis to FDA approval has consistently gone up from 8.1 years for the drugs approved in the 1960s to 11.6 years in the 1970s to 14.2 years in the 1980s to 14.9 years between 1990 and 1996.\textsuperscript{46}

In a similar vein, costs of manufacturing drugs have also been on the rise in the last several years. Although manufacturing for traditional drugs remains relatively less capital intensive than research and marketing activities, such appears to not be true in the case of new chemical entities.\textsuperscript{47} In the 1990s, manufacturing costs associated with them have begun to take on the proportion and risk characteristics of R&D. The out-of-pocket costs of a standard new manufacturing facility for new chemical entities has been estimated to be anywhere between $100 million and $400 million, depending upon the nature of the products. Similarly, the costs associated with new facilities for launching a new biotechnology product have been estimated to be around $100 million.\textsuperscript{48} The reasons for this apparent explosion in costs of manufacturing new drugs are thought to be the need for highly specialized equipment to produce new chemical compounds and biotechnology products, and the stringent process control requirements by the Food and Drug Administration.\textsuperscript{49}

\textbf{Conclusion}

In summary, then, breakthroughs in medical knowledge and in laboratory techniques present both opportunities and challenges for firms in the pharmaceutical industry. On the one hand, technological advancements present new opportunities to address difficult old illnesses – and for at least temporarily relieving downward pressure on prices. On the other hand, technological advancements are rapidly raising the complexity and attendant costs of the discovery, development, manufacture, and marketing of drugs.

It is difficult to say what the net effect of these two forces will be on the margins of competitors in the industry. Even so, it appears that pressures so generated will almost certainly strengthen the incentives for firms to increase expenditures on research. The sharp incentives to innovate, along with an ever-deepening scientific knowledge about diseases, lead many industry analysts to claim that the next century will be a golden age for the industry.

Such optimism is already visible in the products-in-the-making in key ethical sectors. Under development, for example, are new drugs to treat central nervous system illnesses such as Alzheimer’s disease, Lou Gehrig’s disease, and Multiple Sclerosis. New drugs are also in the pipeline to challenge drugs that dominate the market for treating debilitating illnesses such as schizophrenia, depression, and arthritis. A large number of drugs are already available to treat high cholesterol and hypertension, and new cardiovasculars continue to enter the market at a rapid pace. Several drugs compete aggressively to treat the large population suffering from ulcers. New drugs with newer mechanisms to treat diabetes have recently

\textit{Pharmaceuticals/Massachusetts}

\textit{Anurag Sharma, May 1999}
come on the market, as have new anti-infectives for AIDS and for older infectious microbes that have mutated to reduce the effectiveness of older antibiotics.

Hence, although the industry is populated with large multinationals with formidable resources, these firms compete aggressively with one another to defend their market positions and to find new markets for their research outputs. Such competition is driven, moreover, by science-based innovation that demands uninterrupted investments into the research function. Given the high stakes, investment-intensive inter-firm competition is likely to persist into the foreseeable future and, in the process, it is likely to generate an ever-growing pool of innovative products.
End-Notes

1 The following has been cited as part of Dr. H.I. Silverman’s presentation during the 106th Annual meeting of The Proprietary Association: “Bedridden because of a streptococcal infection and fever, General Washington was given a mixture of molasses, vinegar, and fermented butter. He was made to eat a menthol salve, bled a pint, his throat wrapped in salve-soaked flannel, and his feet bathed in warm water. A blistering poulce of Spanish flies was applied to his throat. He was then bled an addition pint, made to gargle with a sage and vinegar tea, and bled again. Unfortunately, the General’s condition worsened. He was then bled a full quart, given a laxative of mild mercurous chloride and an emetic of tartar…Washington died sometime between ten and eleven the same night.”


3 Ibid. George Gifford. P. 279.


5 See Stephen W. Williams, 1842, A Medical History Of The County Of Franklin In The Commonwealth Of Massachusetts. [No publisher indicated in the manuscript that was read at the Annual Meeting of the Medical Society on May 25, 1842].

6 For a well-written history of pharmaceutical discovery, see M. Weatherall’s In Search Of A Cure, 1990, Oxford University Press.

7 For a history of drug regulation in the United States, see Peter Temin’s Taking Your Medicine, 1980, Harvard University Press.


9 Ibid. Russell. p. 25.

10 This discussion of manufacturing is drawn largely from Jonathan Liebenau’s Medical Science and Medical Industry, The John Hopkins University Press.

11 Ibid. Jonathan Liebenau.


13 Ibid. Weatherall, p. 176.

14 Weatherall, p. 181. Gary Pisano reports that “considering that average U. S. pharmaceutical companies spent $15 million annually between 1946 and 1950 on new plant and equipment, the financial impact of such productivity gain [in the production of penicillin] was likely quite large.” See p. 54 in The Development Factory, 1997, Harvard Business School Press. Yet, most of those gains seems to have been passed on to consumers in the form of lower prices.

15 Some respite to this came from the Hatch-Waxman Act of 1984, which in combination with easing FDA approval of generics also effectively increased the patent life of drugs that met certain criteria.

16 Over $17 billion of this worldwide total was spent on R&D in the United States. See p. 92, Industry Profile 1998, Pharmaceutical Research and Manufacturers of America. This trend in the growth of investments in research has continued unabated since the 1950s, which is when the industry shifted from being largely manufacturing-based to being research intensive. In fact, the period 1950 through 1990 is considered very good for the industry because the increasing levels of research expenditures -- encouraged by a “treatment-starved target-rich” medical environment -- were accompanied with stable growth in revenues and high accounting profits.
In fact, the domestic R&D outlays by research-based pharmaceutical companies increased substantially in the 1980s during which period it grew at an average annual real rate of over 10 percent. Even in the 1990s, except for the years 1994 and 1995, domestic R&D outlays have increased at an annual rate in double digits.

Some researchers have alluded to the “racing” behavior where compete with each other via heavy investments in research and development in a race to develop patent-protected monopoly positions in financially attractive therapeutic classes. Evidence for this hypothesis is elusive, however, and it remains speculative. See F. M. Scherer’s Commentary (pp. 269-273) on a set of articles in (ed.) Robert Helms, Competitive Strategies In The Pharmaceutical Industry, 1996, The AEI Press.

In the late eighties and early nineties, for example, the industry was spending $1 billion more on marketing than on research and development. See Chapter 2 in Stuart O. Schweitzer’s Pharmaceutical Economics and Policy, 1997, Oxford University Press. There is, of course, considerable variance in such expenditures across the large firms in the industry. See Anita McGahan’s The Pharmaceutical Industry in the 1990s, Case # 9-796-058, 1996, Harvard Business School Publishing.

See Grabowski, H. & Vernon, J. 1996. “Prospect For Returns To Pharmaceutical R&D Under Health Care Reform,” in (ed.) Robert Helms, Competitive Strategies In The Pharmaceutical Industry, 1996, The AEI Press. The authors estimate this patent life based on their sample of new chemical entities introduced between 1980 and 1984. They also speculate that for another of their sample of new chemical entities developed between 1985 and 1989, the patent life was even shorter by a few years.

For an excellent discussion of the role of doctors and their behavior in prescribing medicines, see Chapter 5, “Doctors and Drugs” in Peter Temin’s Taking Your Medicine, 1980, Harvard University Press.

By late 1980s and early 1990s, there was an increasing trend for large pharmaceutical firms to move away from captive or in-house production of active ingredients. Assuming that capital would be more productive in research and marketing rather than in manufacturing of fine chemicals, and given that there was then excess production capacity worldwide, firms increasingly used a complex of outside suppliers to complement their more limited captive production. See “Chemical & Allied Products” in Encyclopedia of American Industries, Second Edition.

Economic theory would predict that in the absence of research (technical effectiveness), patents (temporary and porous monopoly), and marketing (differentiation), profits of the industry would dissipate as competition ruthlessly drove selling price toward the marginal cost.

In addition, drug therapies sometimes compete with non-drug therapies or other systems of medicine (e.g., homeopath). The presence of close substitutes and alternative forms of treatment lead, therefore, to imperfect competition where innovator firms earn higher profit than they would in perfect competition but lower than what they would in a pure monopoly.

Another significant source of vulnerability for patent-protected innovator drugs is the side effects that most of them inevitably have for small or large proportion of patients. New formulations that become successful at the expense of incumbents are often those that cure while effectively minimizing or (in rare cases) eliminating undesirable consequences for the patients. A case in point is the well-known example of Glaxo’s Zantac dethroning Smithkline’s Tagamet as pre-eminent antiulcer therapy several years before expiration of the latter’s patents. Ironically, Tagamet itself had replaced another class of antiulcer drugs that had severe side effects.

The rapid incursions of generic drugs are said to have been greatly enabled by the passage of the Hatch-Waxman Act in 1984. The act streamlined and expedited the process for FDA approval of generic drugs but requiring only that they demonstrate “bioequivalence” — or the same rate of absorption in the bloodstream for generics as that for an already approved “innovator” drug. Prior to that, the approval for generics was very rigorous and, evidently, unnecessarily burdensome.

In addition, by 1984, most states changed laws to allow pharmacists the previously prohibited practice of dispensing a generic version even when a brand-name drug was specified in the prescription. By 1989, this practice of substituting generics for brand-name drugs was firmly in place across the country, and it contributed significantly to the growth of the generics in the United States.

See p. 7 in Standard & Poor’s Industry Survey, Healthcare: Pharmaceuticals, June 18, 1998. The CBO study uses 1994 data compiled by Scott-Levin to report that, for a sample of about 300 drugs, the average price of generics was 53% that of patented or “innovator drugs. The average price for generic copies of innovator drugs was even lower when there were more than 10 suppliers.

From a review of six empirical studies done in the 1990s, the CBO study states that, “Overall, brand-name prices frequently continue to rise after generic entry. Whether they rise more quickly or more slowly than would be the case without competition from generic drugs, however, is unclear based on these studies” (1998, p. 30).

Prices for pharmaceuticals may also be affected by the trend toward capitated contracts, where managed care organizations pay a fixed fee for healthcare providers (e.g., doctors or hospitals) to serve their members. Fixed fee per patient not only creates incentives to cut costs of inputs such as drugs but it may also encourage providers such as hospitals to demand their own fixed fee per patient contracts with drug companies eager to get a large volume account.

It is not clear, however, how the profits of pharmaceutical products are affected by the rise of managed care organizations. On the one hand, pharmaceutical companies are now forced to give heavy discounts to their large customers. On the other hand, the insurance and co-payment structure in HMS and PPOs encourages greater use of drugs, thereby increasing the volume sold by the pharmaceutical companies. The net effect on profits of the producers is, therefore, believed to be only marginal, if any.

Of course, when drugs are still under the protection of patents and they do not have close substitutes on the market, the pressure for lower prices is somewhat attenuated. Yet, economic theory predicts that higher profits for particular products create strong incentives for potential entrants to intensify their research efforts and to develop their own versions of innovator drugs.

Pharmaceutical reimbursement by Medicaid and private third parties has grown from 37% of the dollar share of retail market in 1990 to 71% in 1997. See page 54 in “Industry Profile 1998” by PhRMA which sources the data from IMS Health, 1998. Along the same line, the consumer out-of-pocket payments for outpatient prescription drugs is reported to have been reduced from 82.4% in 1970 to 33.9% in 1990. See page 51 in “Industry Profile 1998” by PhRMA which cites the original source as the Health Care Financing Administration (HCFA), 1998.

The breakthrough actually came in 1973 when Herbert Cohen and Stanley Boyer of the University of California developed a technique to manipulate the genetic structure of cells. This technique made it possible for researchers to induce living cells to produce specific protein molecules which, because of their complexity and large size, could not be synthesized via known chemical means. Researchers now had the means to attack a wider range of diseases than ever.

See The Biotechnology Industry, 1997, Office of Technology Policy, U.S. Department of Commerce. Also, in 1997, one source estimated that the distribution of biotechnology drugs in the various stages of development was as follows: Early Development 1,264), Phase I Clinical Trials (357), Phase II Clinical Trials (527), Phase III Clinical Trials (258),

Pharmaceuticals/Massachusetts
Anurag Sharma, May 1999
and FDA Review (62). This same source estimated the cost of failures as: Preclinical ($1 million to $2 million), Phase I Clinical Trials ($500,000 to $800,000), Phase II Clinical Trials ($2 million to $20 million), and Phase III Clinical Trials ($10 million to $40 million). Presentation entitled, “The Relevance Of Failure In Drug Development,” by Mathew J. Palazzolo, December 3, 1998, Cambridge, MA.

41 A 1979 study estimated the cost of drug development to be $54 million in 1976. More recent estimates put that figure anywhere from $200 million in the early 1980s to as much as $500 million in 1990.

42 One of many indications of the web of relationships now commonplace in the industry is the increasing frequency of alliances from 121 in 1986 to 319 in 1990 to 635 in 1997. See page 58 in “Industry Profile 1998” by PhRMA citing the original source as Windhover’s Pharmaceutical Strategic Alliances, 1998.


44 PhRMA reports that, in 1996, the research pharmaceutical companies allocated 29.5% of their domestic U.S. R&D budget to Phase I-III clinical trials mandated by the FDA. Another 6.3% was allocated to post-launch Phase IV clinical evaluation. See page 17 in “Industry Profile, 1998.”

45 In “Industry Profile 1998,” PhRMA reports that the number of patients required for each new drug application (NDA) increased 169% from 1,576 in the 1997-1980 period to 4,237 in 1994-1995 (p. 27). Similarly, the number of medical procedures per patient during the Phase I-III clinical trials increased 61% from 1992 through 1997 (p. 28).

46 The average time taken for the three phases of mandated clinical trials increased from 2.5 years in the 1960s to 6.7 years in the 1990-1996 period. See page 25 in “Industry Profile 1998” by PhRMA. Original source cited is the Tufts Center for the Study of Drug Development, 1998.

47 According to one study, for a sample of seventeen large pharmaceutical firms, manufacturing costs as a percent of sales increased from 10 percent in 1980 to 20 percent in 1990. For this statistic and other trends in manufacturing of drugs, see pp. 71-78 in Gary Pisano’s “The Development Factory,” 1997, Harvard Business School Press.

48 Ibid. 42.

49 According to an executive in the construction industry in Massachusetts, the cost of building a typical manufacturing plant is between $45 and $60 per square foot. For a manufacturing plant to produce biotechnology drugs, on the other hand, the costs rise to between $900 and $1400 per square foot. Personal telephone conversation with Peter Malkowski, January 6, 1998.
Appendix 3

NOTE ON DRUG DISCOVERY & DEVELOPMENT

Two important features characterize product development in the drug industry (see Figure A3.1 for an overview). First, the process of discovering drugs is built on a vast edifice of scientific knowledge. Although applied research is important to translate abstract science into concrete products that solve real problems, basic research is also a crucial element in drug discovery and development. In fact, the process of drug development is rooted in the open-ended biomedical research done in the National Institutes of Health, in the laboratories of private firms and foundations, and in the research universities.

The cumulative pool of knowledge in the biomedical sciences, along with decades of hands-on experience in the laboratories, then becomes the starting point for researchers to use a variety of techniques to extract or synthesize compounds that might have desirable therapeutic effects on diseases. The result of such effort is construction of often privately-held, expensive, and ever-growing libraries of chemical compounds, from which researchers periodically draw to address particular research problems.

Upon defining a general target area (e.g., type of disease), for instance, researchers start the process by drawing thousands of compounds from their firm’s library and other public or professional sources. These large numbers of compounds are then put through “screens” to assess the chemical and pharmacological properties of each compound. Next, each of the (up to 5,000) compounds in the shortlist so generated is tested in the laboratory for its biological activity against target diseases and for its safety for use in live animals. The compounds that pass these various tests are then selected for committed development by filing the Investigational New Drug Application (IND) with the Food and Drug Administration (FDA).

The second noteworthy feature of drug development is that it is heavily regulated by the FDA – principally because the end products have potentially profound impact on the health and lives of consumers. The IND application, for instance, documents in detail such things as therapeutic objectives and chemical structure of compounds under consideration, the descriptions and results of tests conducted during pre-clinical trials, and specifics of proposed human clinical trials. Once the FDA allows an IND application to go unchallenged for 30 days, the applicant is free to proceed with developing particular drugs for particular diseases.

Upon proceeding to develop a drug, the onus is entirely on IND applicants to demonstrate their safety and effectiveness. Such is accomplished by conducting FDA-mandated 3-phase human clinical trials to obtain the necessary scientific data. In Phase I, 20 to 80 healthy volunteers are given the drug to determine its safety at various dosage levels, and to understand its biological characteristics such as absorption, distribution, and metabolism in the human body. If considered safe, Phase II tests are conducted with between 100 and 300 patient volunteers to assess the drug’s effectiveness. If these are successful, then more extensive (and more expensive) Phase III tests are conducted with several thousand patient volunteers.
Extending over several years, this phase of human clinical trials has the objective of confirming safety and efficacy of the drug being tested and to also document adverse reactions in the volunteer patient population.

If satisfied with the results obtained thus far, and if still comfortable with market potential of the drug being tested, the applicant then files a New Drug Application (NDA) with the FDA. This application runs into thousands of pages and it contains the test data as well as scientific analysis to conclusively demonstrate to FDA the safety and efficacy of the drug.

FDA’s role does not end with the approval of the drug, however. It continues to regulate and monitor the drug as it moves through manufacturing to marketing and after. FDA requires, in fact, that the company responsible for the drug continue to file periodic reports that contain analysis of data relating to experiences (e.g., adverse reactions) with the general patient population. In some cases where effects of the drug are expected to be long term, applicants are required to do Phase IV post-launch clinical evaluations.

According to industry sources, regulation of drug development in the United States is considered the most rigorous in the world. Such is evident in a widely quoted statistic that, of the 5000 compounds entering the pre-clinical stage, only 5 enter human clinical trials – indicating that firms are very selective in what they commit to developing in the face of regulatory rigor. Of the 5 drugs that do enter human clinical evaluation, moreover, only one is eventually approved by the FDA. The others are either disapproved by the FDA or withdrawn by applicants in the face of empirical data that do not support the theoretical claims.

As a result, perhaps, the development of a new drug (based on a new chemical entity) can take up to 15 years and it is estimated by industry sources to have capitalized costs of up to $500 million.

The high costs of drug development are often justified by potentially high returns that breakthrough drugs can yield. High sales volumes and very lucrative returns are possible from a drug that brings significant scientific breakthrough and a clearly superior remedy for a difficult (and widespread) illness. According to industry convention, a drug is considered to be a blockbuster when it reaches annual sales of $750 million, and there are examples of drugs on the market today (e.g., Amgen’s Epogen, Merck’s Prilosec and Zocor, Eli Lilly’s Prozac) that had 1997 domestic sales of more than $1 billion.

Yet, about seven in ten new chemical entities that make it to the market do not even break even on average capitalized cost of research and development. Of the three in ten drugs that do have a positive net present value, only one can be expected to yield sales that, after a few years on the market, reach over $1 billion a year. The skewed nature of distribution of returns suggests that a large part of the support for a company’s overall infrastructure for research is provided by their blockbuster drugs. Such dependence means, in turn, that firms have strong incentives to intensify investment in research – in the hope of raising the odds of developing additional blockbusters.

Once a new chemical entity has been in the market for about ten years, moreover, its patents expire and it becomes vulnerable to competition on price from generic copies – or chemical equivalents. Innovator drug makers then try to fend off price competition by making incremental improvements in the original
drugs, such that doctors and patients continue to see value that justifies premium prices vis-à-vis lower priced copies. Yet, the price differentials between generics and originals are often quite drastic. For instance, when Glaxo Wellcome’s blockbuster drug Zantac (anti-ulcer) and Bristol-Myers Squibb’s blockbuster Capoten (heart) lost patent protection, generic versions came on the market at prices 80% to 90% below those of the branded products.

Another response firms have to expiration of patents is to obtain FDA approval for over-the-counter (OTC) formulations that can be branded and mass marketed to the general public. The relatively lower margins for OTC products are justified by the larger volumes and product life extension that such actions sometimes bring. Glaxo’s Zantac 75, for instance, is a successful OTC version of its original namesake. Similarly, Advil and Nuprin are both OTC formulations of Upjohn’s prescription drug Motrin, which is now also available over the counter.

__________________

End-Notes

1 According to PhRMA, in 1996, human clinical trials absorbed 29.5% (or over $5 billion) of the approximately $17 billion in domestic R&D expenditures by U.S. pharmaceutical companies. See page 17, “Industry Profile, 1998.”

2 According to a study cited by the Congressional Budget Office, the ratio (Approved NDA/IND) was as follows: (38/160) for the period 1975-1978; (47/185) for the period 1979-1982; and (40/223) for the period 1983-1986. See p. 22 in How Increased Competition From Generic Drugs Has Affected Prices And Returns In The Pharmaceutical Industry, A Congressional Budget Office Study, July, 1998.

NOTE ON DRUG MANUFACTURING

The manufacturing sector of the drug industry is divided into four broad categories.\(^1\) In order to evaluate the activities therein, discussed below are some basic economic aspects of drug manufacture.

\textit{Input-Output Analysis}

Like other industries, drug manufacturing is deeply embedded in the larger economy around it. For instance, in the 1982 data made available in 1991 by the Department of Commerce, the drug industry is shown to obtain inputs from several other sectors of the economy. As shown in Table A4.1, the chief sectors that feed into the drug sector are: Manufacturing (34%),\(^2\) Services (29%),\(^1\) Imports (16%), Trade (9%),\(^4\) Utilities (5%), and Finance/Real Estate (3%). Consequently, the impact of the industry activities is felt both nationally and internationally. In addition, since the services, wholesale trade, and utilities are often present near or in the immediate surroundings of manufacturing establishments, it is likely that a large proportion of the total inputs directly impact the local and regional economies as well.

On the output side, as shown in Table A4.2, personal consumption with 48% represented the largest aggregate, followed by the manufacturing sector (17%),\(^5\) services (14%),\(^6\) government (11%),\(^7\) and exports (8%). Given the nature of the product and the manner in which drugs are typically marketed, these numbers do not reveal how much of the output is consumed in the locality of manufacturing establishments. It seems, in fact, that a vast majority (92%) of the total output would be absorbed by individuals (directly or via institutions) nationwide, since drugs made in one region of the country are often readily available in other regions.

Note that although the input-output analysis suggests that manufacturing of drugs is deeply embedded in a complex web of economic activities, it does not reveal the geographical nature of the interconnections between the sectors. Such connections can only be assessed qualitatively from general knowledge of activities involved.

Note also that the latest data available is for 1982.\(^8\) Hence, the proportions mentioned in the preceding paragraphs need to be adjusted to incorporate changes that have occurred in the industry since the early eighties. Once again, absent concrete data, only qualitative assessment of such changes can be made. It is likely, for example, that the input of manufacturing may have increased in proportion because, as production of biotechnology-based drugs and larger chemical entities has increased, more specialized (and more expensive) equipment is now perhaps needed. Since the new chemistry and biotechnology still represent a relatively small share of the overall drug market, however, the relative increase in
manufacturing inputs is likely to be only marginal. The proportions mentioned above are, therefore, likely to be in the same range in the 1990s as they were in the early 1980s.

**Occupations Analysis**

In 1994, workers employed in the manufacture of drugs represented at least thirty different occupations. According to the data reported by *Manufacturing USA*, the five largest occupations represented in the drug manufacturing group (SIC 283) were: packaging and filling machine operators (7.8%), science and mathematics technicians (5.7%), biological scientists (5.5%), secretarial staff (5.3%), and chemists (4.9%). Overall, of the occupations reported, those relating to scientific and technical work represented 20% of total employment. The other broad classifications were: skilled workers (24%), administrative and management staff (16%), sales and marketing (7%), and unskilled workers (6%). Twenty seven percent of the employees in SIC 283 were not categorized because they belonged to occupations that made up less than 1 percent of total employment in the 3-digit industry group.

As shown in Table A4.3, *Manufacturing USA* also reports the growth projections for each occupation as estimated by the Bureau of Labor Statistics. By 2005, for instance, the number of systems analysts employed in the SIC 283 industry grouping will increase by 97.7% over the numbers employed in 1994. The other five occupations with most significant growth projections between 1994 and 2005 are: biological scientists (49.6%), medical scientist (48.3%), professional workers, nec (48.3%), and engineering, mathematical, and science managers (40.4%). In addition, each of the following three occupations are projected to grow by 36% between 1994 and 2005: science and mathematics technicians, industry machinery mechanics, and extruding and forming machine workers. On the other hand, the number of bookkeeping, accounting, and auditing clerks employed by this industry group is expected to decline by 7.3% during the same period.

In essence, although these projections are subject to (sometimes quite drastic) revisions, they suggest that the industry is likely to favor scientific, technical, and other skilled workers during the next several years. Given the trends in industry toward more and more sophisticated manufacturing to produce increasingly sophisticated products, such general sentiment in the data seems reasonable.

**Drug Manufacturing in Context**

In comparing the drug manufacturing establishments with other overall manufacturing sector, *Manufacturing USA* reports several useful ratios. These ratios are computed by dividing the values computed for select variables in each 4-digit SIC industry by corresponding variables averaged over the entire manufacturing sector. These variables pertain to employment, payroll, wages, value added, costs, shipments, and investments.

As shown in Table A4.4, except a few cases, the four parts of the drug industry indices were above 100, suggesting that manufacturing of drugs had higher than average values for the variables reported. For instance, the indices for “employees per establishment” vary from a low of 122 (SIC 2833) to a high of 329
(SIC 2835). This indicates that, depending on the type of product, drug manufacturing establishments were estimated to have 22 to 229 percent more employment than an “average” manufacturing plant in the larger economy. Yet, the indices for “hours per production worker” are all less than hundred, indicating that, perhaps, workers did less than average overtime work at these establishments.

With respect to other variables, the drug manufacturing establishments had higher than average wages, payroll, costs, value added, shipments, and investments. Of particular note are suggestions in the data that, in 1994, there was significantly more investment in drug manufacturing sector (particularly in SIC 2833, 2834, and 2835; but also in 2836) than in the manufacturing sector at large. Similarly, value added in drug manufacturing was also much higher (particularly in SIC 2834 and 2835) than in average manufacturing establishments at large.

Overall, the ratios indicate that, relative to the manufacturing sector at large, the average drug manufacturing establishment had larger workforce at higher wages and higher total payroll. In addition, the average drug manufacturing establishment had relatively higher costs, but much higher value added, shipments, and investments. All in all, from the data for 1994, it appears that the drug manufacturing is a high cost, capital intensive, high volume, and high gross margin business relative to manufacturing in most other sectors of the U.S. economy.

____________________

End-Notes

1 See Chapter 2, “Definitions & Data Sources.”

2 Note, however, that – as is typical with most economic sectors -- drugs themselves represent 19.2% of the total inputs into the SIC 283 establishments.

3 The three major service sectors were (1) accounting, auditing, and bookkeeping – 12.9 percent, (2) management & consulting services & labs – 7.2 percent, and (3) advertising – 2.9 percent.

4 Trade represents (1) wholesale trade – 8.4 percent, and (2) eating & drinking places – 0.8 percent.

5 Once again, 12.3 percent, the drug industry itself was a major consumer of the output of SIC 283.

6 The three major service sectors were (1) hospitals – 9.9 percent, (2) medical & health facilities, nec. – 2.5 percent, and (3) nursing & personal care – 1.0 percent.

7 State and local governments consumed 8.6 percent of the industry’s output, with the federal government consuming the remaining 2.2 percent.

8 See “Benchmark Study of the U.S. Economy, 1982,” published in the fall of 1991 by the Department of Commerce. The data reported here is drawn from the 5th Edition of Manufacturing USA, published in 1996 by Gale Research. Because the gathering and compilation of such data are very complex and expensive endeavors, this Department of Commerce publication is made available infrequently and with substantial time lag.
In an industry that is dominated by giants, a small Massachusetts company has finessed an ingeniously simple strategy to create an enviable position for itself. Located in Marlborough, the company, Sepracor, targets highly successful drugs already on the market, and then, using the latest technology and high-powered expertise in chiral chemistry and pharmacology, it develops purified formulations that have greater efficacy and fewer side effects. The Company patents these so-called improved chemical entities, or ICEs, and then negotiates favorable business arrangements with the large pharmaceutical companies behind the original formulations.

Sepracor’s most important successes to date have entailed addressing an oddity shared by a number of blockbuster drugs on the market. It is widely known that many organic molecules (and active ingredients in drugs) exist as mixtures of mirror images, or optical isomers that were originally named S (“sinister”) for left and R for right. Only one of these isomers is responsible for the drug’s benefits, however. The other, or the evil twin, is sometimes innocuous, sometimes inconvenient, and, at times, highly dangerous to the patients because of severe harmful side effects it causes.

Until Sepracor came along in 1984, both isomers were left together in the drug, partly because the technology did not exist to actually separate them, but partly also because the big companies had no great incentives to do so. The Company has developed technology and equipment to just that, and a good portion of its research and development efforts are focused on separating the desirable isomer from the undesirable isomer.

In a second, more recent strategy, Sepracor has honed in on the fact that the body itself transforms drugs into a variety of related chemical forms (metabolites), not all of which are therapeutically active or useful for the patient. On again, therefore, by directly developing active metabolites in drug form, the company attempts to improve the side effect or efficacy profiles for widely prescribed drugs on the market.

Sepracor has applied its aggressive research strategy in the areas of allergy, asthma, urology, psychiatry and gastroenterology. Because the Company’s research deliberately builds on work done by other firms in developing the original drug, it typically is cost-effective, speedier, and less risky than doing original research and pushing one or more compounds though the stringent FDA approval process.
Nineteen ninety-eight was a banner year for Sepracor. During the spring of the year, Johnson & Johnson (J&J) agreed to a second very lucrative deal in which Sepracor would work on developing a safer version of J&J’s best-selling antihistimine; an earlier agreement covered improvement of a J&J product used to treat a serious form of heartburn. Similarly, in December of 1998, Eli Lilly agreed to pay up to $90 million plus future royalties to obtain Sepracor’s improved version of its fabulously successful antidepressant, Prozac.

Despite the fact that it had yet to turn a profit, Sepracor’s share price doubled in 1998. A number of Massachusetts-based players, including Fidelity, Putnam, John Hancock, Fleet Investment Advisors, MFS, Boston College and the Boston Museum of Fine Arts, were among the young Company’s happy shareholders.

But how did the multinational pharmaceutical giants find themselves in such a vulnerable position in the first place? How could an upstart snatch patents for some of their most valuable product from under their corporate noses? And what are they going to do about it? Sepracor’s president and CEO, Timothy Barberich, believes that part of the problem of the large companies has been cultural, and part of it has been legal. The glamour work among researchers at the big companies is in developing new drugs, not tinkering with those that someone else discovered or synthesized. And, in any case, uncovering problems with successful drugs already in wide use could create legal and ethical dilemmas the original makers would rather avoid.

Their well-earned successes to date notwithstanding, Sepracor’s nimble entrepreneurs face significant challenges in the years ahead. Not surprisingly, industry giants are moving, if belatedly, to bring the work of “cleaning up” their products in-house, and the FDA is encouraging – even requiring – them to do so. Hence, although it is well capitalized and ensured healthy revenues under existing agreements for at least the next ten years, Sepracor has already begun to respond to the changing environment by diversifying into a riskier, perhaps even more lucrative, part of the pharmaceutical business. In the future, the Company will also seek to develop, test, manufacture and market its own drugs from scratch.

Last but not least, a price-to-earnings ratio – which stands at this writing at an astronomical 154 – will require much skill and a heavy dose of luck, as well as an extra measure of patience from the investment community.
Risky Business of Innovation

Studying a surprising failure can sometimes be more instructive than applauding a straight-ahead success. Consider, for example, the high drama played out recently at Ergo Science Corporation, a small biopharmaceutical firm incorporated in 1990 in Delaware, but located in Charlestown, MA to take advantage of heavy concentration of medical researchers in the area.

The Company was founded to develop treatments for metabolic disorders, as well as immune disorders and some types of cancer. Using what is called Neuroendocrine Resetting Therapy (NRT), Ergo Science was developing drugs to target a vast primary market comprising 16 million Americans who suffer from Type 2 diabetes – also called adult-onset diabetes. The drug’s other market, the country’s obese, was even larger. The Company’s secondary research focus, using the same technology, was on immune disorders and breast cancer.

The Company’s founding scientists were bright and had high pedigrees. They had, in fact, spent over 30 years researching the role of neurotransmitters in regulating glucose and lipid metabolism. And, they were committed to developing a drug that operated through the central nervous system to alter how patients metabolize sugar and fat. Moreover, they would design the drug such that the patients would take orally and only one dose a day.

The drug, Ergoset, was to be a fast-release reformulation of bromocriptine, which was sold by Novartis as a treatment for Parkinson’s disease. Ergoset would compete with other drugs on the market to treat Type 2 diabetes – Warner-Lambert’s Resulin and Bristol-Myers Squibb’s Glucophase, both of which had 1997 sales running into several million dollars. Ergoset was to also be the flagship product that would be at the core of all of the Company’s other proposed drugs.

Ergo Science was considered to be very successful in developing various novel treatments. In 1997, seven years of hard work was rewarded when the company successfully completed a pivotal clinical trial for Ergoset. The potential for the drug was considered so great that, in February of 1998, the pharmaceutical giant Johnson & Johnson invested $10 million for a fraction of the company’s outstanding shares. Johnson & Johnson also agreed to pay another $10 million for an up front license to Ergoset and the underlying technology. An additional twenty million dollars were conditional upon the small company’s ability to meet certain milestone.

Then, in May, Ergo Science sustained a body blow from the Food and Drug Administration (FDA). A panel of the FDA’s outside experts concluded unanimously that to approve Ergoset they would need evidence of its long-term effects on human subjects. This was because the drug was to be marketed as lifelong medication for Type 2 diabetics. Based on an earlier understanding with the FDA, the company had clinical data for only six months. Under the new guidelines, which were still in draft form, the FDA panel wanted more data to assess the long-term effects of the drug. They also wanted more data to help them understand how the drug achieved its effects in the human body.
The company’s stock fell by fifty-five percent. Over the summer, the number of employees on the payroll was reduced from 65 to forty.

In late November came a second, near-fatal blow. The FDA sent Ergo Science a formal letter of non-approval for Ergoset tablets. The rejection letter cited the same reasons as its outside experts had in May: (1) It was not clear how Ergoset worked, and (2) It was not clear how the drug might affect brain chemicals and the metabolism of glucose in the long run.

In early December, Johnson & Johnson, which had recently pulled out of a diabetes deal with another company and which had announced plans to slash its 100,000-strong workforce by 4% literally the day before, terminated its relationship with Ergo Science.

The news was enough to bring about another sharp drop in the share price of Ergo Science. The company was in crisis. It cut its workforce from 40 to twenty.

The principals of the company were now faced some unpleasant choices. They knew that it would be prohibitively expensive to conclusively demonstrate Ergoset’s long-term safety and efficacy, particularly now that Ergo Science was financially quite weak. Yet, failure to prove long-term safety and efficacy to the FDA’s satisfaction would mean that a promising new drug with a range of important potential applications could not go to market.

In 1999, perhaps the Company’s only hope for the time being was some positive news from a 300-patient, double blind, placebo-controlled trial of Ergoset’s efficacy in treating obesity. Results for these trials were expected sometime during the summer.