Pennsylvania's Biotechnology and Pharmaceutical Industry

Taking the Initiative for Growth

Ben Franklin Technology Center of Southeastern Pennsylvania

Contents

Pennsylvania's Biotechnology and Pharmaceutical Industry:

Taking the Initiative for Growth

COMMONWEALTH OF PENNSYLVANIA
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THE GOVERNOR

Greetings:

The biotechnology industry in Pennsylvania is leading the way in developing solutions to some of the world's most pressing medical problems. Supported by tremendous resources, this industry is a growth engine for Pennsylvania in the new economy of the 21st century.

To nurture and expand technology-intensive industries in our state, we launched the Technology 21 initiative. Hundreds of industry leaders, including executives from major biotechnology firms, helped formulate our Tech 21 strategy and they identified biotechnology as a primary growth industry for Pennsylvania. Today, we rank fifth in the number of small biotech firms and we have the second-largest concentration of bio-pharmaceutical firms in the nation.

The industry is well positioned for growth in Pennsylvania and my administration is committed to being your best business partner. Since 1995, Pennsylvania families and businesses are saving $5.6 billion - thanks to tax cuts, electric deregulation, workers comp reform and reduced red tape. Our world-renowned universities deliver high-tech, skilled graduates and offer unique partnership opportunities with private sector firms. Our strategic location provides easy access to the regulatory agencies in Washington, D.C. and the financial community in New York. Also our research centers provide the intellectual infrastructure that is critical to biotech growth.

This report examines the state of biotechnology in Pennsylvania and the industry's importance to job creation in the Commonwealth. I look forward to working with the Ben Franklin Technology Center of Southeastern Pennsylvania and the Pennsylvania Biotechnology Association to strengthen the biotechnology industry in the Commonwealth.

Sincerely,

Tom Ridge

Tom Ridge

Executive Summary

Biotechnology, Bioscience, Biopharmaceuticals, Biorobotics, Bioinformatics, Biopharmacogenomics—these terms describe elements of a relatively new science that is expanding daily and altering many other disciplines. These emerging life sciences develop human, animal and agricultural products to reduce medical problems, prolong life, remedy environmental problems and aid farming.

The biotechnology industry cluster—referred to as "biotech"—will be among the next century's leading global influences, economically and socially. Noted MIT economist, Lester Thurow, says biotech "...is going to change the world and probably change the nature of mankind itself..."[1]

Pennsylvania, ranked fifth in the nation in small biotechnology firms, hosts many biopharmaceutical and life sciences companies, medical devices firms and private contract laboratories. The state's research universities, institutions and medical centers from which biotech innovations emerge attract more than $2 billion of federal research funding. Located near other areas of industry strength in the United States and Canada, Pennsylvania's network of bioscience business relationships spans the world.

In conjunction with private industry, led by the Pennsylvania Biotechnology Association (PBA), the Commonwealth brought renewed focus to the importance of biotech through the *Technology 21*[2] initiative. A report produced by the Biotechnology Network of *Technology 21*[3] outlined challenges and offered recommendations for action at the legislative and administrative levels.

This report builds on that initial work. It provides the first examination of biotech cluster data and integrates its findings with those of the Biotechnology Network of Technology 21 and the new strategy for the Ben Franklin Technology Centers completed by the Battelle Memorial Institute. This report and the Battelle Strategy for the Ben Franklin Technology Centers are activities of *Technology 21*, conducted under the auspices of the Ben Franklin/IRC Partnership Board and the Department of Community and Economic Development (DCED).

The complexity of the biotech cluster, its geographic dispersion across Pennsylvania, and the early stage of its development contribute to a lack of understanding about Pennsylvania's biotech sector. While this report makes a first effort at increasing information, there needs to be periodic monitoring, measurement and evaluation of successes, obstacles and issues, in order to benefit fully from what biotech offers.

Several key constituencies are central or ancillary to the biotech sector in Pennsylvania. These include:

- Biotech product and process companies
- Biotech-related product service firms and organizations
- Pharmaceutical companies
- Medical device and diagnostics manufacturers
- Suppliers of services, products or materials
- Trade associations and industry organizations such as the Pennsylvania Biotechnology Association
- Academic health and research centers (including colleges, medical schools and universities)
- Financiers in biotech and related areas (such as venture capitalists, private "angel" investors, corporate investment programs, etc.)
- Government agencies and legislative bodies
- Primary and secondary school districts
- The Ben Franklin/IRC Partnership and other economic development groups
- Health maintenance organizations (HMOs) and other providers

The Commonwealth's Ben Franklin/IRC Partnership has been the source of state support for emerging biotech companies. Biotech offers great economic potential through the formation of new firms, the expansion of existing businesses and increased high-paying employment generated directly or by supplier and servicing industries. In 1997, the average biotech sector wage was 180 percent of the average for all sectors in the Commonwealth. Such benefits need to accrue and remain in Pennsylvania—permanently. By taking a leading position in biotech, Pennsylvania will attract and grow other key technology firms and industries—objectives of *Technology 21*. Collaborative opportunities exist between biotech and agribusiness, information technology and the state's other high tech growth clusters.

To further aid biotech cluster growth in Pennsylvania, this report recommends that the Commonwealth act in seven key areas:

1. Accelerate biotech entrepreneurship.
2. Expand financial resources and address tax issues.
3. Develop a biotech-ready workforce.
4. Advance biotech research excellence.
5. Publicize Pennsylvania's strength as a world-class biotech center.
6. Foster retention of biotech firms while attracting new ones.
7. Adapt electronic tools to develop networks.

Full details of these initiatives are presented in the Recommendations section of this report. The Ben Franklin Technology Centers join the Pennsylvania Biotechnology Association in the belief that the state can achieve leadership in this new industry. With foresight, planning, coordination and informed implementation, biotech can become a significant force in Pennsylvania's business economy.

The Biotechnology Cluster in Pennsylvania

Biotechnological, pharmaceutical and related industries provide about 59,000 jobs in 1,100 establishments in Pennsylvania (Figures A, B, F-L). This *biotech cluster* yields $3 billion in wages statewide, with the average wage at $52,250. Counting indirect compensation (benefits, stock, etc.), industry sales and purchases, and secondary (i.e., indirect or, "multiplier") activity generated by the cluster, the total impact within Pennsylvania—for example, as measured by Gross Regional Product—is even greater. Hospitals and diagnostic laboratories account for an additional 276,000 jobs. Recent trends indicate that the impact of biotech is growing due to sectoral gains in employment and wages and to the declining importance of the state's traditional large industries.

Biotechnology Cluster: Statewide Facts & Figures

59,000	Number of Biotech Employees
$3 billion	Total Annual Wages
1,100	Number of Establishments
*$52,250**	Average Sector Wage *$29,200=Average PA Wage (all sectors)

* The biotechnology cluster includes workers in "core" biotechnology, pharmaceutical and related industries.

Source: ES 202: 1997 Q2

Figure A

Figure B

The Biotechnology Cluster in Southeastern and Southwestern Pennsylvania

REGION	*TOTAL ESTABLISHMENTS*	*TOTAL EMPLOYEES*	*TOTAL WAGES*	*AVG. BIO WAGE*
Southeastern PA*	500	35,000	$2,000,000,000	$58,000
% of PA Total	*43%*	*59%*	*67%*	*113%*
Philadelphia Cty.	100	6,000	$300,000,000	$50,500
Montgomery Cty.	160	18,000	$1,200,000,000	$66,600
Southwestern PA*	200	10,000	$500,000,000	$48,700
% of PA Total	*19%*	*17%*	*16%*	*93%*
Allegheny Cty.	170	8,000	$400,000,000	$49,900

*Southeastern PA includes Bucks, Chester, Delaware, Montgomery and Philadelphia Counties
*Southwestern PA includes Allegheny, Beaver, Butler, Fayette, Washington and Westmoreland Counties

Source: ES202: 1997 Q2

The Biotechnology Cluster

Figure C

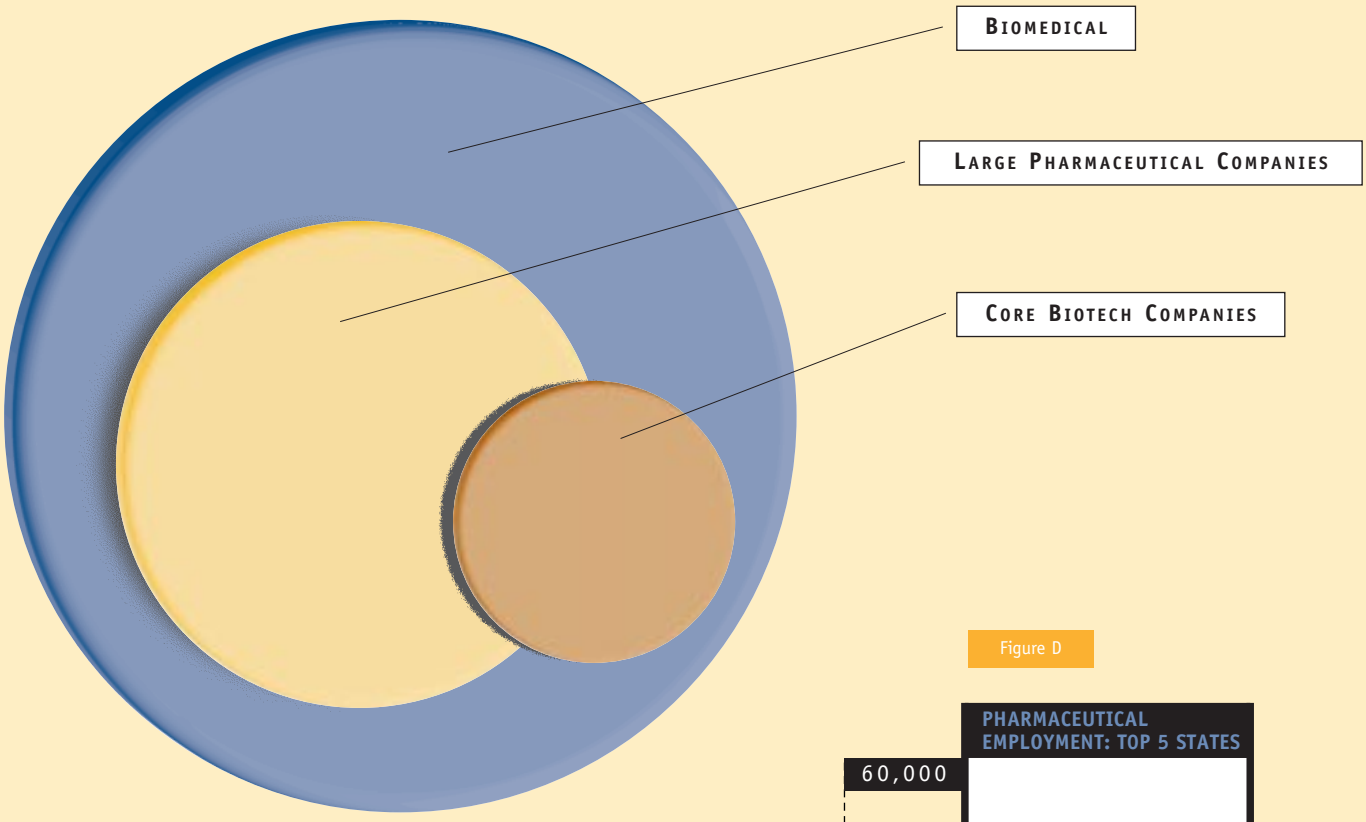
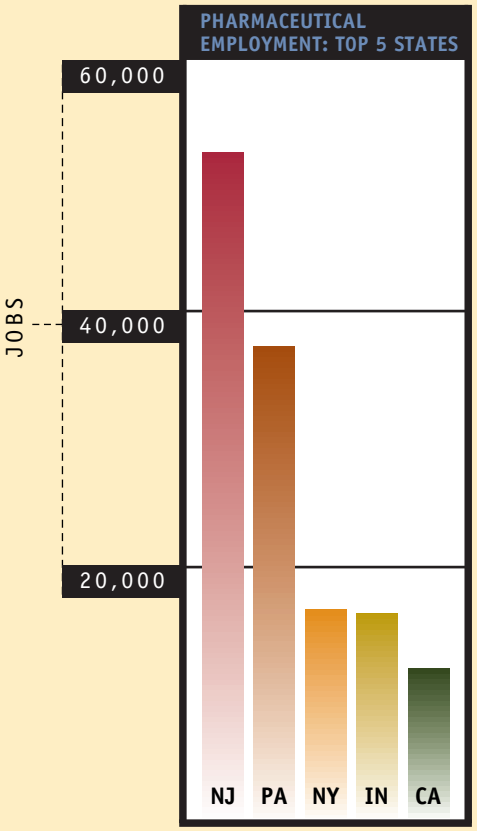


Figure D



Source: Pharmaceutical Industry in Pennsylvania (Pennsylvania Healthcare Technology Network: October 1997)

Within the biotechnology cluster, two industry segments deserve special attention: pharmaceuticals (long associated with Pennsylvania) and "core" biotechnology (Figure C). The remaining components of the cluster include instrumentation and device manufacturers, cosmetics, related chemicals and others.

The Pharmaceutical Industry

Pennsylvania's pharmaceutical industry includes 44 establishments representing 9 companies and 37,000 employees. Wages total $1.8 billion; the average wage is $50,000. Pennsylvania ranks second nationally in pharmaceutical employment (Figure D). Nationwide, from 1986 to 1996, the pharmaceutical industry grew by 25 percent (about 52,000 jobs), while Pennsylvania's tally grew by 36 percent (about 7,200 jobs). Most of the state's pharmaceutical industry, about 80 percent, is situated in and around Philadelphia. A second, smaller concentration exists around Pittsburgh (Figure B).

The Biotech Industry

The core biotech industry in Pennsylvania includes between 100 and 150 establishments with a total of about 6,000 employees. Research spans a broad array of topics. Firms specialize in agriculture, food processing, environmental and plant research, animal and veterinary diagnostics and therapeutics, and process control (e.g., fermentation) activities. Human biotechnology efforts develop diagnostics, therapeutics and vaccines. Clinical specialties include cardiovascular, cancer, neurologic, hepatitis and HIV/AIDs research, reflecting areas of expertise in the Commonwealth's universities and medical centers.

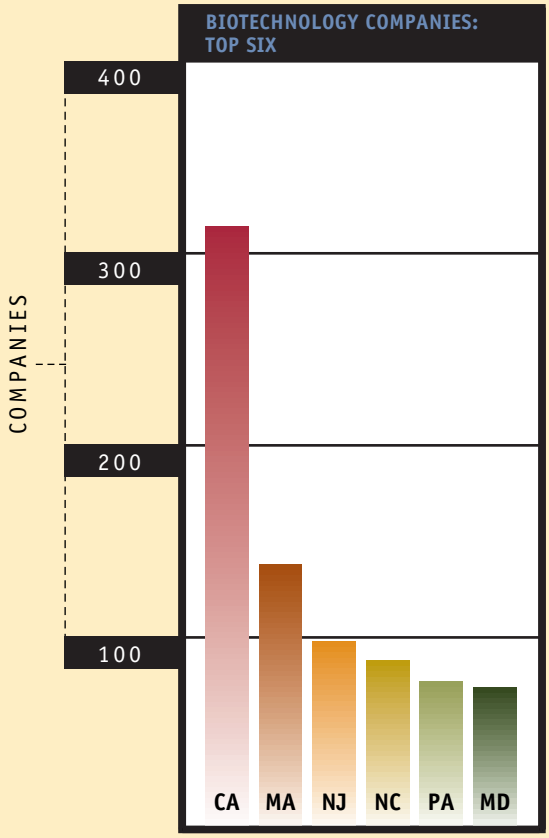
Because most biotech companies are privately held and very small when first established and because ownership often changes rapidly in the first few years, it is difficult to establish precisely the number of *biotech* firms in any state. The Pennsylvania companies we identified came from several sources identified at the end of this report.

Approximately 20 firms are publicly traded. Some firms are almost 20 years old; the youngest are less than a year old. New firms form and then may be sold or restructured—i.e., there is constant "churn." Significantly, Pennsylvania's oldest, largest public biotech companies are all home-grown, developed around technology originating at research universities within the state.

The road to profitability for a biotech company spans many years and consumes hundreds of millions of dollars. Globally, only about a dozen biotech firms are profitable. One Pennsylvania firm has achieved that status; industry analysts regard at least two other companies in the state as near-term candidates to succeed. Pennsylvania's long-term success in biotech cannot be taken for granted. Only states which take an active role addressing the needs of all biotech firms—from startup through maturity—will be able to compete.

Based on the number of companies listed in the BIO International directory, Pennsylvania ranks fifth in the nation (Figure E).

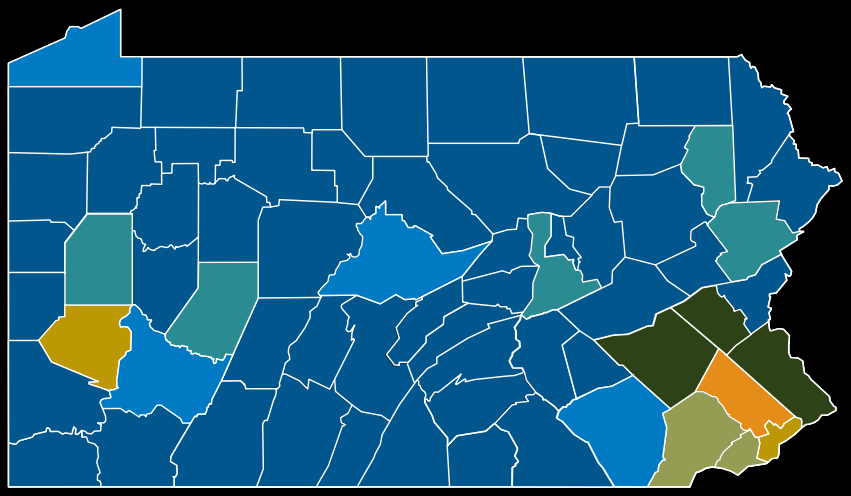
Figure E



Source: BIO online directory (October 1998)

Pennsylvania Biotechnology Cluster: Employment Distribution

Figure F



Employees per County

- 0-500
- 501-1000
- 1001-1500
- 1501-3000
- 3001-6000
- 6001-10000
- over 10000

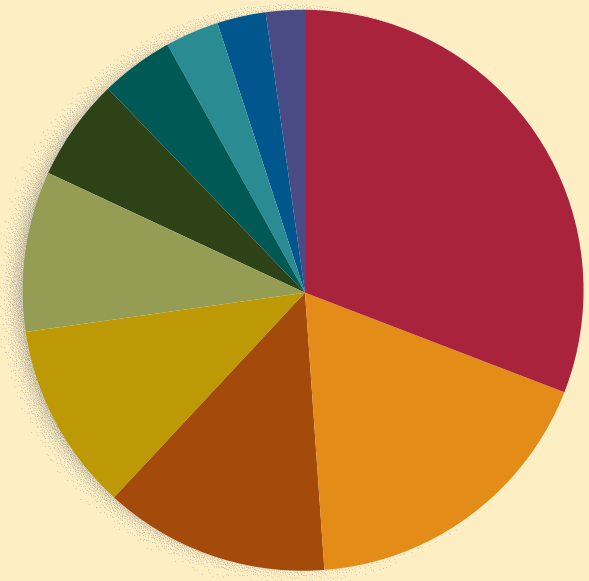
Employment Distribution

- Employment is concentrated around Southeastern and Southwestern Pennsylvania.
- Other, less dense concentrations occur in Centre and Erie Counties and along the spine of the Poconos (i.e., Allentown-Bethlehem–Easton through Wilkes Barre-Scranton).
- Montgomery County, home to many of the Commonwealth's pharmaceutical manufacturers, shows the greatest concentration of jobs.

Source: ES202: 1997Q2

Distribution of Biotechnology Cluster Employees by County

Figure G

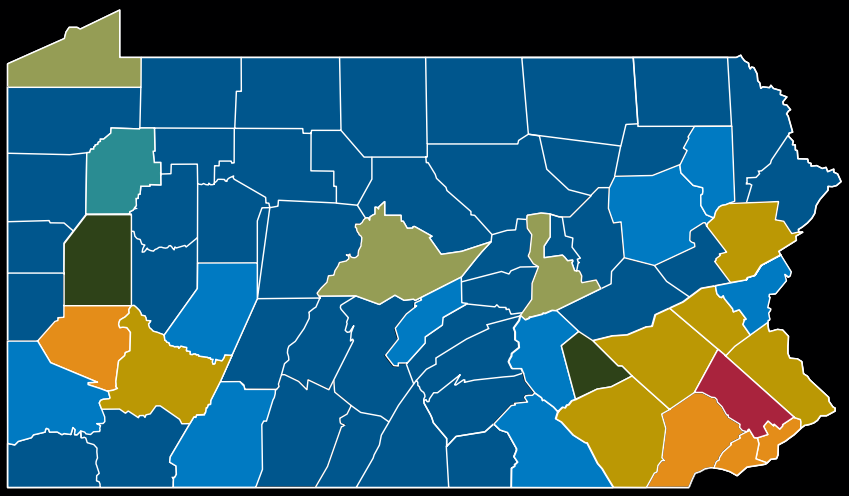


- Montgomery 31%
- Allegheny 13%
- Philadelphia 11%
- Chester 9%
- Delaware 6%
- Bucks 4%
- Berks 3%
- Lehigh 3%
- Lancaster 2%
- Other PA Counties 18%

Source: ES202: 97Q2

Pennsylvania Biotechnology Cluster: Distribution of Wages

Figure H



Total Annual Wage per County ($ Million)

- 0-3
- 4-7
- 8-20
- 21-30
- 31-50
- 51-100
- 101-999
- over 1000

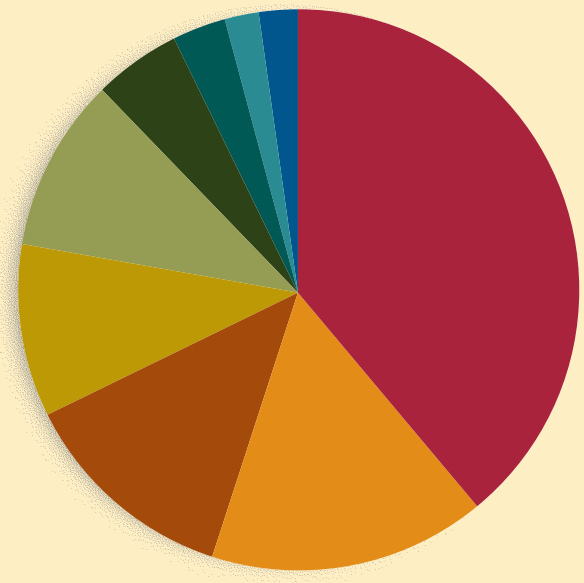
Wages

- Wages and jobs show similar concentrations around the Commonwealth (i.e., Southeastern and Southwestern Pennsylvania).
- Montgomery County, home to many of the Commonwealth's pharmaceutical manufacturers, shows the greatest concentration of wages.

Source: ES202: 97Q2

Distribution of Biotechnology Cluster Wages by County

Figure I



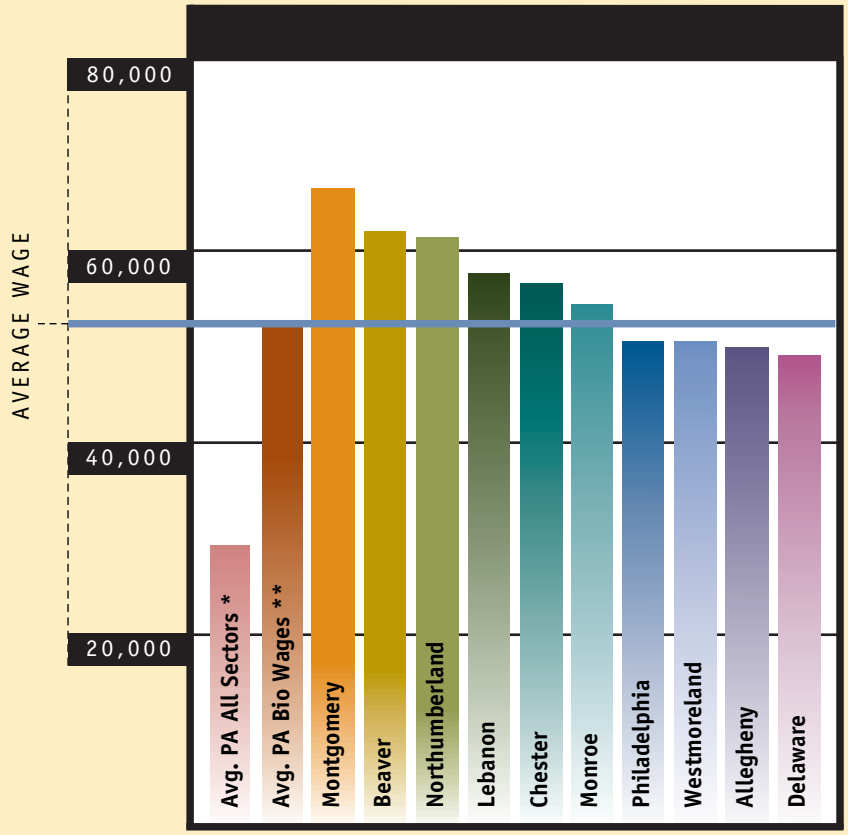
- Montgomery 39%
- Allegheny 13%
- Philadelphia 10%
- Chester 10%
- Delaware 5%
- Bucks 3%
- Berks 2%
- Lehigh 2%
- Other PA Counties 16%

Source: ES202: 97Q2

Biotechnology Cluster: Average Wages by County

Figure J

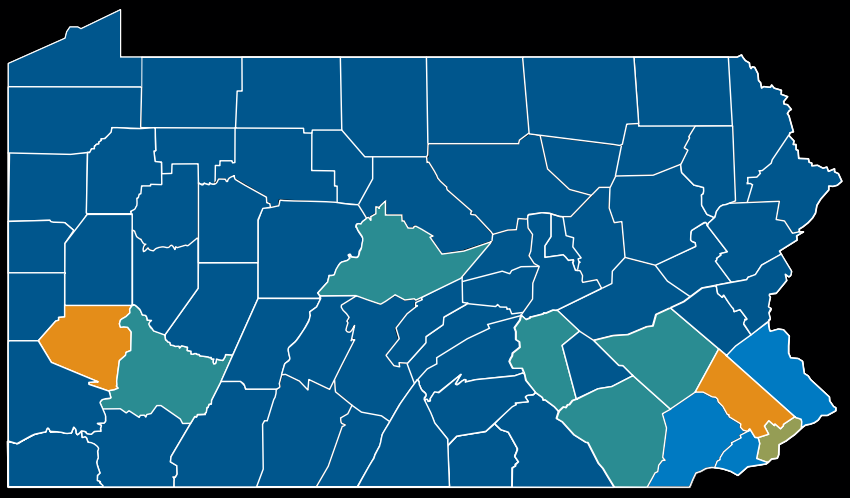
Source: ES202: 97Q2



* Average PA All Sectors Wage = $29,200
** Average PA Bio Wages = $52,250

Pennsylvania Biotechnology Cluster: Distribution of Establishments

Figure K



Establishments per County

- 0-25
- 26-50
- 51-100
- 101-125
- 126-150
- over 151

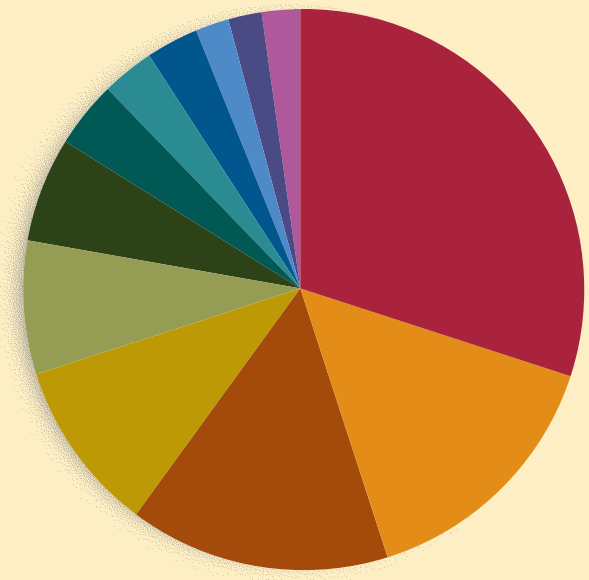
Establishments

- Like wages and jobs, the largest concentrations of establishments fall in Southeastern and Southwestern Pennsylvania.
- Other regions of the Commonwealth also show biotech cluster establishment activity; firms in these areas are smaller (and thus, account for fewer jobs and wages).
- Over time, small firms that are less concentrated (i.e. scattered) exhibit multiple behavior patterns:
  - *Remain where they form;*
  - *Relocate within the state to an area of concentrated biotech activity;*
  - *Relocate out of state to another region of the U.S. with concentrated biotech activity.*

Source: ES202: 97Q2

Distribution of Biotechnology Cluster Establishments By County

Figure L



- Allegheny 15%
- Montgomery 15%
- Philadelphia 10%
- Chester 8%
- Bucks 6%
- Delaware 4%
- Berks 3%
- Centre 3%
- Dauphin 2%
- Lancaster 2%
- Westmoreland 2%
- Other PA Counties 30%

The Economic Environment for Biotech Cluster Growth in Pennsylvania

Changing patterns of employment and increased global competitiveness

The U.S. economy at the end of the 1990s does not resemble the economy of the preceding four decades. In addition to low unemployment and low inflation, there is rapid technological change and increased global competitiveness. Large organizations and industries are being restructured, traditional employment sectors are consolidating, and a new mix of companies, jobs and industries is being created.

Two trends stand out:

- The increased importance of small and medium-sized employers (SMEs) to the US economy;[4]
- The shift from traditional manufacturing and service-producing industries to knowledge-workers in high technology fields.[5]

Leaders in the public and private sectors are looking to develop policies which foster growth in small business and in new sectors. Growth in high technology firms is attractive for several reasons:[6]

- High tech firms improve the competitiveness of existing industries.
- High tech firms attract, retain and support a skilled labor force.
- High tech firms provide direct regional economic benefits through export activity.

Changes in the pharmaceutical industry

The modern pharmaceutical industry began one hundred years ago, with the synthesis of the compound now known as aspirin. Today, global medicine sales are estimated to be $300 billion annually, with the 11 largest firms sharing almost two-thirds of the market (Figure M). Profit margins of the largest drug firms run close to 35 percent.

Figure M

Top Pharmaceutical Companies by Revenue

Company	Revenue ($bn)
Merck	23.6
Johnson & Johnson	22.6
Novartis	21.5
Aventis (Hoechst/Rhone Poulenc)	20.0
Bristol-Myers Squibb	16.7
American Home Products	14.2
AstraZeneca	14.1
Glaxo Wellcome	13.1
Roche	12.9
SmithKline Beecham	12.8
Pfizer	12.5

Source: Financial Times; December 9, 1998; p. 8.

Rapid advances in technology are fueling the discovery and creation of new compounds at unprecedented rates. At present, 10,000 new molecules are synthesized and undergo some degree of testing for every drug that is approved and reaches market. Considering all of the pre-clinical and clinical costs of drug discovery and testing, it now costs over $300 million and takes an average of 13 years for a new drug to come to market (Figure N).

Drug Development and Approval Process

The drug development and approval process takes up to a dozen years and $300 Million on average

Figure N

Development Stage	Pre-Clinical	IND	Clinical Testing (human) Phase I	Clinical Testing (human) Phase II	Clinical Testing (human) Phase III	NDA	Post NDA Marketing Studies
Activity	Synthesis & Development Animal efficacy/safety studies: * Bioavailability * Pharmacokinetics * Toxicology	Investigational New Drug Application Filed	Safety Trials on volunteers * 20-100 human volunteers * Ensure safety of therapy	Safety & Efficacy in Patients * Several hundred patients * Assess safety & effectiveness of therapy	Controlled Safety & Efficacy in Patients * Several thousand patients * Assess safety, effectiveness & dosage	New drug application filed * Report detailing pre-clinical trials including: * Results * Manufacturing * Labeling information	
Average Cost	$205M		Average Total Cost (All Phases) $99 Million				
Average Time	18 months - 4 years		6-18 months	24 months	1-4 years	2 years	
Success Rate			70% of trials	33% of trials	25%-30% of trials		

Some large pharmaceutical manufacturers have shrinking "pipelines" and will not have new compounds to market when patents expire on current revenue-producing commodities. Between 1990 and 1994, the 10 largest pharmaceutical companies together launched an average of five new drugs per year. To maintain revenue growth at its current 10 percent per year, output must rise to five new drugs per company per year, each with annual sales of $350 million. At present, half of the new drugs introduced each year have market values under $100 million annually.

Rising costs and slow revenue growth are spurring mergers among the world's pharmaceutical giants. There is also merger activity among pharmaceutical companies and agricultural chemical producers. Through mergers, the new giants hope to cut costs and increase market size by creating common "life sciences" technology platforms—applicable across disciplines as diverse as human and animal health, plant engineering and crop production.

The pharmaceutical industry is also facing increased pressure to control the costs of drugs as a result of changes to reimbursement policies. In the U.S., health maintenance organizations (government purchasers, abroad) are implementing cost policies that exert pressure on physicians, hospitals and drug manufacturers alike.

Economic potential of the biotech cluster

The opportunities that lay ahead for the pharmaceutical industry are technological and are also at the core of the biotech industry. Advances in recombinant molecular chemistry, genomics and bioinformatics are creating research and business opportunities at unprecedented rates. Today there are over 1,300 biotech companies around the world. Over 350 companies are publicly traded. Of those, a dozen are profitable—that represents almost a doubling of companies in the category from a year ago. Analysts expect the category to expand by 16 to 20 firms during the next year. The combined sales of the biotech cluster now run to $13 billion annually (Figure 0).

Figure 0

Top Biotechnology Companies by Revenue

Company	Revenue ($M)
Amgen	*2,303*
Chiron	*1,313*
Genetech	*967*
Genzyme	*536*
Alza	*466*
Biogen	*277*
Immunex	*153*

Source: A Survey of the Pharmaceutical Industry," in The Economist: February 21, 1998; p. 4.

The profit outlook for biotech companies has brightened as more companies have more drugs in late-stage development. Also, the Food and Drug Administration (FDA) has streamlined the U.S. regulatory process and shortened the time for drug review leading to approval. In 1997, the FDA approved 126 new drugs, a 75 percent increase from 1993. At present, over 50 companies have about 200 drugs in the final stages of clinical testing. More than half of all compounds currently undergoing some phase of clinical testing were developed in laboratories other than those belonging to the pharmaceutical giants.

Biotech companies represent a divergence from the fully integrated pharmaceutical companies *(FIPCOs)* of the past. They exploit the rapid technological changes of the research and development process. While a few of the first biotech success stories have integrated vertically, many choose to specialize somewhere along the spectrum of drug development. The industry is diversifying at every step of the process: drug discovery (e.g., high-throughput screening, combinatorial chemistry), pre-clinical research (e.g., toxicity, bioavailability, pharmacokinetic and efficacy testing), clinical trials (e.g., contract research organizations—CROs), regulatory approval and manufacturing.

Each round of industrial diversification creates more opportunities for financial success or risk for biotech firms. It also creates strategic partnering opportunities with the pharmaceutical giants. This has accelerated the trend toward outsourcing by large pharmaceutical companies. Expenditures on contract services as a share of total research and development have more than doubled over the past decade.

Several business models exist for new biotech companies. The earliest and most developed have become nearly fully integrated pharmaceutical companies, with smaller, "targeted" product lines than larger firms. At the other end of the business model continuum are the "virtual" companies, which assemble various specialist entities (through partnering and licensing agreements, etc.) such as university researchers, CROs, management agencies, et al., to tackle challenges in a cost-effective fashion. The middle ground is occupied by a range of public and private configurations.

No business model prevails in biotech, perhaps because the industry is still rapidly evolving. Despite efficiencies forced by increased competition, the long and expensive road between discovery, development, approval, scaled-up manufacturing and distribution presents significant obstacles and barriers to entry. Just as it is costly for the pharmaceutical giants to bring a new drug to market, so the process is arduous and expensive for startups.

Investors are still waiting to break even (let alone profit) from the publicly traded biotech companies, or they are staying away altogether as the slide in new biotech initial public offerings (IPOs) and the lack of new venture capital inflow illustrates. During 1998, the U.S. biotech industry raised a total of $4.0 billion in financing, compared with $7.1 billion in 1997, according to Burrill & Company, a San Francisco-based merchant bank biotech industry specialist. There were 14 IPOs completed during the period, accounting for $371 million, as compared with 27 and $709 million, respectively, during 1997.

When biotech companies "strike paydirt," however, they have had a tendency to hit the mother lode. For example, Amgen, with only two products, was able to produce a gross margin of 87 percent in 1997. Similarly, Biogen and Chiron both have gross margins above 80 percent.

How Pennsylvania's economic environment suits the biotech industry

Pennsylvania is at the center of many current U.S. economic shifts. The Commonwealth has seen large reductions in its traditional industrial base. At the same time, there has been significant growth in the state's high tech sectors. The importance of small and medium-sized employers, especially business births and startups, has been a parallel-related phenomenon. Nationwide, such firms have shown their economic importance. Between 1988 and 1993 firms with fewer than 500 employees created 18 million net new jobs, while larger firms created just 100,000 jobs.[7]

Pennsylvania has numerous academic health organizations specializing in healthcare delivery and research. The Commonwealth and nearby states are also home to many of the world's largest pharmaceutical manufacturers, including much of their administrative, sales, research and manufacturing staff. Pennsylvania also houses several health maintenance organizations and insurers.

Those resources, combined with adequate financial support and sound business management, create an environment conducive to biotech startups. Activity is scattered across the state, not only in southeastern and southwestern Pennsylvania, although analysis of the data over time shows that biotech companies grow best when they cluster within the state's two major metropolitan areas (Philadelphia and Pittsburgh).

Pennsylvania's suitability as a haven for biotech is enhanced by the presence of a strong trade group, the Pennsylvania Biotechnology Association. PBA works to support biotechnology by improving business networking, strengthening the public understanding of biotech, and working with state government to formulate an industry strategy.

How Biotech Companies Develop and Cluster

The biotech entrepreneur in Pennsylvania

Interviews held with entrepreneurs from biotech startups statewide revealed that many company founders are, or were, university researchers. Many have tenured appointments. The technology around which they are building companies comes from the academic laboratory setting, often from research in which they were the principal investigators. Some saw entrepreneurship as an additional means of funding their research or moving it in directions that did not conform to the terms of their research grants. Other Pennsylvania biotech entrepreneurs come from larger pharmaceutical or biotech companies, and maintain ties with those organizations.

Whatever their background, the entrepreneurs' strengths lie most often with scientific or technological knowledge, not business. Some had prior experience with a startup or small business, but most were first-timers. The only formal business training most had was from a government program—e.g., Ben Franklin Technology Center, Small Business Administration (SBA) or Small Business Development Center (SBDC)—or entrepreneur forums and seminars.

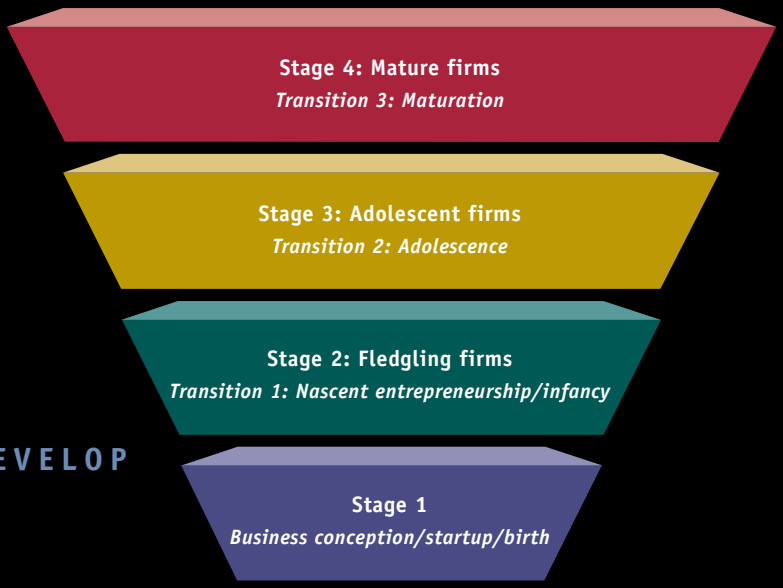
Profile of the biotech startup firm

The typical biotech startup consists of not more than three employees—one or two founders and a full- or part-time graduate student or post-doctoral researcher. Startups usually locate in space near the founder's former employer and the most eligible pool of labor, or in rental space previously used for a similar biotech startup firm.

Entrepreneurial business stages

Consider the entrepreneurial process as four stages, marked by three intermediate transitions.[8] Businesses have specific needs at each of these stages and transitions (Figure P):

Figure P



Economic growth strategies for a region or state need to consider the mix of firms at different developmental stages. Too many startups with few experienced firms make for a weak industry with little experience to draw upon. Likewise, if not enough attention is given to the needs of fledgling firms, they may leave and cluster elsewhere for survival. Firms may grow to maturity but flee a region due to restrictive tax policies, high business costs, transit and congestion issues, environmental constraints or labor shortages.

The biotech cluster includes firms at all stages of maturity. Early mortality is high due to the business risks associated with startups in general, the slow path from research to commercialization, and significant cluster-specific financial needs.

Biotech companies at Stage 1

(conception/startup/birth)

Biotech startups work on proof-of-concept activities, including product refinement and, for therapeutics, toxicity testing. Most have no revenues. When they generate revenues, they are unlikely to show profits. They need cash to cover operating expenses and expertise to solve technical and business problems. Financial obligations include staff salaries (although founders may not pay themselves during this phase), rent, capital equipment purchases, etc.

Market information, competition, research, production, marketing, growth and financial strategies must be established and refined. Founding entrepreneurs must continue to work on technology but they cannot ignore the management issues facing a new business. The tendency however is to spend more time in the laboratory than on tactical, operational and strategic business issues.

Business information and advice is especially useful to entrepreneurs if it can be gained at little or no cost in either time or money. They can benefit substantially from the mentoring expertise of those who have "been there" and from collaborative relationships with larger partners who can provide practical know-how as well as cash.

Larger firms also have good reasons for partnering. Small firm relationships provide access to radical innovations and new products in which large firms are otherwise unlikely to risk investment.[9] Evidence shows large firms have marketing and distribution competency but lack innovative technical competency.[10]

Mortality for startups is extremely high. Rates of business births and survival are influenced positively by government assistance programs[11] and collaborative partnerships.[12]

Stage one challenges:

- Intellectual property ownership/technology transfer
- Technical feasibility
- Adequate financial support
- Tactical and strategic business planning
- Legal assistance for IP, contracts, etc.
- Little to no prior business experience among entrepreneurs
- Location and proximity to resources
- Time management issues for founders

Biotech companies at Stage 2 *(fledgling firms)*

The difference between startup and fledgling is not a matter of size as much as a matter of duration. The fledgling has overcome the immediate challenges of birth and is on the way to longer-term survival and some growth—perhaps in employment, if not sales.

Some activities related to encouraging entrepreneurship are less likely to have an impact on firm survival.[13] Founders may better aid survival by learning from others and entering into successful partnerships for production, research and financial support. The entrepreneur is unlikely to be able to identify all of the financial, manufacturing, legal, space and infrastructure resources needed. Those are likely to be spread across the Commonwealth and may even reach across the nation or world.

Formal mentor relationships may provide the business knowledge important to entrepreneurs at this stage of the firm's life, however they are not easy to build. The public sector, in cooperation with industry trade associations, can facilitate the process.

Financial requirements grow, but remain under $3 million. Work focuses on toxicity testing and achieving Phase I FDA approval. Scaled up production (for testing) costs more (if it can be found, given quantities remain relatively small), just as salaries, rent and legal fees are multiplying. Fledgling biotech entrepreneurs remain many years from the marketplace and profitability. The ability to locate and arrange financing and manage expenditures can be a determinant of success. Survival also depends on knowing when to bring in professional management talent.

Stage two challenges:

- Intellectual property ownership/licensing arrangements
- Technical feasibility/testing
- Ongoing financial support
- Production scale up
- Business planning for production, research and distribution
- Networking-collaborative partnerships (in-and out-of-state)
- Legal/regulatory advice
- Accounting assistance
- Changing location needs
- Next-stage financing

Biotech companies at Stage 3 *(adolescent firms)*

The diversity of experience here is greater than in earlier stages. Adolescent biotech firms have larger average employment than both startups and fledglings, with significantly larger expenses (up to tens of millions of dollars). They may have achieved positive sales growth but may not be profitable. Such companies use many techniques to obtain financing, including stock offerings.

Stage 3 companies have professional management. Most managers come from other biotech or pharmaceutical firms. There may be a legacy of management turnover, as unsuccessful teams are replaced.

Adolescent biotech firms are probably still involved with their initial products, but are also at work on new products in order to avoid obsolescence. They focus on regulatory approval and commercial success and are likely to be close to all stages of research, testing, manufacturing, marketing and distribution.

Some are "virtual" corporations that outsource core functions. Production capabilities for new compounds or devices, the success of testing and achievement of regulatory hurdles, confidence in management, strong financial statements (even without profits) and depth of strategic planning are factors that contribute to the ease with which financing is obtained.

Firms that reach adolescence may engage in collaborative partnerships, although some partnerships prove restrictive.[14] Partnerships may cause emergent firms to choose between short-term gains and long-term viability.

Biotech firms may need to hire skilled labor from similar organizations, so adolescent firms may grow in regions that have been identified as "biotech centers." By clustering in such areas, executives also create the density necessary for informal networks and mentoring opportunities to grow. They may also face financial challenges related to growth. The need to conserve cash for research and development, the lack of profits, combined with the absence of suitable, affordable financing mechanisms, constrain physical development at this critical stage.

Stage Three Challenges:

- Licensing arrangements
- Regulatory approval
- Multiple financing arrangements
- Production scale manufacturing
- Ongoing business and strategic planning
- Increased business costs
- Labor market concerns
- Access to markets
- Capital needs—both for continued research & development/physical expansion
- Innovations

Biotech companies at Stage 4 *(mature firms)*

Mature companies have achieved profitability and are working to remain competitive. They are publicly traded, incorporated, multidisciplinary organizations with products in all phases of development. In some cases, they obtain technology through acquisition rather than research. With their focus on growth through volume and economies of scale, mature firms tend to be conservative[15] and engage in less costly risk-taking activities.

There is a natural tension between mature firms (10 to 15 years old) and those that are just starting out. However, information flow in both directions can result in "win-win" outcomes for both firms as well as for the regions in which they exist.

In the current biotech sector, there are probably no more than a dozen organizations worldwide that can be identified as mature firms. Many struggled for ten years or more before achieving profitability. Several are on the edge of profitability.

Stage Four Challenges:

- Sustained profitability and commercial viability
- Market dominance
- Economies of scale
- New market entry
- Research and development
- Mergers and acquisitions
- Import-export possibilities
- Labor force concerns
- Raw materials
- Regulatory demands
- Environmental impact

Figure Q

Biotech Cluster Entrepreneurial Business Stages

Stage One Challenges:

- Intellectual property ownership/technology transfer
- Technical feasibility
- Adequate financial support
- Tactical and strategic business planning
- Legal assistance for IP, contracts, etc.
- Little to no prior business experience among entrepreneurs
- Location and proximity to resources
- Time management issues for founders

Stage Two Challenges:

- Intellectual property ownership/licensing
- Technical feasibility/testing
- Ongoing financial support
- Production scale up
- Business planning for production, research and distribution
- Networking and collaborative partnerships
- Legal/regulatory advice
- Accounting assistance
- Changing location needs
- Next-stage financing

Stage Three Challenges:

- Licensing arrangements
- Regulatory approval
- Multiple financing arrangements
- Production scale manufacturing
- Ongoing business and strategic planning
- Increased business costs
- Labor market concerns
- Access to markets
- Capital needs
- Innovations

Stage Four Challenges:

- Sustained profitability and commercial viability
- Market dominance
- Economies of scale
- New market entry
- Research and development
- Mergers and acquisitions
- Import-export possibilities
- Labor force concerns
- Raw materials
- Regulatory demands
- Environmental impact

Conclusion

With the support of the Pennsylvania Biotechnology Association, the Ben Franklin Technology Centers, and other public and private sector organizations, Pennsylvania can move into significant leadership nationally and internationally as a home for biotechnology development and growth.

The state's mix of young biotech companies, established multinational pharmaceutical giants, premier teaching hospitals, academic research laboratories and related enterprises, already ranks among the richest in the world. In combination with a well-planned collaborative effort, Pennsylvania can achieve and surpass the goals of Technology 21.

Methodology

This report advances the work begun by the Ben Franklin Technology Center of Southeastern PA, in 1997 and 1998, to promote the goals of *Technology 21*. It summarizes research conducted in 1998, by Ben Franklin Technology Center of Southeastern PA, about the biotechnology cluster in Pennsylvania. This research was preceded by the joint efforts of Ben Franklin Technology Center of Southeastern PA and Greater Philadelphia First (GPF), as well as the *Biotechnology Network of Technology 21*.

During the spring of 1997, Ben Franklin Technology Center of Southeastern PA, in conjunction with GPF, began to examine the biotechnology cluster in southeastern Pennsylvania. That research grew out of a report by GPF ("Reports of the GPF Cluster Teams," May 1997) which identified the biopharmaceutical sector as one of the industry clusters important to the welfare of the regional economy. As part of the work with GPF, interviews with major stakeholders were held throughout southeastern Pennsylvania and in Harrisburg, to assess the industry's health and develop recommendations for strengthening its presence in the region.

That research was expanded to cover the entire Commonwealth, in order to complete this study. The literature review was expanded accordingly, and a series of individual interviews and moderated focus groups were conducted at locations across the state. Ben Franklin Technology Center of Southeastern PA, solicited input from representatives of the "core" biotech industry, pharmaceuticals, related industry and other sectors. The information collected in the course of those sessions was combined with other research findings to produce this report. The cooperation and assistance of the Pennsylvania Biotechnology Association was critical and without peer, as this work was completed.

The questions used to focus discussion during the course of individual and group interviews always included the following:

- What is your perception of the state of the industry in Pennsylvania today?
- What are the challenges/obstacles facing the industry in Pennsylvania today?
- What can the industry do for itself to strengthen its presence in Pennsylvania?
- What can the public sector do for the industry to strengthen its presence in Pennsylvania?

Typically, these questions were sufficient to instigate lively discussion by session participants.

Data Sources

The primary source of data for this report is the ES-202 Universal Database. The ES-202 database consists of data collected by the Pennsylvania Department of Labor and Industry, in compliance with the Commonwealth's Unemployment Insurance (UI) program. The ES-202 program (or, "Covered Employment and Wages Program") is a cooperative endeavor between the Commonwealth and the U.S. Bureau of Labor Statistics. The ES-202 database is the most complete census of monthly employment and quarterly wage information by industry, county and state.[16] Records collected under this program include firm classification by primary Standard Industrial Classification (SIC), the number of covered workers who earned wages during the monthly pay period and quarterly average wages. Other data, such as year of startup, is also available from the database.

Data from the ES-202 program was aggregated to ensure confidentiality, then used to develop a census of the biotechnology cluster within Pennsylvania. Data collected during the second quarter of 1997 was utilized, and the following SIC codes were included in the census:

SIC	Description
283-	Drugs
2833	Medicinal Chemicals and Botanical Products
2834	Pharmaceutical Preparations
2835	In Vitro and In Vivo Diagnostic Substances
2836	Biological Products, Except Diagnostic Substances
2869	Industrial Organic Chemicals, Not Elsewhere Classified
382-	Laboratory Apparatus and Analytical, Optical, Measuring and Controlling Instruments
3826	Laboratory Analytical Instruments
384-	Surgical, Medical and Dental Instruments and Supplies
3841	Surgical and Medical Instruments and Apparatus
3842	Orthopedic, Prosthetic and Surgical Appliances and Supplies
3844	X-Ray Apparatus and Tubes and Related Irradiation Apparatus
3845	Electromedical and Electrotherapeutic Apparatus
873-	Research, Development and Testing Services
8731	Commercial Physical and Biological Research
8733	Non-commercial Research Organizations
8734	Testing Laboratories

Because of confidentiality issues, ES-202 data was supplemented with data obtained from other sources to identify the constituents of the "core" biotechnology sector and the pharmaceutical sector. These sources include proprietary databases such as BioScan and CorpTech, the members' registry of BIO, as well as data prepared for a report on Pennsylvania's pharmaceutical sector ("The Pharmaceutical Industry: Economic Growth in Pennsylvania"; Pennsylvania Healthcare Technology Network, Oct. 97.) In each case, data sources were cross-checked against each other, to ensure accuracy.

Footnotes

1 Thurow, Lester. The Future of Capitalism: How Today's Economic Forces Shape Tomorrow's World; William Morrow & Co., 1996.

2 Technology 21—The Keystone Spirit: Putting Technology to Work; Harrisburg, PA: DCED, 1997.

3 Technology 21—Biotechnology Network Final Report and Recommendations; Harrisburg, PA: DCED, 1997.

4 Acs, Zoltan J. and Bruce D. Phillips. "Why Does the Relative Share of Employment Stay Constant?" in Frontiers of Entrepreneurship Research (Reynolds, Paul D., et al, Eds.); Wellesley, MA: Babson College, 1997.

5 American Electronics Association. Cyberstates: A State-By-State Overview of the High Technology Industry; Washington, DC: AEA, 1997.

6 Stearns, Timothy M. "Strategic Alliances and Performance of High Technology New Firms" in Frontiers of Entrepreneurship Research (Reynolds, Paul D., et al, Eds.); Wellesley, MA: Babson College, 1996.

7 Acs, Phillips; p. 10.

8 The model used here is derived from that described by Paul Reynolds, Coordinator, Entrepreneurial Research Consortium and Paul T. Babson Professor of Entrepreneurial Studies, Babson College, in a presentation entitled, "National Panel Studies of Business Start-Ups: Research Program Status Report and Policy Implications." That talk was delivered to the Working Party on Small Medium Enterprises, 9th Session, November 6, 1997, in Seoul, Republic of Korea.

9 Katila, Rita. "Technology Strategies for Growth and Innovation: A Study of Biotechnology Ventures," in Frontiers of Entrepreneurship Research (Reynolds, Paul D., et al, Eds.); Wellesley, MA: Babson College, 1997; p. 3.

10 Stearns; p. 12.

11 White, Sammis B. and Paul D. Reynolds. "What Can the Public Sector Do to Increase New Business Starts?" in Frontiers of Entrepreneurship Research (Reynolds, Paul D., et al, Eds.); Wellesley, MA: Babson College, 1994.

12 Katila; p. 4.

13 Slevin, Dennis P. and Jeffrey G. Covin. "New Ventures and Total Competitiveness: A Conceptual Model, Empirical Results, and Case Study Examples" in Frontiers of Entrepreneurship Research (Reynolds, Paul D., et al, Eds.); Wellesley, MA: Babson College, 1995.

14 Katila; p. 1.

15 Katila; p. 2.

16 US Department of Labor, Bureau of Labor Statistics. BLS Handbook of Methods; Washington, DC: BLS, 1997; p. 46.

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