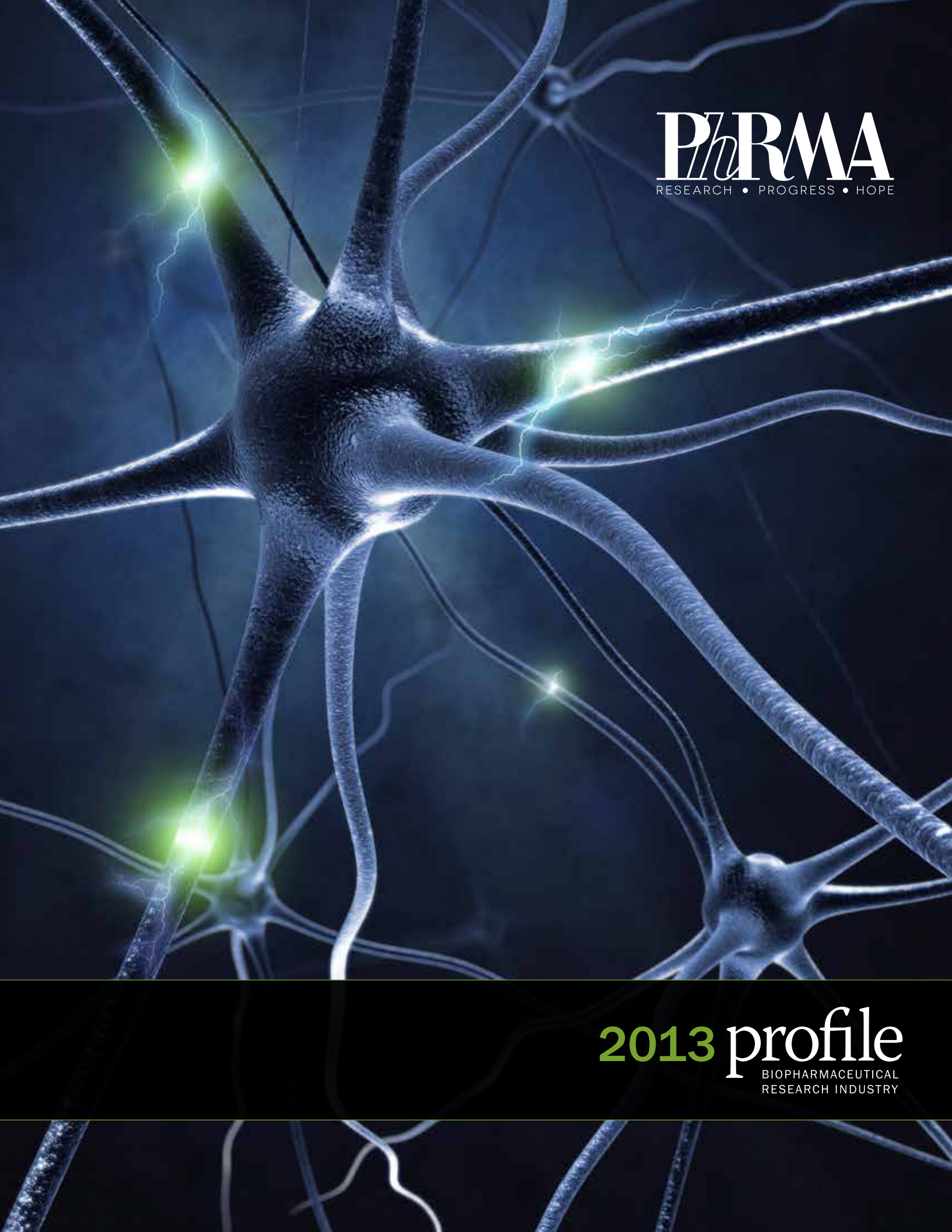
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BIOPHARMACEUTICAL
RESEARCH INDUSTRY

Key Facts

Research and Development (R&D)

Time to develop a drug = 10 to 15 years[1, 2, 3]

Development Costs

Average cost to develop a drug (including the cost of failures): [4, 5]

- Early 2000s = $1.2 billion* (some more recent studies estimate the costs to be even higher [6])
- Late 1990s = $800 million*
- Mid 1980s = $320 million*
- 1970s = $140 million*

R&D Spending

Year	PhRMA members[7]
2012	$48.5 billion (*est.*)
2011	$48.6 billion
2010	$50.7 billion
2009	$46.4 billion
2008	$47.4 billion
2007	$47.9 billion
2006	$43.4 billion
2005	$39.9 billion
2000	$26.0 billion
1990	$8.4 billion
1980	$2.0 billion

Percentage of Sales That Went to R&D in 2012[8]

Domestic R&D as a percentage of domestic sales = 20.7%

Total R&D as a percentage of total sales = 16.4%

Economic Impact of the Biopharmaceutical Sector[9]

Direct jobs = more than 810,000

Total jobs (including indirect and induced jobs) = nearly 3.4 million

Approvals

- Medicines approved 2000–2012 = more than 400[10, 11, 12]
- In the 30 years since the Orphan Drug Act was established, more than 400 orphan drugs have been approved.[13]
- Only 2 of 10 marketed drugs return revenues that match or exceed R&D costs.[14]

Medicines in Development

- Global development in 2011 = 5,400 compounds[15]
- U.S. development 2013 = 3,400[16] — an increase of 40% since 2005[17]
- Potential first-in-class medicines** in clinical development globally = 70%[18]

Value of Medicines

- **Cancer:** Since 1980, 83% of life expectancy gains for cancer patients are attributable to new treatments, including medicines.[19] Another study found that medicines specifically account for 50% to 60% of increases in survival rates since 1975.[20]
- **Cardiovascular Disease:** According to a 2013 statistics update by the American Heart Association, death rates for cardiovascular disease fell a dramatic 33% between 1999 and 2009.[21]
- **HIV/AIDS:** Since the approval of antiretroviral treatments in 1995, the HIV/AIDS death rate has dropped by 85%.[22, 23]

Sales

Generic share of prescriptions filled:[24]

2000 = 49%

2012 = 84%

See inside back cover for references.

* Note: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.

**Note: First-in-class medicines are those that use a different mechanism of action from any other already approved medicine.

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To enhance the content in the print version of this year's Profile, we have included quick response (QR) codes that link you directly to additional materials online. You can find QR code readers for your smart phone or tablet in your device's app store, or you can access the Industry Profile online at www.phrma.org/industryprofile2013.

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Pharmaceutical Research and Manufacturers of America
Washington, DC
www.phrma.org
July 2013

Cover image: Neurons firing in the brain.

Letter from PhRMA's President and CEO

Hear more from John J. Castellani here.
◄ Scan QR code

Today in America and around the world we confront daunting health care challenges. The incidence and costs of preventable and manageable chronic diseases like diabetes and asthma are growing. The medical needs of our rapidly aging population are unprecedented. And we face extremely complex diseases like cancer and Alzheimer's disease.

Each of these alone represents an enormous challenge and, in combination, a threat to both individual health and to the U.S. economy. To overcome these challenges we will need many innovative solutions, and research in the biopharmaceutical sector offers an important part of the answer.

Biopharmaceutical research is an engine of progress in the fight against disease and in building a stronger economy. More importantly, drug discovery offers patients around the globe real hope — hope that a once-deadly disease may be prevented, treated, and even cured, hope that a patient may stop being a patient and live a longer, healthier life.

Researchers continue to work toward these goals in spite of many barriers. The science and technology of drug development are increasingly complex, and the length and cost of research and development have continued to grow. Regulatory and business environments add uncertainty to the process.

Still, researchers in our industry are inspired to improve life for patients. This is why biopharmaceutical research companies invested an estimated $48.5 billion in new R&D in 2012 — the largest R&D investment of any sector in the U.S. economy. PhRMA members invest in order to realize the promise of incredible advances in our understanding of basic biology; to help solve the puzzle of cancers and rare diseases; and to help reduce the cost and health burden of disease.

I am pleased to present the ***2013 Biopharmaceutical Research Industry Profile***, which lays out both the challenges we face and the progress we have made. I am proud of the story it tells of a sector striving to achieve the hope we all share for a longer life and a healthier future.

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

Table of Contents

Committed to Patients, Health, and the Economy

New medicines have been an important part of transforming many diseases in recent years. They are putting rheumatoid arthritis into remission, greatly increasing the chances of survival for children with cancer, curing hepatitis in many patients, and reducing hospitalizations for HIV patients.

The biopharmaceutical industry is a dynamic, knowledge-driven sector. The work of its researchers brings hope to millions of patients and benefits to local and national economies. Biopharmaceutical companies invest heavily in research and development; in the past year, Pharmaceutical Research and Manufacturers of America (PhRMA) members surpassed the $500 billion mark in research and development (R&D) spending since 2000.

Developing a new medicine is challenging and the chances of success are extremely low, particularly in recent years. The 44 new medicines approved by the U.S. Food and Drug Administration (FDA) in 2012 represented the highest total in 15 years, a proud landmark for an industry whose mission is to save and improve lives.

In addition to their health benefits, medicines are an important part of the solution to rising health care costs through their role in reducing the need for hospital stays, surgeries, and

other costly interventions. The biopharmaceutical sector also supports hundreds of thousands of high-quality, well-paying jobs in the United States that contribute significantly to the health of our communities and the nation's economy.

The *2013 Biopharmaceutical Research Industry Profile* provides an overview of the essential contributions the industry makes to the lives and health of people and to the U.S. economy. Chapter 1 examines the enormous value of medicines developed by biopharmaceutical companies for patients around the world. Chapter 2 discusses the role that prescription medicines play in improving the quality and value of health care, and in controlling its cost. Chapter 3 describes the impact of the biopharmaceutical industry on local, state, and the national economies. Chapter 4 captures the R&D process that brings us new medicines. Chapter 5 reflects on our growing knowledge of disease, which is providing the most promising platform ever for developing new medicines and new ways to save lives. And Chapter 6 looks ahead at the hurdles facing the sector and how biopharmaceutical companies are meeting those challenges.

1 Impacting Patients

Impacting Patients

New medicines save and improve lives every day. For patients, new medicines can mean getting back to work, avoiding doctors visits and surgeries, feeling better, and living longer.

In recent years, we have seen accelerated progress in the fight against many diseases as a result of biopharmaceutical innovation. In 2012, the U.S. Food and Drug Administration (FDA) approved 44 new medicines[1,2] — the largest number in 15 years.[3] Of those, 39 were approved by the Center for Drug Evaluation and Research and 5 by the Center for Biologics Evaluation and Research.

Novel therapies were approved in a wide variety of disease areas, including:[4]

- **Cystic Fibrosis:** The first therapy that targets the underlying cause of cystic fibrosis. This personalized medicine treats a subset of patients with a specific mutation.[5]
- **Skin Cancer:** The first medicine approved for treatment of metastatic basal cell carcinoma, the most common form of skin cancer.[6]

- **Tuberculosis:** The first new tuberculosis medicine in 40 years, which will be used in combination with other medicines to treat multi-drug resistant tuberculosis infection.[7]
- **Leukemia:** Three new therapies that treat chronic myelogenous leukemia, a rare blood and bone marrow disease.[8]
- **Cushing's Disease:** Two new medicines to treat Cushing's disease, a rare disease that affects the pituitary gland causing a host of problems throughout the body. One medicine treats patients with endogenous Cushing's syndrome and the other is the first medicine that addresses the underlying mechanism of the disease.[9,10]
- **Respiratory Distress Syndrome:** A new medicine to treat respiratory distress syndrome in premature infants.[11]

> *These accomplishments could not have been achieved without the innovations of the biopharmaceutical industry and the dedication and skill of FDA's drug review staff.*[12]
>
> ► Food and Drug Administration on 2012 approvals

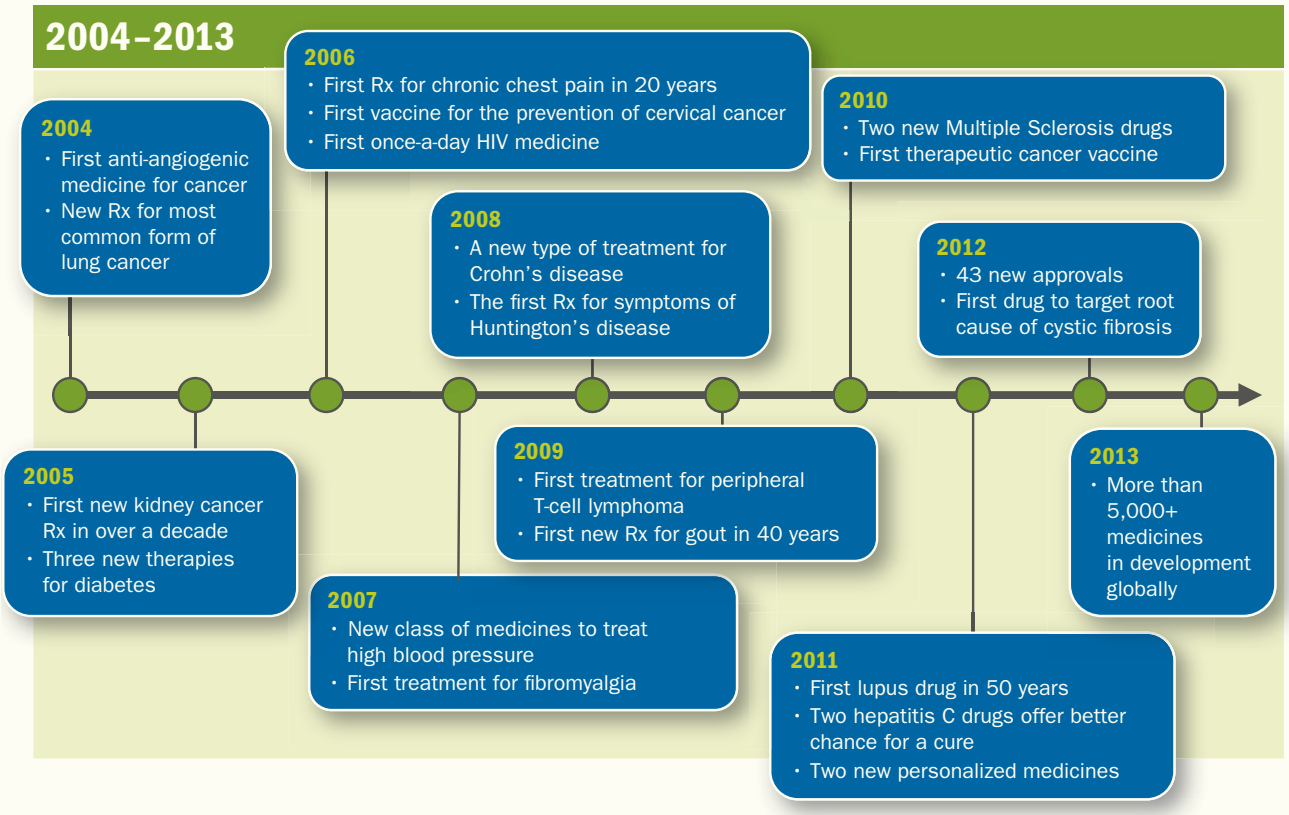
Fighting Rare Diseases

This year marks the 30th anniversary of the enactment of the Orphan Drug Act, which was pivotal in creating incentives for the development of new treatments for rare diseases. The Act transformed the landscape of drug development for rare diseases: more than 400 medicines have been approved to treat rare diseases since 1983, compared with fewer than 10 in the 1970s.[13,14]

Researchers have made tremendous progress against rare diseases in recent years. In fact, the FDA notes that approximately one-third of all new medicines approved in the last 5 years have been designated as "orphan drugs" — the term used for medicines that treat rare diseases affecting fewer than 200,000 patients in the United States.[15] In 2012, 13 orphan drugs were approved by the FDA.[16]

Although each of the nearly 7,000 rare conditions affects a small number of people, their impact on public health is anything but small; rare diseases overall affect more than 30 million Americans.[17] Because 85% to 90% of rare diseases are serious or life threatening, bringing new medicines to patients is especially important.[18] (See Chapter 5, page 46 for information about treatments currently in development for rare diseases.)

Figure 1: A Decade of Innovation—Selected Advances



SOURCES: U.S. Food and Drug Administration. Available at www.fda.gov (accessed February 2013); Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

Progress Against Disease

Medicines improve patients' lives in many different ways. Appropriate use of medications can have a huge impact on the health and well-being of patients and their caregivers by extending life, halting or slowing disease progression, minimizing complications, improving quality of life, preventing hospitalizations and surgeries, preventing disease, and reducing side effects. Following are just a few specific examples of the positive impact therapies have had on patient care.

Extending Lives

Childhood Cancers: The chance of survival for children with cancer has greatly improved in recent years. The 5-year relative survival rate increased from 58% in the mid-1970s to 83% in the most recent time period (2002–2008) — a 25 percentage point increase.[19] (See Figure 2.) The American Cancer Society noted that "survival for all invasive childhood cancers combined has improved markedly over the past 30 years due to new and improved treatments."[20]

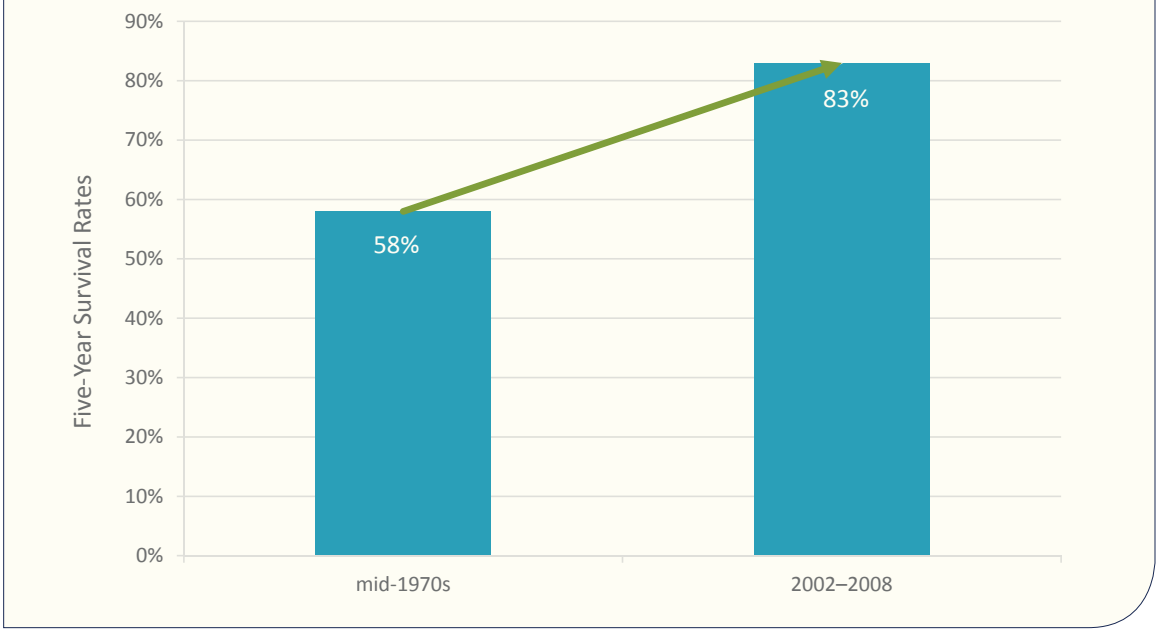
Slowing and Preventing Disease Progression

Cardiovascular Disease: Despite rising obesity levels, Americans have reached a milestone in controlling high cholesterol. The U.S. Centers for Disease Control and Prevention (CDC) reported in 2007 that U.S. adults reached an average cholesterol level in the ideal range (below 200) for the first time in 50 years.[21] (See Figure 3.) Authors of the report attribute the drop to the increased use of cholesterol-lowering medicines in the over-60 population.[22]

Hepatitis C: This viral disease, which affects 3.2 million people in the United States, attacks the liver leading to many complications, including cirrhosis, liver transplants, liver cancer, and death.[23] Sustained virologic response rates improved from 10% in the 1990s to 80% today among hepatitis C patients.[24] Sustained virologic response, defined as the suppression of the virus below detectable levels for 24 weeks after treatment, rose as understanding of the disease grew and treatment moved to today's triple therapy regimens, which include recently approved "direct acting antivirals."[25]

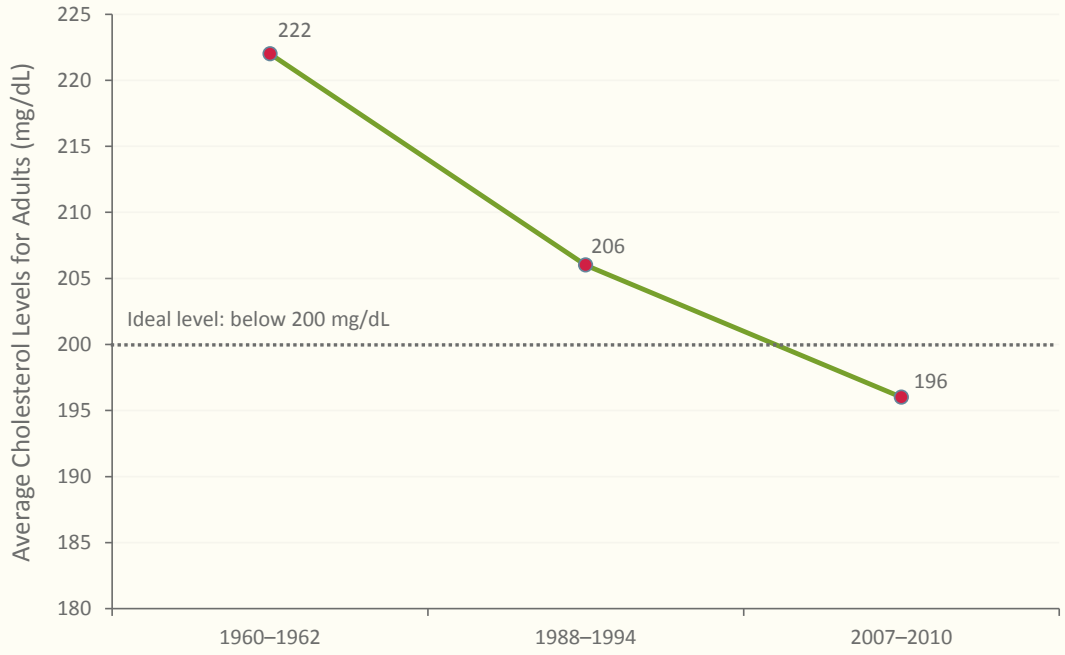
> *We are living in very exciting times. While years ago there were no specific therapies for liver diseases, we now have many different therapies for patients with different types of liver disease and at different stages of disease. One of the most exciting areas is the therapy of hepatitis C, one of the main causes of liver disease in the world.*[26]
>
> ► Guadalupe Garcia-Tsao, M.D., President, American Association for the Study of Liver Diseases

Figure 2: Survival Rates for Childhood Cancers Have Increased 25 Percentage Points over the Last Several Decades



SOURCE: American Cancer Society. "Cancer Facts & Figures, 2013." Atlanta, GA: American Cancer Society, 2013. Available at www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf (accessed February 2013).

Figure 3: In 2007, the Average Cholesterol Level for Adults Reached the Ideal Range, Below 200 mg/dL



SOURCES: S.E. Schober, et al. "High Serum Total Cholesterol—an Indicator for Monitoring Cholesterol Lowering Efforts: U.S. Adults, 2005–2006." *NCHS Data Brief* 2007; 2: 1–8. Hyattsville, MD: National Center for Health Statistics; M.D. Carroll, et al. "Trends in Lipids and Lipoproteins in U.S. Adults, 1988–2010." *JAMA* 2012; 308(15): 1545–1554.

> ***Protein enzymes, receptors, or channels identified by the pharmaceutical industry as 'drugable targets' have led to striking, remarkable, and repeated achievement.***[27]
>
> ► Drs. Myron Weisfeldt and Susan Zieman, Johns Hopkins University, "Advances in the Prevention and Treatment of Cardiovascular Disease," *Health Affairs*, 2007

Preventing Hospitalizations

HIV/AIDS: Since anti-retroviral treatments became available in the mid-1990s, survival rates for HIV patients have grown rapidly, increasing the number of people living with the disease between 1996 and 2000 by 28%. Despite this increase in survival, hospitalization rates fell by 32% in this period.[28] In more recent years, hospitalization rates have continued to fall. Between 2002 and 2007, the hospitalization rate fell from 35 per 100 HIV patients to 27 per 100 patients, a 23% drop.[29]

Diabetes: Over the last several years, many innovative medications for the treatment of diabetes have emerged, giving patients important tools for managing their disease. A recent study found that emergency room visits of patients who took their diabetes medicines as directed were 46% lower than for patients who took their medicines less than 50% of the time. Similarly, the hospitalization rate and the number of days spent in the hospital were 23% and 24% lower, respectively, for adherent patients.[30]

Check out an infographic on the impact of innovation and adherence in improving the lives of diabetes patients.

Scan QR code ▼

HIV/AIDS

THEN... "In the early years of the AIDS epidemic before ART (anti-retroviral treatment) was available, the median survival after an AIDS diagnosis was measured in weeks to months and patient care was confined to diagnosing and treating a complex array of opportunistic infections and AIDS-related types of cancer..."

NOW... "In stark contrast to the early and mid-1980s, if a person aged 20 years is newly infected with HIV today and guideline recommended therapy is initiated, researchers can predict by using mathematical modeling that this person will live at least an additional 50 years — that is, a close-to-normal life expectancy."[31]

► Drs. Carl W. Dieffenbach and Anthony S. Fauci, *Annals of Internal Medicine*, 2011

Learn about progress against HIV from an activist who has seen the disease go from acute and fatal to chronic and manageable.

Scan QR code ►

Improving Quality of Life

Rheumatoid Arthritis: Clinical remission is now possible for patients with severe rheumatoid arthritis (RA).[32] A recent study found that patients treated with combination therapy consisting of both a new and older medicine had a 50% chance of complete clinical remission after 52 weeks of treatment, compared with 28% for those taking only the older medicine. These results would have been "unthinkable" prior to new disease-modifying biological medicines.[33]

Rheumatoid Arthritis

THEN... "Previously the progression of RA from symptom onset to significant disability was often inevitable and, in some cases, rapid."

NOW... "With the availability of medications that can slow or halt disease progression and prevent irreversible joint damage, joint replacement surgery is not always the ultimate outcome and patients with RA may live comfortable and productive lives on medical therapy."[34]

▶ Drs. Katherine Upchurch and Jonathan Kay, University of Massachusetts Medical School

The Evolving Value of Medicines

Advances against disease like those illustrated above are not typically driven by large, dramatic developments, but more commonly result from a series of incremental gains in knowledge over time. New medicines build on one another step by step. In addition, the best clinical role and full value of a therapy typically emerges years after initial approval as further research is conducted and physicians gain real-world experience. Initial FDA approval often marks the starting point for this additional research, generating a larger body of evidence to help us understand the full value of the medicine and how best to treat patients.

This step-wise transformation in knowledge has led to increased survival, improved patient outcomes, and enhanced quality of life for many patients. In fact, in recent years we have seen the transformation of several diseases that were once thought of as acute and sometimes fatal to chronic, manageable conditions for patients who have access to medication.

Some forms of cancer provide a useful illustration of the different pathways by which our understanding of value can evolve:[35]

- **Use earlier in treatment line or disease state**
  For example: Trastuzumab (Herceptin®) received an additional indication for use as a potential first-line adjuvant therapy, 10 years after originally being approved as a second-line treatment for HER2+ metastatic breast cancer.

- **Use in combination with other therapeutics or biomarkers**
  For example: Subsequent studies of Cetuximab (Erbitux®) indicated that mutations of the KRAS gene could predict response to treatment for patients with a form of metastatic colorectal cancer, allowing for more targeted treatment.

- **Use in additional indications**
  For example: Docetaxel (Taxotere®) was initially approved for the treatment of non-small cell lung cancer, but continued research revealed a significant survival benefit in squamous cell carcinoma of the head and neck; initial evaluation based on early trial results would have substantially underestimated its impact on survival by more than 4.5 years.

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[1]U.S. Food and Drug Administration. "New Molecular Entity Approvals for 2012." 28 January 2013. Available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm336115.htm (accessed February 2013).

[2]U.S. Food and Drug Administration. "2012 Biological License Application Approvals." 21 February 2013. Available at www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/ucm289008.htm (accessed April 2013).

[3]Pharmaceutical Research and Manufacturers of America. "New Drug Approvals." Washington, DC: PhRMA, 1997–2012; U.S. Food and Drug Administration. "New Molecular Entity Approvals for 2012." 28 January 2013. Available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm336115.htm (accessed February 2013); U.S. Food and Drug Administration. "2012 Biological License Application Approvals." 21 February 2013. Available at www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/ucm289008.htm (accessed April 2013).

[4]"CDER's Novel Approvals in 2012." *The Pink Sheet*, 7 January 2013.

[5]Cystic Fibrosis Foundation. "Kalydeco™." 8 February 2012. Available at www.cff.org/treatments/Therapies/Kalydeco/ (accessed February 2013).

[6]U.S. Food and Drug Administration. "FDA Approves New Treatment for Most Common Type of Skin Cancer." Silver Spring, MD: FDA, 30 January 2012. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm289545.htm (accessed February 2013).

[7]U.S. Food and Drug Administration. "FDA Approves First Drug to Treat Multi-drug Resistant Tuberculosis." Silver Spring, MD: FDA, 31 December 2012. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333695.htm (accessed February 2013).

[8]S. Merville. "Three New Therapies Increase Options for CML and Some ALL Patients." *Cancer Frontline*. MD Anderson Cancer Center, 21 December 2012. Available at www2.mdanderson.org/cancerfrontline/2012/12/three-new-therapies-increase-options-for-cml-patients-1.html (accessed February 2013).

[9]U.S. Food and Drug Administration. "FDA Approves Korlym for Patients with Endogenous Cushing's Syndrome." Silver Spring, MD: FDA, 17 February 2012. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm292462.htm (accessed February 2013).

[10]U.S. Food and Drug Administration. "FDA Approves Signifor, A New Orphan Drug for Cushing's Disease." Silver Spring, MD: FDA, 14 December 2012. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm332351.htm (accessed February 2013).

[11]U.S. Food and Drug Administration. "FDA Approves Surfaxin to Prevent Breathing Disorder in Premature Infants." Silver Spring, MD: FDA, 6 March 2012. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm294984.htm (accessed December 2012).

[12]U.S. Food and Drug Administration. "FY 2012 Innovative Drug Approvals: Bringing Life-saving Drugs to Patients Quickly and Efficiently." Silver Spring, MD: FDA, December 2012. Available at www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm (accessed February 2013).

[13]U.S. Food and Drug Administration, Office of Orphan Product Development. "Orphan Drug Designations and Approvals Database." Available at www.accessdata.fda.gov/scripts/opdlisting/oopd/ (accessed February 2013).

[14]U.S. Food and Drug Administration. "Developing Products for Rare Diseases & Conditions." 6 February 2013. Available at www.fda.gov/ForIndustryDevelopingProductsforRareDiseasesConditions/default.htm (accessed February 2013).

[15]U.S. Food and Drug Administration. "FY 2012 Innovative Drug Approvals: Bringing Life-saving Drugs to Patients Quickly and Efficiently." Silver Spring, MD: FDA, December 2012. Available at www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm (accessed February 2013).

[16]U.S. Food and Drug Administration, Center for Drug Evaluation and Research. "2012 Novel New Drugs Summary." Silver Spring, MD: FDA, January 2013. Available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM337830.pdf (accessed February 2013).

[17]U.S. Food and Drug Administration. "Helping Rare Disease Patients Find Their Voice." 27 February 2011. Available at www.fda.gov/ForConsumers/ConsumerUpdates/ucm293213.htm (accessed February 2013).

[18]U.S. Food and Drug Administration, Office of Orphan Products Development. "Food and Drug Administration Fiscal Year 2011 Justification of Budget." Silver Spring, MD: FDA, 2011. Available at www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM205391.pdf (accessed February 2013).

[19]American Cancer Society. "Cancer Facts & Figures 2013." Atlanta, GA: American Cancer Society, 2013. Available at www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf (accessed February 2013).

[20]*Ibid*.

[21]S.E. Schober, et al. "High Serum Total Cholesterol—An Indicator for Monitoring Cholesterol Lowering Efforts: U.S. Adults, 2005–2006." *NCHS Data Brief* 2007; 2: 1–8. Hyattsville, MD: National Center for Health Statistics.

[22]Associated Press. "First Time in 50 Years, Average American Adult's Cholesterol in Ideal Range." *Fox News*, 12 December 2007. Available at www.foxnews.com/story/0,2933,316562,00.html (accessed December 2012).

[23]U.S. Centers for Disease Control and Prevention. "Hepatitis C FAQs for the Public," 22 October 2012. www.cdc.gov/hepatitis/c/cfaq.htm#cFAQ22 (accessed February 2013).

[24]M. Pacanowski, S. Amur, and I. Zineh. "New Genetic Discoveries and Treatment for Hepatitis C." *JAMA* 2012; 307(18): 1921–1922.

[25]*Ibid*.

[26]PR Newswire. "Six Late-Breaking Abstracts Selected for Oral Presentation at The Liver Meeting®." *Boston Business Journal*, 2 November 2012. Available at www.bizjournals.com/boston/prnewswire/press_releases/Massachusetts/2012/11/02/FL05188 (accessed February 2013).

[27]M.L. Weisfeldt and S.J. Zieman. "Advances in the Prevention and Treatment of Cardiovascular Disease." *Health Affairs* 2007; 26(1): 25–37.

[28]F.J. Hellinger. "HIV Patients in the HCUP Database: A Study of Hospital Utilization and Costs." *Inquiry* 2004; 41(1): 95–105.

[29]B.R. Yehia, et al. "Inpatient Health Services Utilization Among HIV-Infected Adult Patients in Care 2002–2007." *Journal of Acquired Immune Deficiency Syndromes* 2010; 53(3): 397–404.

[30]W.E. Encinosa, D. Bernard, and A. Dor. "Does Prescription Drug Adherence Reduce Hospitalizations and Costs?" National Bureau of Economic Research Working Paper No. 15691. Cambridge, MA: National Bureau of Economic Research, January 2010.

[31]C.W. Dieffenbach and A.S. Fauci. "Thirty Years of HIV and AIDS: Future Challenges and Opportunities." *Annals of Internal Medicine* 2011; 154(11): 766–771.

[32]P. Emery, et al. "Comparison of Methotrexate Monotherapy with a Combination of Methotrexate and Etanercept in Active, Early, Moderate to Severe Rheumatoid Arthritis (COMET): A Randomized, Double-Blind, Parallel Treatment Trial." *The Lancet* 2008; 372(9636): 375–382.

[33]J.M. Kremer. "COMET's Path, and the New Biologicals in Rheumatoid Arthritis." *The Lancet* 2008; 372(9636): 347–348.

[34]K.S. Upchurch and J. Kay. "Evolution of Treatment for Rheumatoid Arthritis." *Rheumatology (Oxford)* 2012; 51(Suppl 6): vi28–vi36.

[35]T.F. Goss, E.H. Picard, and A. Tarab. "Recognizing the Value in Oncology Innovation." Boston, MA: Boston Healthcare Associates, Inc., June 2012. Available at www.phrma.org/sites/default/files/phrma_bha recognizingvalueinoncology innovation_20120604.pdf (accessed February 2013).

2 Improving the Quality and Value of Health Care

Improving the Quality and Value of Health Care

Improving the quality and value of health care — and controlling its costs — are imperatives for the health of Americans and for our economy. Prescription medicines play an important role in achieving both of those goals, especially in light of our aging population and the large number of people living with chronic conditions.

With optimal use, medicines can improve health outcomes and help to reduce the need for costly health care services, such as emergency room admissions, hospital stays, surgeries, and long-term care. Patients are healthier, and unnecessary medical expenditures are avoided.

As more Americans gain access to health care, it is important that they also have access to the medicines they need. Suboptimal use of prescription medications remains a challenge, and there is a large opportunity for patients and their health care providers to improve the quality and the efficiency of the health care system by improving the use of medicines.

Better Use of Medicines Improves Outcomes

For patients to receive the clinical benefits of medicines, several actions must occur:

- Appropriate and timely diagnosis and prescribing
- Prompt initiation of therapy
- Adherence to prescribed medicines (i.e., patients must take the medicines as prescribed at the right dose and right time)
- Periodic reviews and updates of the medication regimen

All of these dimensions are key to achieving better health outcomes, particularly for patients with chronic diseases. For example:

- **Preventing Hospitalizations:** Poor adherence to prescribed medicines is associated with increased hospitalizations, nursing home admissions, and physician visits.[1,2,3] For instance, research demonstrates that patients who did not consistently take their diabetes medicine were 2.5 times more likely to be hospitalized than were patients who took their medicine as directed more than 80% of the time.[4]
- **Preventing Disease:** Nonadherent patients were 7%, 13%, and 42% more likely to develop coronary heart disease, cerebrovascular disease, and chronic heart failure, respectively, over 3 years than were patients who took antihypertension medicine as directed.[5]
- **Preventing Adverse Events:** Providing counseling to patients to clarify their medication regimen following hospital discharge can dramatically reduce the likelihood of adverse drug events.[6]

Figure 4: Recommended Medicines Can Save Lives and Dramatically Improve Health

"...achieving effective blood pressure control would be approximately equivalent to eliminating all deaths from accidents, or from influenza and pneumonia combined."

—David Cutler, Ph.D., Harvard University

Annual Hospitalizations and Deaths Avoided through Use of Recommended Antihypertensive Medications

	Annual Hospitalizations Avoided	Annual Premature Deaths Avoided
Prevention Achieved: Based on Current Treatment Rates	833,000	86,000
Potential Additional Prevention: If Untreated Patients Received Recommended Medicines	420,000	89,000

SOURCE: D.M. Cutler, et al. "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation." *Health Affairs* 2007; 26(1): 97–110.

The Economic Value of Better Use of Medicines

Used appropriately, medicines also can generate positive economic outcomes across many common diseases. A wide range of studies have shown that improved use of recommended medications is associated with reduced total health care costs.[7] In fact, the link between use of prescription medicines and spending on other health care services was recently acknowledged by the Congressional Budget Office (CBO). In 2012, the CBO announced a change to its scoring methodology to reflect savings in medical spending associated with increased use of medicines in Medicare.[8] (For more on the value of better use of medicines in Medicare Part D, see sidebar on page 15.)

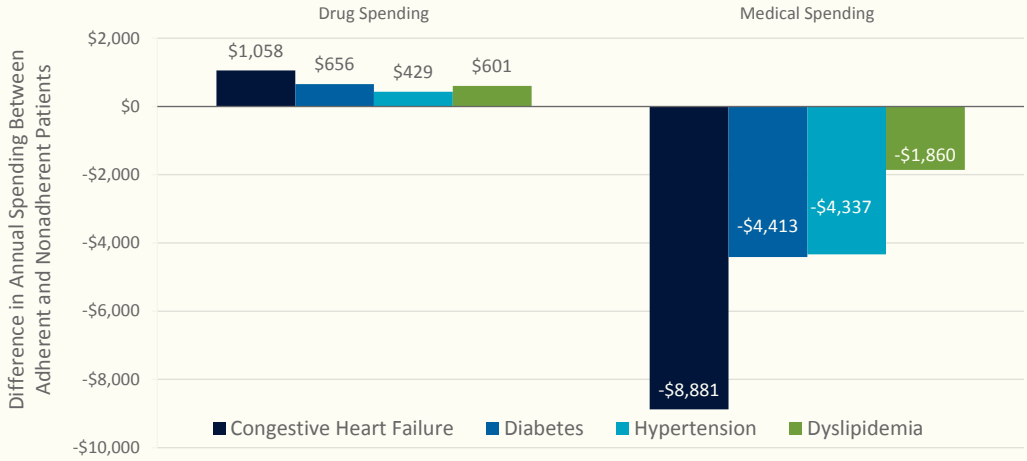
It is estimated that the cost of suboptimal medicine use including nonadherence, undertreatment, administration errors, and underdiagnosis is between $100 and $290 billion annually.[9,10]

Examples of the medical savings resulting from better use of medicine include:

- **High Blood Pressure:** Treating patients with high blood pressure in accordance with clinical guidelines would result in fewer strokes and heart attacks, preventing up to 89,000 deaths and 420,000 hospitalizations annually and saving $15.6 billion a year.[11] (See Figure 4.)
- **Diabetes:** Improving adherence to diabetes medicines would result in an estimated reduction of more than 1 million emergency room visits and hospitalizations annually, for potential savings of $8.3 billion each year.[12]
- **High Cholesterol:** Research has shown that statin therapy reduces low-density lipoprotein cholesterol levels by an average of 19%. Over one year, this reduction in bad cholesterol was associated with roughly 40,000 fewer deaths, 60,000 fewer hospitalizations for

Figure 5: Adherence to Medicines Lowers Total Health Spending for Chronically Ill Patients

Better use of medicines reduces use of avoidable medical care, resulting in reductions in medical spending.



SOURCE: M.C. Roebuck, et al. "Medical Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending." *Health Affairs* 2011; 30(1): 91–99.

heart attacks, and 22,000 fewer hospitalizations for strokes in the United States. From an economic perspective, those prevented hospitalizations translated into gross savings of nearly $5 billion.[13]

- **Chronic Conditions:** For conditions such as diabetes, dyslipidemia, hypertension, and congestive heart failure, patients who had better adherence to prescribed medicines experienced savings of $3 to $10 in non-drug spending for each additional dollar spent on prescriptions — a net savings of $1,200 to $7,800 per patient per year.[14] (See Figure 5.)

Another aspect of the economic impact of medicines is their potential to improve productivity in the workplace through reduced absenteeism or disability leave, which benefits both the individual patient and the economy as a whole. Several of the most common chronic conditions are estimated to cost the economy more than $1 trillion annually in lost productivity.[15] Examples of improved productivity include:

- **Rheumatoid Arthritis:** Researchers at the Integrated Benefits Institute found that high cost sharing for rheumatoid arthritis medications decreased adherence and led to increased incidence and longer duration of short-term disability leave. Researchers estimated that lowering patient copays would improve medication adherence, reducing lost productivity among workers with this disease by 26%.[16]
- **Chronic Conditions:** Research shows that workers diagnosed with diabetes, hypertension, dyslipidemia, asthma, or chronic obstructive pulmonary disease who are adherent to prescribed medicines were absent up to 7 fewer days from work and used 5 fewer days of short-term disability compared with nonadherent workers.[17]

Gaps in Optimal Use of Medicines

Poor use of medicines is a widespread challenge throughout the health care system. Because of the broad scope

Medicare Part D: Improving Seniors' Access to Medicine and Reducing the Cost of Care

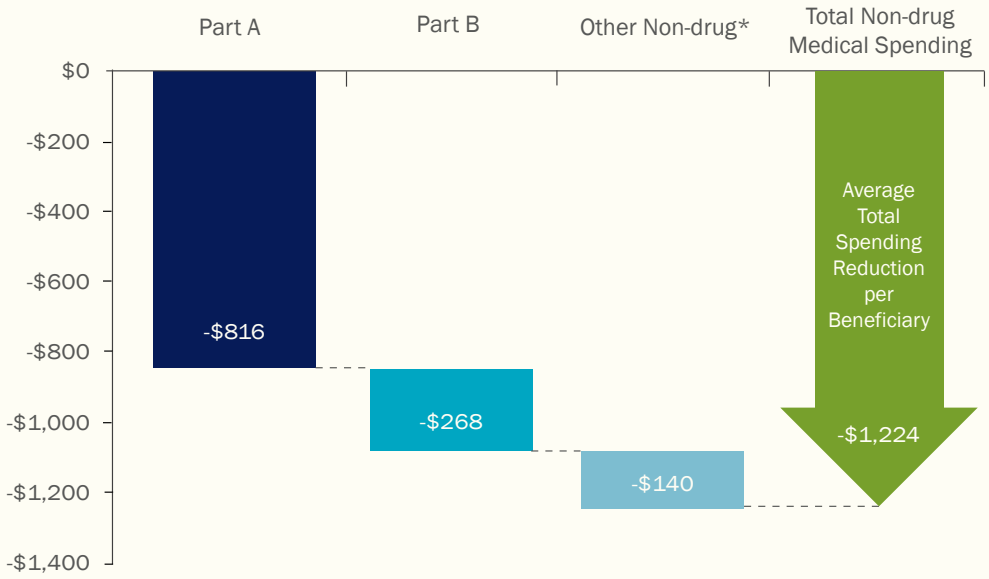
Passed into law in 2003, the Medicare prescription drug program (Part D) began in 2006. The program is working well and exceeding expectations. The current estimates for total spending over the first 10 years of the program are $346 billion lower than initial projections.[18] Additionally, health outcomes for seniors have improved, and beneficiary satisfaction is high.[19] Medicare Part D has improved access to needed medicines and reduced hospitalizations and use of other medical care.[20]

A 2011 study in the *Journal of the American Medical Association* found that for those with limited prior drug coverage who subsequently enrolled in Part D, there was an average savings of $1,200 per beneficiary in total non-drug medical costs in both 2006 and 2007.[21] (See Figure 6.) Better access to medicines through Medicare Part D also has led to declines in costly hospitalizations and skilled nursing care, which provides significant savings to the Medicare program.[22,23]

Today, 32 million people, or almost two-thirds of all Medicare beneficiaries, are enrolled in a Part D plan,[24] and the overwhelming majority of them rate their coverage highly. A recent survey reported that 96% of respondents were satisfied with their Medicare drug coverage, and 96% said their coverage worked well.[25] To learn more about the successes of Medicare's Part D program, visit www.phrma.org/issues/medicare.

Figure 6: Gaining Drug Coverage Reduced Other Medical Spending

The Medicare drug benefit increased access to medicines, reducing non-drug medical spending — an overall savings of $13.4 billion in 2007, the first full year of the program.

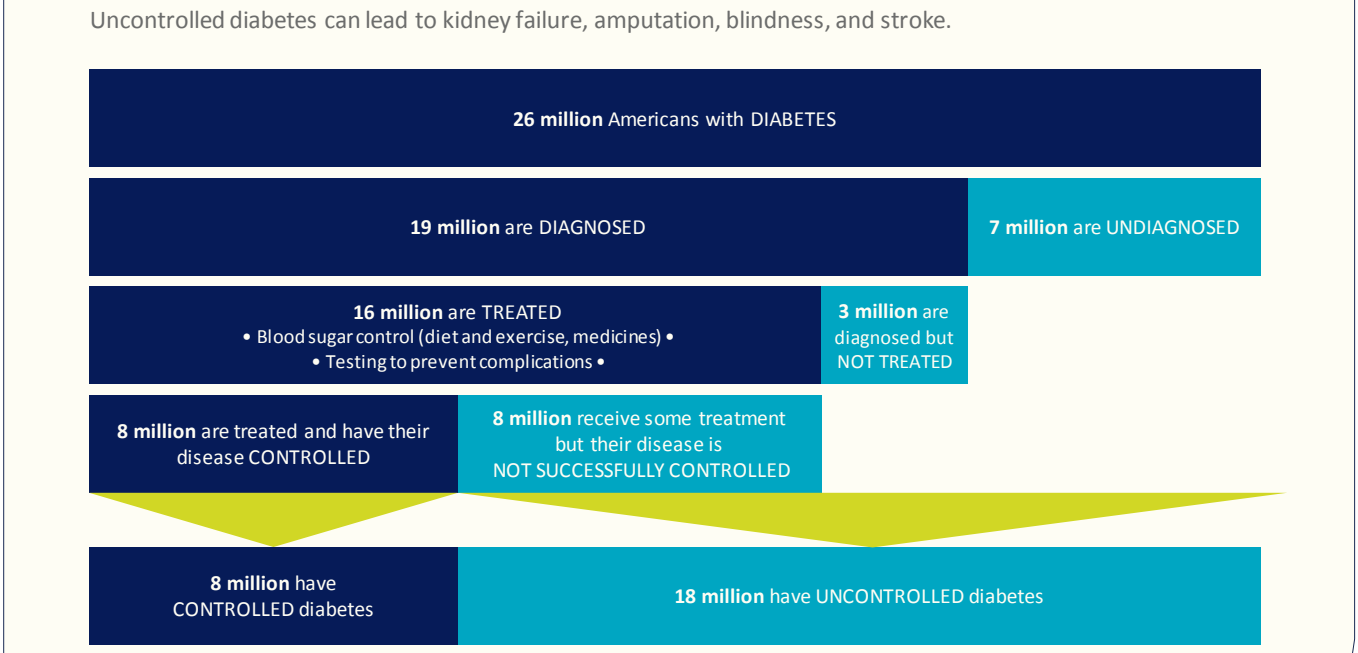


*Home health, durable medical equipment, hospice, and outpatient institutional services.

SOURCES: J.M. McWilliams, A.M. Zaslavsky, and H.A. Huskamp. "Implementation of Medicare Part D and Nondrug Medical Spending for Elderly Adults with Limited Prior Drug Coverage." *JAMA* 2011; 306(4): 402–409; C.C. Afendulis and M.E. Chernew. "State-level Impacts of Medicare Part D." *American Journal of Managed Care* 2011; 17 Suppl 12: S.

Find out more about the successes of Medicare's Part D Program.
Scan QR code ▶

Figure 7: Diabetes: An Example of Underdiagnosis and Undertreatment



SOURCES: U.S. Centers for Disease Control and Prevention (CDC). "National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011." Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2011. www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf (accessed December 2012); IHS Global Insight Analysis of 2010 NHANES. Available at http://meps.ahrq.gov/mepsweb/ (accessed December 2012).

of the problem, there is a significant opportunity for improving patients' health and the efficiency of the health care system.

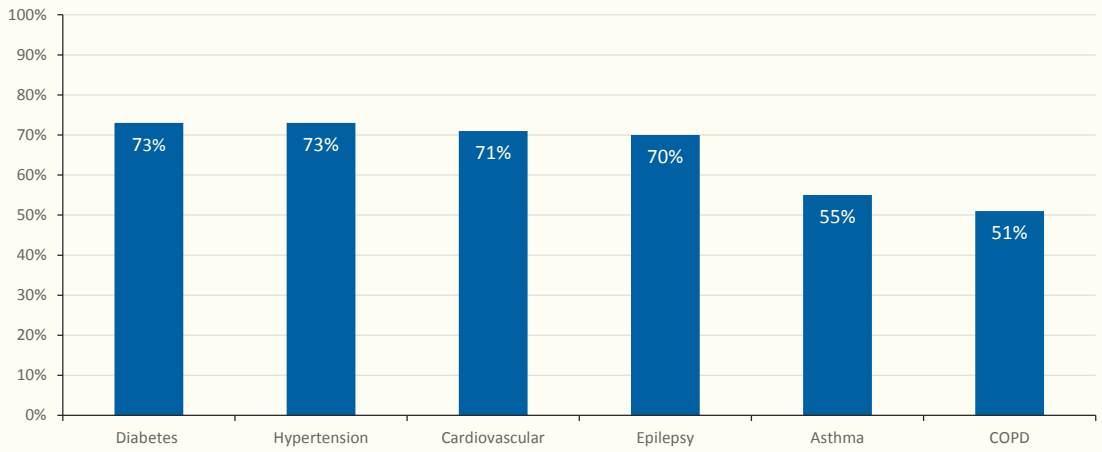
- More than 25% of newly written prescriptions, including those for high blood pressure, diabetes, and high cholesterol, are never brought to the pharmacy to be filled.[26]
- Approximately 50% of medications for chronic diseases are not taken as prescribed.[27]
- Among elderly patients, underuse of recommended medicines outweighs overuse by about 17 to 1.[28]
- A National Community Pharmacists Association poll showed that nearly 75% of adults do not follow their doctors' prescription orders, including not filling the prescription in the first place or taking less than the recommended dose.[29]

Patients do not follow their doctors' prescription recommendations for a wide variety of reasons. Patients may not believe that the treatment will help them or they may not adequately understand their illness and the need for treatment. Some patients may experience or fear potential side effects. Others suffer from cognitive or physical impairments that can reduce their adherence to medication regimens. Complex medication regimens, limited access to medicines, and poor relationships between prescribers and patients may also contribute to nonadherence.[30]

Improving Use of Medicines

Given the potential for better use of medicines, there are clear opportunities for various parts of the health care system to contribute to improvement. Employers, health plans, pharmacists, manufacturers, and other health care

Figure 8: Percentage of Doses Patients Take as Prescribed



SOURCE: A.J. Claxton, J. Cramer, and C. Pierce. "A Systematic Review of the Associations Between Dose Regimens and Medication Compliance." *Clinical Therapeutics* 2001; 23(8): 1296–1310.

stakeholders have taken on the challenge in differing ways. For example:

- To reduce their medical costs, employers and health plans are focusing on comprehensive medication management and decreasing cost sharing, which can pose a significant barrier to taking prescribed medicines.[31]
- Advances in information technology are enabling pharmacies to synchronize refills for patients who have multiple prescriptions to reduce the number of times a patient must go to the pharmacy. Some pharmacies now send out reminders to patients when they need to pick up a prescription and allow physicians to access their patients' medication fill histories to prevent drug interactions.
- The Centers for Medicare and Medicaid Services is tracking medication adherence rates for Part D Medicare Advantage and standalone prescription drug plans.
- Biopharmaceutical companies are continuing to develop innovative new therapies that make it easier for patients to take medicines by simplifying dosing regimens or reducing side effects.

There is no single solution to improving use of medicines. With diverse approaches, patients will gain more value from the medicines prescribed to keep them healthy.

[1]F.H. Gwadry-Sridhar, et al. "A Framework for Planning and Critiquing Medication Compliance and Persistence Using Prospective Study Designs." *Clinical Therapeutics* 2009; 31(2): 421–435.

[2]D.T. Lau and D.P. Nau. "Oral Antihyperglycemic Medication Nonadherence and Subsequent Hospitalization Among Individuals With Type 2 Diabetes." *Diabetes Care* 2004; 27(9): 2149–2153.

[3]American Pharmacists Association. "Medication Compliance-Adherence-Persistence (CAP) Digest." Washington, DC: American Pharmacists Association, 2003.

[4]D.T. Lau and D.P. Nau. *Op. cit.*

[5]A. Dragomir, et al. "Impact of Adherence to Antihypertensive Agents on Clinical Outcomes and Hospitalization Costs." *Medical Care* 2010; 48(5): 418–425.

[6]J.L. Schnipper, et al. "Role of Pharmacist Counseling in Preventing Adverse Drug Events After Hospitalization." *Archives of Internal Medicine* 2006; 166(5): 565–571.

[7]Congressional Budget Office. "Offsetting Effects of Prescription Drug Use on Medicare's Spending for Medical Services." Washington, DC: CBO, November 2012. Available at www.cbo.gov/sites/default/files/cbofiles/attachments/43741-MedicalOffsets-11-29-12.pdf (accessed February 2013).

[8]*Ibid.*

[9]L. Osterberg and T. Blaschke. "Adherence to Medication." *The New England Journal of Medicine* 2005; 353: 487–497.

[10]New England Healthcare Institute. "Thinking Outside the Pillbox: A System-wide Approach to Improving Patient Medication Adherence for Chronic Disease." Cambridge, MA: NEHI, August 2009.

[11]D.M. Cutler, et al. "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation." *Health Affairs* 2007; 26(1): 97–110.

[12]A.K. Jha, et al. "Greater Adherence to Diabetes Drugs is Linked to Less Hospital Use and Could Save Nearly $5 Billion Annually." *Health Affairs* 2012; 31(8): 1836–1846.

[13]D.C. Grabowski, et al. "The Large Social Value Resulting from Use of Statins Warrants Steps to Improve Adherence and Broaden Treatment," *Health Affairs* 2012; 31(10): 2276–2285.

[14]M.C. Roebuck, et al. "Medical Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending." *Health Affairs* 2011; 30(1): 91–99.

[15]R. DeVol and A. Bedroussian. "An Unhealthy America: The Economic Burden of Chronic Disease—Charting a New Course to Save Lives and Increase Productivity and Economic Growth." Santa Monica, CA: Milken Institute, October 2007. Available at www.milkeninstitute.org/pdf/chronic_disease_report.pdf (accessed February 2013).

[16]Integrated Benefits Institute. "A Broader Reach for Pharmacy Plan Design." San Francisco, CA: IBI, May 2007.

[17]G.S. Carls, et al. "Impact of Medication Adherence on Absenteeism and Short-Term Disability for Five Chronic Diseases." *Journal of Occupational and Environmental Medicine* 2012; 54(7): 792–805.

[18]See Congressional Budget Office baseline spending estimates for Medicare from 2004 through 2013. Available at www.cbo.gov/topics/retirement/medicare/data-and-technical-information (accessed February 2013).

[19]KRC Research. "Seniors' Opinions About Medicare Rx: 7th Year Update." KRC Survey for *Medicare Today*, September 2012.

[20]C.C. Afendulis and M.E. Chernew. "State-level Impacts of Medicare Part D." *American Journal of Managed Care* 2011; 17(Suppl 12): S.

[21]J.M. McWilliams, A.M. Zaslavsky, and H.A. Huskamp. "Implementation of Medicare Part D and Nondrug Medical Spending for Elderly Adults with Limited Prior Drug Coverage." *JAMA* 2011; 306(4): 402–409.

[22]C.C. Afendulis and M.E. Chernew. *Op.cit.*

[23]J.M. McWilliams, A.M. Zaslavsky, and H.A. Huskamp, *Op. cit.*

[24]Centers for Medicare & Medicaid Services. "Medicare Enrollment Reports." Available at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/MedicareEnrpts/index.html (accessed February 2013).

[25]KRC Research, *Op. cit.*

[26]M.A. Fischer, et al. "Primary Medication Non-Adherence: Analysis of 195,930 Electronic Prescriptions." *Journal of General Internal Medicine* 2010; 25(4): 284–290.

[27]R.B. Haynes, et al. "Interventions for Enhancing Medication Adherence." *Cochrane Database of Systematic Reviews* 2008; 16(2): CD000011.

[28]T. Higashi, et al. "The Quality of Pharmacologic Care for Vulnerable Older Patients." *Annals of Internal Medicine* 2004; 140(9): 714–720.

[29]National Community Pharmacists Association. "Take as Directed: A Prescription Not Followed." Research conducted by The Polling Company™. Alexandria, VA: National Community Pharmacists Association, December 16, 2006.

[30]L. Osterberg and T. Blaschke. *Op. cit.*

[31]The University of Michigan Center for Value-Based Insurance Design. "The Evidence for V-BID: Validating an Intuitive Concept." *V-BID Center Brief*, November 2012.

3 Supporting the Economy

Supporting the Economy

The biopharmaceutical industry continues to make major contributions to the U.S. economy. This sector generates high-quality jobs and powers economic output for the U.S. economy, serving as "the foundation upon which one of the United States' most dynamic innovation and business ecosystems is built."[1] The U.S. biopharmaceutical sector employs more than 810,000 workers, supports a total of nearly 3.4 million jobs across the country, and contributes nearly $790 billion in economic output on an annual basis when direct, indirect, and induced effects are considered.[2]

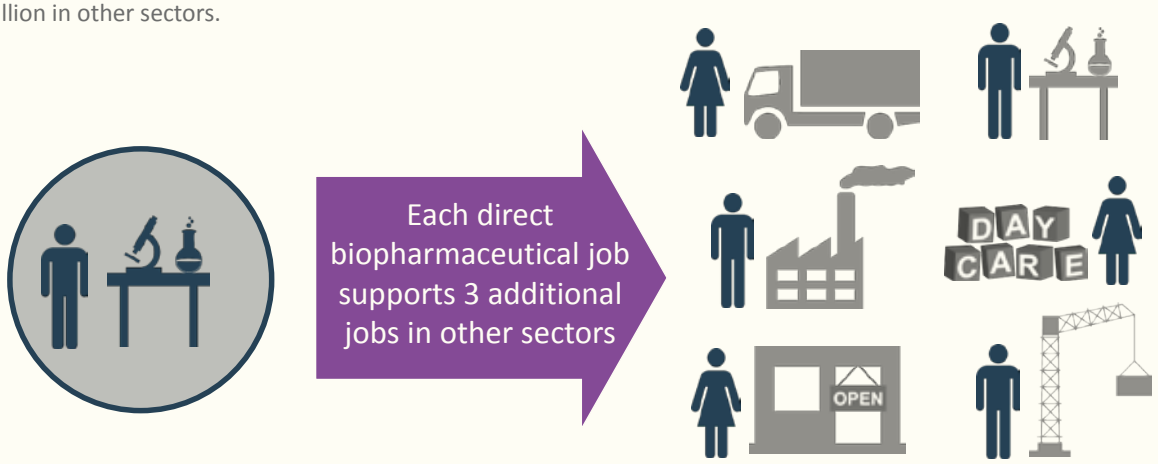
These economic impacts are driven by the industry's research and development (R&D) enterprise. (See Chapter 4 for more on investment in R&D.) The U.S. biopharmaceutical sector accounts for the single largest share of all U.S. business R&D, representing nearly 20% of all domestic R&D funded by U.S. businesses, according to data from the National Science Foundation.[3]

The high number of jobs that are supported indirectly reflects the fact that the industry is a "jobs multiplier," meaning that each biopharmaceutical sector job supports a total of four jobs throughout the economy. (See Figure 9 and sidebar, "Mapping the Impact.") The industry helps support a vibrant scientific and economic ecosystem that is vital to the U.S. economy and our country's competitiveness in the global market. Biopharmaceutical companies put down roots in communities across the country, helping to generate jobs across a whole range of sectors, from suppliers to retail to personal services.

The jobs the industry creates have high wages and require a workforce with diverse skills and educational levels, from Ph.D. scientists, to entry-level technicians, to support staff of all kinds.

Figure 9: The Ripple Effect of High-Value Biopharmaceutical Jobs

The biopharmaceutical sector supported nearly 3.4 million jobs across the economy in 2009, including about 3.3 million in other sectors.



Biopharma Jobs

More than 810,000 Jobs in the U.S. Biopharmaceutical Sector

Total Jobs Supported

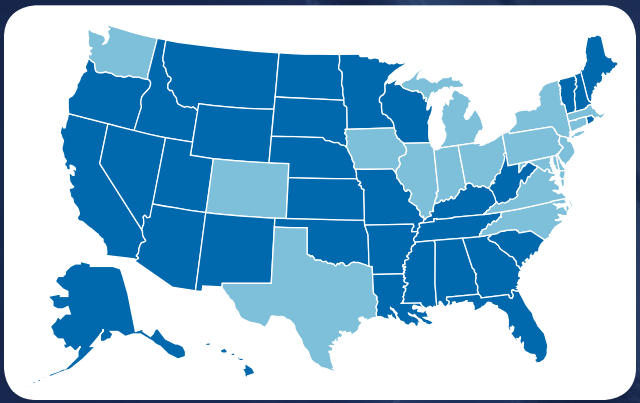
Nearly 3.4 million total U.S. Jobs Supported by the Biopharmaceutical Sector

SOURCE: Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013.

Mapping the Impact

In accomplishing the mission of bringing new medical treatments to the market, the biopharmaceutical industry sustains a very large-scale supply chain — both in R&D and in support of the production and distribution of biopharmaceutical products.

To provide insight into the breadth and depth of the industry's impact in the form of business relationships with vendors large and small, a recent analysis aggregated data from 17 innovative biopharmaceutical companies across 17 states. The analysis found that in 2011, these biopharmaceutical companies spent approximately $53 billion in transactions with vendors and suppliers in these states.[4] The recipient companies provided services and supplies to the industry. Although just a snapshot of the sector's total impact, these findings demonstrate the importance of a strong and vibrant biopharmaceutical industry in helping other businesses to grow and contribute to a strong local economy.



Vendor data from this analysis, broken down by congressional and state legislative district, can be viewed at www.weworkforhealth.org.

WEWORKFORHEALTH
WEWORKFORHEALTH.ORG

> *Science, technology, engineering, and mathematics (STEM) workers drive our nation's innovation and competitiveness by generating new ideas, new companies, and new industries. STEM workers play a key role in the sustained growth and stability of the U.S. economy and are critical components to helping the U.S. win the future.*[5]
>
> ► U.S. Department of Commerce

In 2011, the more than 810,000 direct jobs generated $89.9 billion in total personal income—averaging $110,490 in wages and benefits per worker. This was twice the average U.S. private sector compensation of $54,455, an indication of the high-quality jobs the biopharmaceutical industry provides to U.S. workers.[6]

Boosting State and Regional Economies

Clinical trials are the most costly portion of the drug development process, usually accounting for 45% to 75% of the $1.2 billion average cost of developing a new medicine.[7] Trials on average last 7 years and represent a large investment into the communities where they are conducted. Biopharmaceutical companies collaborate with local research institutions across the country — including clinical research centers, university medical schools, hospitals, and foundations — to carry out clinical trials, providing patients access to potential new treatments as well as creating local jobs.

A PhRMA program called "Research in Your Backyard" helps to illustrate the impact trials have on communities around the country. Sixteen state reports developed by the program have been released, highlighting the biopharmaceutical economic impact on these communities through clinical trials. For example, in Washington State, job growth in the biopharmaceutical industry grew 12% from 2007 through 2011, compared with a 2% decline in jobs for all other industries.[8] Since 1999,

biopharmaceutical companies working with local research institutions have conducted, or are conducting:

- Nearly 3,500 clinical trials in Maryland, including 1,775 for six major chronic diseases (asthma, cancer, diabetes, heart disease, mental illness, and stroke)[9]
- More than 3,000 trials in Colorado, including 1,400 for major chronic diseases[10]
- More than 3,600 trials in Georgia, including 1,800 targeting major chronic diseases[11]
- More than 3,400 trials in Virginia, including more than 1,500 for major chronic diseases[12]

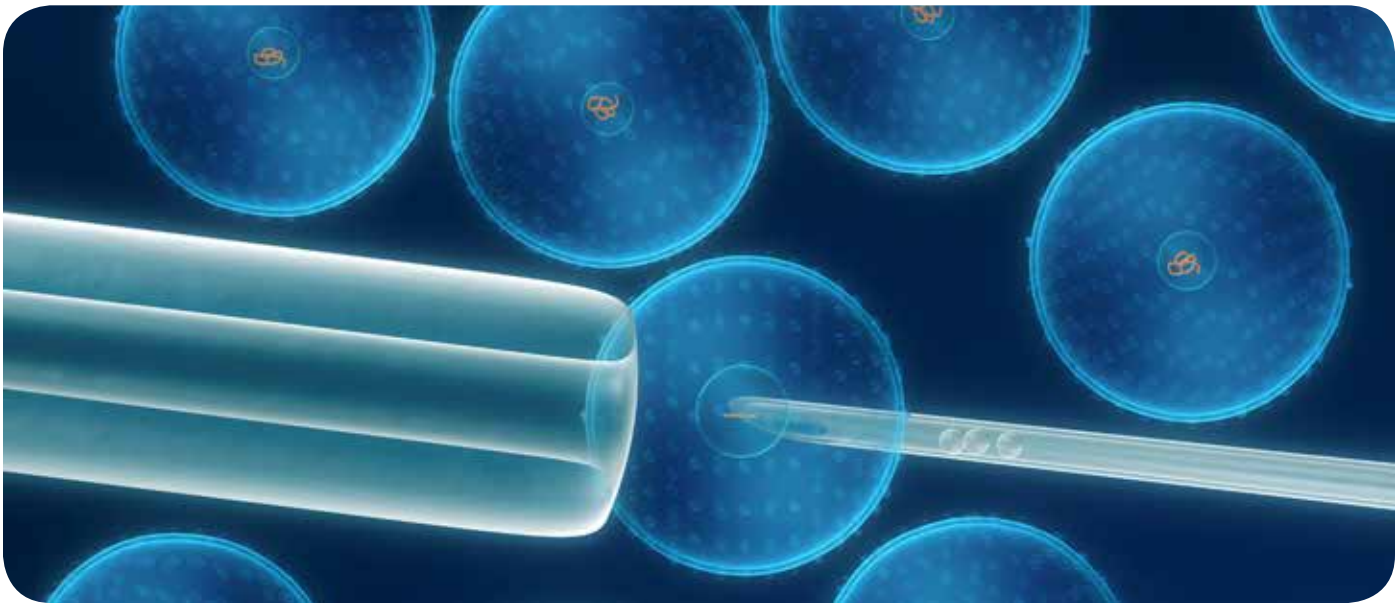
Although clinical trials provide an economic boost for communities, their primary benefit is to offer patients potential therapeutic options. Clinical trials may provide a new avenue of care for some chronic disease sufferers who are searching for the medicines that are best for them.

Ripple Effect of Industry R&D Support

Biopharmaceutical R&D continues to have a strong impact on the overall U.S. economy. PhRMA members have invested more than half a trillion dollars in R&D since 2000, including an estimated $48.5 billion in 2012 alone.[13] The impacts of this spending and the sector's broad support for biomedical research ripple across the economy.

Support for the R&D enterprise extends beyond the confines of any given company. In addition to supporting science, technology, engineering, and mathematics (STEM) education

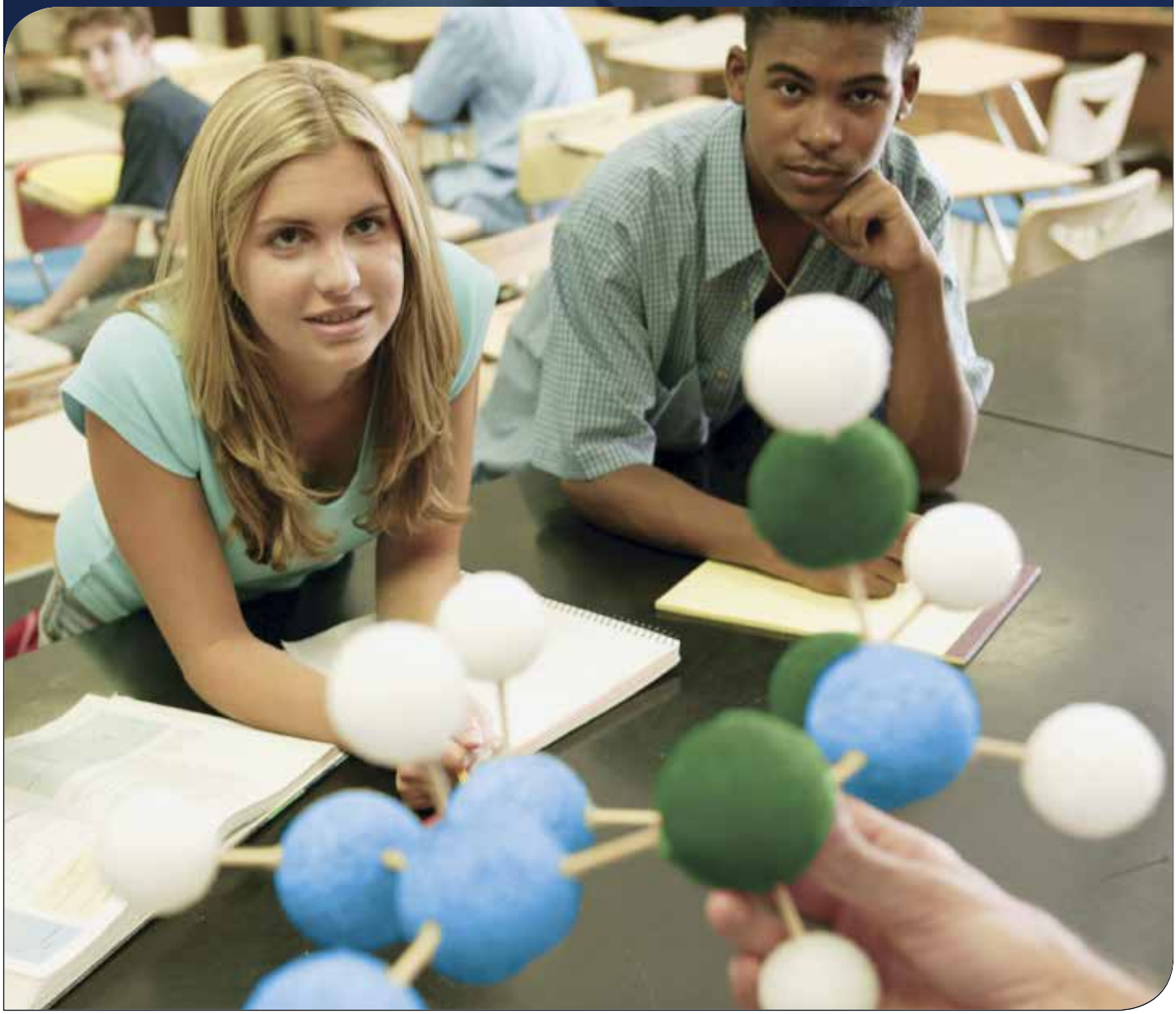
> *The STEM fields and those who work in them are critical engines of innovation and growth: according to one recent estimate, while only about five percent of the U.S. workforce is employed in STEM fields, the STEM workforce accounts for more than fifty percent of the nation's sustained economic growth.*[14]
>
> ► U.S. Department of Labor



STEM Jobs and Education: A Critical Focus for Today and Tomorrow

Science, technology, engineering, and mathematics (STEM) education is critical to continued U.S. global leadership. A workforce with strong STEM skills is essential to providing an adequate supply of workers with the skills necessary for the increasingly complex mission of developing 21st century medicines, and for the U.S. biopharmaceutical industry to maintain its competitive edge globally.

From 2001 to 2008, the biopharmaceutical industry outperformed other major STEM industries in generating jobs, and it is one of the few high-tech manufacturing sectors projected to add STEM-related jobs between 2010 and 2020.[15] However, many of these high-wage, high-value jobs may go unfilled if the United States continues to fall behind other countries in the quality of STEM education it provides its students. Improvements in this area would not only help the industry but also would benefit American workers as the average earnings for STEM workers are nearly twice as high as those of all workers, and STEM workers are also much less likely to experience joblessness.[16] Increasingly, biopharmaceutical companies are supporting STEM efforts around the country in many ways, including providing scholarships, mentoring students in local school districts, and funding and supporting teacher workshops and other professional development in STEM fields.



(see sidebar on page 24), innovative biopharmaceutical companies are engaged in a range of precompetitive research collaborations and partnerships with academic medical centers as well as increasingly supporting start-up and emerging companies through the establishment of corporate venture capital funds. These innovative collaborations not only help to ensure a robust future for the industry and the biopharmaceutical ecosystem, but benefit the larger national economy as well.

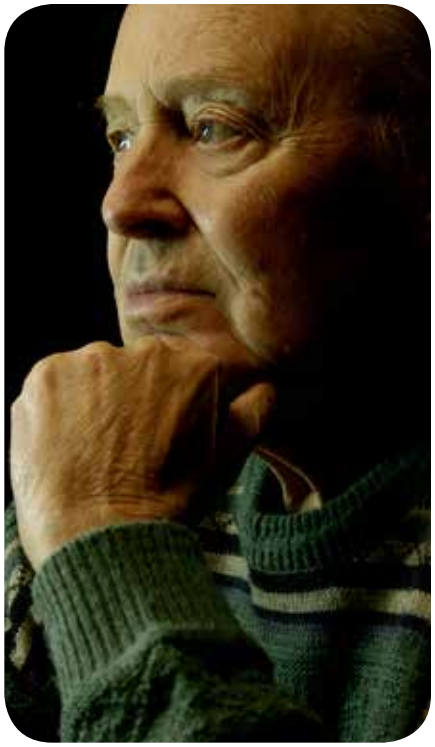
Partnerships Across Sectors

In recent years, biopharmaceutical companies have formed a growing number of partnerships with researchers in government, academia, smaller companies, and other parts of the biomedical ecosystem. The close and synergistic relationship between sectors in the biomedical research ecosystem is critical to ensuring a robust national biomedical research capacity in the United States.

The Tufts Center for the Study of Drug Development recently conducted an analysis of more than 3,000 partnerships of biopharmaceutical companies with academic medical centers (AMCs).[17] The analysis found that the partnerships benefit both industry and academia by providing opportunities for the sectors to work together to explore promising new technologies and address scientific problems that may lead to breakthroughs in treatments for the most challenging diseases and conditions. According to a report by PwC's Health Research Institute, "all large pharmaceutical companies have established at least one AMC partnership, often specific to a disease," and the number of partnerships is rising as the industry adopts a more collaborative approach to R&D.[18]

These relationships vary significantly and are continually evolving. Common partnership models include unrestricted research support, academic drug discovery centers, and precompetitive research centers, which incorporate a collaborative research model that brings together various institutions that ordinarily are commercial competitors to perform early-stage research collectively.

One prominent example of a precompetitive research collaboration is the Alzheimer's Disease Neuroimaging Initiative (ADNI), which includes federal agencies, nonprofit organizations, and industry members. The goal is to identify physical changes in the brain prior to the onset of Alzheimer's disease, track their progression, establish quality standards for imaging data collection and sharing, and validate biomarkers to be used in clinical trials.[19] Data collected from ADNI are made available at no cost to other researchers to analyze and use when designing Alzheimer's disease clinical trials and research projects.[20]



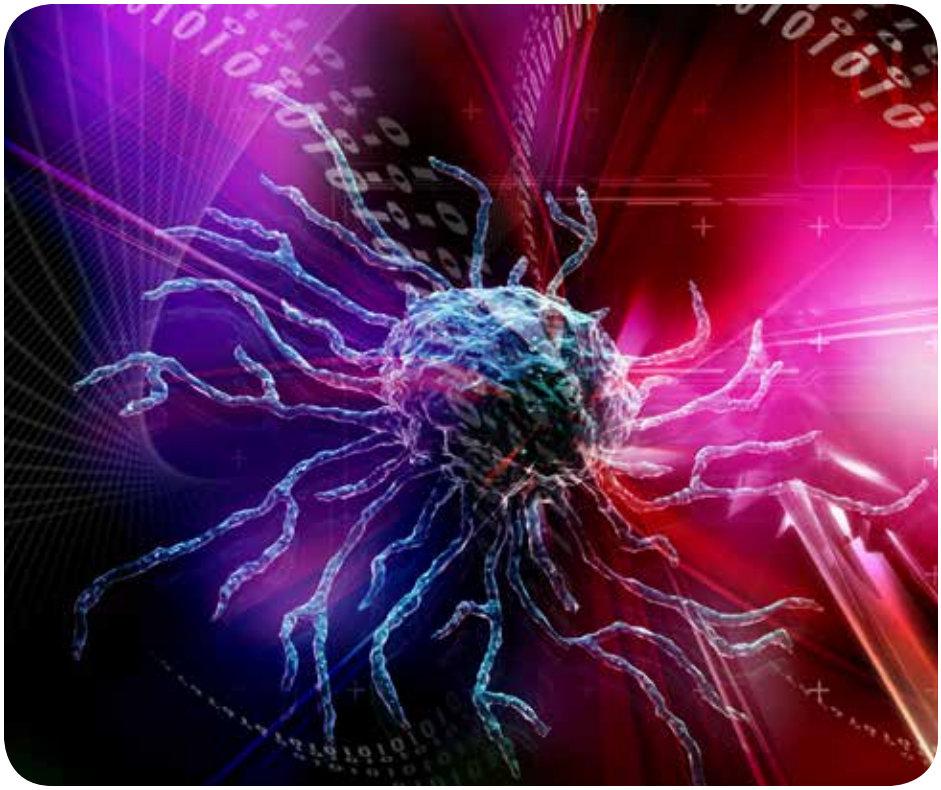
> ***The industry is funding and working collaboratively with the academic component of the public sector on basic research that contributes broadly across the entire spectrum of biomedical R&D, not just for products in its portfolio.[21]***
>
> ► Tufts Center for the Study of Drug Development, 2012

Corporate Venture Capital Investments

Venture capital (VC) and other forms of private capital are a key form of financing for start-up and emerging biopharmaceutical companies.

As traditional VC has recently declined due to several factors, including regulatory challenges and concerns about coverage and payment for new medical innovations, the corporate venture arms of established biopharmaceutical companies have become an increasingly important source of capital to help fill this gap. Between 2010 and 2012, biopharmaceutical corporate venture capital funds invested nearly $1.2 billion in biotechnology start-ups.[22] And corporate venture activity is on the rise. According to a recent report by the Boston Consulting Group, 63% of the 30 largest biopharmaceutical companies currently participate in corporate venture capital investments — up from 50% in 2007.[23]

> *Corporate venture funds may provide biotech startups with strategic benefits beyond investment capital. These include the opportunity to access technology, research knowledge and capacity, drug development expertise, marketing competence, and (often) a global presence ... Corporate venturing by multinational pharmaceutical and large biotech companies is playing an increasingly important role in financing the development of early stage innovation... and an essential role in the sustainability of the biotech ecosystem, advancing the future of pharmaceutical innovation and biotech entrepreneurship.*[24]
>
> ► Georg von Krogh, et al., *Nature Biotechnology*, 2012



Ensuring Access to Needed Medicines

The Partnership for Prescription Assistance

The biopharmaceutical industry has long provided access to medicines for patients who cannot afford them. The Partnership for Prescription Assistance (PPA) has helped nearly 8 million uninsured and financially struggling patients gain free and confidential access to 475 public and private patient assistance programs, including nearly 200 that are offered by pharmaceutical companies.[25] PPA member programs offer more than 2,500 brand-name medicines and generic drugs. More than 1,300 major national, state, and local organizations have joined the PPA, including the American Academy for Family Physicians, American Cancer Society, American College of Emergency Physicians, Easter Seals, National Association of Chain Drug Stores, United Way, and the Urban League.

Patients can learn about and apply to the PPA by visiting www.pparx.org or calling toll-free 1-888-4PPA-NOW. The call center can provide help in English, Spanish, and about 150 other languages.

Rx Response

Ensuring access to medicines following a major disaster is a critical priority for biopharmaceutical companies. In the aftermath of Hurricane Katrina, the industry realized that the absence of a single point of contact through which federal and state officials could reach the biopharmaceutical supply chain was a serious problem.

Rx Response is a unique collaborative initiative that brings together biopharmaceutical companies, distributors, and dispensers, along with the American Red Cross, to help ensure the continued flow of medicines following a major disaster. In the 6 years since its inception, Rx Response has become an indispensable homeland security and public health asset. In October 2012, Rx Response was activated to address threats to the supply chain posed by Super Storm Sandy.

Among its most valuable resources is the Pharmacy Status Reporting Tool, an online resource that maps the location of open pharmacies in disaster-stricken areas. For additional disaster planning resources and more information about Rx Response, visit RxResponse at www.rxresponse.org.

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[1]Battelle Technology Partnership Practice. "The U.S. Biopharmaceuticals Sector: Economic Contribution of the Nation." Columbus, OH: Battelle Memorial Institute, July 2011. Prepared for Pharmaceutical Research and Manufacturers of America.

[2]Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013. Note: The economic impact estimates developed by Battelle and presented here reflect several methodological refinements and thus are not directly comparable to previous estimates prepared for PhRMA. These estimates now more accurately capture the core functions of today's innovative biopharmaceutical industry and better capture headquarters' jobs.

[3]National Science Board. "Science and Engineering Indicators 2012." Arlington VA: National Science Foundation (NSB 12-01), 2012.

[4]We Work for Health. "Working with Local Businesses." Available at www.weworkforhealth.org (accessed February 2013).

[5]D. Langdon, et al. "STEM: Good Jobs Now and for the Future." ESA Issue Brief #03-11. Washington, DC: U.S. Department of Commerce, July 2011. Available at www.esa.doc.gov/sites/default/files/reports/documents/stemfinalyjuly14_1.pdf (accessed February 2013).

[6]Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013.

[7]J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479.

[8]Pharmaceutical Research and Manufacturers of America. "Research in Your Backyard: Developing Cures, Creating Jobs: Pharmaceutical Clinical Trials in Washington." Washington, DC: PhRMA, 2012. Available at http://phrma.org/sites/default/files/344/2013washingtonriyb.pdf (accessed February 2013).

[9]Pharmaceutical Research and Manufacturers of America. "Research in Your Backyard: Developing Cures, Creating Jobs: Pharmaceutical Clinical Trials in Maryland." Washington, DC: PhRMA, 2012. Available at http://phrma.org/sites/default/files/344/2012marylandresearchinyourbackyard.pdf (accessed February 2013).

[10]Pharmaceutical Research and Manufacturers of America. "Research in Your Backyard: Developing Cures, Creating Jobs: Pharmaceutical Clinical Trials in Colorado." Washington, DC: PhRMA, 2012. Available at www.phrma.org/sites/default/files/344/phrmaresearchinyourbackyardcolorado20120319.pdf (accessed February 2013).

[11]Pharmaceutical Research and Manufacturers of America. "Research in Your Backyard: Developing Cures, Creating Jobs: Pharmaceutical Clinical Trials in Georgia." Washington, DC: PhRMA, 2012. Available at www.phrma.org/sites/default/files/344/phrmaresearchinyourbackyardgeorgia201201.pdf (accessed February 2013).

[12]Pharmaceutical Research and Manufacturers of America. "Research in Your Backyard: Developing Cures, Creating Jobs: Pharmaceutical Clinical Trials in Virginia." Washington, DC: PhRMA, 2012. Available at http://phrma.org/sites/default/files/344/2013virginiariyb.pdf (accessed February 2013).

[13]Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013.

[14]U.S. Department of Labor. "The STEM Workforce Challenge: The Role of the Public Workforce System in a National Solution for a Competitive Science, Technology, Engineering, and Mathematics (STEM) Workforce." Washington, DC: DOL, April 2007. Available at www.doleta.gov/youth_services/pdf/STEM_Report_4%2007.pdf (accessed February 2013).

[15]PhRMA analysis based on Bureau of Labor Statistics. "Employment and Output by Industry (2012)." Washington, DC: BLS, 2012. Available at www.bls.gov/emp/ep_table_207.htm (accessed December 2012).

[16]National Science Board, *Op. cit.*

[17]C.P. Milne and A. Malins. "Academic–Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Boston, MA: Tufts Center for the Study of Drug Development, April 2012.

[18]PwC Health Research Institute. "New Chemistry: Getting the Biopharmaceutical Talent Formula Right." New York, NY: PricewaterhouseCoopers LLP, February 2013.

[19]National Institutes of Health. "Alzheimer's Disease Neuroimaging Initiative Enters Next Phase of Research." Bethesda, MD: NIH, 21 October 2010.

[20]Foundation for the National Institutes of Health. "Alzheimer's Disease Neuroimaging Initiative (ADNI)." Available at www.fnih.org/work/areas/chronic-disease/adni (accessed August 2012).

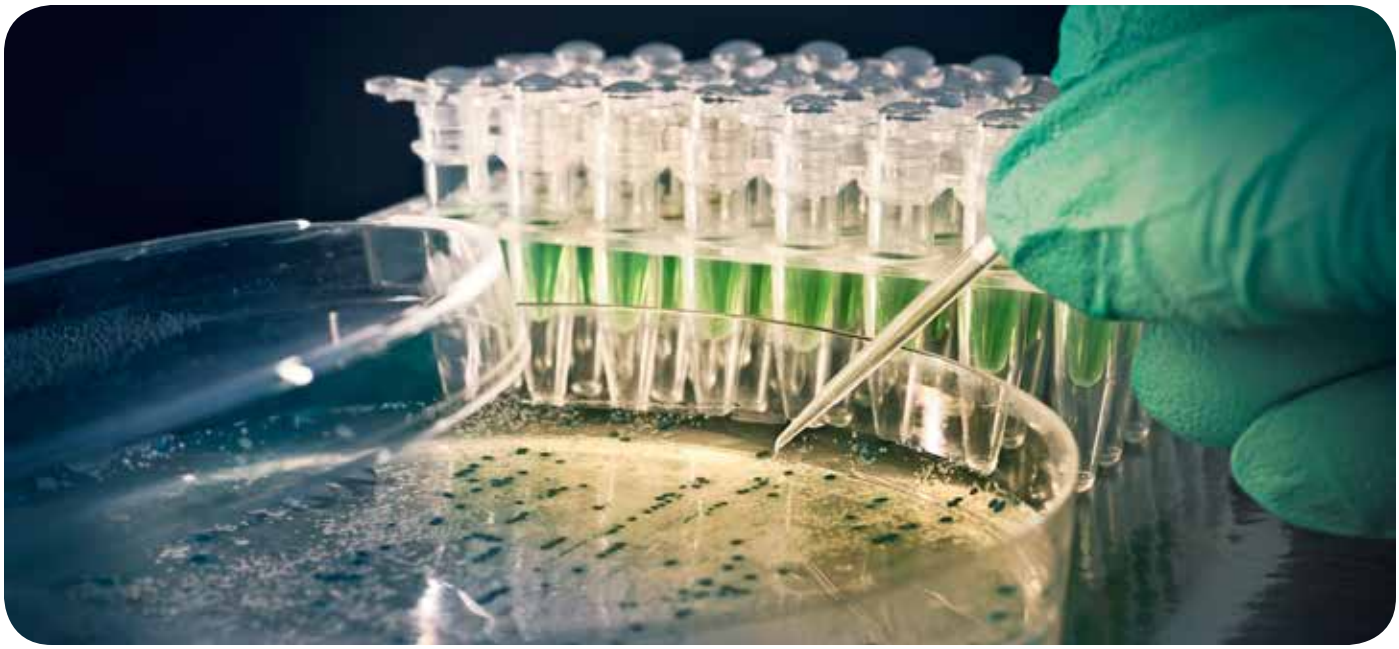
[21]C.P. Milne and A. Malins, *Op. cit.*

[22]PricewaterhouseCoopers LLP and National Venture Capital Association. "2012 MoneyTree Report." New York, NY: PricewaterhouseCoopers LLP, January 2013.

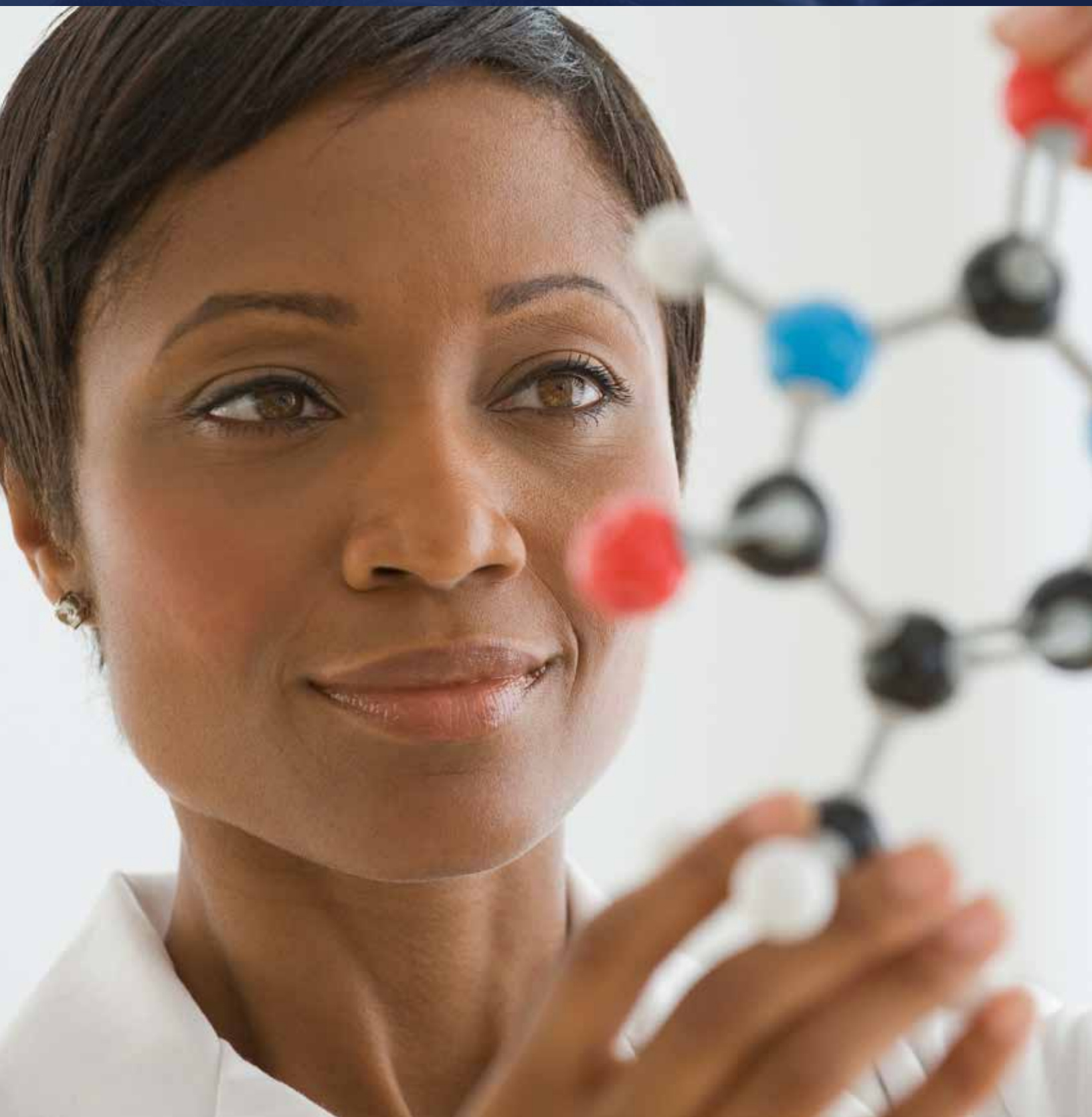
[23]F. Bielesch, et. al. "Corporate Venture Capital: Avoid the Risk, Miss the Rewards." Boston, MA: Boston Consulting Group, October 2012.

[24]G. von Krogh, et al. "The Changing Face of Corporate Venturing in Biotechnology." *Nature Biotechnology* 2012; 30(10): 911–915.

[25]The Partnership for Prescription Assistance. "Facts About PPA." Available at www.pparx.org/en/about_us/facts_about_ppa (accessed April 2013).



4 R&D: Delivering Innovation



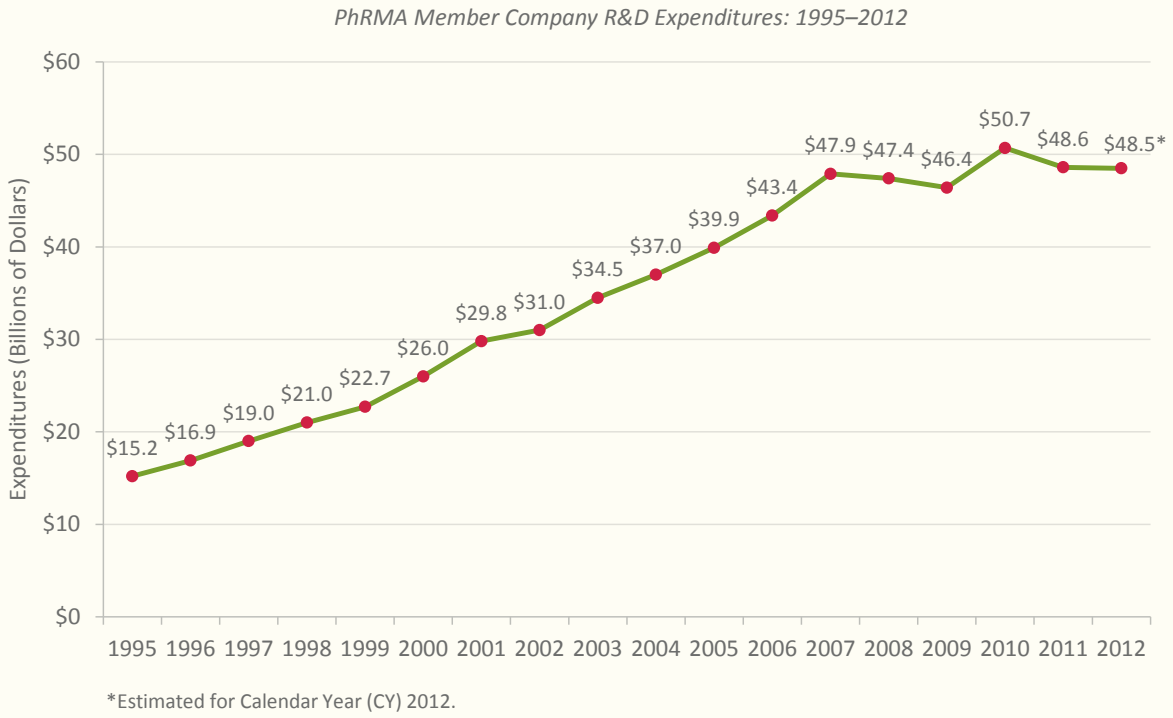
R&D: Delivering Innovation

Discovering and developing new medicines is a long, complex, and costly process, but biopharmaceutical researchers devote their careers to this often frustrating but tremendously gratifying task. The research and development (R&D) process is the road to new medicines — and more often than not it entails many turns, stops, and starts. Substantial progress typically occurs in increments over time, as advances build on each other.

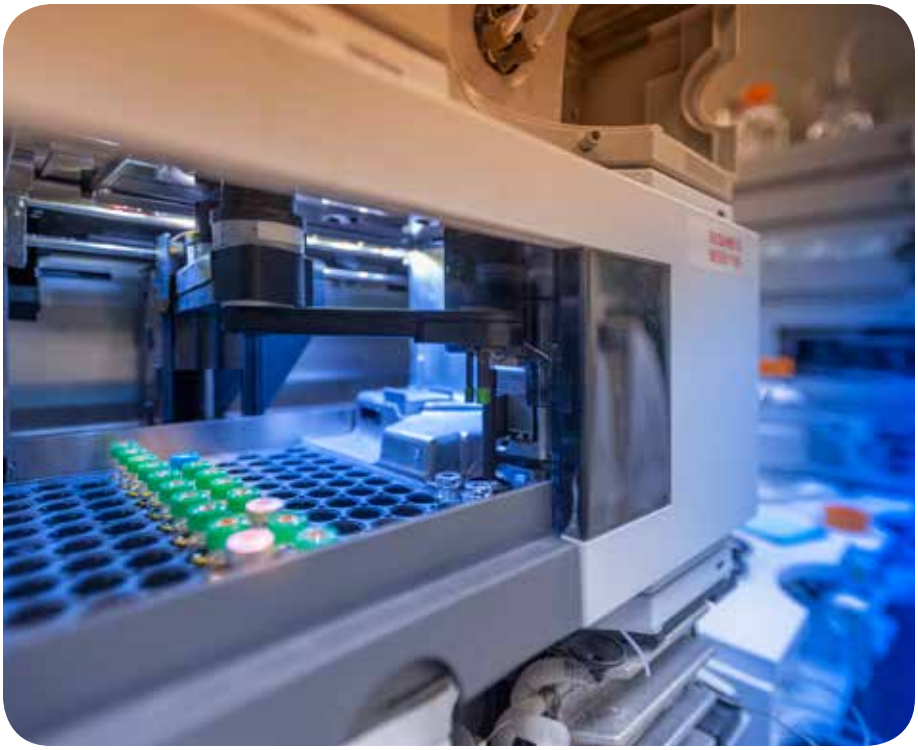
In 2012, Pharmaceutical Research and Manufacturers of America (PhRMA) member companies invested an estimated $48.5 billion in R&D.[1] This strong investment is part of the industry's ongoing commitment to innovation; since 2000, PhRMA members have spent more than half a trillion dollars on R&D.[2] PhRMA members' yearly investments represent the majority of all biopharmaceutical R&D spending in the United States.[3]

According to the Congressional Budget Office, "The pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest

Figure 10: Biopharmaceutical Companies Continue to Invest Strongly in R&D



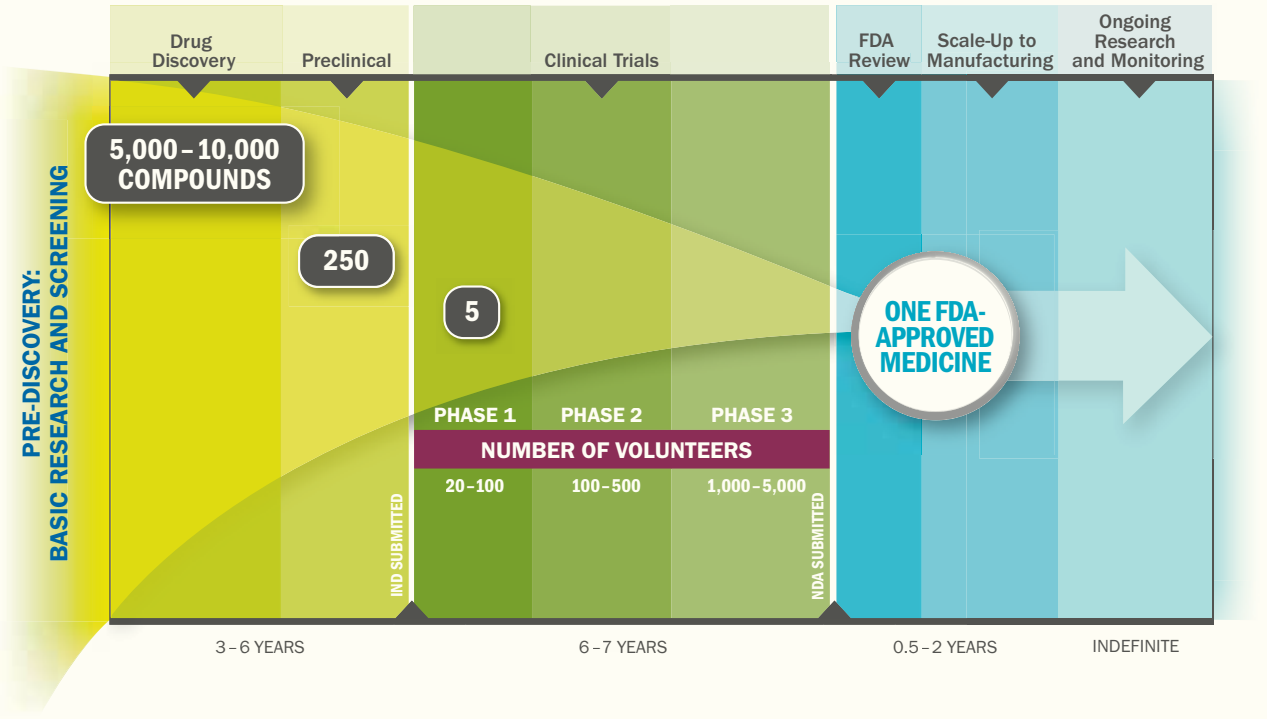
SOURCE: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 1996–2013.



as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm."[4]

Today, more than 5,000 medicines are in clinical trials globally or in U.S. Food and Drug Administration (FDA) review.[5] All of these have the potential to benefit U.S. patients, and each must undergo the same rigorous process to determine safety and efficacy for patient use. (For more information about the many innovative medicines in the pipeline, see Chapter 5.)

Figure 11: The Research and Development Process



Overview of the R&D Process

For those who do not work directly in drug development, the difficulty of the process can be hard to grasp. Numbers can help give a sense of the gauntlet of challenges each candidate medicine must pass through, and those numbers are daunting:

- On average, it takes about 10 to 15 years for a new medicine to complete the journey from initial discovery to the marketplace.[6,7,8]
- For every 5,000 to 10,000 compounds that enter the pipeline, only one receives approval. Even medicines that reach clinical trials have only a 16% chance of being approved.[9]
- The process is costly. The average R&D investment for each new medicine is $1.2 billion, including the cost of failures,[10] with more recent studies estimating the costs to be even higher.[11]

Each potential new medicine goes through a long series of steps on its way to patients. Figure 11 outlines this process.

Drug Discovery

The first step in developing a new medicine is to understand the disease or condition as thoroughly as possible. The entire biomedical research community contributes to this body of knowledge. In the United States, we are fortunate to have a have a dynamic, collaborative research ecosystem that includes researchers from government, industry, and academia.

From the earliest stages of basic research to drug approval, this collaborative ecosystem is among our greatest strengths in moving medical advances forward and making the United States the worldwide leader in biopharmaceutical innovation. (For more information on this ecosystem and these partnerships, see page 25 in Chapter 3 and Figure 12 below.)

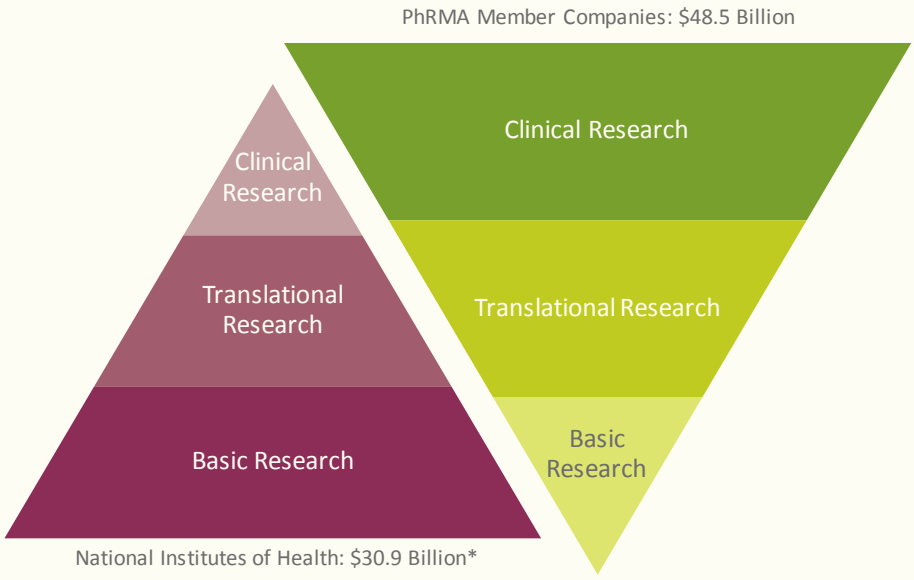
Basic research provides clues about how to treat diseases and potential ways to target the symptoms or underlying causes. Armed with an idea, researchers work to understand biological targets for a potential medicine. A drug target can be a protein, RNA, DNA, or other molecule that is somehow involved in the disease. The investigators conduct studies in cells, tissues, and animal models to determine whether the target can be influenced by a medicine.

Then researchers look for a lead compound — a promising molecule that could influence the target and, potentially, become a medicine. They do this in various ways, including creating a molecule from scratch, using high-throughput screening techniques to select a few promising possibilities from among thousands of potential candidates, finding compounds from nature, and using biotechnology to genetically engineer living systems to produce disease-fighting molecules.

Even at this early stage, investigators already are thinking about the final product. Issues such as the formulation (or "recipe") of a medicine and its delivery system (for example, whether it is taken in pill form, injected, or inhaled) are critical if a compound is to become a successful new medicine.

Figure 12: Government and Industry Roles in Research & Development

Government and biopharmaceutical industry research complement one another.



*NIH spending is for FY 2012. PhRMA member companies' spending is estimated for CY 2012. PhRMA member companies account for the majority of private biopharmaceutical R&D spending. Non-member company data are not included.

SOURCES: Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013; National Institutes of Health (NIH), Office of Budget. "History of Congressional Appropriations, Fiscal Years 2000–2012." Bethesda, MD: NIH, 2012. http://officeofbudget.od.nih.gov/pdfs/FY12/Approp.%20History%20by%20IC)2012.pdf (accessed February 2013); Adapted from E. Zerhouni. "Transforming Health: NIH and the Promise of Research." Transforming Health: Fulfilling the Promise of Research. Washington, DC. November 2007. Keynote address. www.researchamerica.org/transforming_health_transcript (accessed January 2013).

Preclinical Testing

The drug discovery phase whittles down thousands of compounds to a few hundred promising possibilities that are ready for preclinical testing. In this stage, scientists conduct laboratory and animal studies to determine whether a compound is suitable for human testing. At the end of this process, which can take several years, around five compounds move to the next stage of testing in humans. The company files an Investigational New Drug Application with the FDA to begin clinical trials.

Clinical Trials

During this stage, a compound is tested in human volunteers. The clinical trials process occurs in several phases and takes on average 6 to 7 years. A potential medicine must successfully complete each phase before being submitted to the FDA for review.

Because this process involves both benefits and risks, companies take great care to protect the safety of trial participants and to ensure that they are thoroughly informed about the trial and its potential risks so that they can provide informed consent to participate, as required by federal regulations. Companies also ensure that the trials are conducted correctly and with integrity and that clinical trial results are disclosed at the appropriate time.

Clinical Trial Principles

PhRMA members have had a longstanding commitment to sponsoring clinical research that fully complies with all legal and regulatory requirements as well as international agreements. In addition, PhRMA has set out voluntary principles to fortify member companies' commitment to the highest standards for ethics and transparency in the conduct of clinical trials. PhRMA's *Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results* are designed to help ensure that clinical research conducted by America's pharmaceutical research and biotechnology companies continues to be carefully conducted and that meaningful medical research results are communicated to health care professionals and patients.

Learn more about PhRMA's *Principles on Conduct of Clinical Trials.*
Scan QR code ▶

The study design and the informed consent are reviewed, approved, and monitored by an Institutional Review Board (IRB). The IRB is made up of physicians, researchers, and members of the community. Its role is to make sure that the study is ethical and the rights and welfare of participants are protected. This includes ensuring that research risks are minimized and are reasonable in relation to any potential benefits.[12]

Following is a general description of the three primary phases of clinical research:

- **Phase 1** trials test a compound in a small group (e.g., 20 to 100) of healthy volunteers to determine the safety of the compound.
- **Phase 2** trials test the compound in a somewhat larger group (e.g., 100 to 500) of volunteers who have the disease or condition the compound is designed to treat. Phase 2 trials determine effectiveness of the compound, examine possible short-term side effects and risks, and identify optimal dose and schedule.
- **Phase 3** trials test the compound in a much larger group (e.g., 1,000 to 5,000) of participants to generate statistically significant information about safety and efficacy and to determine the overall benefit-risk ratio.

FDA Review and Approval

If the results of all three clinical trial phases indicate that the compound is safe and effective, the company submits a New Drug Application or Biologics License Application to the FDA. This application, which includes reams of data from all stages of testing, is a request for FDA approval to market the new medicine.

Scientists at the FDA carefully review all the data from all of the studies on the compound and, after weighing the benefits and risks of the potential medicine, decide whether to grant approval. Occasionally, the FDA will ask for additional research before granting approval or convene an independent expert panel to consider data presented by the FDA and the company. The panel will then advise the agency on whether to approve the application and under what conditions.

Manufacturing

Approved medicines may be used by millions of people or a small, specific population. Medicines often are in the marketplace for many years. As a result, manufacturing facilities must be carefully planned so that medicines can be consistently and efficiently produced.

Manufacturing facilities must be constructed to the highest standards to ensure that safety and quality are built into each step of the manufacturing process.[13] Companies must adhere to FDA's Good Manufacturing Practices regulations, and they also must constantly update, overhaul, or even rebuild facilities when new medicines are approved, as each new medicine is manufactured differently.

Drug Lifecycle

The R&D process is part of a larger prescription drug lifecycle. The cycle begins with the initial development of the medicine and it ends with generic drugs. Generics provide low-cost access to effective medicines for many years. But we would not have generics if innovator companies did not commit the time, resources, and investment to research and develop new, innovative medicines.

After FDA approval, the average effective patent life of a brand name medicine is about 12 years.[14] Competition often begins soon after approval, with generics frequently coming to the market even earlier through patent challenges, and other competing brand drugs commonly coming to market. During the period of patent protection, the medicine must earn enough revenue to fund the drug development pipeline for other candidates that may someday become new drugs. Only 2 of every 10 brand name medicines earn sufficient revenues to recoup average R&D costs.[15]

After patent protection expires, other companies are allowed to sell generic copies of the innovative drug. These medicines, which are often adopted rapidly, can be offered at low cost because the generic companies can base their approval on the extensive research already conducted to develop the brand name medicine. Today, we estimate that 84% of all drug prescriptions are filled generically,[16] yielding a savings of $1.1 trillion dollars in the past decade.[17] With the passage of the Affordable Care Act, an abbreviated approval pathway was created for biosimilars, which will further increase competition.

Post-Approval Research and Monitoring

Research on a new medicine does not end when the discovery and development phases are over and the product is on the market. On the contrary, companies conduct extensive post-approval research to monitor safety and long-term side effects in patients using the medicine. The FDA requires that companies monitor a medicine for as long as it stays on the market and submit periodic reports on safety issues. Companies must report any adverse events that occur from use of the medicine.

FDA sometimes requires companies to conduct phase 4 clinical trials, which evaluate long-term safety or effects in specific patient subgroups. Companies may conduct post-approval studies to assess the benefits of a medicine for different populations or in other disease areas. In some cases, they may also develop improved delivery systems or dosage forms.

This research phase is critical to improving researchers' and clinicians' understanding of a medicine's potential uses and its full benefits for health and quality of life. Continued research can show whether a medicine has a greater impact on an outcome when it is used earlier in a disease, in combination with other medicines, in different disease indications, or in combination with specific biomarkers (see the section "The Evolving Value of Medicines" in Chapter 1, page 9).

The Evolving R&D Process

As science advances and opens new doors, the R&D process continually changes and adapts. New scientific advances are bringing greater promise but also increasing complexity. Here are just a few examples of the forces that are changing the R&D process:

Working on the molecular level: In recent years, scientists' deepening understanding of the molecular and genetic underpinnings of disease has brought unprecedented opportunities and dramatically changed many aspects of drug development.

Figure 13: Increasing Complexity of Clinical Trials

During the last decade, clinical trial designs and procedures have become much more complex, demanding more staff time and effort, and discouraging patient enrollment and retention.

Trends in Clinical Trial Protocol Complexity

	2000–2003	2008–2011	Percentage Change
Total Procedures per Trial Protocol (median) (e.g., bloodwork, routine exams, x-rays, etc.)	105.9	166.6	57%
Total Investigative Site Work Burden (median units)	28.9	47.5	64%
Total Eligibility Criteria	31	46	58%
Clinical Trial Treatment Period (median days)*	140	175	25%
Number of Case Report Form Pages per Protocol (median)	55	171	227%

*These numbers reflect only the "treatment duration" of the protocol.

SOURCE: K.A. Getz, R.A. Campo, and K.I. Kaitin. "Variability in Protocol Design Complexity by Phase and Therapeutic Area." *Drug Information Journal* 2011; 45(4): 413–420. Updated data provided through correspondence with Tufts Center for the Study of Drug Development.

Researching more complex diseases: Increasingly, clinical investigators are exploring treatment options for more complex diseases such as neurological disorders, cancer, and many rare diseases. For example, in 2003 there were 26 medicines in development for Alzheimer's disease in the United States; today there are 94.[18,19] New scientific opportunities make these new avenues of exploration possible, but the complexities of these uncharted areas also can in some cases mean that research projects are less likely to succeed.

Advancing personalized medicine: With the emergence of personalized medicine — in which the use of a medicine is linked to a diagnostic to determine if a patient will respond well to a medicine — the R&D process has become more complex. Drug developers must coordinate research on a new medicine along with a corresponding diagnostic.

In this increasingly complicated research scheme, it is necessary to dig deeper into how each patient may respond to a therapy and to keep pace with expanding regulatory requirements. As a result of these changes, the burden of executing a clinical trial is growing, with more procedures required, more data collected, more numerous and complex eligibility criteria for study enrollment, and longer study duration.[20] (See Figure 13.) In fact, the form used to collect data from each patient expanded in length by 227% between 2000 and 2011, reflecting the growing challenges of conducting clinical trials.[21]

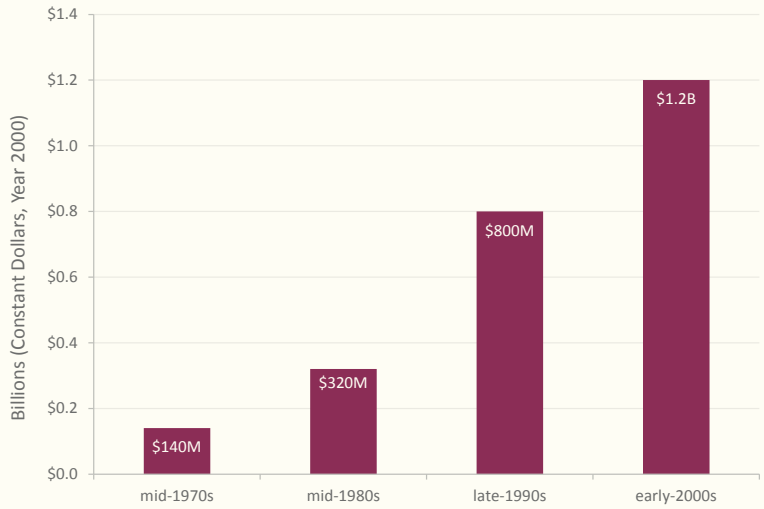
Recruitment of patient volunteers is also an ongoing and growing challenge for researchers. Difficulty recruiting volunteers extends the original timeline of phase 2 to 4 trials by nearly double on average across all therapeutic areas.[22]

The increased complexity of the research environment has contributed to the rising costs of clinical research.[23] Treatment failures and setbacks also contribute to the cost of research. According to the Tufts Center for the Study of Drug Development, the cost of developing a drug (including the cost of failures) grew from $800 million in

Figure 14: Average Cost to Develop One New Medicine

It costs an average of $1.2 billion to develop one new drug, with more recent studies estimating the costs to be even higher.

The Average Cost to Develop One New Approved Drug — Including the Cost of Failures



SOURCES: J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185; J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479; More recent estimates range from $1.5 billion to more than $1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.
NOTE: Data is adjusted to 2000 dollars based on correspondence with J.A. DiMasi.

the late 1990s to about $1.2 billion in the early 2000s.[24] (See Figure 14.) Other more recent studies have put the total cost even higher.[25]

Adapting to Changes and Challenges

The biopharmaceutical industry is continually adapting to produce innovative treatments more efficiently. Researchers are exploring ways to reduce development times and increase the odds of success using new research tools, new approaches to patient recruitment, and sophisticated methods of analyzing data.

Companies are working to develop innovative partnerships and collaborative relationships with researchers in academia, government, and in other companies. Precompetitive partnerships, which seek to advance basic research, are a growing part of this approach.[26]

Improving the clinical trials process is another area of active exploration. For example, phase 0 or "microdosing" trials allow researchers to test a very small dose in fewer human volunteers to eliminate more quickly drug candidates that may be metabolically or biologically ineffective.

No one change will transform the R&D process on its own, but with many diverse efforts biopharmaceutical companies will continue to improve the process of innovation.

> ***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."[27]***
>
> ► Tufts Center for the Study of Drug Development, 2011

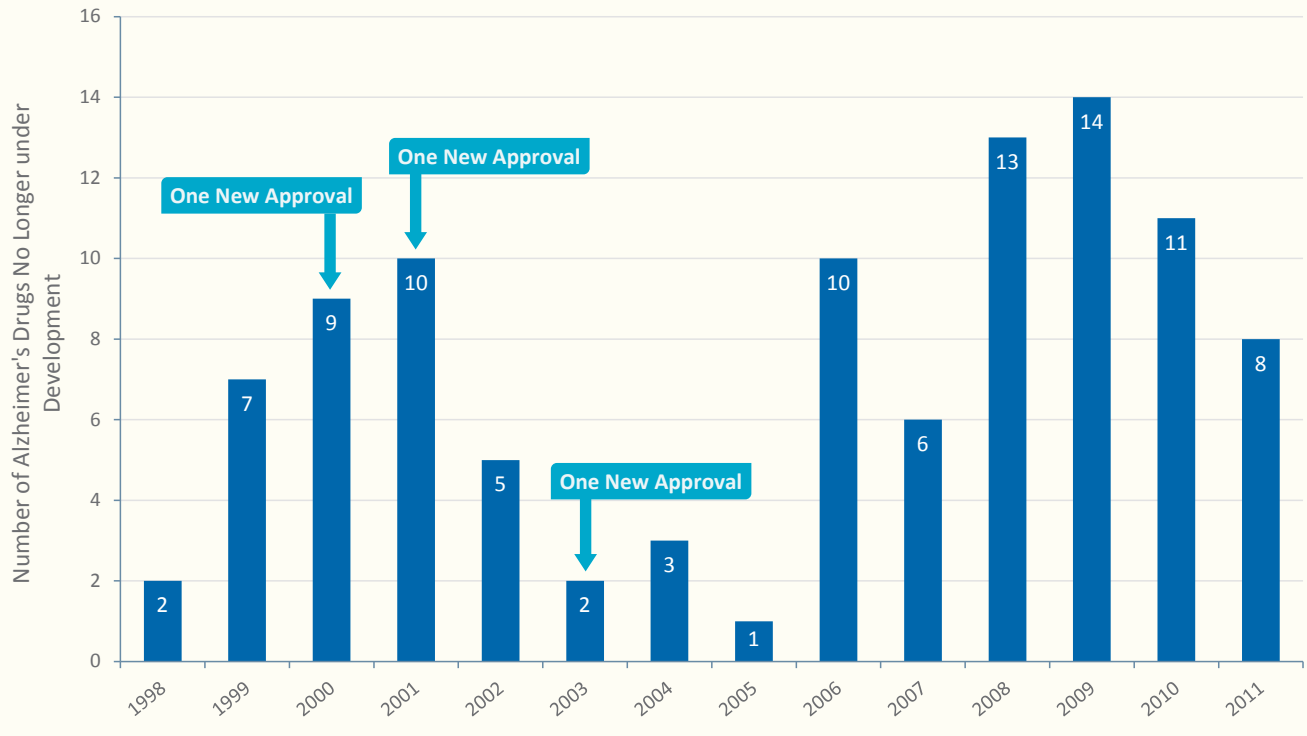
Learning from Setbacks in Alzheimer's Disease Research

Not only do successes build over time, but so do lessons learned from seemingly failed projects and research. Alzheimer's disease is commonly considered one of the most devastating conditions anyone can face and is the sixth leading cause of death in the United States.[28] The disease progressively robs people of their memory, their personality, and their health.[29] What's more, the Alzheimer's Association projects that the disease will cost the U.S. health care system $1.1 trillion annually by 2050.[30]

Today's medicines can address symptoms of Alzheimer's, but medicines that prevent or slow the disease are needed. Although researchers continue to discover and learn more, the underlying causes and mechanisms of this disease remain elusive, and the complex nature of the disease presents huge challenges to scientists.

Since 1998, biopharmaceutical companies have made 101 unsuccessful attempts to develop medicines to treat Alzheimer's while, in the same period, only three medicines have been approved. That means that for every success, companies have experienced 34 so-called "failures."[31] (See Figure 15.) Although these setbacks may be disheartening, they are certainly not failures because they contribute valuable knowledge about Alzheimer's that can be used as building blocks to point researchers in more fruitful directions.

Figure 15: Unsuccessful Alzheimer's Drugs in Development, 1998 – 2011
Total unsuccessful drugs=101



SOURCE: Pharmaceutical Research and Manufacturers of America. "Researching Alzheimer's Medicines: Setbacks and Stepping Stones." Washington, DC: PhRMA, September 2012. Available at http://phrma.org/sites/default/files/1864/alzheimersetbacksreportfinal912.pdf (accessed February 2013).

Understanding the Nature of Progress and Innovation

Occasionally one breakthrough will transform treatment of a disease, but most often discoveries and approvals build on each other over time in a cumulative process resulting in significant clinical advances. To progress from no treatments to effective treatments, the R&D process must be repeated over many years for many drugs, which build upon one another incrementally.

Research on individual medicines also accumulates over time. Although initial market approval by the FDA is a critical first step in ensuring a medicine is reaching patients, the approval often lays the foundation for additional learning and research that will shape the way a product is used in years to come. (See the section on the evolving value of medicines in Chapter 1, page 9.)

Recognizing the step-wise nature of innovation is essential to ensuring that progress continues.

> *Incremental advances can add up to transformative changes.*[32]
>
> ▶ Dr. Siddhartha Mukherjee, *The Emperor of All Maladies*, 2010

Recognizing Researchers and Patient Advocates for Alzheimer's Disease

In September 2012, PhRMA bestowed the first annual Research and Hope Award, honoring individuals and organizations in academia, the biopharmaceutical research sector, as well as the patient and caregiving communities that have contributed significantly to the advancement of medical progress and patient care for Alzheimer's. Information about the award recipients is available at www.phrma.org/awards.

Biopharmaceutical researchers are responding to this complex scientific challenge and are committed to finding treatments for Alzheimer's disease. There are nearly 100 new medicines in development in the United States.[33] As researchers examine the science and clinical data behind both the successes and the stumbling blocks, there is hope for a future in which this devastating disease can be managed successfully or even cured or prevented altogether.

Key Legislation in 2012 Fosters Innovation

In 1992, the Prescription Drug User Fee Act (PDUFA) authorized the FDA to collect user fees from the biopharmaceutical industry to hire additional drug reviewers and safety specialists. These funds supplement Congressional appropriations. In its first 20 years, PDUFA has helped to bring more than 1,500 new medicines to market. It also has increased FDA's staffing and resources and preserved and strengthened FDA's high safety standards, resulting in a drop in approval times for new medicines from 29 months in the early 1990s to an estimated 10 months in 2010.[34,35]

In 2012, the fifth authorization of PDUFA (called PDUFA-V) was enacted as part of the Food and Drug Administration Safety and Innovation Act. In addition to enabling more timely patient access to safe and effective new medicines, PDUFA-V promotes future research and prepares the FDA for a 21st century regulatory framework. It also supports the development of a framework to facilitate evaluations of the benefits and risks of new medicines (including orphan drugs) and integrates patient perspectives into the review process.

Congress also acted last year to make two provisions affecting pediatric research permanent. These provisions, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), work together to encourage pediatric research. The combination of BPCA and PREA, often referred to as the "carrot" and "stick" approach, has resulted in a wealth of useful information about administering drugs to children, including information on dosing, safety, and efficacy. Together, BPCA and PREA have driven research and greatly advanced American children's medical care. Making these two provisions permanent will help create a more predictable and efficient pediatric drug development process, resulting in continued progress to develop new medicines for children. BPCA and PREA already have resulted in significant accomplishments:

- As of December 2012, 193 drugs have received pediatric exclusivity under BPCA.[36,37]
- Following the reauthorization of BPCA and PREA in 2007 and through June 2012, 405 pediatric studies were completed, involving 174,273 patients.[38]
- Since 1998, BPCA and PREA have resulted in 463 labeling changes reflecting important pediatric information.[39]

[1]Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013.

[2]Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2001–2013.

[3]Burrill & Company. Unpublished analysis for PhRMA. 31 January 2012.

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

[5]Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

[6]PAREXEL International. "PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2010/2011." Waltham, MA: PAREXEL International, 2010.

[7]M. Dickson and J.P. Gagnon. "Key Factors in the Rising Cost of New Drug Discovery and Development." *Nature Reviews Drug Discovery* 2004; 3(5): 417–429.

[8]J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185.

[9]Tufts Center for the Study of Drug Development. "Large Pharma Success Rate for Drugs Entering Clinical Trials in 1993–2004: 16%." *Impact Report* 2009; 11(4).

[10]J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479.

[11]More recent estimates range from $1.5 billion to more than $1.8 billion. See for exampleJ. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

[12]National Institutes of Health. "ClinicalTrials.gov: A Service of the U.S. National Institutes of Health." Available at www.clinicaltrials.gov (accessed February 2013).

[13]U.S. Food and Drug Administration. "Facts about Current Good Manufacturing Practices (cGMPs)." 25 June 2009. Available at www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm (accessed February 2013).

[14]H.G. Grabowski, et al. "Evolving Brand-name and Generic Drug Competition may Warrant a Revision of the Hatch-Waxman Act." *Health Affairs* 2011; 30(11): 2157–2166.

[15]J.A. Vernon, J.H. Golec, and J.A. DiMasi. "Drug Development Costs When Financial Risk is Measured Using the Fama-French Three-factor Model." *Health Economics* 2009; 19(8): 1002–1005.

[16]IMS Health. "National Prescription Audit™." December 2012. Danbury, CT: IMS Health, 2012.

[17]Generic Pharmaceutical Association. "Generic Drug Savings in the U.S. (Fourth Annual Edition: 2012)." Washington, DC: Generic Pharmaceutical Association, 2012.

[18]Pharmaceutical Research and Manufacturers of America. "Medicines in Development for Neurological Disorders." Washington, DC: PhRMA, 2003.

[19]Pharmaceutical Research and Manufacturers of America. "Medicines in Development for Alzheimer's Disease." Washington, DC: PhRMA, September 2012.

[20]K.A. Getz, R.A. Campo, and K.I. Kaitin. "Variability in Protocol Design Complexity by Phase and Therapeutic Area." *Drug Information Journal* 2011; 45(4): 413–420.

[21]*Ibid*.

[22]Tufts Center for the Study of Drug Development. "89% of Trials Meet Enrollment, but Timelines Slip, Half of Sites Under-Enroll." *Impact Report* 2013; 15(1).

[23]M. Allison. "Reinventing Clinical Trials." *Nature Biotechnology* 2012; 30(1): 41–49.

[24]J.A. DiMasi and H.G. Grabowski, *Op. cit*.

[25]More recent estimates range from $1.5 billion to more than $1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

[26]C.P. Milne and A. Malins. "Academic-Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Boston, MA: Tufts Center for the Study of Drug Development, April 2012.

[27]Tufts Center for the Study of Drug Development. "Outlook 2011." Boston, MA: Tufts University, January 2011.

[28]Alzheimer's Association. "Alzheimer's Facts and Figures." Available at www.alz.org/alzheimers_disease_facts_and_figures.asp (accessed February 2013).

[29]Alzheimer's Association. "2012 Alzheimer's Disease Facts and Figures." *Alzheimer's & Dementia* 2012; 8(2). Available at www.alz.org/downloads/facts_figures_2012.pdf (accessed February 2013).

[30]Alzheimer's Association. "Changing the Trajectory of Alzheimer's Disease: A National Imperative." Washington, DC: Alzheimer's Association, May 2010.

[31]Pharmaceutical Research and Manufacturers Association. "Researching Alzheimer's Medicines: Setbacks and Stepping Stones." Washington, DC: PhRMA, 2012.

[32]S. Mukherjee. *The Emperor of All Maladies: A Biography of Cancer*. New York, NY: Scribner, 2010.

[33]Pharmaceutical Research and Manufacturers Association. "Medicines in Development for Alzheimer's Disease." Washington, DC: PhRMA, September 2012. Available at http://phrma.org/sites/default/files/422/alzheimers2012.pdf (accessed February 2013).

[34]U.S. Food and Drug Administration. "Third Annual Performance Report: Prescription Drug User Fee Act of 1992, Fiscal Year 1995 Report to Congress." Silver Spring, MD: FDA, December 1995.

[35]U.S. Food and Drug Administration. "FY 2011 Performance Report to the President and Congress for the Prescription Drug User Fee Act." Silver Spring, MD: FDA, March 2012.

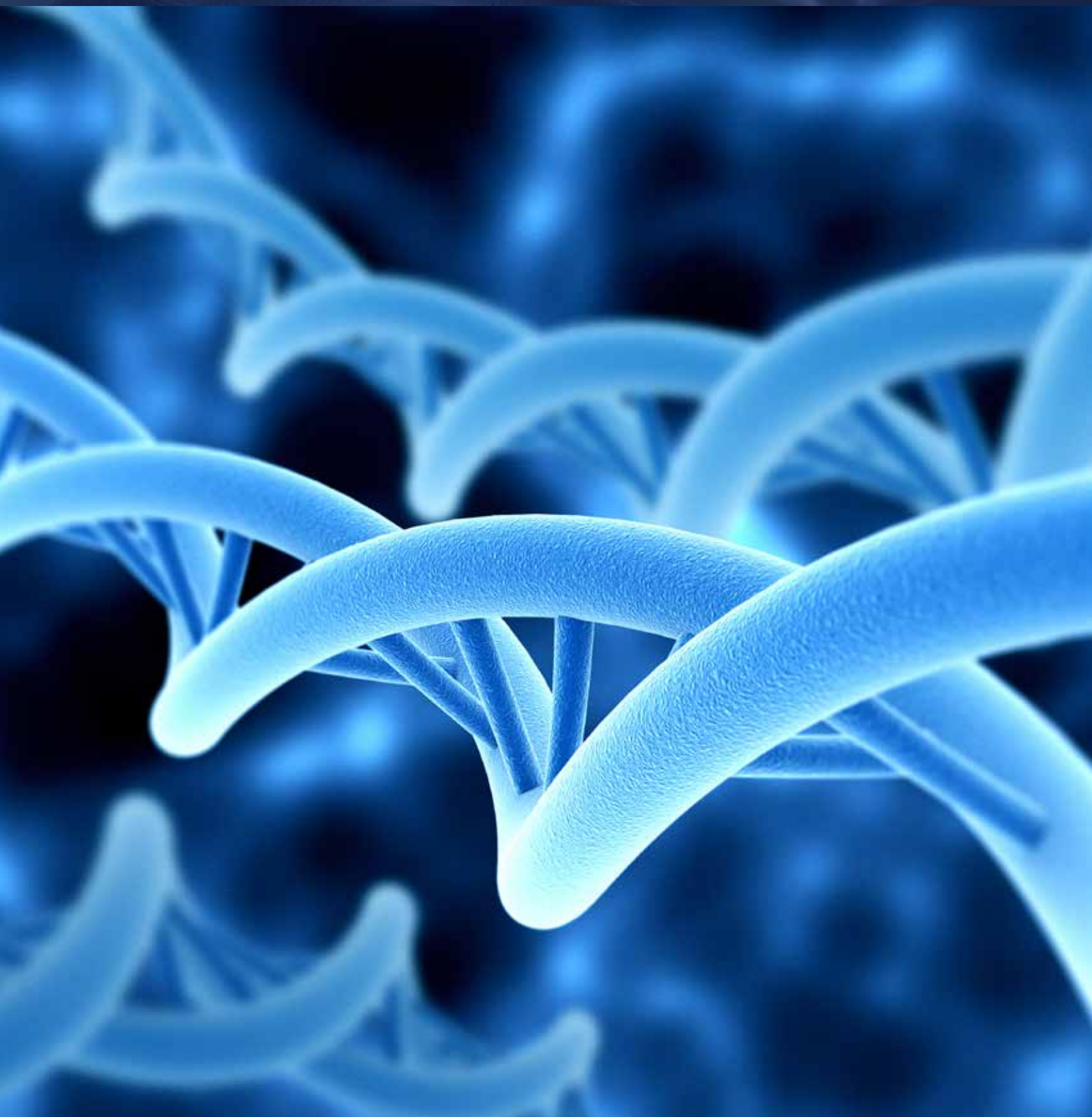
[36]*Ibid*.

[37]U.S. Food and Drug Administration. "Pediatric Exclusivity Granted." January 2013. Available at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM223058.pdf (accessed February 2013).

[38]U.S. Food and Drug Administration. "Breakdown of FDAAA Completed Pediatric Studies." 6 December 2012. Available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm (accessed February 2013).

[39]U.S. Food and Drug Administration. "New Pediatric Labeling Information Database." 13 December 2012. Available at www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase (accessed February 2013).

5 A Promising Pipeline



A Promising Pipeline

Our growing understanding of human disease gives us the most promising platform ever to find medicines that treat disease in new ways. Today, more than 5,000 medicines are in development globally, all of which have the potential to help patients in the United States and around the world.[1] (See Figure 16.) According to another data source, there are 3,400 medicines in development today just in the United States, an increase of 40% since 2005.[2,3] The quantity and quality of new drugs in the pipeline reflect a robust research ecosystem. Both basic research and the biopharmaceutical pipeline are thriving. As a result, the potential for new treatments and cures for patients is unprecedented.

Biopharmaceutical researchers are working tirelessly to develop medicines that attack diseases in novel ways. They are exploring new scientific approaches while expanding their knowledge and understanding of human diseases. The increase in the number and variety of scientific tools over the last 20 years has enabled researchers to better understand the molecular and genetic bases of disease and to develop targeted treatments that work more precisely and effectively. Researchers are steadily applying this knowledge to a range of different diseases and conditions, and the result is unprecedented potential for improvements in human health around the world.

Examining the Pipeline

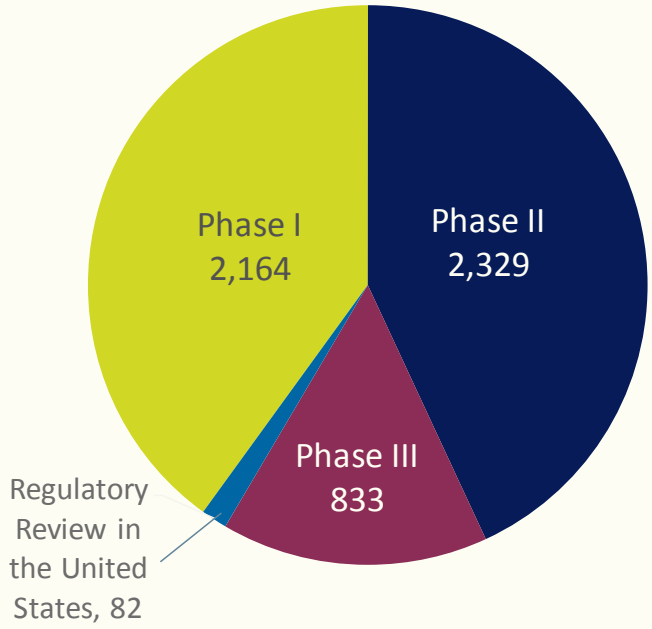
According to a recent report by Analysis Group, which uses various data sources to examine innovation in the pipeline from several different angles, 70% of the more than 5,000 new molecular entities (NMEs) being investigated are potential first-in-class medicines, meaning that they are in a unique pharmacologic class distinct from any other marketed drugs.[4] Such medicines offer new potential treatment options for patients, particularly for those who have not responded to existing therapies or for whom no existing treatment options are available. These medicines may improve the outlook for patients by providing greater efficacy or fewer side effects. Subsequent medicines in the class may provide patients with different side effect or efficacy profiles.

These data "hint at an exciting new Spring of medical innovation for patients. The last thing we want to do — or can afford to do — is stop it cold."[5]

► John C. Lechleiter, Ph.D., Chairman, President, Chief Executive Officer, Eli Lilly and Company

Figure 16: Medicines in Development by Regulatory Phase

In 2011, 5,408 medicines* were in clinical development worldwide.

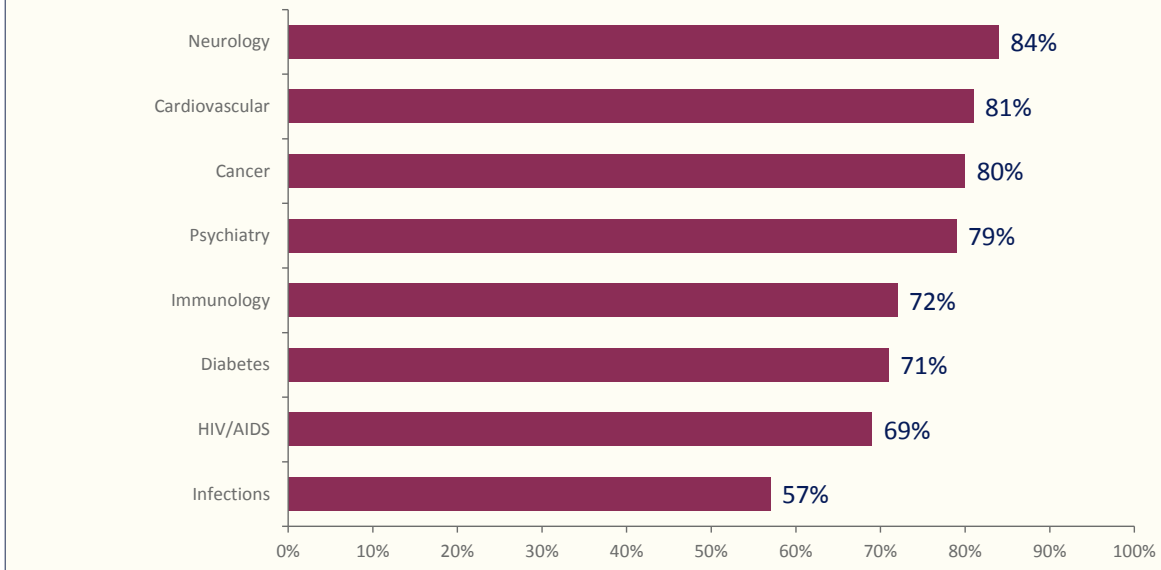


Because many of the 5,408 medicines in development are in trials for more than one indication, the total number of projects in development is close to 8,000.

*Defined as single products which are counted exactly once regardless of the number of indications pursued.

SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

Figure 17: Percentage of Potential First-In-Class Medicines in Selected Therapeutic Areas, 2011



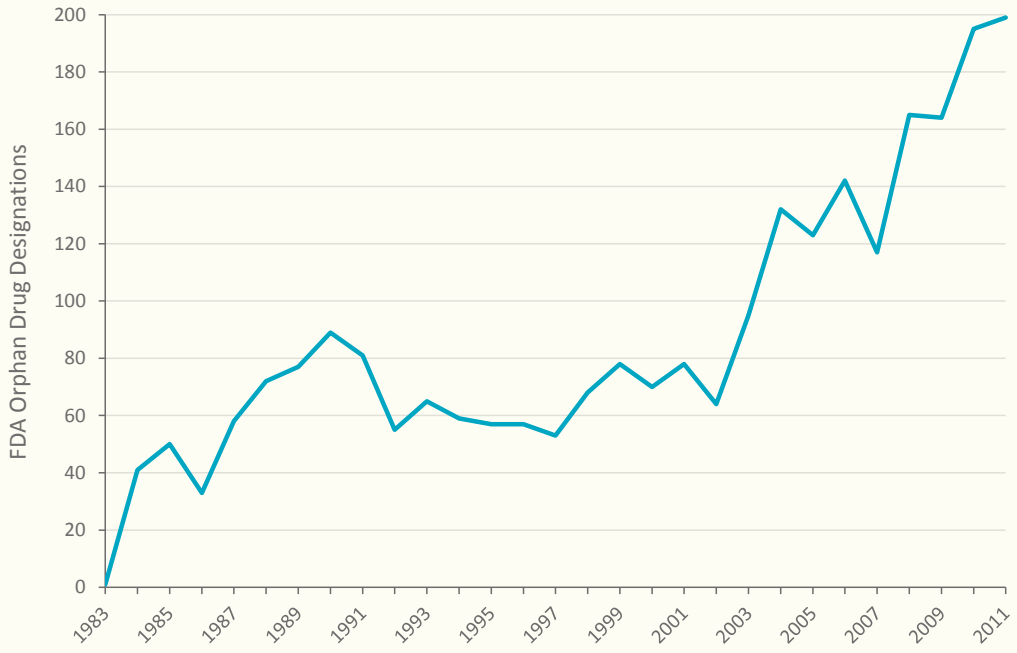
SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed January 2013).

The proportion of projects in development that could become first-in-class varies by therapeutic area but is particularly high in areas such as neurology (84%), cancer (80%), and psychiatry (79%).[6] (See Figure 17.) The high number of potential first-in-class drugs being researched in these areas likely reflects researchers' growing knowledge of the underpinnings of these disease areas and new opportunities for advances.

According to Analysis Group, biopharmaceutical companies are making significant progress in a number of key areas:[7]

- **Rare diseases.** There are nearly 7,000 rare diseases[8] — many of which are serious or life-threatening and have few treatment options. In 2011, 1,795 projects in development focused on rare diseases, which each affect fewer than 200,000 persons in the United States. The U.S. Food and Drug Administration (FDA) designations of orphan drugs in development have been increasing. In the past 10 years, an average of 140 drugs were designated as orphan drugs each year compared with 64 in the previous 10 years.[9]
- **Diseases that do not yet have approved treatments.** Scientists are increasingly developing medicines for diseases for which no therapies have been approved in the last 10 years and that have significant gaps in treatment options. For example, there are 61 medicines in development for amyotrophic lateral sclerosis or Lou Gehrig's disease, 41 for small cell lung cancer, 19 for sickle cell disease, and 158 for ovarian cancer.[10]
- **Medicines that are among the first to apply new scientific strategies to address disease.** New discoveries in basic science are leading to new therapeutic approaches that were never before possible. Among the potential new approaches under investigation today are:

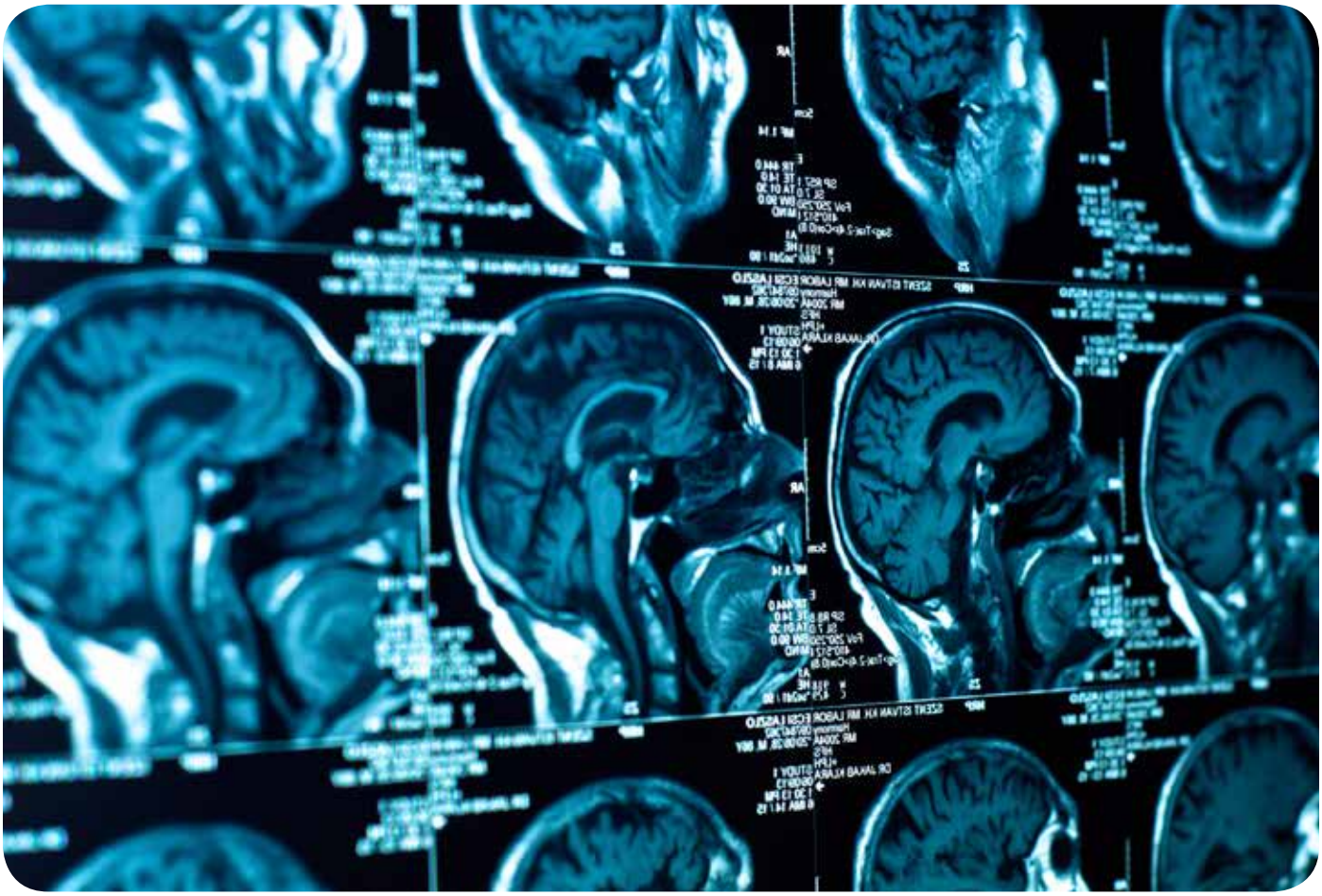
Figure 18: Number of Projects with Orphan Drug Designation by Year 1983–2011



SOURCE: Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

- **RNAi therapy.** While most drugs target proteins such as enzymes and cellular receptors, this new approach opens up opportunities to target RNA, which carries genetic information to create proteins in the cell. Antisense RNA interference (RNAi) therapy can help to silence harmful gene expression. In the past 20 years, this work has advanced from the laboratory bench to the bedside, and two RNAi therapies already have been approved. More than 127 RNAi projects are in the pipeline.[11]
- **Therapeutic cancer vaccines.** Unlike traditional vaccines, these new vaccines harness the power of the immune system to fight cancer rather than to prevent it. This idea first emerged in the late 1990s, and the first therapeutic cancer vaccine was approved in 2010. More than 20 therapeutic vaccines for cancer are in development.[12,13]

> *If you're a patient with a terrible disease, a serious cancer or something like that, I think you ought to take heart from what we are seeing.*[14]
>
> ► Janet Woodcock, M.D., Director of the U.S. Food and Drug Administration's Center for Drug Evaluation and Research



Our progress in understanding the specific pathways of disease has identified hundreds of new targets for potentially life-saving drugs that hold the potential to treat individual patients much more effectively. The result of this understanding is an emerging paradigm shift for the development of new medicines.[15]

► Mark McClellan, M.D., Ph.D., Engelberg Center for Health Care Reform, Brookings Institution, and Ellen Sigal, Ph.D., Friends of Cancer Research, 2012

New Horizons in Personalized Medicine

Personalized medicine presents a new set of tools to help diagnose and treat patients based on our growing understanding of the genetic and molecular basis of disease. This approach is becoming more widespread, particularly in the treatment of cancer, and it holds potential to prevent disease, find the correct treatment more quickly, prevent side effects, improve patients' quality of life, and treat disease more effectively. As the overall cost of health care continues to rise, personalized medicine could help to control costs by reducing unnecessary treatments and side effects.[16]

The role of personalized medicine is growing. According to the Personalized Medicine Coalition, there were 13 prominent examples of personalized medicines, treatments, and diagnostics available in 2006; by 2011, there were 72.[17] Likewise, a 2010 survey by the Tufts Center for the Study of Drug Development found that companies saw a roughly 75% increase in personalized medicine investment between 2005 and 2010 and expected to see an additional 53% increase from 2010 to 2015.[18] Of the companies surveyed, 94% of biopharmaceutical companies are investing in personalized medicine research, and 12% to 50% of the products in their pipelines are personalized medicines.[19]

> *The industry as a whole is committed to pushing strongly ahead … Early indications show that development of personalized medicines is commanding more resources and fomenting more corresponding organization change than is generally appreciated outside the industry.*[20]
>
> ► Tufts Center for the Study of Drug Development, 2010

Spotlight on Medicines in the Pipeline

Treating a Dangerous Mutation in Infants

Hypophosphatasia is a rare inherited bone disease that is caused by a genetic mutation. The mutation results in low levels of an enzyme called alkaline phosphatase. This deficiency hinders the formation of bones and teeth and can result in substantial skeletal abnormalities. No medicine has been approved for this disease. A potential therapy in development would provide the enzyme necessary for proper bone growth in those with this devastating, rare disease.[21]

Addressing Difficult-to-Treat Symptoms of Schizophrenia

Schizophrenia is a severe and complex mental illness that impairs the patient mentally and emotionally. Although some medicines target symptoms like hallucinations and delusions, they are generally not able to improve other symptoms such as lack of motivation and interest in social activities. A new medicine in development could be the first in a new class that has the potential to target these difficult-to-treat symptoms by improving transmission of a chemical needed in the brain for proper communication between neurons.[22]

[1]Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

[2]Adis Insight. "R&D Insight Database." 19 February 2013.

[3]Adis Insight. Customized analysis for PhRMA based on R&D Insight Database. October 2011.

[4]Analysis Group, *Op. cit.*

[5]J. Lechleiter. "A Coming Renaissance in Pharmaceutical Research & Development?" *Forbes*, 28 January 2013. Available at www.forbes.com/sites/johnlechleiter/2013/01/28/a-coming-renaissance-in-pharmaceutical-research-development/ (accessed February 2013).

[6]Analysis Group, *Op. cit.*

[7]*Ibid.*

[8]National Institutes of Health, Office of Rare Diseases Research. "Rare Diseases Information." Available at http://rarediseases.info.nih.gov/Resources/Rare_Diseases_Information.aspx (accessed February 2013).

[9]Analysis Group, *Op. cit.*

[10]*Ibid.*

[11]*Ibid.*

[12]*Ibid.*

[13]T. Gryta. "Enlisting the Body to Fight Cancer." *Wall Street Journal*, 14 June 2011. Available at http://online.wsj.com/article/SB10001424052702303478304576377892911572686.html?mod=googlenews_wsj (accessed December 2012).

[14]J.D. Rockoff and R. Winslow. "Drug Makers Refill Parched Pipelines." *Wall Street Journal*, 11 July 2011. Available at http://online.wsj.com/article/SB10001424052702303499204576387423702555648.html (accessed January 2013).

[15]M. McClellan and E. Sigal. "Getting Drugs to Market Place Faster." The Hill's Congress Blog. *The Hill*, 20 April 2012. Available at http://thehill.com/blogs/congress-blog/healthcare/222771-getting-drugs-to-market-place-faster (accessed February 2013).

[16]Personalized Medicine Coalition. "The Case for Personalized Medicine: 3rd Edition." Washington, DC: PMC, October 2011. Available at www.personalizedmedicinecoalition.org/sites/default/files/files/Case_for_PM_3rd_edition.pdf (accessed February 2013).

[17]Personalized Medicine Coalition. "Personalized Medicine by the Numbers." Washington, DC: PMC: October 2011. Available at www.personalizedmedicinecoalition.org/sites/default/files/files/PM_by_the_Numbers.pdf (accessed February 2013).

[18]Tufts Center for the Study of Drug Development. "Personalized Medicine Is Playing a Growing Role in Development Pipelines." *Impact Report*. 2010; 12(6).

[19]*Ibid.*

[20]*Ibid.*

[21]Pharmaceutical Research and Manufacturers of America. "The Biopharmaceutical Pipeline: Evolving Science, Hope for Patients." Washington DC, PhRMA: 17 January 2013. Available at http://phrma.org/sites/default/files/2435/phrmapipelinereportfinal11713.pdf (accessed February 2013).

[22]Analysis Group, *Op. cit.*

6 Looking Ahead

Looking Ahead

Despite an extremely promising scientific landscape and ongoing positive impact of the biopharmaceutical sector on patients, the health care system, and the economy, the biopharmaceutical industry faces growing challenges.

Higher Hurdles

Changing Science

The drug development process is becoming more costly and complex. In part, this is due to today's need for medicines to treat increasingly challenging and costly chronic diseases, such as arthritis, cancer, diabetes, and neurodegenerative disorders. Scientific opportunities are leading researchers to focus on increasingly complex diseases and new approaches such as personalized medicine. This sophisticated science requires equally sophisticated tools, technologies, and expertise.

Regulatory Environment

Today's regulatory environment requires complex and extensive research to establish the safety and effectiveness of new medicines and an ever-growing amount of information on each new medicine. This typically means that companies must sponsor clinical trials with large numbers of participants. Patient recruitment and retention in clinical trials are continuing challenges.

International Competition

Many countries are now focusing on building an innovative biomedical sector because they recognize its benefits for their economies and their patients — posing a challenge to U.S. leadership in biomedical research. They are forming industry clusters, often in partnership with regional governments. They are also helping to grow their knowledge-based economies through strategies such as building research and development (R&D) infrastructure; emphasizing science, technology, engineering, and math (STEM) education; ensuring access to financial capital; and building and retaining a skilled workforce.[1] For example:

- **Singapore** invested significantly in R&D infrastructure, most famously by creating the Biopolis Research Park. More than 30 companies have located to Biopolis, including many well-known multinational companies.[2]
- **China** has increased R&D investment by 10% each year over the last decade for a total investment of $154 billion — second only to the United States. China also has established programs and incentives to attract talented scientists and foreign investment.[3]

Meeting Challenges

America's biopharmaceutical companies are adapting and seeking creative solutions to meet these growing economic, scientific, business, regulatory, and policy challenges. For example, companies are working to make the clinical trials process as efficient as possible and are focusing on diseases with the greatest unmet needs. They are developing partnerships and unique collaborations to expand the capacity to address complex disease targets. Companies are also working with the U.S. Food and Drug Administration, the National Institutes of Health, and related research agencies

to advance regulatory science and to foster the integration of emerging data and innovation into the development and review of new medicines.

These responses, combined with positive, forward-looking public policies that sustain a market-based system and incentives for innovators, such as strong intellectual property protections, will help ensure America's continued role as the worldwide leader in biopharmaceutical research.

To foster innovation and the medical advances and economic impact that go with it, we must:

- Continue to advance regulatory science and foster the integration of emerging scientific data and innovative approaches into the development and review of new medicines more efficiently, promoting public health in areas such as biomarkers, pharmacogenomics, and rare and orphan drug development.
- Advance medical innovation policies as a solution to health-system problems. For example, to help realize the potential of medical innovation as a solution for improving patient outcomes and controlling rising health care costs, it is important to recognize across all policy areas that the full value of medical advances emerges over time, and to support the ability of physicians and patients to choose from the full range of medically appropriate treatment options.
- Support coverage and payment policies that foster the introduction and availability of new medical advances to America's patients.
- Support the development of STEM workers to increase the nation's ability to develop and manufacture tomorrow's new treatments and to compete globally.
- Support strong intellectual property rights and enforcement in the United States and abroad.
- Sustain U.S. global leadership in the biosciences through economic, trade, and related policies to promote a level playing field globally.

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[1] Battelle Technology Partnership Practice. "The Biopharmaceutical Research and Development Enterprise: Growth Platforms for Economies Around the World." Washington, DC: Battelle Technology Partnership Practice, May 2012.

[2] *Ibid.*

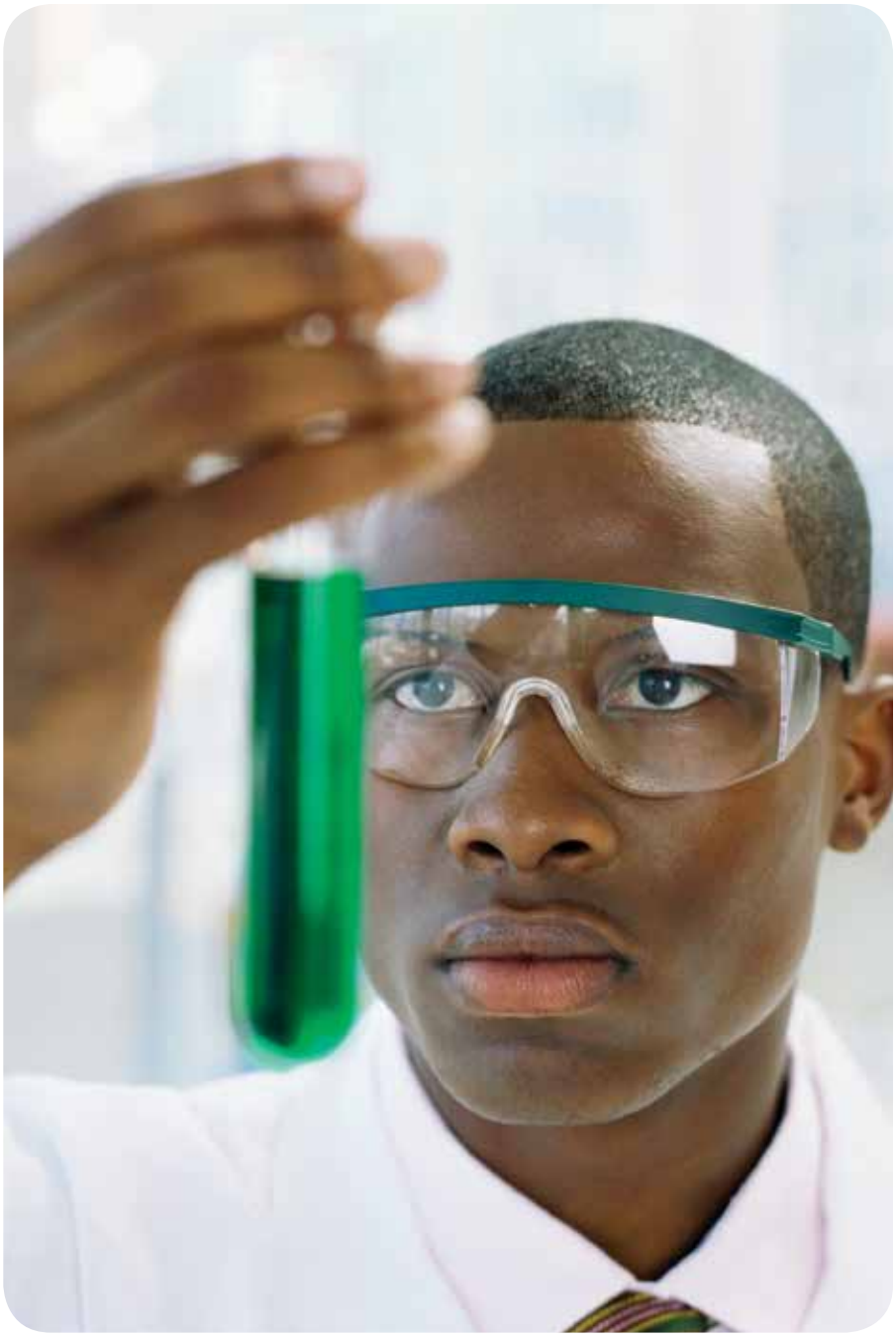
[3] *Ibid.*

Committed to Progress

The challenges facing the biopharmaceutical industry are many and substantial — complex scientific issues, an evolving regulatory environment, and stiff competition at home and abroad. But the scientific opportunities and the promise of medicines in the pipeline are remarkable. And the positive impact of the industry is far reaching.

The biopharmaceutical sector is meeting the challenges before it with innovative scientific work, creative approaches to building and sustaining the industry, and an unending commitment to saving lives and improving the health and quality of life of patients.

This commitment is reflected in the many advances that we have already seen across a wide spectrum of diseases that affect millions. And it brings many benefits such as good jobs and economic investment to communities and states across the nation. The future holds great promise for continued advancements, and with sustained support for innovation, the U.S. biopharmaceutical sector will continue to lead the world.



Appendix

RESEARCH • PROGRESS • HOPE

PhRMA: Who We Are

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading biopharmaceutical companies, which are committed to discovering and developing medicines that save and improve lives. The work of the biopharmaceutical research sector brings hope to millions of patients, allowing them to live longer, healthier lives, while helping to manage health care costs. PhRMA member companies have invested more than $500 billion in research and development into medical innovations since 2000, and an estimated $48.5 billion in 2012 alone. This investment also helps drive the industry's significant contributions to the U.S. economy, including the generation of hundreds of thousands of American jobs and vital support for local communities.

Our Mission

PhRMA's mission is to conduct effective advocacy for public policies that encourage discovery of important new medicines for patients by pharmaceutical and biotechnology research companies. To accomplish this mission, PhRMA is dedicated to achieving these goals in Washington, D.C., the states, and the world:

- Broad patient access to safe and effective medicines through a free market, without price controls
- Strong intellectual property incentives
- Transparent, efficient regulation and a free flow of information to patients

To learn more about PhRMA, go to www.PhRMA.org/about.

PhRMA Member Companies

Full Members & Research Associate Members

Members & Subsidiaries

AbbVie, Inc.
North Chicago, IL

Alkermes plc
Waltham, MA

Amgen Inc.
Thousand Oaks, CA

Astellas Pharma US, Inc.
Northbrook, IL

AstraZeneca Pharmaceuticals LP
Wilmington, DE

Bausch + Lomb
Rochester, NY

Bayer
Wayne, NJ

Biogen Idec Inc.
Weston, MA

Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT

Bristol-Myers Squibb Company
New York, NY

Celgene Corporation
Summit, NJ

Cubist Pharmaceuticals, Inc.
Lexington, MA

Daiichi Sankyo, Inc.
Parsippany, NJ

Dendreon Corporation
Seattle, WA

Eisai Inc.
Woodcliff Lake, NJ

EMD Serono
Rockland, MA

Endo Pharmaceuticals, Inc.
Chadds Ford, PA

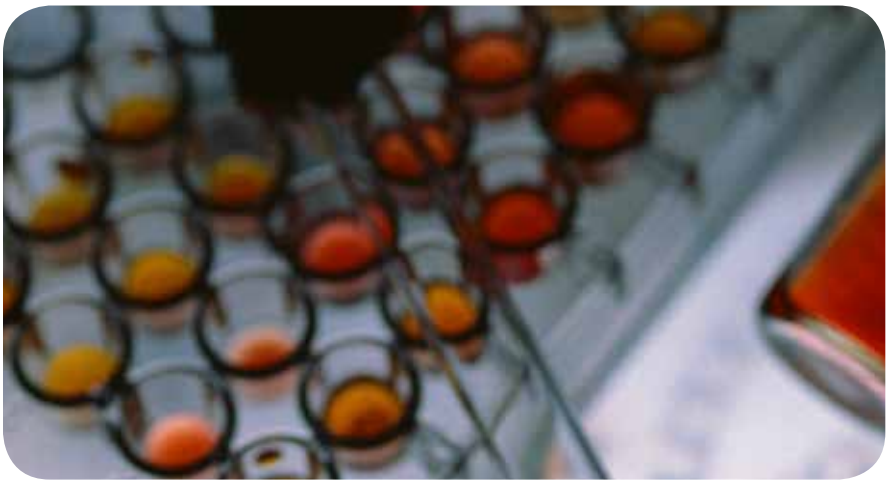
GlaxoSmithKline
Research Triangle Park, NC

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
East Hanover, NJ

Novo Nordisk Inc.
Princeton, NJ

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

Pfizer Inc.
New York, NY

Purdue Pharma L.P.
Stamford, CT

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Bridgewater, NJ
- *Sanofi Pasteur*

Sunovion Pharmaceuticals Inc.
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Sigma-Tau Pharmaceuticals, Inc.
Gaithersburg, MD

Takeda Pharmaceuticals U.S.A., Inc.
Deerfield, IL

Research Associate Members

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San Diego, CA

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Chesterbrook, PA

BioMarin Pharmaceutical Inc.
Novato, CA

CSL Behring, LLC
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Parsippany, NJ

Grifols USA, LLC
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Ikaria, Inc.
Hampton, NJ

Ipsen Pharmaceuticals Inc.
Basking Ridge, NJ

Onyx Pharmaceuticals
South San Francisco, CA

Orexigen Therapeutics, Inc.
La Jolla, CA

Shionogi Inc.
Florham Park, NJ

Sucampo Pharmaceuticals, Inc.
Bethesda, MD

Theravance, Inc.
South San Francisco, CA

Vifor Pharma
Basking Ridge, NJ

VIVUS Inc.
Mountain View, CA

XOMA Corporation
Berkeley, CA

PhRMA Annual Membership 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.

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 decision.

Phase 4 Clinical Testing: Any post-marketing R&D activities performed.

Uncategorized: Represents data for which detailed classifications were unavailable.

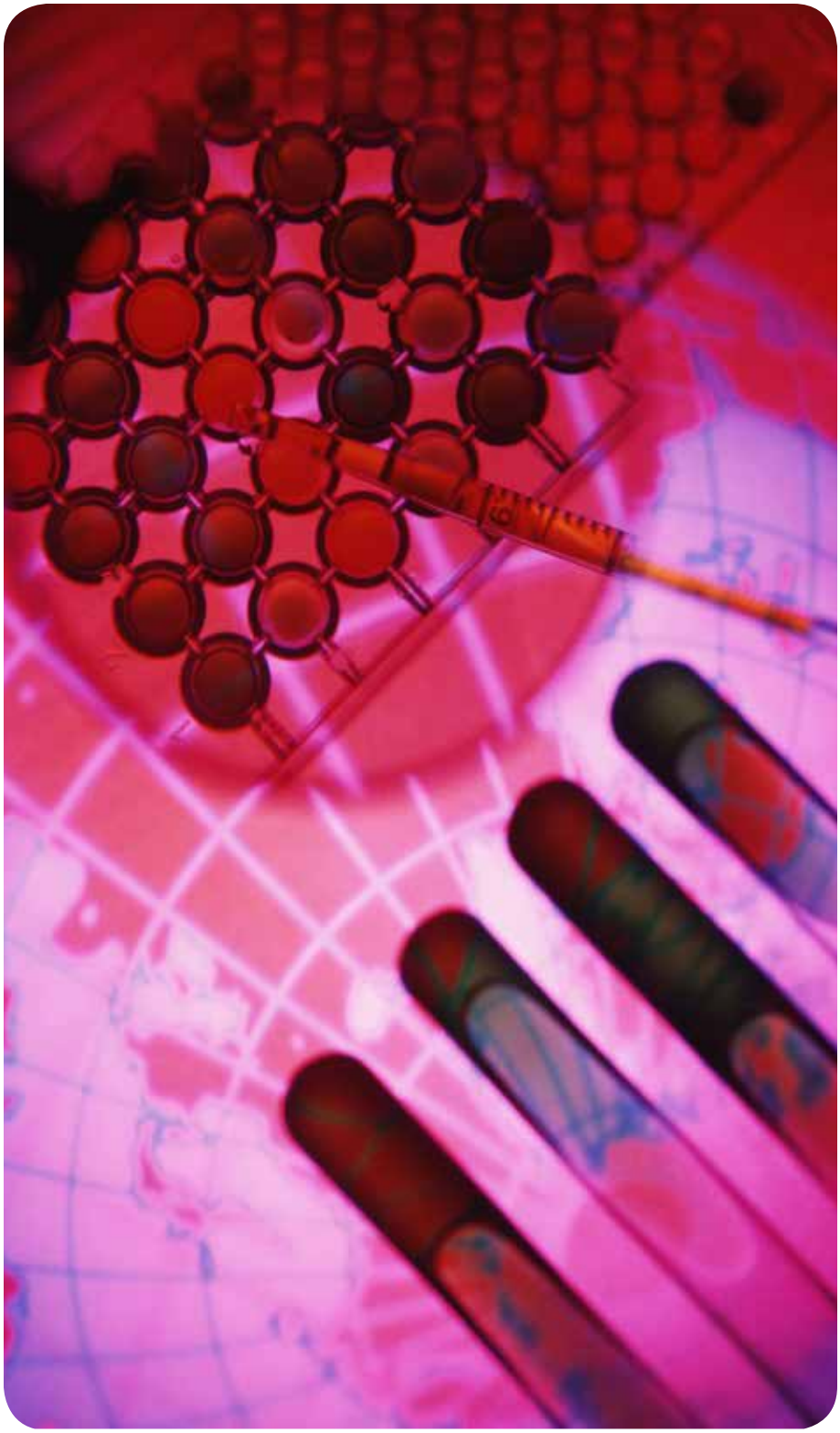
Sales Definitions

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.



List of Tables

Detailed Results from the PhRMA Annual Membership Survey

R&D, PhRMA Member Companies

Sales, PhRMA Member Companies

TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1975–2012

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2012**	$36,810.4	1.2%	$11,674.7	-4.9%	$48,485.1	-0.3%
2011	36,373.6	-10.6	12,271.4	22.4	48,645.0	-4.1
2010	40,688.1	15.1	10,021.7	-9.6	50,709.8	9.2
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		**10.8%**		**12.2%**		**11.1%**

*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 Membership Survey, 2013.

TABLE 2: R&D as a Percentage of Sales, PhRMA Member Companies: 1975–2012

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2012*	20.7%	16.4%
2011	19.4	15.9
2010	22.0	17.4
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 Membership Survey, 2013.

TABLE 3: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 2011

(dollar figures in millions)

R&D Expenditures for Human-use Pharmaceuticals	Dollars	Share
Domestic	$35,923.9	73.8%
Abroad*	$11,982.5	24.6%
Total Human-use R&D	**$47,906.4**	**98.5%**
R&D Expenditures for Veterinary-use Pharmaceuticals		
Domestic	$449.7	0.9%
Abroad*	$288.9	0.6%
Total Vet-use R&D	**$738.7**	**1.5%**
TOTAL R&D	**$48,645.0**	**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 Membership Survey, 2013.

TABLE 4: R&D by Function, PhRMA Member Companies: 2011

(dollar figures in millions)

Function	Dollars	Share
Prehuman/Preclinical	$10,466.3	21.5%
Phase 1	4,211.0	8.7
Phase 2	6,096.4	12.5
Phase 3	17,392.9	35.8
Approval	4,033.4	8.3
Phase 4	4,760.9	9.8
Uncategorized	1,684.0	3.5
TOTAL R&D	**$48,645.0**	**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 Membership Survey, 2013.

TABLE 5: R&D by Geographic Area,* PhRMA Member Companies: 2011

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$3.7	0.0%
South Africa	50.1	0.1
Other Africa	5.2	0.0
Americas		
United States	$36,373.6	74.8%
Canada	781.0	1.6
Mexico	114.6	0.2
Brazil	181.1	0.4
Argentina	101.1	0.2
Venezuela	5.3	0.0
Columbia	29.1	0.1
Chile	21.5	0.0
Peru	16.9	0.0
Other Latin America (Other South America, Central America, and all Caribbean nations)	77.6	0.2
Asia-Pacific		
Japan	$1,027.7	2.1%
China	327.6	0.7
India	48.7	0.1
Taiwan	38.7	0.1
South Korea	103.9	0.2
Other Asia-Pacific	272.3	0.6
Australia		
Australia and New Zealand	$274.7	0.6%
Europe		
France	$509.6	1.0%
Germany	659.2	1.4
Italy	190.6	0.4
Spain	230.7	0.5
United Kingdom	1,770.5	3.6
Other Western European	4,009.6	8.2
Czech Republic	50.6	0.1
Hungary	40.1	0.1
Poland	73.5	0.2
Turkey	48.2	0.1
Russia	73.3	0.2
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	538.7	1.1
Middle East		
Saudi Arabia	$7.3	0.0%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	74.8	0.2
Uncategorized	$513.6	1.1%
TOTAL R&D	**$48,645.00**	**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 Membership Survey, 2013.

TABLE 6: Domestic Sales and Sales Abroad,* PhRMA Member Companies: 1975–2012

(dollar figures in millions)

Year	Domestic Sales	Annual Percentage Change	Sales Abroad*	Annual Percentage Change	Total Sales	Annual Percentage Change
2012**	$177,506.9	-3.9%	$117,293.1	10.0%	$294,800.0	1.2%
2011	187,870.7	3.7	117,138.5	23.1	305,009.2	10.4
2010	184,660.3	2.0	106,593.2	12.0	291,253.5	5.4
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		**9.4%**		**9.9%**		**9.4%**

*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 Membership Survey, 2013.

TABLE 7: Sales by Geographic Area,* PhRMA Member Companies: 2011

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$347.7	0.1%
South Africa	872.3	0.3
Other Africa	1,327.8	0.4
Americas		
United States	$187,870.7	61.6%
Canada	6,793.0	2.2
Mexico	2,576.9	0.8
Brazil	4,387.4	1.4
Argentina	873.9	0.3
Venezuela	1,323.2	0.4
Columbia	771.4	0.3
Chile	320.8	0.1
Peru	167.6	0.1
Other Latin America (Other South America, Central America, and all Caribbean nations)	1,449.8	0.5
Asia-Pacific		
Japan	$17,556.4	5.8%
China	3,391.2	1.1
India	1,635.0	0.5
Taiwan	1,152.2	0.4
South Korea	2,669.7	0.9
Other Asia-Pacific	2,003.6	0.7
Australia		
Australia and New Zealand	$4,008.7	1.3%
Europe		
France	$9,947.9	3.3%
Germany	8,127.0	2.7
Italy	6,761.6	2.2
Spain	5,976.2	2.0
United Kingdom	6,037.0	2.0
Other Western European	11,825.3	3.9
Czech Republic	687.2	0.2
Hungary	499.9	0.2
Poland	942.5	0.3
Turkey	1,518.4	0.5
Russia	1,816.9	0.6
Central and Eastern Europe (Cyprus, Estonia, Slovenia, Bulgaria, Lithuania, Latvia, Romania, Slovakia, Malta, and other Eastern European countries and the Newly Independent States)	5,576.4	1.8
Middle East		
Saudi Arabia	$716.3	0.2%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	1,268.8	0.4
Uncategorized	$1,808.3	0.6%
TOTAL SALES	**$305,009.2**	**100.0%**

*Sales abroad include 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, include 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 Membership Survey, 2013.

References

(continued from inside front cover)

[1]PAREXEL International. "PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2010/2011." Waltham, MA: PAREXEL International, 2010.

[2]M. Dickson and J.P. Gagnon. "Key Factors in the Rising Cost of New Drug Discovery and Development." *Nature Reviews Drug Discovery* 2004; 3(5): 417–429.

[3]J.A. DiMasi, R.W. Hansen, and H.G. Grabowski. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22(2): 151–185.

[4]J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28(4–5): 469–479.

[5]J.A. DiMasi, R.W. Hansen, and H.G. Grabowski, *Op. cit.*

[6]These estimates range from $1.5 billion to more than $1.8 billion. See for example J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London, UK: Office of Health Economics, 2012; S.M. Paul, et al. "How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge." *Nature Reviews Drug Discovery* 2010; 9: 203–214.

[7]Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 1981–2013.

[8]Pharmaceutical Research and Manufacturers of America. "PhRMA Annual Membership Survey." 2013.

[9]Battelle Technology Partnership Practice. "The Economic Impact of the U.S. Biopharmaceutical Industry." Washington, DC: Battelle Technology Partnership Practice, July 2013.

[10]Pharmaceutical Research and Manufacturers of America. "New Drug Approvals, 2001–2011." Washington DC: PhRMA, 2002–2011.

[11]U.S. Food and Drug Administration. "New Molecular Entity Approvals for 2012." 28 January 2013. Available at www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm336115.htm (accessed February 2013).

[12]U.S. Food and Drug Administration. "2012 Biological License Application Approvals." 9 January 2013. Available at www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicalApprovalsbyYear/ucm289008.htm (accessed February 2013).

[13]U.S. Food and Drug Administration, Office of Orphan Product Development. "Orphan Drug Designations and Approvals Database." Available at www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm (accessed February 2013).

[14]J.A. Vernon, J.H. Golec, and J.A. DiMasi. "Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-Factor Model." *Health Economics* 2010; 19(8): 1002–1005.

[15]Analysis Group. "Innovation in the Biopharmaceutical Pipeline: A Multidimensional View." Boston, MA: Analysis Group, January 2013. Available at www.analysisgroup.com/uploadedFiles/Publishing/Articles/2012_Innovation_in_the_Biopharmaceutical_Pipeline.pdf (accessed February 2013).

[16]Adis Insight. "R&D Insight Database." 19 February 2013.

[17]Adis Insight. Customized analysis for PhRMA based on R&D Insight Database. October 2011.

[18]Analysis Group, *Op. cit.*

[19]E. Sun, et al. "The Determinants of Recent Gains in Cancer Survival: An Analysis of the Surveillance, Epidemiology, and End Results (SEER) Database." *Journal of Clinical Oncology* 2008; 26(Suppl 15): Abstract 6616.

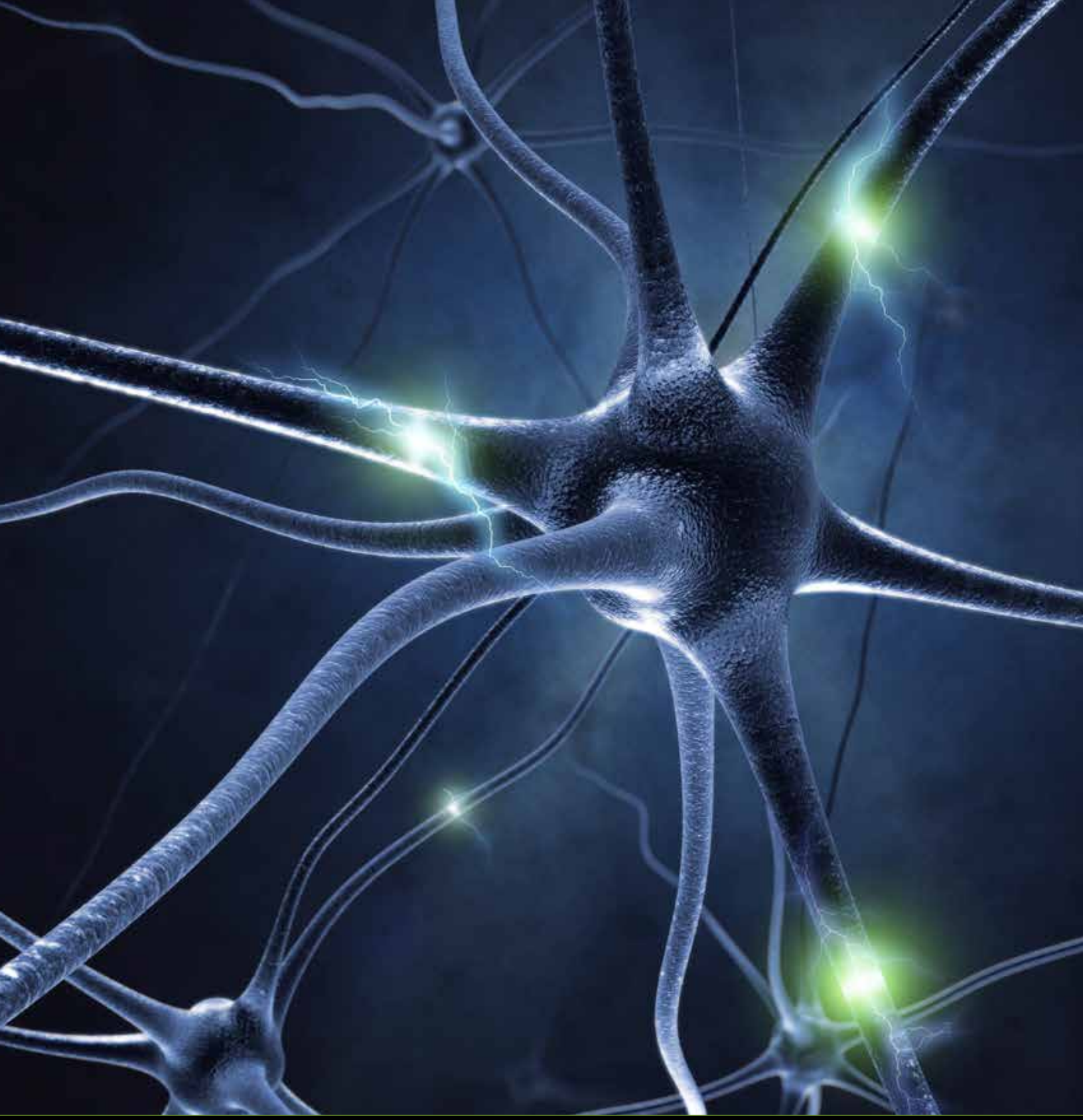
[20]F. Lichtenberg. "The Expanding Pharmaceutical Arsenal in the War on Cancer." National Bureau of Economic Research Working Paper No. 10328. Cambridge, MA: National Bureau of Economic Research, February 2004.

[21]A.S. Go, et al. "Heart Disease and Stroke Statistics—2013 Update: A Report from the American Heart Association." *Circulation* 2013; 127(1):e6–e245.

[22]U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. "Health, United States, 2010: With Special Feature on Death and Dying, table 35." Hyattsville, MD: HHS, 2011. Available at www.cdc.gov/nchs/data/hus/hus10.pdf#045 (accessed February 2013).

[23]D.L. Hoyert and J. Xu. "Deaths: Preliminary Data for 2011." *National Vital Statistics Reports* 2012; 61(6): 38. Hyattsville, MD: NCHS. www.cdc.gov/nchs/data/nvsr/nvsr61/nvsr61_06.pdf (accessed December 2012).

[24]IMS Health. "National Prescription Audit™." December 2012. Danbury, CT: IMS Health, 2012.



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