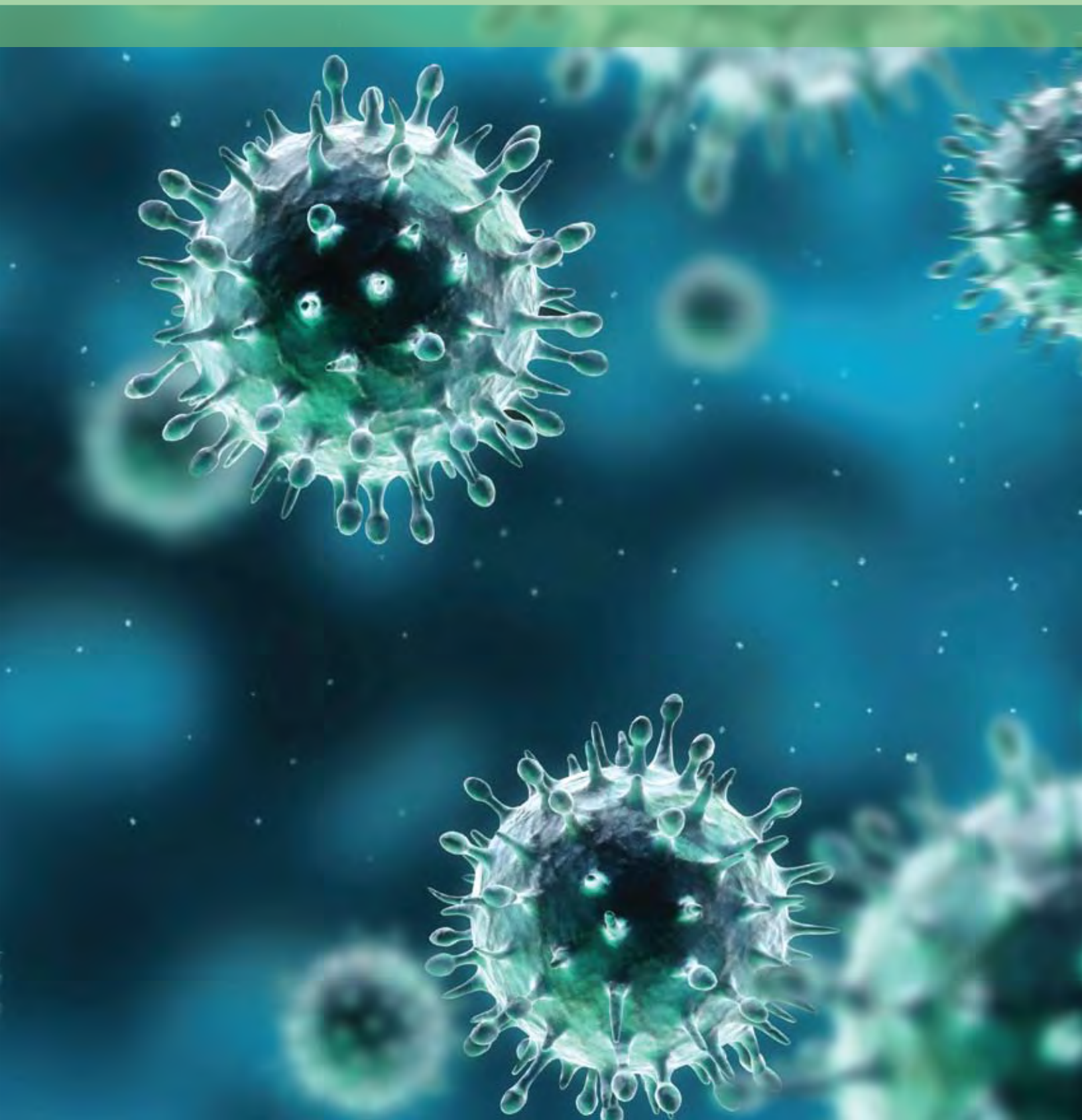
2011 profile

PhRMA

PHARMACEUTICAL INDUSTRY



Key Facts

Research and Development (R&D)

- Time to develop a drug = 10 to 15 years[1]

Development Costs

- Cost to develop a drug
  2005 = $1.3 billion[2]
  2001 = $802 million[3]
  1987 = $318 million[3]
  1975 = $138 million[3]
- Cost to develop a biologic
  2005 = $1.2 billion[4]

R&D Spending

Year	PhRMA members[5]	Total industry[6]
2010	$49.4 billion *(est.)*	$67.4 billion *(est.)*
2009	$46.4 billion	$65.9 billion
2008	$47.4 billion	$63.7 billion
2007	$47.9 billion	$63.2 billion
2006	$43.4 billion	$56.1 billion
2005	$39.9 billion	$51.8 billion
2004	$37.0 billion	$47.6 billion
2000	$26.0 billion	not available
1990	$8.4 billion	not available
1980	$2.0 billion	not available

Percentage of Sales That Went to R&D in 2010[7]

Domestic R&D
as a percentage of domestic sales = 20.5%

Total R&D
as a percentage of total sales = 17.0%

Economic Impact of the Biopharmaceutical Sector[8]

Direct jobs = 655,025 in 2008 *(most recent data)*

Total jobs (including indirect and induced jobs)
= 3.1 million in 2008 *(most recent data)*

Approvals

- Drugs and biologics approved in 2000–2010 = 333[9]
- In the 28 years since the Orphan Drug Act was established, more than 360 orphan drugs have been approved.[10]
- Only 2 of 10 marketed drugs return revenues that match or exceed R&D costs.[11]

Medicines in Development

2010 = 3,050 compounds[12]

2001 = 2,040 compounds[13]

Value of Medicines

- **Cancer:** Since 1980, life expectancy for cancer patients has increased about **3 years,** and 83% of those gains are attributable to new treatments, including medicines.[14] Another study found that medicines specifically account for 50% to 60% of increases in survival rates since 1975.[15]
- **Cardiovascular Disease:** According to a 2010 statistics update by the American Heart Association (AHA), death rates for cardiovascular disease fell a dramatic **28%** between 1997 and 2007.[16]
- **HIV/AIDS:** Since the approval of the antiretroviral treatments in 1995, the U.S. AIDS death rate has dropped by **more than 75%.**[17]

Sales

- Generic share of market[18]
  2000 = 49%
  2010 = 78%

See inside back cover for endnotes.

2011 profile

PhRMA

PHARMACEUTICAL
INDUSTRY

PhRMA

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Pharmaceutical Research and Manufacturers of America

Washington, DC

www.phrma.org

2011

Letter from PhRMA's President and CEO

America's biopharmaceutical research companies are among the most innovative, research-driven enterprises anywhere. Together they are the recognized global leaders in developing new medicines, which help to save and improve lives.

Last year, America's biopharmaceutical companies continued to lead the world in drug discovery, investing an estimated $67.4 billion in R&D. PhRMA members alone contributed an estimated $49.4 billion of the total for 2010. As a result of this ongoing investment, more than 3,000 new medicines are in development to help treat debilitating and costly conditions ranging from cancers to diabetes to rare diseases.

This industry is also a vibrant economic engine. Every one of the nearly 650,000 direct jobs created by one of America's biopharmaceutical companies results in an additional 3.7 jobs in other sectors – totaling more than 3.1 million jobs across the economy.

However, our sector faces real challenges. The time it takes to bring a new medicine to patients – navigating the complicated clinical development and regulatory processes – is growing, and the science of drug discovery is getting harder. The more we understand about biology, genetics and the potential for personalized medicine, the more complex and costly R&D has become.

Additionally, international competition for R&D investment is growing stronger as more and more countries around the globe understand that a robust, innovative biopharmaceutical research sector can help improve the health and quality of life of their people as well their national economies.

At a time when our innovation, entrepreneurialism and jobs dominate the national dialogue, our industry should be held up and preserved as a national treasure. It should be supported by policies that encourage growth and that reward innovation, investment and risk taking.

Our companies are dedicated to helping people live longer, healthier, more productive lives through better prevention and disease management; the discovery of new treatments; and advocacy for policies that enable people to access needed care. This year, the *Pharmaceutical Industry Profile* highlights that commitment and the vital role biopharmaceutical companies play in both improving lives and driving the economy.

John J. Castellani
President and Chief Executive Officer
Pharmaceutical Research and Manufacturers of America

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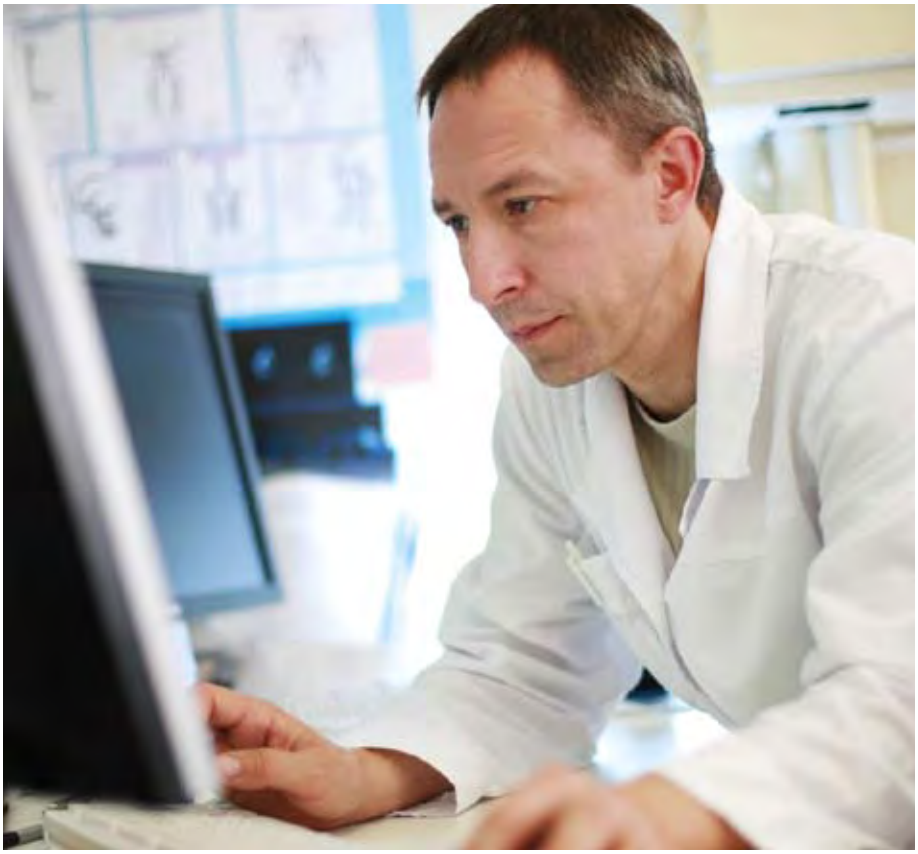
Dynamic Research: Vital Effects

Dynamic scientific research is at the core of the work conducted by America's biopharmaceutical companies. This research leads to treatments that save lives and improve health for patients around the world; it also helps drive the U.S. economy by supporting millions of high-quality jobs.

The biopharmaceutical research sector invests tens of billions of dollars each year to support research that advances the boundaries of scientific knowledge and brings new medicines to patients. Through their research and development (R&D) investments and interconnections with local businesses, biopharmaceutical companies are strong drivers of local and national economies. In addition to directly providing hundreds of thousands of well-paying jobs, they indirectly support millions more.

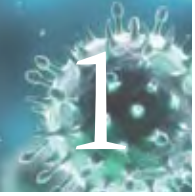
Although the research process is long and expensive, with low odds of success, the medicines that do eventually gain approval greatly improve patients' lives. For example, in recent years we have seen great progress in the fight against cancer, heart disease, and HIV/AIDS. In addition to improving health, medicines often help manage health care costs by preventing hospitalizations, surgeries and other costly care.



Improving the lives of patients is what drives America's biopharmaceutical research companies. This means not only discovering better treatments, but also making sure that patients have access to medicines when they need them. Therefore, the sector supports programs that promote access to medicines, along with wellness and prevention programs to help reduce the burden of disease.

The 2011 *Pharmaceutical Industry Profile* examines the vital impact of the research-intensive biopharmaceutical sector on patients and the economy. The research investments of the industry mean the promise of a better life for millions of patients and a stronger economy for all Americans.

1 Vibrant Innovation: Strengthening the U.S. Economy



Vibrant Innovation: Strengthening the U.S. Economy

Biopharmaceutical companies support some of the most advanced, cutting-edge research in the world. Driven by unmatched R&D investment, a highly skilled workforce, unprecedented scientific potential and new partnerships, this vibrant innovation is also an essential engine of U.S. economic vitality. The sector is an economic resource and a national asset, particularly as the country works to create high-value jobs, increase exports, and restart the economy.

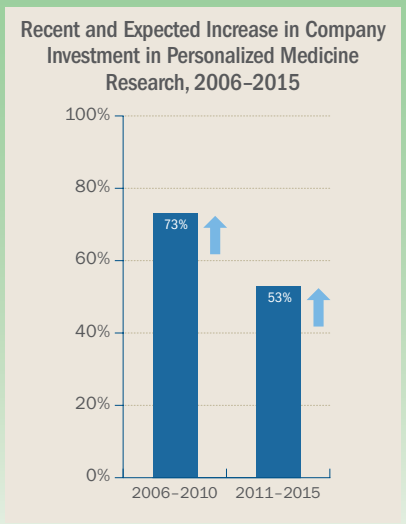
> *"The pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm."*[1]
>
> — CONGRESSIONAL BUDGET OFFICE, 2006

Scientific Potential

Greater knowledge of how diseases work at the genetic and molecular level has allowed researchers to pursue new treatment mechanisms and better target medicines to the underlying disease causes. For example, researchers are working on developing medicines that specifically attack diseased or cancerous cells, sparing healthy cells. Researchers across the sector are also actively working to advance personalized medicine, which uses an individual's genetic information to guide diagnosis, prevention and treatment. (See box on page 3.)

The scientific potential for making real progress against complex diseases has never been greater, and biopharmaceutical companies are working to turn that promise into new medicines. The R&D pipeline in the United States includes more than 3,000 medicines in clinical trials or awaiting Food and Drug Administration (FDA) review.[2] This includes 98 potential medicines for Alzheimer's disease,[3] 861 for cancers,[4] 235 for diabetes,[5] 100 for HIV/AIDS,[6] 300 for rare diseases,[7] and 299 for heart disease and stroke.[8]

FIGURE 1: Biopharmaceutical Companies Report Increases in Personalized Medicine Spending



SOURCE: Tufts Center for the Study of Drug Development, "Personalized Medicine Is Playing a Growing Role in Development Pipelines," *Impact Report* no. 12 (November/December 2010): 6.

"The industry as a whole is committed to pushing strongly ahead . . . . [and] early indications show that development of personalized medicines is commanding more resources and fomenting more corresponding organizational change than is generally appreciated outside the industry."

— TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT, 2010

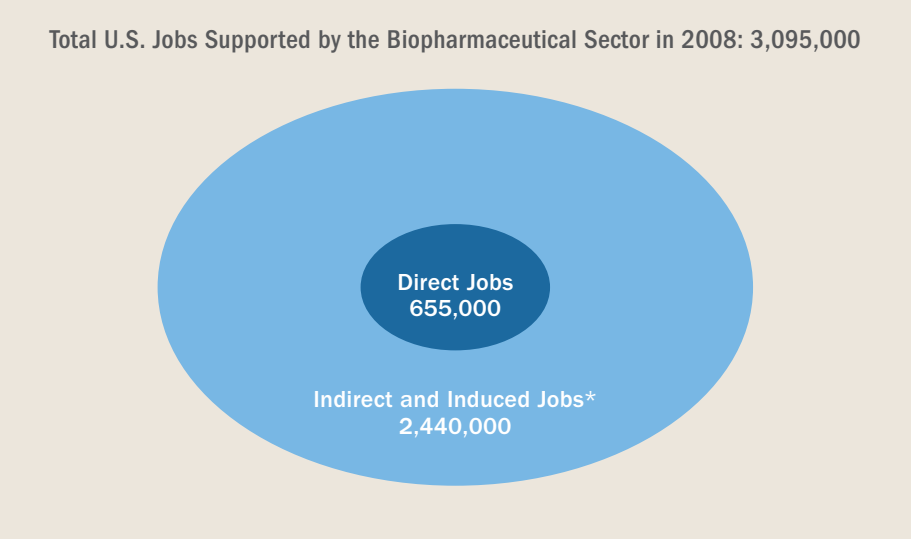
Biopharmaceutical Companies Pursuing Scientific Potential of Personalized Medicine

A new report from the Tufts Center for the Study of Drug Development quantifies the depth of biopharmaceutical companies' commitment to advancing personalized medicine (PM), which is genetically guided diagnosis, treatment, and prevention:[9]

- Of the companies surveyed, 94% are investing in PM research, which often requires substantial investment in new technologies.
- In many instances, companies' investments are translating into the development of therapies that have a companion diagnostic, which guides use of the treatment based on a patient's genetic information. Companies report that within their development pipelines, 12% to 50% of compounds are personalized medicines.
- In the last five years, companies report that they have increased their investment in PM by roughly 75%. What's more, they expect an additional 53% increase in the next five years. (See Figure 1, page 2.)
- Personalized medicine is changing the way biopharmaceutical companies develop new medicines. One hundred percent of companies surveyed said that they are using biomarkers (characteristics which can guide treatment and diagnosis and are integral to PM) in the discovery stage of research to help learn more about a compound.

1 Vibrant Innovation: Strengthening the U.S. Economy

FIGURE 2: **Biopharmaceutical Jobs Create Ripple Effect – Each Job Supports 3.7 Others**



* Indirect jobs are jobs that produce goods or services used to support biopharmaceutical companies. Induced jobs are jobs supported by the spending of direct and indirect employees of the biopharmaceutical sector.

SOURCE: Archstone Consulting and R. L. Burns, The Biopharmaceutical Sector's Impact on the Economy of the United States (Fact Sheet) (Washington, DC: Archstone Consulting, LLC, 2010).

Innovation Fuels Economic Vitality

Innovation not only fosters medical advances, but it continues to be an engine of job creation and U.S. global competitiveness. By investing in and focusing on innovation, America's biopharmaceutical research companies are playing a critical role in contributing to the national economy and making the United States the worldwide hub for scientific and medical research.

The industry directly sustains more than 650,000 high-quality jobs across a range of professions and skill levels, with an average salary of $96,563.[10] (See Figure 2.) Each of those jobs supports an additional 3.7 jobs across the economy, for a total of more than 3 million jobs.

The U.S. biopharmaceutical sector is one of the few U.S. sectors to continue to show export growth over time – in fact, U.S. biopharmaceutical exports rose nearly 60% between 2005 and 2009, from $29 billion to $46 billion.[11] According to the National Export Initiative, exports are projected to support millions of good jobs, increase production and wages, and generate more high-paying jobs in the United States over the next five years.[12]

Vital Effects: Industry's Economic Contributions

Even during the recent downturn, the biopharmaceutical sector contributed substantially to the U.S. economy.[13] For example, in 2008 (the latest comprehensive analysis):

- The sector directly employed **655,025** people.
- The sector directly and indirectly supported **3.1 million** jobs.
- The personal taxes paid per direct employee averaged **$3,653,** which is **three** times higher than those paid by employees in the rest of the economy.
- The sector's direct, indirect and induced contribution to the U.S. Gross Domestic Product was **$333 billion,** an increase of **$39 billion** since 2006.

States' Perspectives on the Bioscience Sector

> *"The Delaware Biotechnology Institute, an interdisciplinary center for life sciences research at the University of Delaware that was created nearly a decade ago, has rapidly evolved into 'one of the principal economic engines in the State of Delaware.'"*
>
> — DELAWARE BIOTECHNOLOGY INSTITUTE PRESS RELEASE QUOTING SENATOR THOMAS CARPER, 2009

> *"The BIO 2020 Initiative is a comprehensive, targeted plan to leverage Maryland's science and technology assets and nationally acclaimed workforce to attract and grow the bioscience opportunities of tomorrow in Maryland."*
>
> — MARYLAND GOVERNOR MARTIN O'MALLEY, 2008

> *"Work being done in Boulder and Fort Collins and at the Anschutz Medical Campus at Fitzsimons is making Colorado a regional bioscience hub. My administration has made the biosciences one of the focal points of our overall economic development strategy, and by elevating the stature of this crucial industry of the future, we are competing on a national and international level."*
>
> — THEN-COLORADO GOVERNOR BILL RITTER, JR., 2008

Driving State and Regional Economies

Many state governments recognize that the biopharmaceutical industry and the larger bioscience sector are economic engines[14] that generate more than just good jobs. The sector provides valuable tax revenues and additional income for a state's research institutions, hospitals, suppliers, and educational institutions. It also creates a biosciences infrastructure, which results in new medical treatments for citizens of the state.

Biopharmaceutical development often occurs as part of a larger bioscience or life sciences industry cluster. To attract and grow their life sciences sector, some states are using strategies such as building bioscience research capacity, facilitating the availability of early-stage capital, and enacting tax policies to attract and nurture a robust life sciences sector. These clusters can create a collaborative local environment in which startup firms can receive vital public/private support to sustain activity during lengthy product development cycles. In addition, biopharmaceutical companies have access to talent, specialized scientific facilities, clinical research partners to test new products, and public/private partnerships that link companies, researchers and clinicians.

1 Vibrant Innovation: Strengthening the U.S. Economy

Global Leadership

Historically, America has provided a climate that values and encourages investment and entrepreneurialism in the biopharmaceutical sector. Today, much of the pharmaceutical research formerly done in other countries – especially in Europe – is conducted in the United States. In fact, a recent study found that about 64% of research on new medicines approved in the last 10 years was done in this country.[15] In addition, the United States generates 80% of global biotechnology R&D.[16]

While the United States currently is the global leader in biopharmaceutical research, other countries are increasingly seeking to challenge that role. As the U.S. National Economic Council states, "Other countries understand that innovation is fundamental to their economic well-being and are finding new ways to advance their innovation agendas… . Innovation is the key to global competitiveness, new and better jobs, a resilient economy, and the attainment of essential national goals."[17]

Collaborative efforts between the public and private sectors and incentives to

Examples of International Efforts to Attract and Grow the Biopharmaceutical Sector

China

In 2009, the Chinese government earmarked US$9.2 billion for new technology, including biotechnology, to stimulate economic growth.[18] The infrastructure investments were accompanied by other policy changes to foster R&D investment, including the establishment of national hubs and efforts to improve intellectual property protection.

India

The government of India is building more than 20 biotechnology parks throughout the country[19] and allocating US$1.7 billion over five years to grow the country's biotechnology industry.[20] One of the most prominent biotechnology parks in India is the ICICI Knowledge Park in Hyderabad – a world-class center for leading-edge business-driven research in India, including a Life Science Incubator.

Singapore

The government of Singapore launched a biomedical sciences initiative in June 2000 "to develop the Biomedical Sciences cluster as one of the key pillars of Singapore's economy."[21] In 2003, the government of Singapore unveiled a 46-acre bioscience complex. The country's ultimate vision is "to be the Biopolis of Asia, a leading international biomedical sciences cluster advancing human health by achieving excellence across the entire value chain."[22]

European Union

In addition to country-specific efforts throughout the continent, the European Union is implementing a public-private partnership with the European Federation of Pharmaceutical Industries and Associations that seeks to reinvigorate the biopharmaceutical sector in Europe. Over the period of 2008 to 2013, €2 billion (approximately US$2.9 billion) is budgeted to implement a focused and coherent industrial R&D program that "supports collaborative research projects and builds networks of industrial and academic experts in Europe that will boost innovation in healthcare."[23]

Argentina

The Argentine government has identified biotechnology as a critical industry for economic development, as evidenced by such measures as enacting a biotechnology promotion law in 2007 aimed at fostering the development of the biotech industry through a variety of tax and other financial incentives.

> *The first step in winning the future is encouraging American innovation… . In America, innovation doesn't just change our lives. It is how we make our living."*[24]
>
> — PRESIDENT BARACK OBAMA
> STATE OF THE UNION ADDRESS, JANUARY 2011

attract R&D investment and the R&D enterprise are taking place in Europe, Australia, China, India, Singapore, Argentina, Brazil, South Africa, and many other regions. (See box on page 6.) Related strategies include: government funding to support the development of critical R&D infrastructure, such as bioparks, fellowships and other efforts to attract and retain scientists; efforts to support commercialization of R&D; R&D tax credits and reduced corporate tax rates; government-funded venture capital funds; and targeted economic policies.

This underscores a recent statement from the U.S. National Economic Council: "We must redouble our efforts to give our world-leading innovators every chance to succeed. We cannot rest on our laurels while other countries catch up."[25]

Opportunities to Foster Innovation

Accelerating medical advances is good for patients and for our society. As countries around the world are recognizing the opportunities and value of pursuing medical advances, it is

becoming more pressing for the United States to bolster its scientific research environment. U.S. innovation and ingenuity represent our comparative advantage in the global trading arena, and will continue to be essential to America's future prosperity and growth. By embracing positive, proactive policies, the United States could create a more favorable environment for innovation and retain its global leadership position in biopharmaceutical R&D. In order to continue to foster economic growth and the much-needed medical breakthroughs that will save lives and lower overall health care costs, we must continue to pursue public policies that promote innovation, including:

- Strengthening the science base to meet 21st-century challenges.
- Promoting coverage and reimbursement policies that ensure the continued introduction and availability of new medical advances.
- Strengthening the U.S. biosciences infrastructure and increasing U.S. global competitiveness.
- Supporting strong intellectual property rights and enforcement in the United States and abroad.
- Building the 21st-century biosciences workforce to increase U.S. ability to compete globally.

Vibrant Innovation: Strengthening the U.S. Economy

[1] Congressional Budget Office, Research and Development in the Pharmaceutical Industry (Washington, DC: CBO, October 2006).

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[4] Pharmaceutical Research and Manufacturers of America, Medicines in Development for Cancer (Washington, DC; PhRMA, April 2009), www.phrma.org/research/publications/fact-sheets-and-policy-papers (accessed 14 February 2011).

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[6] Pharmaceutical Research and Manufacturers of America, Medicines in Development for HIV/AIDS (Washington, DC; PhRMA, December 2010), www.phrma.org/research/publications/fact-sheets-and-policy-papers (accessed 14 February 2011).

[7] Pharmaceutical Research and Manufacturers of America, Medicines in Development for Rare Diseases (Washington, DC; PhRMA, February 2011), http://www.phrma.org/sites/default/files/878/rarediseases2011.pdf (accessed 14 February 2011).

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[9] Tufts Center for the Study of Drug Development, "Personalized Medicine Is Playing a Growing Role in Development Pipelines," *Impact Report* no. 12 (November/December 2010): 6.

[10] Archstone Consulting and R. L. Burns, The Biopharmaceutical Sector's Impact on the Economy of the United States (Fact Sheet) (Washington, DC: Archstone Consulting, LLC, 2010). Types of direct biopharmaceutical jobs in 2008 are from the U.S. Bureau of Labor Statistics, 2008 Occupational Employment Statistics (NAICS codes 3254 and 54171).

[11] Archstone Consulting and R. L. Burns, *op. cit.*

[12] Export Promotion Cabinet, National Export Initiative, Report to the President on the National Export Initiative: The Export Promotion Cabinet's Plan for Doubling Exports in Five Years (Washington, DC: NEI, September 2010), p.2, www.whitehouse.gov/sites/default/files/nei_report_091510_extended.pdf.

[13] Archstone Consulting and R. L. Burns, *op. cit.*

[14] Battelle Technology Partnership Practice, Driving State Economic Growth in the 21st Century: Advancing the Biopharmaceutical Sector (Columbus, OH: Battelle Memorial Institute, November 2010), http://webstage2.innova-partners.com/~ccunningham/phrma/sites/default/files/159/phrmafinal_report_11_15_2010_.pdf (accessed 14 February 2011).

[15] Pharmaceutical Research and Manufacturers of America analysis of Y. Friedman, "Location of Pharmaceutical Innovation: 2000–2009," Nature Reviews Drug Discovery, 9 (November 2010): 835–836.

[16] Burrill & Co. analysis for PhRMA based on publicly available data, August 2009.

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[23] Innovative Medicines Initiative, "Mission," www.imi.europa.eu/content/mission (accessed 18 February 2011).

[24] President Barack Obama, State of the Union Address, January 2011, www.whitehouse.gov/the-press-office/2011/01/25/remarks-president-state-union-address (accessed 18 February 2011).

[25] National Economic Council, *op. cit.*

2 The R&D Process: Innovation and Collaboration

2

The R&D Process: Innovation and Collaboration

Every day, scientists in the biopharmaceutical industry research the molecular underpinnings of disease, screen compounds against new disease targets, and conduct clinical trials with thousands of patients at locations around the globe. The driving goal of the sector is to find new medicines that improve medical care and address unmet medical needs.

In 2010, despite the challenging economic environment, the sector maintained its strong support for innovation. Biopharmaceutical companies invested an estimated $67.4 billion in the search for new medicines.[1] (See Figure 3, page 11.)

Developing a new medicine is a long and complex process, with many setbacks and challenges. The R&D process is becoming increasingly difficult, expensive, time-consuming and risky, costing $1.3 billion on average.[2]

Researchers are working to find new ways to approach the R&D process to make it more efficient while maintaining the highest safety and efficacy standards. The process is evolving to make use of the latest statistical techniques and research tools.

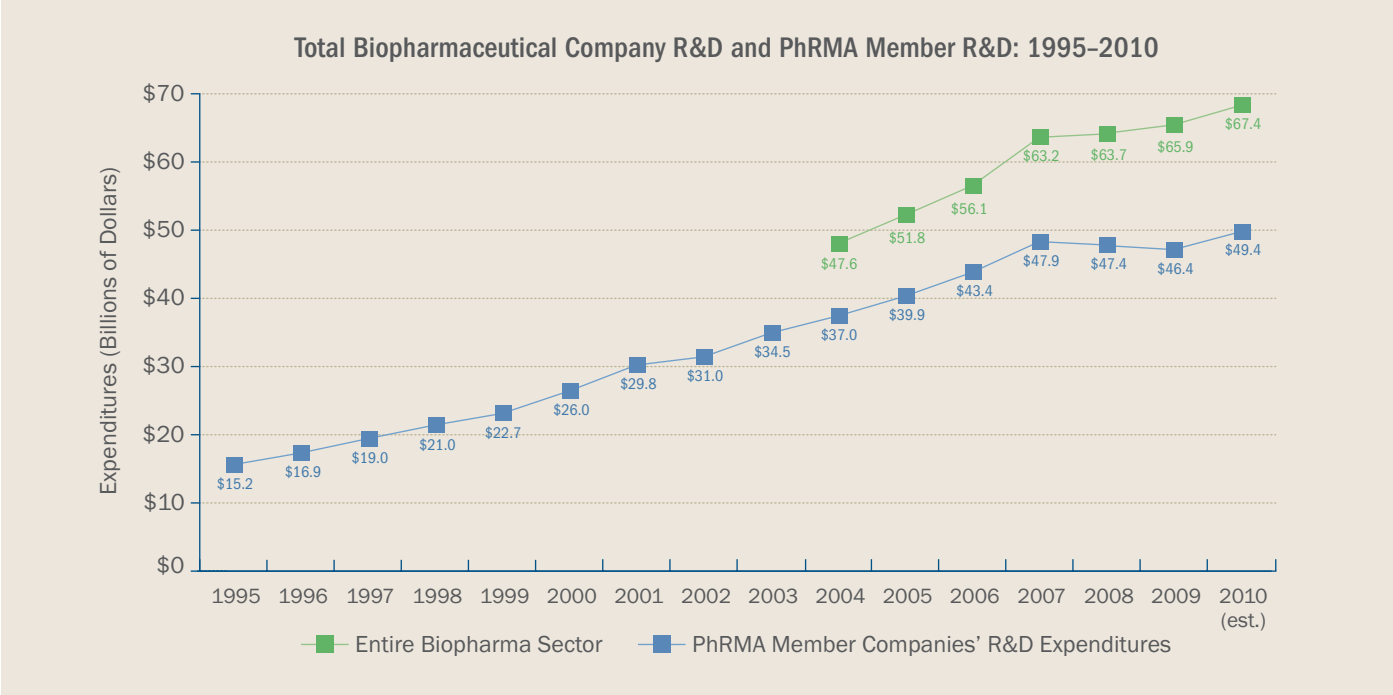
The R&D Process

Only about one in six drug candidates that enter clinical trials are ultimately submitted to and approved by the FDA, according to a study of the 50 largest companies[3] – many candidates fail as late as phase 3 trials. For the small share of drug candidates that do become approved drugs, it takes about 10 to 15 years[4] from the initial discovery to availability for treating patients. The process requires both flashes of inspiration and persistent dedication. Researchers must creatively tackle unforeseen challenges and thoroughly collect data on all aspects of the drug's safety and efficacy. The graphic on page 12 shows the stages that the average drug passes through on the road to approval. (See Figure 4.)

Drug Discovery and Preclinical Testing

Extensive basic research lays the groundwork for understanding the disease to be treated and, if possible, the underlying cause. Researchers may contribute to this work from across sectors, including academic institutions, government labs and biopharmaceutical companies.

FIGURE 3: Biopharmaceutical Company R&D Spending Remains Strong

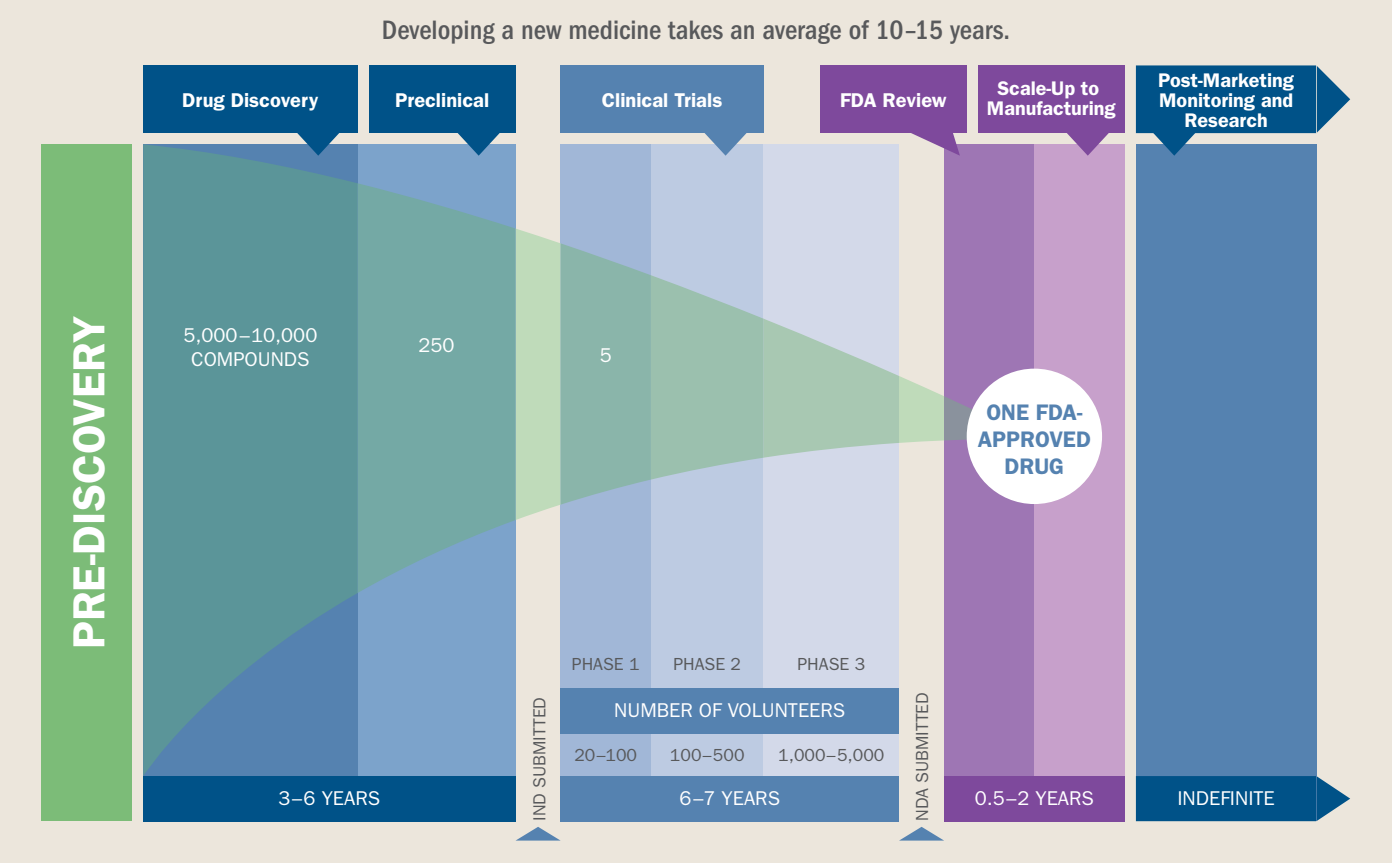


Note: The "Entire Biopharma Sector" figures include PhRMA research associates and nonmembers; these are not included in "PhRMA Member Companies' R&D Expenditures." PhRMA first reported this data in 2004.

SOURCES: Burrill & Co., analysis for PhRMA, 2006–2011 (includes PhRMA research associates and nonmembers); Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey* (Washington, DC: PhRMA, 2011).

2 The R&D Process: Innovation and Collaboration

FIGURE 4: The Research and Development Process



SOURCE: Pharmaceutical Research and Manufacturers of America, Drug Discovery and Development: Understanding the R&D Process, www.innovation.org.

With this knowledge, biopharmaceutical researchers look for a molecule or "lead compound" that may alter the disease course. They may screen compound libraries, develop a molecule from scratch or use some substance from nature as the starting point. After many safety and efficacy tests, they often redesign the most promising compounds to optimize their disease-fighting properties. Often, hundreds of variations are pursued.

The next step is to test the optimized compounds in the laboratory to find the most effective lead with a safety profile that supports initial introduction into humans. Scientists try to determine how a compound works and describe its safety profile.

If the compound appears to be safe and effective, the company submits an Investigational New Drug Application to the FDA to seek approval to begin clinical trials.

Clinical Trials Are Increasingly Complex

A recent report by the Tufts Center for the Study of Drug Development finds that clinical trials are continuing to become more complex and time-consuming.[5] Between 2000–2003 and 2004–2007, the median number of procedures per clinical trial increased by 49%, while the total work burden per protocol grew by 54%.

As complexity increases, so do eligibility criteria for volunteers, leading to lower volunteer recruitment and retention rates. The average number of eligibility criteria for volunteers increased by 58%, and volunteer enrollment and retention rates declined by 21% and 30%, respectively. (See Figure 5.)

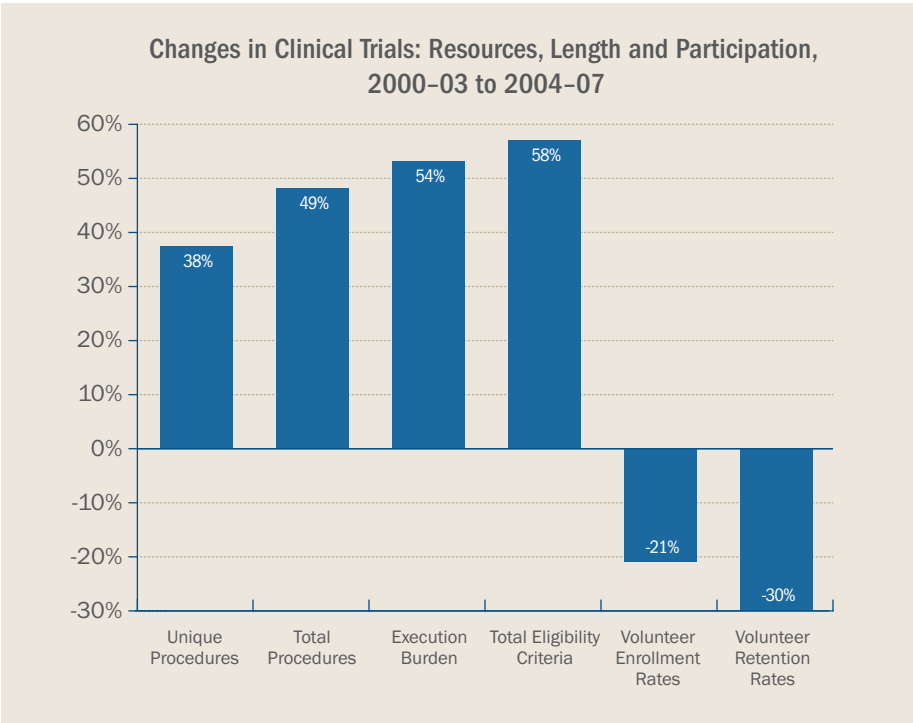
Clinical Trials

A critical part of the R&D process is clinical research, the study of a pharmaceutical product in people. Clinical research involves both potential benefits and potential risks to the participants, and research-based biopharmaceutical companies place great importance on respecting and protecting the safety of research participants, ensuring scientific integrity, and disclosing clinical trial results.

Before a trial begins, researchers develop a protocol, or plan, for the trial, laying out exactly what information they are collecting and how patients' safety will be protected. The clinical trials process lasts an average of six to seven years and usually involves thousands of patients and several different phases of research:

Phase 1 trials (20 to 100 volunteers) – Phase 1 trials are usually performed in healthy volunteers. These studies are designed to determine if a drug is safe

FIGURE 5: Clinical Trials Are Increasingly Complex



Definitions

Procedures:
Including lab and blood work, routine exams, x-rays and imaging, questionnaire and subjective assessments, invasive procedures, heart assessment, etc.

Execution Burden:
Clinical trial staff work burden.

Enrollment Rate:
Percentage of volunteers meeting the increasing number of protocol eligibility criteria (percentage screened who were then enrolled).

Retention Rates:
Percentage of volunteers enrolled who then completed the study; declining retention rates mean that firms must enroll more patients initially and/or recruit more patients during the trial.

SOURCE: Tufts Center for the Study of Drug Development, "Rising protocol complexity, execution burden varies widely by phase and TA," *Impact Report* 12, No. 3 (May/June 2010).

in humans, what the safe dosing range is, and if the drug should move on for further testing.

Phase 2 trials (100 to 500 patients) – In phase 2 trials, researchers study a drug's effectiveness in about 100 to 500 patients with the disease or condition in question, and also identify common, short-term side effects associated with the treatment.

Phase 3 trials (1,000 to 5,000 patients) – Phase 3 trials study a drug in a much larger patient population and allow researchers to collect data on a drug's safety and efficacy for the evaluation of the overall benefit-risk profile of the treatment for a particular patient population. Phase 3 trials are the longest trials, and often take place in literally hundreds of sites across the United States and throughout the world.

New Drug Application/ Biologic License Application

If clinical trial findings indicate that a drug is both safe and effective, the company files a New Drug Application (NDA) or a Biologic License Application (BLA) with the FDA to request the medicine be reviewed for approval. The FDA reviews the application, which can run 100,000 pages or more, to assess the data from all testing done since the beginning of the process. The FDA uses these data to determine whether a drug or biologic's benefits outweigh any risks, what information should be included in the medicine's labeling, and whether the proposed manufacturing process is appropriate.

Post-Approval Research and Monitoring

Research does not end with FDA approval. Companies continue to monitor the safety of the product as long as it is available to patients, and often research new potential benefits of the medicine in other disease areas or patient populations.

For the entire life of the medicine, teams of scientists and physicians collect safety data on a daily basis and report potential problems to the FDA. For example, the FDA requires:

- Reports on safety issues every three months for the first three years after approval; annual reports as long as the medicine is marketed.

The biopharmaceutical industry is the most R&D-intensive manufacturing sector in the country.[6] (See Figure 6.) In the last five years, these companies have invested $316 billion on research and development of new medicines."[7]

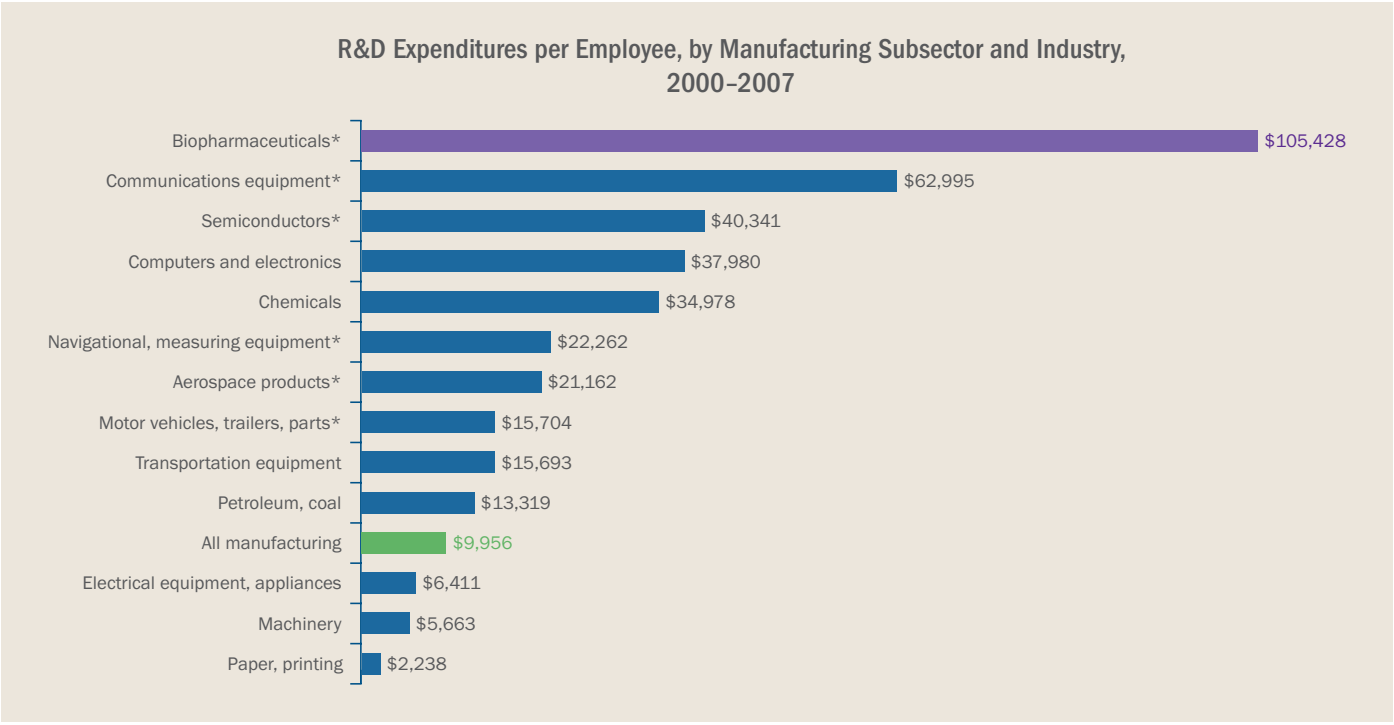
- Adverse events reports within 15 days of event (seven days for a life-threatening event).

As a result of new authorities granted to the FDA in 2007, the agency may require companies to create and conduct a Risk Evaluation and Mitigation Strategy (REMS) to manage any potential risks following approval. For example, this may involve setting special criteria for prescribing the medicine or requiring physician training on its use. Congress has provided specific funding for the FDA's post-approval safety monitoring and directed the FDA to continuously upgrade its efforts.

In addition, the FDA may require companies to conduct "phase 4" studies as a condition of approval to evaluate the long-term safety and effectiveness of a medicine or its effects on a subset of patients.

Companies often also continue to research expanded uses and benefits of a medicine after approval, leading to growing understanding of the full benefits of a given treatment. For instance, the medicine may be able to be used earlier in the disease process,

FIGURE 6: **The Biopharmaceutical Sector is the Most R&D-Intensive in the U.S.**



* Manufacturing subsectors.

SOURCE: Adapted from N. D. Pham, "The Impact of Innovation and the Role of Intellectual Property Rights on U.S. Productivity, Competitiveness, Jobs, Wages, and Exports" (Washington, DC: NDP Consulting, 2010).

2 The R&D Process: Innovation and Collaboration

for different diseases, in combination with another medicine, or in combination with specific biomarkers to better predict response to treatment. As research accumulates after approval, new benefits of a medicine are identified.

Advancing R&D Methods

Research and development of new medicines is not a static process. Researchers are always looking for new and better ways to innovate. As the process has become more complex, expensive, and time-consuming in recent years, researchers have redoubled their efforts to improve the R&D process. They are using new technologies and more sophisticated methods for analyzing data to make the process more efficient while still maintaining the highest safety standards.

According to the Tufts Center for the Study of Drug Development, companies are developing "new approaches to designing and conducting global clinical trials, including simplifying protocols, maximizing investigative site performance, and reducing the number of protocol amendments."[8]

In some cases, restructured trials are helping researchers to gather as much information as possible in the earliest stages and to eliminate compounds that are more likely to fail only after longer, more expensive trials. For example, phase 0 or "microdosing" trials allow researchers to test a very small dose in fewer human volunteers to quickly eliminate drug candidates that are metabolically or biologically ineffective.

A Vibrant Ecosystem of Innovation

The collaborative research ecosystem that exists in the United States among government, academia, and biopharmaceutical companies is one of our country's greatest strengths in moving medical advances forward, and makes the United States the worldwide leader in biopharmaceutical innovation.

In 2010, the National Institutes of Health (NIH) invested more than $31 billion,[9] primarily in basic research, to lay the foundation for medical advances throughout the country. This funding supports important work in universities, medical schools, nonprofit research centers, and government labs.

While small and large companies in the biopharmaceutical industry contribute significantly to basic research, they also conduct the majority of drug discovery and development work to translate the understanding achieved through basic research into medicines that patients can use. In 2010, the biopharmaceutical sector spent $67.4 billion on R&D.[10]

This dynamic, collaborative ecosystem has improved the lives of patients in the United States and around the world.

Partnerships for Collaborative Progress

As scientists have probed more deeply into the causes and signs of disease, the amount of information that is available has greatly increased, but making sense of all this data is a colossal undertaking that no single individual or, increasingly, no single institution can handle alone.

As a result, biopharmaceutical companies are working together with other companies, universities, and the government to share, organize and make sense of huge volumes of information that hold the promise of moving science forward in unparalleled ways. They are working together in innovative ways to share information that once was considered proprietary, with a common goal to advance progress against disease. For example,

- **Sharing results of "failed" clinical trials.** Research that does not lead to an approved medicine can still offer important information. To advance scientific knowledge, some clinical trial sponsors are now sharing their results with other organizations that are undertaking similar endeavors. For example, in an effort to learn from unsuccessful Alzheimer's disease treatment studies, one collaboration of industry and government partners recently launched a shared database.[11] The partner organizations will provide the results of failed clinical trials in the area of Alzheimer's and other neurodegenerative diseases with the goal of accelerating research. Future plans call for similar partnerships regarding Parkinson's disease and tuberculosis.
- **Collaborating in discovery.** Making progress using cutting-edge scientific knowledge and techniques is highly resource intensive. Combining resources to scale up or speed up research can play a crucial role in overcoming key scientific challenges and spurring more rapid progress. For example, a public/private partnership among the NIH, the Foundation for NIH, PhRMA, FDA, and others is working to discover and validate biomarkers (molecular, biological, or physical characteristics that help identify risk of disease, make a diagnosis, or guide treatment). This work is foundational to advancing personalized medicine, but no single organization has the resources to undertake it alone. This partnership has already made important findings, such as the discovery in 2009 of adiponectin as a predictive biomarker for Type 2 diabetes.[12]

Some of the other objectives of current industry/academic partnerships include: testing of innovative compounds with potential for treating cancer, metabolic diseases, and neurologic diseases; collaborating on developing new treatments for specific diseases such as tuberculosis, schizophrenia, and depression; and finding new uses for existing compounds.

2 The R&D Process: Innovation and Collaboration

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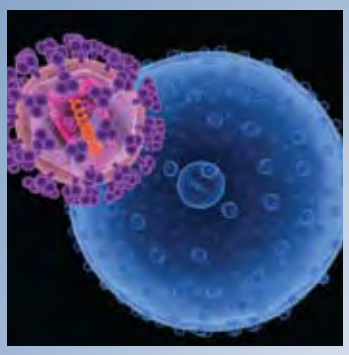
3 New Medicines: Impact on Health and Health Care Costs



New Medicines: Impact on Health and Health Care Costs

Biopharmaceutical research companies work to harness scientific potential to improve the lives of patients. Prescription medicines have dramatically enhanced life for many people by preventing diseases, enhancing quality of life, reducing disability, slowing disease progression, and extending life. By improving health and preventing the need for costly surgeries, hospital visits, and nursing home stays, medicines can help control health care costs and, in many cases, save money.

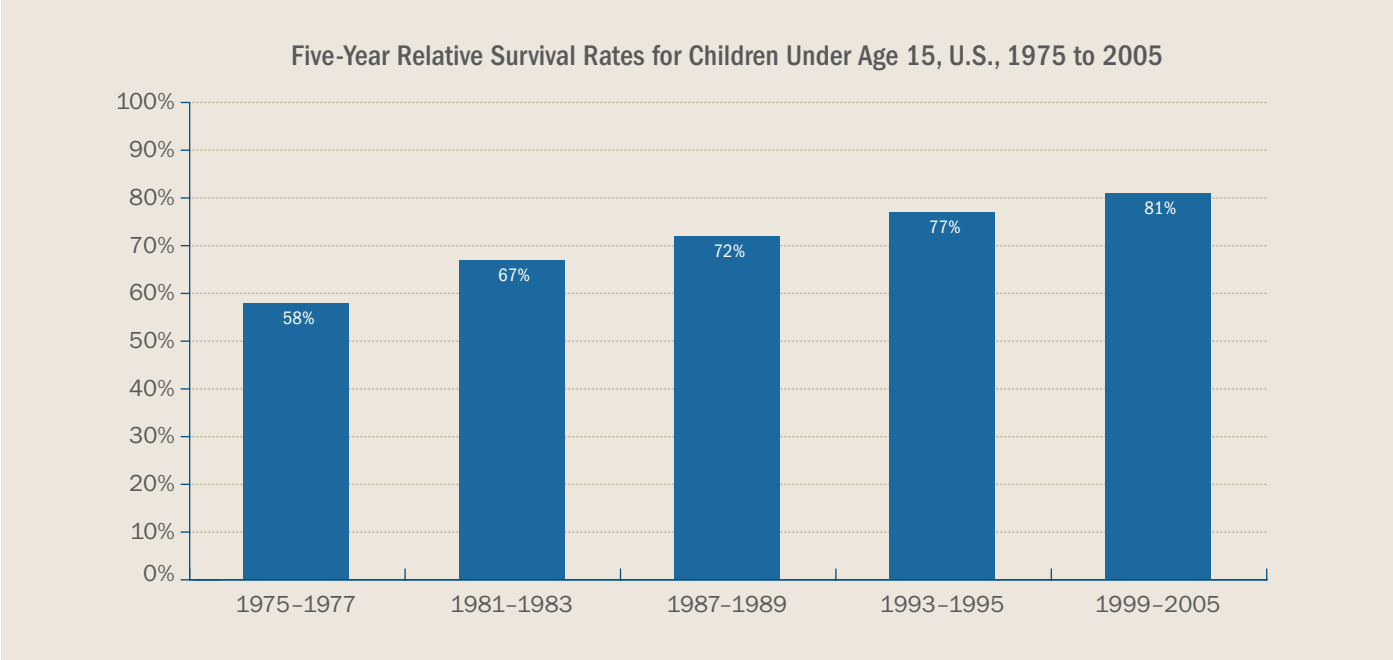
In the last 10 years, 300 new medicines have been approved.[1] They are transforming many cancers into treatable conditions, improving the treatment of patients with cardiovascular disease, offering new options for patients with hard-to-treat diseases like multiple sclerosis and schizophrenia, and fighting even the rarest conditions.

Expanded Treatment Options

In 2010, 21 new medicines[2] improved life and expanded treatment options for patients. For example:

- **Two new treatments for multiple sclerosis (MS):** The first treatment to help improve walking for adults with MS[3] and the first oral drug to reduce relapses and delay disability progression in MS patients.[4]
- **New treatments for prostate cancer:** The first treatment for advanced, hormone-refractory prostate cancer that has worsened with another standard treatment,[5] and the first cancer immunotherapy for certain men with advanced prostate cancer that stimulates their own immune system to fight the disease. Developed specifically for each patient, the treatment is made by obtaining a patient's immune cells from the blood using a process known as leukapheresis, then activating the cells to specifically target cancer cells in the patient.[6]
- **New injectable osteoporosis medicine:** A first-in-class,[7] twice-a-year medicine that works to decrease the destruction of bone and increase bone mass and strength.[8]
- **New treatment to prevent stroke:** The first new oral anticoagulant in 50 years indicated to prevent stroke and blood clots in patients with abnormal heart rhythm.[9]

FIGURE 7: Childhood Cancer Survival Rates Increasing



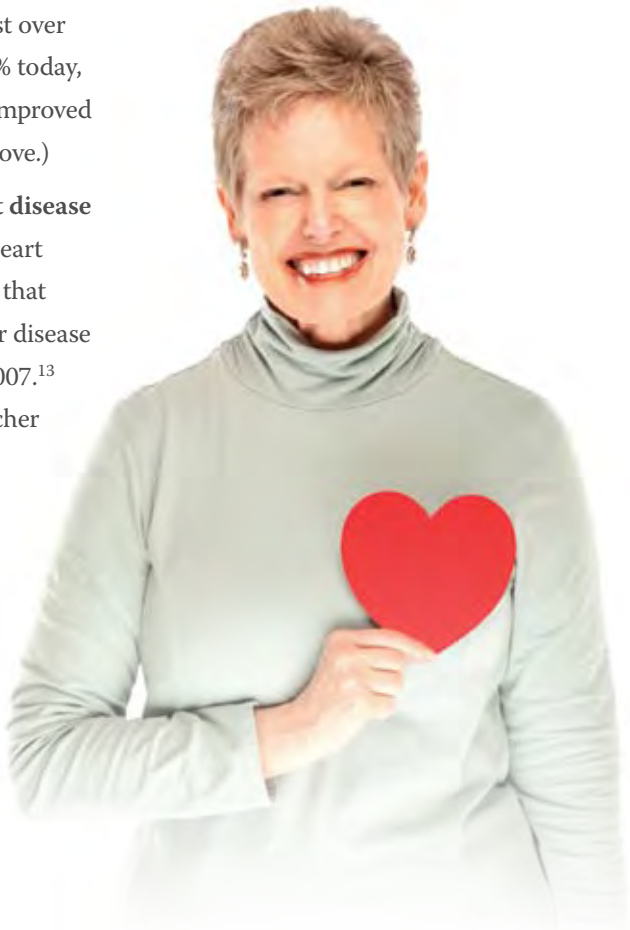
SOURCE: A. Jemal, *et al.*, "Cancer Statistics, 2010," *CA: A Cancer Journal for Clinicians,* published online, 7 July 2010, http://caonline.amcancersoc.org/cgi/content/full/caac.20073v1.

Better Outcomes

In recent decades, better prevention and new medicines have contributed significantly to greater longevity and reduced death and disability.

Since 1950, life expectancy for men and women in the United States has increased by nearly a decade. In 1950, men could expect to live to 66 years, and women 71 years.[10] In 2007, life expectancy rose to 75 years for men and 80 years for women.[11] Life expectancy is continuing to rise as survival rates from many diseases improve. For example:

- **Increasing survival rates for childhood cancers.** The chance of survival for children with cancer is up 40% in the last 35 years. For all childhood cancers combined, the percentage of children surviving five years after diagnosis has grown from just over half in 1975 to more than 80% today, due in large part to new and improved treatments.[12] (See Figure 7 above.)
- **Reducing deaths from heart disease and stroke.** The American Heart Association (AHA) reported that death rates for cardiovascular disease fell 28% between 1997 and 2007.[13] According to the lead researcher of another AHA report, an additional 190,000 deaths would have occurred in 2006 if death rates had remained at 1999 levels.[14]



3 New Medicines: Impact on Health and Health Care Costs

> *"I've been doing drug development for a little more than a decade across a lot of therapeutic areas and without a doubt, the most rewarding day in my career was when I saw individuals who had suffered from the disease, …talking about how important that drug was to them, to their families and that's why I'm in this business. That's why I do what I do."*
>
> — MARK WEINBERG, M.D., MBA,
> VICE PRESIDENT, MEDICAL STRATEGY, LUNDBECK INC.

- **Reducing death from HIV/AIDS.** Since the approval of the antiretroviral treatments (ART) in 1995, the U.S. AIDS death rate has dropped by more than 75%.[15]

In addition to addressing these major public health concerns, advances in scientific knowledge have also led to greater potential to invent medicines for orphan diseases, which are defined by their rarity, each affecting fewer than 200,000 Americans.[16] There are 6,000 to 7,000 rare diseases,[17] and an estimated 85% to 90% of those are serious or life threatening.[18]

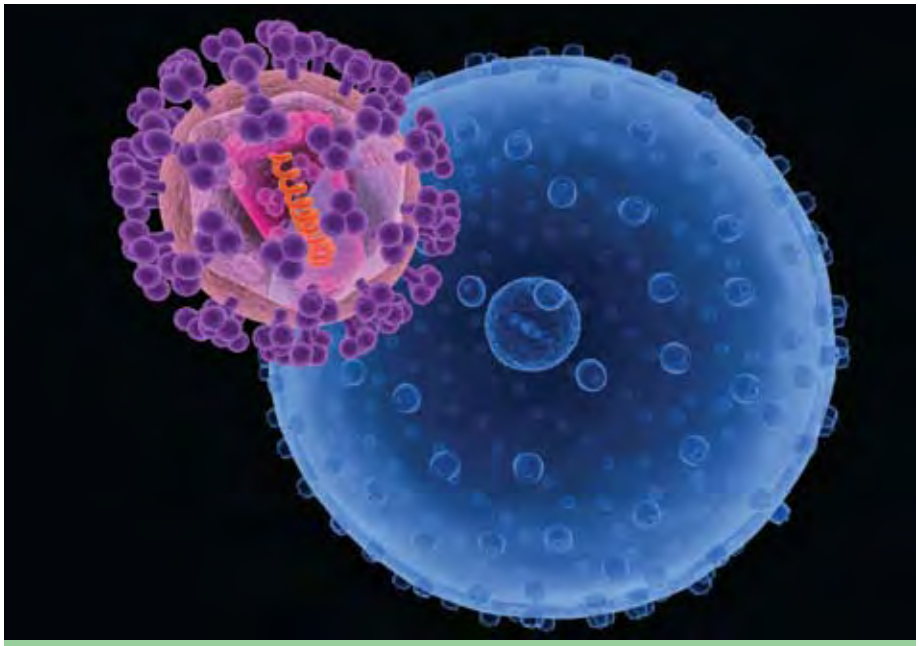
Since the passage of the Orphan Drug Act in 1983, 350 drugs for orphan diseases have received FDA approval.[19] These include:

- The first treatment for ALS, also known as Lou Gehrig's disease.
- Five new treatments for pulmonary hypertension.
- A genetically engineered antibody that is the first treatment for Crohn's disease.
- The first medicine that treats the cause of Fabry disease, rather than its symptoms.
- The first in a new class of medicines to treat acromegaly, a disorder in which excess growth hormone causes enlarged hands feet and facial features, by specifically blocking the effects of excess growth hormone.

Prevention and Reducing Disease Burden

Medicines are a powerful tool for preventing disease progression and complications and the costly care that goes along with them. Such prevention improves clinical outcomes and quality of life for patients, who can remain active and productive.

- **Reducing the risk of fractures in osteoporosis.** Patients who are over 80% adherent to their osteoporosis medicines have a 16% lower rate of fractures compared with those who are less adherent.[20] Patients who are highly compliant cut their risk of fracture by 25%. Those who are the least adherent have a 40% increased risk.
- **Preventing diabetes hospitalizations.** Patients who are less than 80% adherent to their diabetes medicines are two to three times more likely to be hospitalized in the next year compared with patients who are more adherent.[21]
- **Preventing HIV transmission.** A recent study reported in *The Lancet* and carried out in Africa found that initiation of ART reduces the risk of transmission from an infected individual to his or her sexual partner by 92%.[22]



HIV/AIDS: Major Advances — and Savings — Over Time

We have come a long way in recent years in many disease areas, and in addition to saving lives, new advances have helped prevent runaway costs. HIV/AIDS provides a dramatic example.

Before the advent of effective treatments, the prognosis for patients diagnosed with AIDS was grim. Life expectancy was measured in months, during which time patients would be likely to contract a number of opportunistic infections, making their remaining days unpleasant and painful.

In addition, AIDS was very expensive, with repeated hospitalizations a major cost driver. In 1985, it cost the U.S. Army an estimated $500,000 to treat each AIDS patient in its care, and experts warned that the disease had "the potential to bankrupt the system."[23]

Today, ART's are able to save and improve lives while preventing costly hospitalizations. One study reported that hospitalization rates fell by 32% between 1996 and 2000, despite the fact that the number of people with HIV increased by 28% (primarily because of rising survival rates).[24]

In addition to direct savings in health care spending, the societal value is great. University of Chicago economists report that the aggregate value of improved survival resulting from new medicines since the start of the HIV/AIDS epidemic and into the future is $1.4 trillion. Each patient with HIV now lives 15 years longer than they would have in the 1980s.[25]

- **Decreasing disability among seniors.** A 2008 study by Harvard University researchers found that between 1984 and 2004–2005, disability in the elderly population fell by 20%.[26] For cardiovascular disease, the researchers reported that medicines and other treatments increased by 50% the chances that an elderly patient would survive a cardiovascular event without becoming disabled.

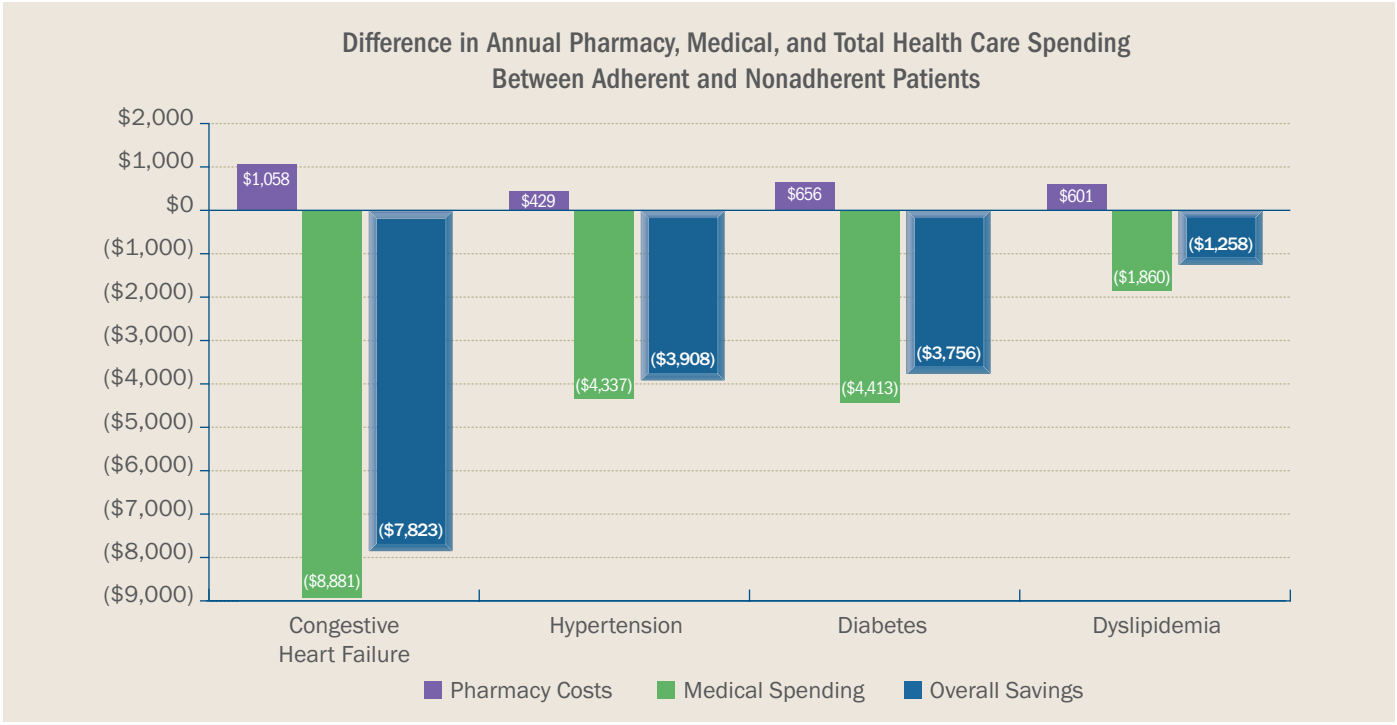
Managing Costs

Because of their role in preventing diseases, slowing progression and averting complications, medicines can reduce the need for costly medical care. When taken appropriately, they can help control health care costs or, in many cases, save money.

A recent study found that adherence to medicines leads to lower total health care costs for commercially insured patients with congestive heart failure,

3 New Medicines: Impact on Health and Health Care Costs

FIGURE 8: Patients Adhering to Their Medicines Have Lower Health Care Costs



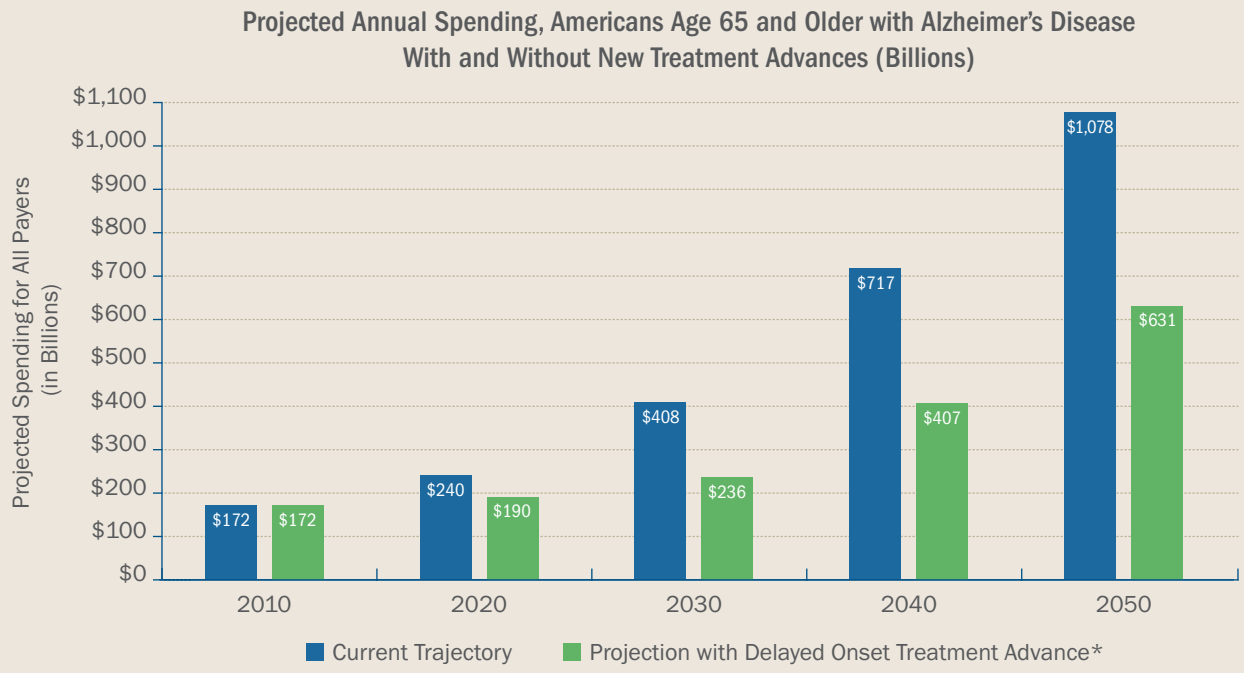
SOURCE: M. C. Roebuck, *et al.*, "Medication Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending," *Health Affairs* 30 no. 1 (January 2011): 91–99.

hypertension, diabetes, or dyslipidemia (lipid disorders including high cholesterol).[27] After accounting for increased pharmacy costs, patients with congestive heart failure who were adherent to their medicines reduced their total annual health care spending by $7,823. Similarly, adherent patients with hypertension saved $3,908, while adherent diabetes patients saved $3,756, and adherent dyslipidemia patients saved $1,258. (See Figure 8 above.)

Medicines can lead to savings in other disease areas as well:

- **Asthma.** Appropriate use of asthma medicines reduced both the severity of asthma and annual costs per patient. Annual savings per patient exceeded the costs of the intervention that increased proper medicine use by almost 11 to one.[28]
- **Parkinson's Disease.** Patients who did not take their medicines as prescribed had more hospital and office visits and used more ancillary services than adherent patients. On average, 12-month total health care costs for the nonadherent group exceeded those of adherent patients by $2,383.[29]

FIGURE 9: New Alzheimer's Medicines Could Save Billions



*Assumes research breakthroughs that delay the average age of onset of Alzheimer's disease by five years beginning in 2010.
SOURCE: Alzheimer's Association, "Changing the Trajectory of Alzheimer's Disease: A National Imperative" (May 2010).

The Potential of Innovation: Alzheimer's Medicines Could Change the Future

Alzheimer's disease (AD) takes a terrible human toll, robbing patients of their identity and their independence. With the aging population, this individual tragedy will become a growing burden on our country.

A new report from the Alzheimer's Association examines the future impact of AD on the U.S. health care system and the potential impact of new treatments.[30] The study finds that on the current trajectory, AD in adults over age 65 will cost $1 trillion per year by 2050. Medicare spending on AD will rise 600%, while costs to Medicaid, other payers and patients will each rise 400%. The number of patients with AD will increase from 5.1 million today to 13.5 million in 2050.

The development of new disease-modifying treatments could change that trajectory. A new treatment that delays the onset of disease by five years would push back the growth in new cases, reducing the number of people with the disease by 43% and saving $447 billion a year by 2050. A treatment that slows the progression of AD by five years would reduce the number of people in the severe stage of the disease by more than 80% and save $197 billion a year by 2050. (See Figure 9 above.)

3 New Medicines: Impact on Health and Health Care Costs

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4 Access: Making Medicines Available to Those in Need

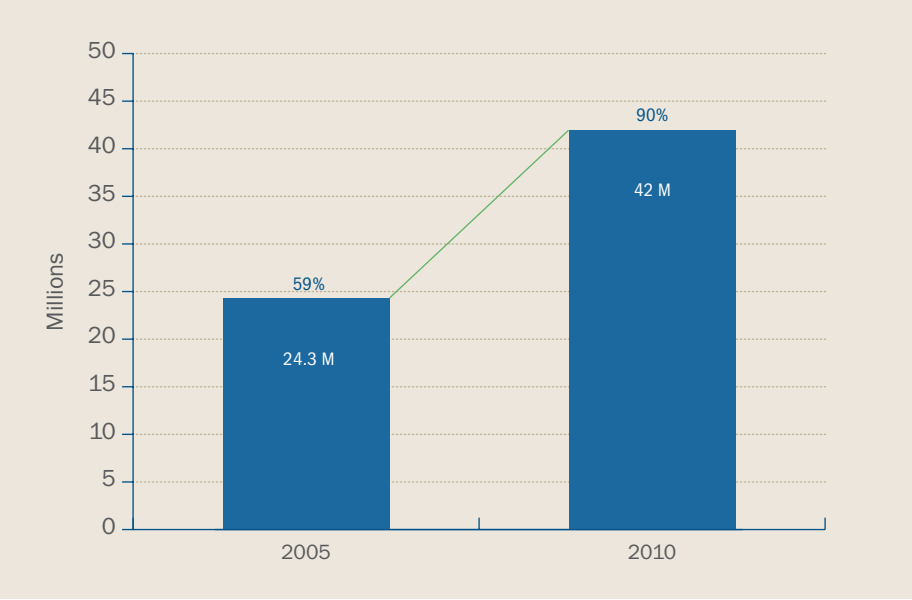
4

Access: Making Medicines Available to Those in Need

Prescription medicines cannot benefit patients if they do not reach the patients who need them. The research-based biopharmaceutical industry supports and directly provides expanded patient access to medicines as part of its commitment to making sure that medicines are available to all those who need them for prevention and treatment of disease.

Biopharmaceutical research companies have supported policies and programs to help people access the medicines they need. For instance, in 2010, the biopharmaceutical sector, along with a range of patient and provider organizations, supported the passage of the Patient Protection and Affordable Care Act (PPACA), which makes strides toward greater access while recognizing the need for significant changes to the law prior to full implementation.

FIGURE 10: More than 90% of People with Medicare Now Have Comprehensive Drug Coverage



Note: Many Medicare beneficiaries had limited drug coverage through Medigap and Medicare Advantage plans in 2005 (high deductibles, high copayments; annual benefit limits). Because these Medigap and Medicare Advantage plans did not offer comprehensive drug coverage, they are excluded in 2005. Drug coverage data obtained from several sources including: CMS, Current Population Survey, Kaiser State Health Fact Sheets, and National Conference of State Legislatures.

SOURCE: The Lewin Group, September 2006; CMS, Medicare Advantage, Cost, PACE, Demo, and Prescription Drug Plan Contract Report – Monthly Summary Report (Data as of February 2010).

The Medicare prescription drug coverage program has greatly increased seniors' access to medicines in recent years, and medicines are becoming more affordable for seniors as a result of health care reform. Access to medicines also continues to be provided through companies' patient assistance programs and the Partnership for Prescription Assistance (PPA), an industry effort that helps patients in financial need connect with company-sponsored and other programs providing free or low-cost prescription medicines.

Medicare Part D

More than 90% of people with Medicare now have comprehensive drug coverage, about 27 million of them through Part D prescription drug benefit plans first introduced in 2006.[1] (See Figure 10, page 28). During the five succeeding years, previously uninsured individuals who enrolled in Part D have markedly increased their access to medicines. For example, the average number of brand and generic prescriptions filled monthly

for this group has increased from 1.7 to 3.5 under the prescription drug program,[2] with a large majority reporting that Part D has resulted in lowering their overall spending on medications.[3] One study notes that Part D has increased coverage "especially for those who need it most."[4] In particular, the number of prescriptions filled for chronic diseases has gone up.[5]

At the same time, the cost profile for Medicare beneficiaries keeps getting better. In 2011, 99% of Part D enrollees will have access to a plan that costs about the same as or less than their 2010 premiums.[6] In addition, federal spending on Part D is far below initial projections. According to the 2010 Medicare Trustees Report, total Part D costs have declined by 41%, or $261 billion, compared with the initial 10-year cost estimate for 2004 to 2013.[7]

In addition, the PPACA includes provisions that reduce the amount eligible beneficiaries must pay for prescriptions when they enter the Part D coverage gap. Beginning in 2011, America's biopharmaceutical research firms will provide a 50% discount on brand-name medicines to beneficiaries who enter the coverage gap. The law phases out the "donut hole" completely in 2020.[8]

Access: Making Medicines Available to Those in Need

Vital Effects: Reduced Costs for Medicare Part D Beneficiaries

Recent peer-reviewed and academic literature confirms the Medicare prescription drug benefit has substantially reduced out-of-pocket costs and increased access to medicine for beneficiaries:

> *An enrollee who moves from paying cash to buying through Medicare Part D pays 24% less for branded prescriptions… .”*[9]
>
> — NATIONAL BUREAU OF ECONOMIC RESEARCH WORKING PAPER

> *[Our] estimates of the overall effect of Part D – an approximate 13.1% decrease in expenditures and an approximate 5.9% increase in prescription utilization – are remarkably similar to other predictors of these estimated based on economic theory.”*[10]
>
> — *ANNALS OF INTERNAL MEDICINE*

> *We estimate that Medicare Part D reduced user cost among the elderly by 18.4 percent, [and] increased their use of prescription drugs by about 12.8 percent… .”*[11]
>
> — *HEALTH AFFAIRS*

The Partnership for Prescription Assistance

The PPA offers financially struggling patients a single point of access to 475 patient assistance programs, almost 200 of which are sponsored by biopharmaceutical companies. More than 2,500 brand-name and generic medicines are available through these programs.

Since its launch in April 2005, the PPA has helped connect more than 6.7 million people to company-sponsored and public programs that provide free or low-cost prescription medicines. The PPA is sponsored by America's biopharmaceutical research companies, who partner with many other health care organizations. Examples include the American Academy of Family Physicians, the American Cancer Society, the American College of Emergency Physicians, Easter Seals, the National Association of Chain Drug Stores, United Way and the Urban League.

Access: Making Medicines Available to Those in Need

[1] Medicare Payment Advisory Commission, A Data Book: Healthcare Spending and the Medicare Program (Washington, DC: MedPAC, June 2010), www.medpac.gov/documents/jun10databookentirereport.pdf (accessed 16 February 2011).

[2] Verispan Longitudinal Data, Amundsen Analysis for PhRMA, May 2008.

[3] KRC Research for Medicare Today, Seniors' Opinions About Medicare Rx: Fifth Year Update (Washington, DC: KRC, September 2010), www.medicaretoday.org/pdfs/KRC%20Medicare%20Today%20Survey%20of%20Seniors%20with%20Medicare%20Rx%202010%20FINAL.pdf.

[4] University of Michigan News Service, "Most Seniors Now Have Drug Coverage UM Study Shows," press release, 9 August 2007.

[5] S. Soumerai, *et al.,* "Cost-Related Medication Non-Adherence Among Elderly and Disabled Patients," *Archives of Internal Medicine* 166 (2006): 1829–1835.

[6] E. P. Walker, "Medicare Part D Premiums Going Up by $1 in 2011," MedPage Today, 19 August 2010.

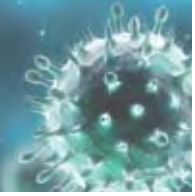
[7] J. Reichard, "CMS: Drug Premiums Just a Buck More Next Year and Benefits Will Improve Too," CQ Healthbeat News, 18 August 2010; The Pink Sheet Daily, "Part D Cost Estimate Drops To $373 Bil. Over 10 Years," 18 August 2010.

[8] Patient Protection and Affordable Care Act, Public Law No. 111-148.

[9] M. G. Duggan and F. M. Scott Morton, "The Effect of Medicare Part D on Pharmaceutical Prices and Utilization," NBER Working Paper No. W13917, April 2008.

[10] W. Yin, *et al.,* "The Effect of the Medicare Part D Prescription Benefit on Drug Utilization and Expenditures," *Annals of Internal Medicine* 148, no.3 (2008): 1–14.

[11] F. Lichtenberg and S. X. Sun, "The Impact of Medicare Part D on Prescription Drug Use by the Elderly," *Health Affairs* 26, no. 6 (2007): 1735–1744.



Vital Effects for People and Prosperity

The ongoing economic downturn has created challenges for all businesses, and the research-based biopharmaceutical sector is no exception. In addition, the United States faces competition from other countries to attract the jobs and economic growth that come with the life sciences sector. Adding to these challenges, the R&D process itself has become more and more complex and costly in recent years, making the already difficult task of developing new medicines harder still.

Despite these and other challenges, the U.S. biopharmaceutical sector remains the strongest in the world. America's biopharmaceutical research companies' commitment to developing groundbreaking new therapies remains strong. In 2010, this sector invested $67.4 billion in researching and developing more than 3,000 new medicines.

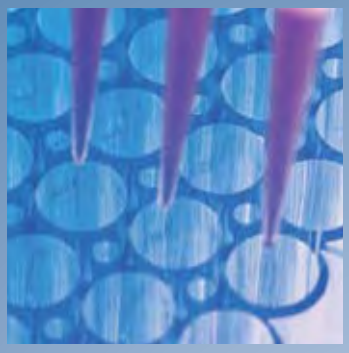
Currently, America continues to lead the world in discovering and developing innovative medicines that are improving health care and helping patients to live longer, healthier and more productive lives. According to the Tufts Center for the Study of Drug Development, a staggering 75% of all new drugs approved worldwide from 2005 to 2007 were first introduced in the United States.[1]

In addition to saving lives, this research investment and continued discovery of newer, more effective medicines supports millions of American jobs and pumps billions of dollars into our nation's economy. Thousands of biopharmaceutical scientists work tirelessly to discover the next medical advances.

Dynamic biopharmaceutical research produces vital effects for people and prosperity, saving lives, improving quality of life, and invigorating the economy. In light of today's scientific opportunities, the potential has never been greater. At the same time, continued medical progress cannot be taken for granted. Continued innovation, and the high-risk, long-term investments it requires, needs to be nurtured by a regulatory environment and public policies that encourage such research. Fostering a strong environment for continued biopharmaceutical R&D will yield tremendous benefits for patients, for health care, and for the economy as a whole.

[1] Tufts Center for the Study of Drug Development, "The U.S. Remains Preferred Market for Launching New Products," press release, 12 November 2008, http://csdd.tufts.edu/files/uploads/12_-_nov_12,_2008_-_trends_-_final.pdf.

Appendix



PhRMA Member Companies

Members

Abbott
Abbott Park, IL

Amgen Inc.
Thousand Oaks, CA

Astellas Pharma US, Inc.
Deerfield, IL

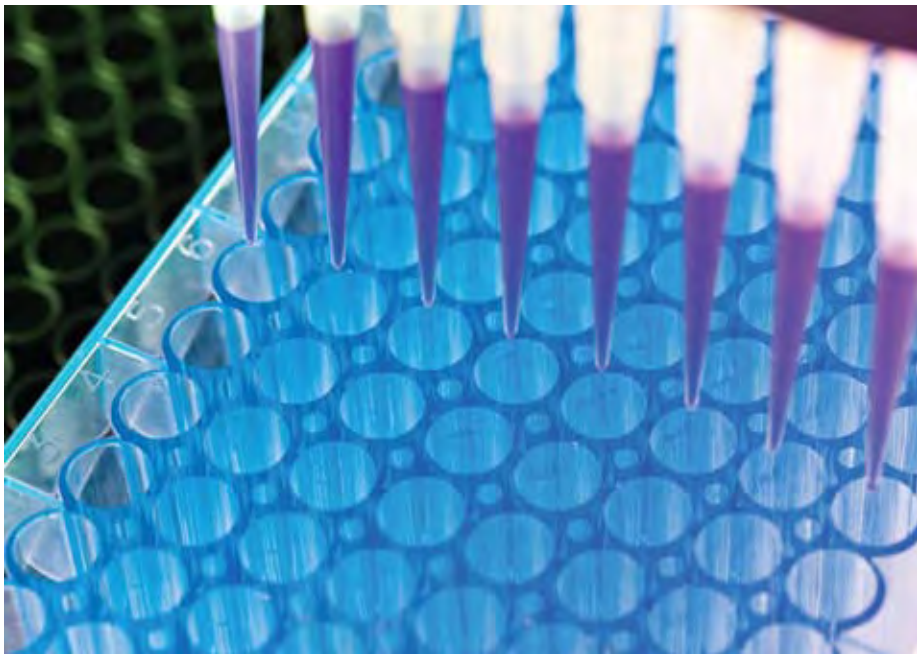
AstraZeneca Pharmaceuticals LP
Wilmington, DE

Bayer HealthCare Pharmaceuticals
Wayne, NJ

Biogen Idec Inc.
Cambridge, MA

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT

Bristol-Myers Squibb Company
New York, NY
Bristol-Myers Squibb Company
Worldwide Medicines Group



Celgene Corporation
Summit, NJ

Cubist Pharmaceuticals, Inc.
Lexington, MA

Daiichi Sankyo, Inc.
Parsippany, NJ

Dainippon Sumitomo Pharma Co., Ltd.
Osaka, Japan
Sunovion Pharmaceuticals Inc.
Marlborough, MA

Eisai Inc.
Woodcliff Lake, NJ

EMD Serono
Rockland, MA

Endo Pharmaceuticals, Inc.
Chadds Ford, PA

Genzyme Corporation
Cambridge, MA

GlaxoSmithKline
Research Triangle Park, NC

Johnson & Johnson
New Brunswick, NJ

Eli Lilly and Company
Indianapolis, IN

Lundbeck Inc.
Deerfield, IL

Merck & Co., Inc.
Whitehouse Station, NJ
- Merck Human Health Division
- Merck Research Laboratories
- Merck Vaccine Division

Novartis Pharmaceuticals Corporation
E. Hanover, NJ

Novo Nordisk, Inc.
Princeton, NJ

Otsuka America Pharmaceutical (OAP)
Princeton, NJ
- Otsuka America Pharmaceutical, Inc.(OAPI)
- Otsuka Pharmaceutical Development & Commercialization, Inc. (OPDC)
- Otsuka Maryland Medicinal Laboratories (OMML)

Pfizer Inc.
New York, NY

Purdue Pharma L.P.
Stamford, CT

sanofi-aventis U.S.
Bridgewater, NJ
- sanofi pasteur
- sanofi-aventis

Sigma-Tau Pharmaceuticals, Inc.
Gaithersburg, MD

Takeda Pharmaceuticals North America, Inc.
Deerfield, IL

Research Associate Members

Alexion Pharmaceuticals Inc.
Cheshire, CT

Alkermes, Inc.
Waltham, MA

Arena Pharmaceuticals, Inc.
San Diego, CA

Depomed, Inc.
Menlo Park, CA

Ferring Pharmaceuticals, Inc.
Parsippany, NJ

Helsinn Therapeutics (U.S.), Inc.
Bridgewater, NJ

Horizon Pharma, Inc.
Northbrook, IL

Ikaria, Inc.
Clinton, NJ

Inspire Pharmaceuticals, Inc.
Raleigh, NC

Orexigen Therapeutics, Inc.
La Jolla, CA

Sucampo Pharmaceuticals, Inc.
Bethesda, MD

Talecris Biotherapeutics
Research Triangle Park, NC

Theravance, Inc.
South San Francisco, CA

United Therapeutics Corporation
Silver Spring, MD

Vertex Pharmaceuticals, Inc.
Cambridge, MA

Vifor Pharma
Basking Ridge, NJ

Xoma Ltd.
Berkeley, CA

PhRMA Annual Member Survey Definition of Terms

Research and Development Expenditure Definitions

R&D Expenditures: Expenditures within PhRMA member companies' U.S. and/or foreign research laboratories plus research and development (R&D) funds contracted or granted to commercial laboratories, private practitioners, consultants, educational and nonprofit research institutions, manufacturing and other companies, or other research-performing organizations located inside/outside of the U.S. Includes basic and applied research, as well as developmental activities carried on or supported in the pharmaceutical, biological, chemical, medical, and related sciences, including psychology and psychiatry, if the purpose of such activities is concerned ultimately with the utilization of scientific principles in understanding diseases or in improving health. Includes the total cost incurred for all pharmaceutical R&D activities, including salaries, materials, supplies used, and a fair share of overhead, as well as the cost of developing quality control. However, it does not include the cost of routine quality control activities, capital expenditures, or any costs incurred for drug or medical R&D conducted under a grant or contract for other companies or organizations.

Domestic R&D: Expenditures within the United States by all PhRMA member companies.

- **Licensed-in:** Products for which a license is held for a compound.
- **Self-originated:** Products for which the company originates the compound.

R&D Abroad: Expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies is excluded.

Prehuman/Preclinical Testing: From synthesis to first testing in humans.

Phase 1/2/3 Clinical Testing: From first testing in designated phase to first testing in subsequent phase.

Approval Phase: From New Drug Application (NDA)/Biologic License Application (BLA) submission to NDA/BLA approval.

Phase 4 Clinical Testing: Any post-marketing testing performed.

Uncategorized: Represents data for which detailed classifications were unavailable.

Sales Definitions

Sales: Product sales calculated as billed, free on board (FOB) plant or warehouse less cash discounts, Medicaid rebates, returns, and allowances. These include all marketing expenses except transportation costs. Also included is the sales value of products bought and resold without further processing or repackaging, as well as the dollar value of products made from the firm's own materials for other manufacturers' resale. Excluded are all royalty payments, interest, and other income.

Domestic Sales: Sales generated within the United States by all PhRMA member companies.

- **Private Sector:** Sales through regular marketing channels for end-use other than by government agency administration or distribution.

- **Public Sector:** Sales or shipments made directly to federal, state, or local government agencies, hospitals, and clinics.

Sales Abroad: Sales generated outside the United States by U.S.-owned PhRMA member companies, and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded.

- **Exports to Other Customers:** Sales to third parties only, FOB U.S. port. Excludes all intrafirm transactions, such as sales or shipments to subsidiaries or affiliates.
- **Foreign Sales:** Sales consummated in foreign countries.

R&D Employment Definitions

Scientific, Professional, and Technical Staff: Full-time employees, as well as full-time equivalents for part-time employees, whose work requires the application of R&D knowledge, skills, and scientific techniques in the life, physical, engineering, mathematical, or statistical sciences, as well as persons engaged in technical work at a level that requires knowledge in one of the above-mentioned fields. Does not include persons who have formal training in the sciences but who are not actively engaged in R&D.

Supported Scientific, Professional, and Technical Nonstaff: Persons whose work requires the application of R&D knowledge, skills, and scientific techniques in the life, physical, engineering, mathematical, or statistical sciences, as well as persons engaged in technical work at a level that requires knowledge in one of the above-mentioned fields who are supported through contracts or grants to commercial laboratories, private practitioners, consultants, educational and nonprofit research institutions, manufacturing and other companies, or other research-performing organizations located in the United States. Does not include persons who have formal training in the sciences but who are not actively engaged in R&D.

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TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1975–2010

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2010**	$37,371.0	5.7%	$12,047.4	8.7%	$49,418.4	6.4%
2009	35,356.0	-0.6	11,085.6	-6.1	46,441.6	-2.0
2008	35,571.1	-2.8	11,812.0	4.6	47,383.1	-1.1
2007	36,608.4	7.8	11,294.8	25.4	47,903.1	11.5
2006	33,967.9	9.7	9,005.6	1.3	42,973.5	7.8
2005	30,969.0	4.8	8,888.9	19.1	39,857.9	7.7
2004	29,555.5	9.2	7,462.6	1.0	37,018.1	7.4
2003	27,064.9	5.5	7,388.4	37.9	34,453.3	11.1
2002	25,655.1	9.2	5,357.2	-13.9	31,012.2	4.2
2001	23,502.0	10.0	6,220.6	33.3	29,772.7	14.4
2000	21,363.7	15.7	4,667.1	10.6	26,030.8	14.7
1999	18,471.1	7.4	4,219.6	9.9	22,690.7	8.2
1998	17,127.9	11.0	3,839.0	9.9	20,966.9	10.8
1997	15,466.0	13.9	3,492.1	6.5	18,958.1	12.4
1996	13,627.1	14.8	3,278.5	-1.6	16,905.6	11.2
1995	11,874.0	7.0	3,333.5	***	15,207.4	***
1994	11,101.6	6.0	2,347.8	3.8	13,449.4	5.6
1993	10,477.1	12.5	2,262.9	5.0	12,740.0	11.1
1992	9,312.1	17.4	2,155.8	21.3	11,467.9	18.2
1991	7,928.6	16.5	1,776.8	9.9	9,705.4	15.3
1990	6,802.9	13.0	1,617.4	23.6	8,420.3	14.9
1989	6,021.4	15.0	1,308.6	0.4	7,330.0	12.1
1988	5,233.9	16.2	1,303.6	30.6	6,537.5	18.8
1987	4,504.1	16.2	998.1	15.4	5,502.2	16.1
1986	3,875.0	14.7	865.1	23.8	4,740.1	16.2
1985	3,378.7	13.3	698.9	17.2	4,077.6	13.9
1984	2,982.4	11.6	596.4	9.2	3,578.8	11.2
1983	2,671.3	17.7	546.3	8.2	3,217.6	16.0
1982	2,268.7	21.3	505.0	7.7	2,773.7	18.6
1981	1,870.4	20.7	469.1	9.7	2,339.5	18.4
1980	1,549.2	16.7	427.5	42.8	1,976.7	21.5
1979	1,327.4	13.8	299.4	25.9	1,626.8	15.9
1978	1,166.1	9.7	237.9	11.6	1,404.0	10.0
1977	1,063.0	8.1	213.1	18.2	1,276.1	9.7
1976	983.4	8.8	180.3	14.1	1,163.7	9.6
1975	903.5	13.9	158.0	7.0	1,061.5	12.8
Average		**11.4%**		**12.9%**		**11.7%**

*R&D Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

**Estimated.

***R&D Abroad affected by merger and acquisition activity.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey*, 2011.

TABLE 2: R&D as a Percentage of Sales, PhRMA Member Companies: 1975–2010

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2010*	20.5%	17.0%
2009	19.5	16.8
2008	19.4	16.6
2007	19.8	17.5
2006	19.4	17.1
2005	18.6	16.9
2004	18.4	16.1**
2003	18.3	16.5**
2002	18.4	16.1
2001	18.0	16.7
2000	18.4	16.2
1999	18.2	15.5
1998	21.1	16.8
1997	21.6	17.1
1996	21.0	16.6
1995	20.8	16.7
1994	21.9	17.3
1993	21.6	17.0
1992	19.4	15.5
1991	17.9	14.6
1990	17.7	14.4
1989	18.4	14.8
1988	18.3	14.1
1987	17.4	13.4
1986	16.4	12.9
1985	16.3	12.9
1984	15.7	12.1
1983	15.9	11.8
1982	15.4	10.9
1981	14.8	10.0
1980	13.1	8.9
1979	12.5	8.6
1978	12.2	8.5
1977	12.4	9.0
1976	12.4	8.9
1975	12.7	9.0

*Estimated.

**Revised in 2007 to reflect updated data.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 3: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 2009

(dollar figures in millions)

R&D Expenditures for Human-use Pharmaceuticals	Dollars	Share
Domestic	$34,986.7	75.3%
Abroad*	$10,751.5	23.2%
Total Human-use R&D	**$45,738.2**	**98.5%**
R&D Expenditures for Veterinary-use Pharmaceuticals		
Domestic	$369.3	0.8%
Abroad*	$334.1	0.7%
Total Vet-use R&D	**$703.4**	**1.5%**
TOTAL R&D	**$46,441.6**	**100.0%**

*R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 4: Domestic R&D by Source, PhRMA Member Companies: 2009

(dollar figures in millions)

Source	Dollars	Share
Licensed-in	$6,339.0	17.9%
Self-originated	29,017.0	82.1
TOTAL R&D	**$35,356.0**	**100.0%**

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 5: R&D by Function, PhRMA Member Companies: 2009

(dollar figures in millions)

Function	Dollars	Share
Prehuman/Preclinical	$11,717.4	25.2%
Phase 1	3,752.9	8.1
Phase 2	7,123.7	15.3
Phase 3	16,300.1	35.1
Approval	2,046.9	4.4
Phase 4	5,302.7	11.4
Uncategorized	197.8	0.4
TOTAL R&D	**$46,441.6**	**100.0%**

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 6: R&D by Geographic Area,* PhRMA Member Companies: 2009

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$1.8	0.0%
South Africa	16.7	0.0
Other Africa	24.6	0.1
Americas		
United States	$35,356.0	76.1%
Canada	444.4	1.0
Mexico	70.9	0.2
Brazil	100.9	0.2
Argentina	24.4	0.1
Venezuela	5.0	0.0
Columbia	16.5	0.0
Chile	4.3	0.0
Peru	14.8	0.0
Other Latin America	178.3	0.4
Asia-Pacific		
Japan	$676.2	1.5%
China	124.4	0.3
India	125.1	0.3
Taiwan	18.0	0.0
South Korea	32.4	0.1
Other Asia-Pacific	345.1	0.7
Australia		
Australia and New Zealand	$181.7	0.4%
Europe		
France	$365.1	0.8%
Germany	583.2	1.3
Italy	210.5	0.5
Spain	223.6	0.5
United Kingdom	1,937.4	4.2
Other Western European	4,315.6	9.3
Czech Republic	97.9	0.2
Hungary	40.3	0.1
Poland	212.4	0.5
Turkey	28.7	0.1
Russia	159.6	0.3
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	384.1	0.8
Middle East		
Saudi Arabia	$2.7	0.0%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	118.0	0.3
Uncategorized	$1.1	0.0%
TOTAL R&D	**$46,441.6**	**100.0%**

*R&D abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 7: Biologics and Biotechnology R&D, PhRMA Member Companies: 2009

(dollar figures in millions)

Type	Dollars	Share
Biotechnology-derived Therapeutic Proteins	$9,691.6	20.9%
Vaccines	1,161.7	2.5
Cell or Gene Therapy	250.6	0.5
All Other Biologics	1,001.8	2.2
Total Biologics/Biotechnology R&D	**$12,105.6**	**26.1%**
Non-biologics/Biotechnology R&D	**$34,336.0**	**73.9%**
TOTAL R&D	**$46,441.6**	**100.0%**

Note: All figures include company-financed R&D only. Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 8: Domestic Sales and Sales Abroad,* PhRMA Member Companies: 1975–2010

(dollar figures in millions)

Year	Domestic Sales	Annual Percentage Change	Sales Abroad*	Annual Percentage Change	Total Sales	Annual Percentage Change
2010**	$182,610.5	0.8%	$108,815.2	14.3%	$291,425.8	5.5%
2009	181,116.8	-1.1	95,162.5	-7.5	276,279.3	-3.4
2008	183,167.2	-1.1	102,842.4	16.6	286,009.6	4.6
2007	185,209.2	4.2	88,213.4	14.8	273,422.6	7.4
2006	177,736.3	7.0	76,870.2	10.0	254,606.4	7.9
2005	166,155.5	3.4	69,881.0	0.1	236,036.5	2.4
2004***	160,751.0	8.6	69,806.9	14.6	230,557.9	10.3
2003***	148,038.6	6.4	60,914.4	13.4	208,953.0	8.4
2002	139,136.4	6.4	53,697.4	12.1	192,833.8	8.0
2001	130,715.9	12.8	47,886.9	5.9	178,602.8	10.9
2000	115,881.8	14.2	45,199.5	1.6	161,081.3	10.4
1999	101,461.8	24.8	44,496.6	2.7	145,958.4	17.1
1998	81,289.2	13.3	43,320.1	10.8	124,609.4	12.4
1997	71,761.9	10.8	39,086.2	6.1	110,848.1	9.1
1996	64,741.4	13.3	36,838.7	8.7	101,580.1	11.6
1995	57,145.5	12.6	33,893.5	****	91,039.0	****
1994	50,740.4	4.4	26,870.7	1.5	77,611.1	3.4
1993	48,590.9	1.0	26,467.3	2.8	75,058.2	1.7
1992	48,095.5	8.6	25,744.2	15.8	73,839.7	11.0
1991	44,304.5	15.1	22,231.1	12.1	66,535.6	14.1
1990	38,486.7	17.7	19,838.3	18.0	58,325.0	17.8
1989	32,706.6	14.4	16,817.9	-4.7	49,524.5	7.1
1988	28,582.6	10.4	17,649.3	17.1	46,231.9	12.9
1987	25,879.1	9.4	15,068.4	15.6	40,947.5	11.6
1986	23,658.8	14.1	13,030.5	19.9	36,689.3	16.1
1985	20,742.5	9.0	10,872.3	4.0	31,614.8	7.3
1984	19,026.1	13.2	10,450.9	0.4	29,477.0	8.3
1983	16,805.0	14.0	10,411.2	-2.4	27,216.2	7.1
1982	14,743.9	16.4	10,667.4	0.1	25,411.3	9.0
1981	12,665.0	7.4	10,658.3	1.4	23,323.3	4.6
1980	11,788.6	10.7	10,515.4	26.9	22,304.0	17.8
1979	10,651.3	11.2	8,287.8	21.0	18,939.1	15.3
1978	9,580.5	12.0	6,850.4	22.2	16,430.9	16.1
1977	8,550.4	7.5	5,605.0	10.2	14,155.4	8.6
1976	7,951.0	11.4	5,084.3	9.7	13,035.3	10.8
1975	7,135.7	10.3	4,633.3	19.1	11,769.0	13.6
Average		**9.8%**		**9.6%**		**9.6%**

*Sales Abroad includes sales generated outside the United States by U.S.-owned PhRMA member companies and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic sales, however, includes sales generated within the United States by all PhRMA member companies.

**Estimated.

***Revised in 2007 to reflect updated data.

****Sales abroad affected by merger and acquisition activity.

Note: Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

TABLE 9: Sales by Geographic Area,* PhRMA Member Companies: 2009

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$314.4	0.1%
South Africa	555.6	0.2
Other Africa	671.8	0.2
Americas		
United States	$181,116.8	65.6%
Canada	6,466.5	2.3
Mexico	2,261.8	0.8
Brazil	2,988.9	1.1
Argentina	486.2	0.2
Venezuela	1,493.9	0.5
Columbia	545.3	0.2
Chile	219.2	0.1
Peru	151.1	0.1
Other Latin America	1,470.9	0.5
Asia-Pacific		
Japan	$11,609.6	4.2%
China	2,722.1	1.0
India	638.4	0.2
Taiwan	653.7	0.2
South Korea	1,091.8	0.4
Other Asia-Pacific	2,139.6	0.8
Australia		
Australia and New Zealand	$3,107.5	1.1%
Europe		
France	$9,229.9	3.3%
Germany	7,410.0	2.7
Italy	6,352.4	2.3
Spain	6,243.9	2.3
United Kingdom	4,938.1	1.8
Other Western European	10,326.0	3.7
Czech Republic	646.9	0.2
Hungary	454.6	0.2
Poland	817.5	0.3
Turkey	1,412.2	0.5
Russia	1,106.5	0.4
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	4,468.4	1.6
Middle East		
Saudi Arabia	$439.3	0.2%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	1,728.4	0.6
Uncategorized	———	0.0%
TOTAL SALES	**$276,279.3**	**100.0%**

*Sales Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies and sales generated abroad by the U.S. divisions of foreign-owned PhRMA member companies. Sales generated abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic sales, however, includes sales generated within the United States by all PhRMA member companies.

Note: Total values may be affected by rounding.

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey*, 2011.

TABLE 10: Domestic R&D Scientific, Professional and Technical Personnel by Function, PhRMA Member Companies: 2009

Function	Personnel	Share
Prehuman/Preclinical	22,725	28.8%
Phase 1	5,748	7.3
Phase 2	10,010	12.7
Phase 3	17,622	22.3
Approval	4,179	5.3
Phase 4	8,843	11.2
Uncategorized	580	0.7
Total R&D Staff	**69,707**	**88.3**
Supported R&D Non-staff	9,243	11.7
TOTAL R&D PERSONNEL	**78,950**	**100.0%**

SOURCE: Pharmaceutical Research and Manufacturers of America, *PhRMA Annual Member Survey,* 2011.

endnotes

(continued from inside front cover)

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