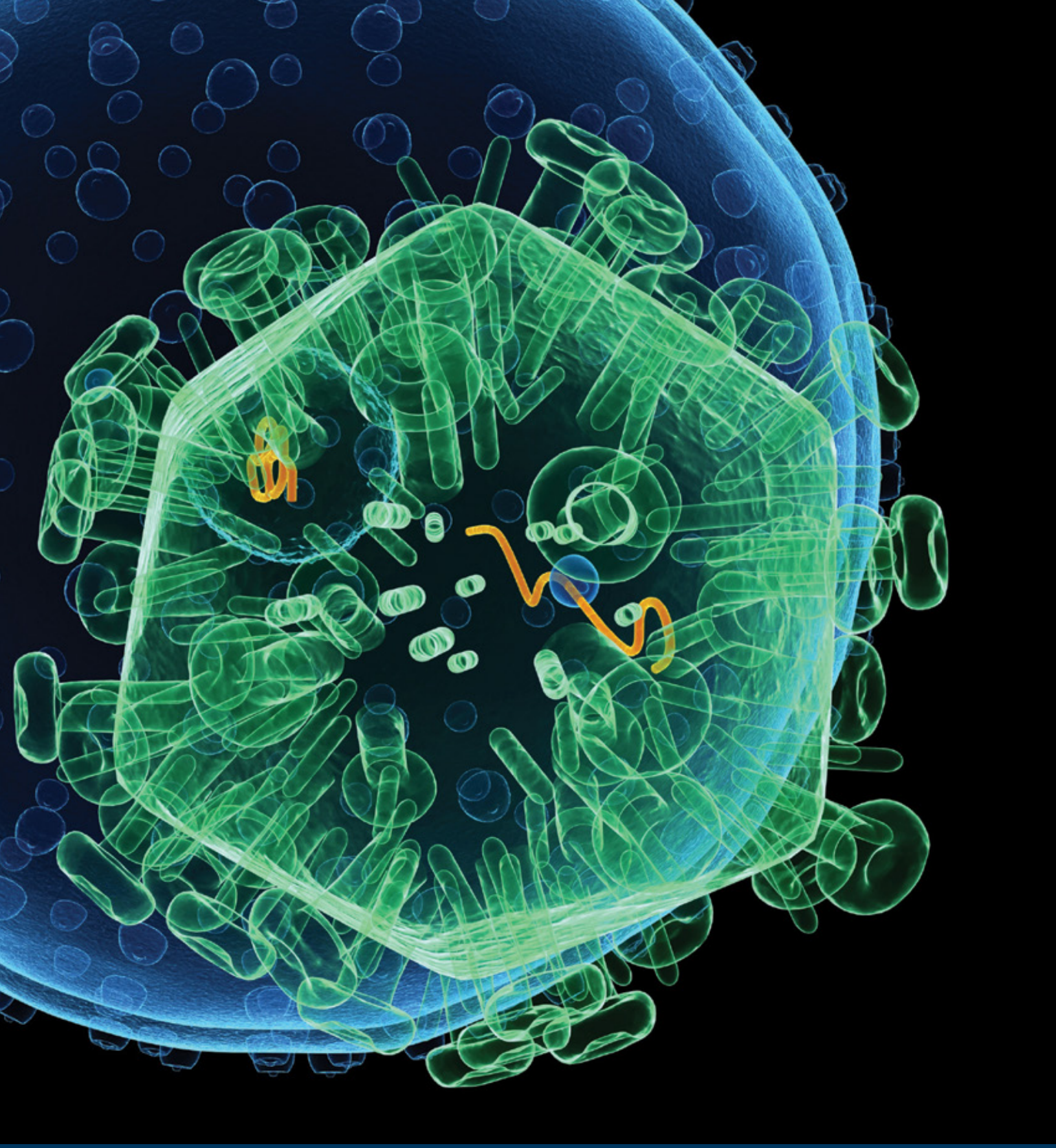


PhRMA
RESEARCH • PROGRESS • HOPE

2014 profile
BIOPHARMACEUTICAL RESEARCH INDUSTRY




KEYFACTS 2014

RESEARCH AND DEVELOPMENT (R&D)

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

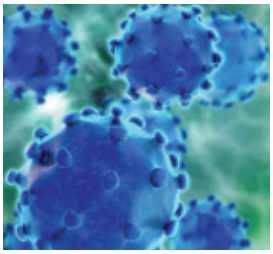
DEVELOPMENT COSTS

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]
2013	$51.1 billion (*est.*)
2012	$49.6 billion
2011	$48.6 billion
2010	$50.7 billion
2009	$46.4 billion
2008	$47.4 billion
2007	$47.9 billion
2006	$43.0 billion
2005	$39.9 billion
2000	$26.0 billion
1990	$8.4 billion
1980	$2.0 billion



SALES

Generic share of prescriptions filled:[8]

2000 = 49%

2013 = 86%

PERCENTAGE OF SALES THAT WENT TO R&D IN 2013

Domestic R&D as a percentage of domestic sales = 22.7%

Total R&D as a percentage of total sales = 17.8%

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 2000–2013 = more than 400[10, 11]
- In the 30 years since the Orphan Drug Act was established, more than 450 orphan drugs have been approved.[12]
- Only 2 of 10 marketed drugs return revenues that match or exceed R&D costs.[13]

MEDICINES IN DEVELOPMENT

- Medicines in development with the potential to aid U.S. patients = 400[14]
- Potential first-in-class medicines** in clinical development globally = 70%[15]
- Biologic medicines in development = More than 900[16]

VALUE OF MEDICINES

- **Cancer:** Since 1980, 83% of life expectancy gains for cancer patients are attributable to new treatments, including medicines.[17]
- **Cardiovascular Disease:** According to a 2013 statistics update by the American Heart Association, death rates for cardiovascular disease fell by about 39% over the past 10 years.[18]
- **HIV/AIDS:** Since the approval of antiretroviral treatments in 1995, the HIV/AIDS death rate has dropped more than 80%.[19] Today, 20-year-olds diagnosed with HIV can expect to live into their early 70s—a life expectancy close to that of the general population.[20]

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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Cover image: Human Immunodeficiency Virus (HIV).

Letter from PhRMA's President and CEO

I am pleased to present the *2014 Biopharmaceutical Research Industry Profile*.

Emerging science and accelerating innovation, dramatic population and lifestyle evolutions, and transitions to new health policies are driving enormous change in the U.S. and global health care systems. How we anticipate, navigate and guide these changes will greatly determine the future health and well-being of people and economies throughout the world. America's biopharmaceutical research companies take this shared obligation very seriously, and our sector is committed to helping lead the way as a catalyst for positive, patient-focused change.

This report demonstrates the profound scope of how innovative medicines—and the collaborative process through which they are discovered and developed—benefit patients, public health and the United States economy. At the core of this process and the value medicines provide is the dedication of researchers to advance biomedical science and bring new treatment options to patients.

Helping patients to live longer, healthier lives. Recent advances in biomedical science have led to significant victories in the fights against cancer, rheumatoid arthritis, HIV/AIDS and scores of other potentially devastating diseases. Death rates have declined, and many previously fatal diagnoses are now often manageable chronic conditions. Since 2000, the biopharmaceutical sector has invested more than half a trillion dollars in R&D—including an estimated $51 billion in 2013 alone. These investments have helped generate incredible progress, but the work is far from done. The more than 5,400 medicines in the global pipeline offer great hope for continued advances in the years ahead.

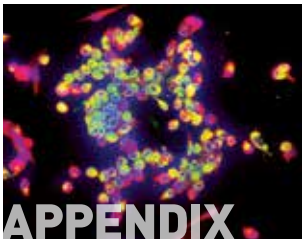
Bringing value to patients and our health system. In addition to the dramatic improvements in patient outcomes generated by medicines, a growing body of evidence demonstrates how innovative medicines are helping patients to avoid costly medical care—for example, by reducing the need for expensive surgeries and hospitalizations. It's a dynamic that necessitates long-term vision and foresight, but it will be proven well worth the investment in the long run.

Strengthening the U.S. economy. Our industry supports nearly 3.4 million jobs across the economy, including more than 810,000 direct jobs. It injects almost $800 billion in economic output on an annual basis. When we bring the strength and breadth of our sector to bear on the world's great challenges, we bolster America's competitive advantage and remind the world that true innovation and economic leadership begin here.

Biopharmaceutical science is a complex, collaborative, resource-intensive enterprise. It requires a highly skilled workforce, sustained investment, and long-term vision. Critical to its success are policies and regulations that foster innovation and broad access to new medicines. By working together—on the science, the research and the policies—we can help ensure that medicines live up to patients' hope for new solutions to our greatest health care challenges.

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

Contents



Biopharmaceutical Innovation: Benefiting Patients and the U.S. Economy

Innovative medicines benefit our lives in many different ways. At the forefront of biomedical science and American ingenuity, new medicines have improved the quality and length of life for millions of patients and enhanced public health in the United States and around the world. What's more, the collaborative biopharmaceutical research and development (R&D) and manufacturing enterprise is a pillar of strength and competitiveness for the U.S. economy.

New medicines have transformed the trajectory of many diseases over the years, providing treatments for diseases for which there were few or no options and increasing patient survival rates for certain cancers, HIV/AIDS, rheumatoid arthritis and Hepatitis C, to name just a few. Among the 27 new molecular entities approved by the U.S. Food and Drug Administration in 2013, one-third represent first-in-class medicines, meaning they use new or unique mechanisms of action, and one-third address rare diseases. Coupled with the tremendous promise in the drug development pipeline, America's biopharmaceutical sector—working hand in hand with stakeholders across the research ecosystem—is on the cusp of transforming many more deadly and costly diseases.

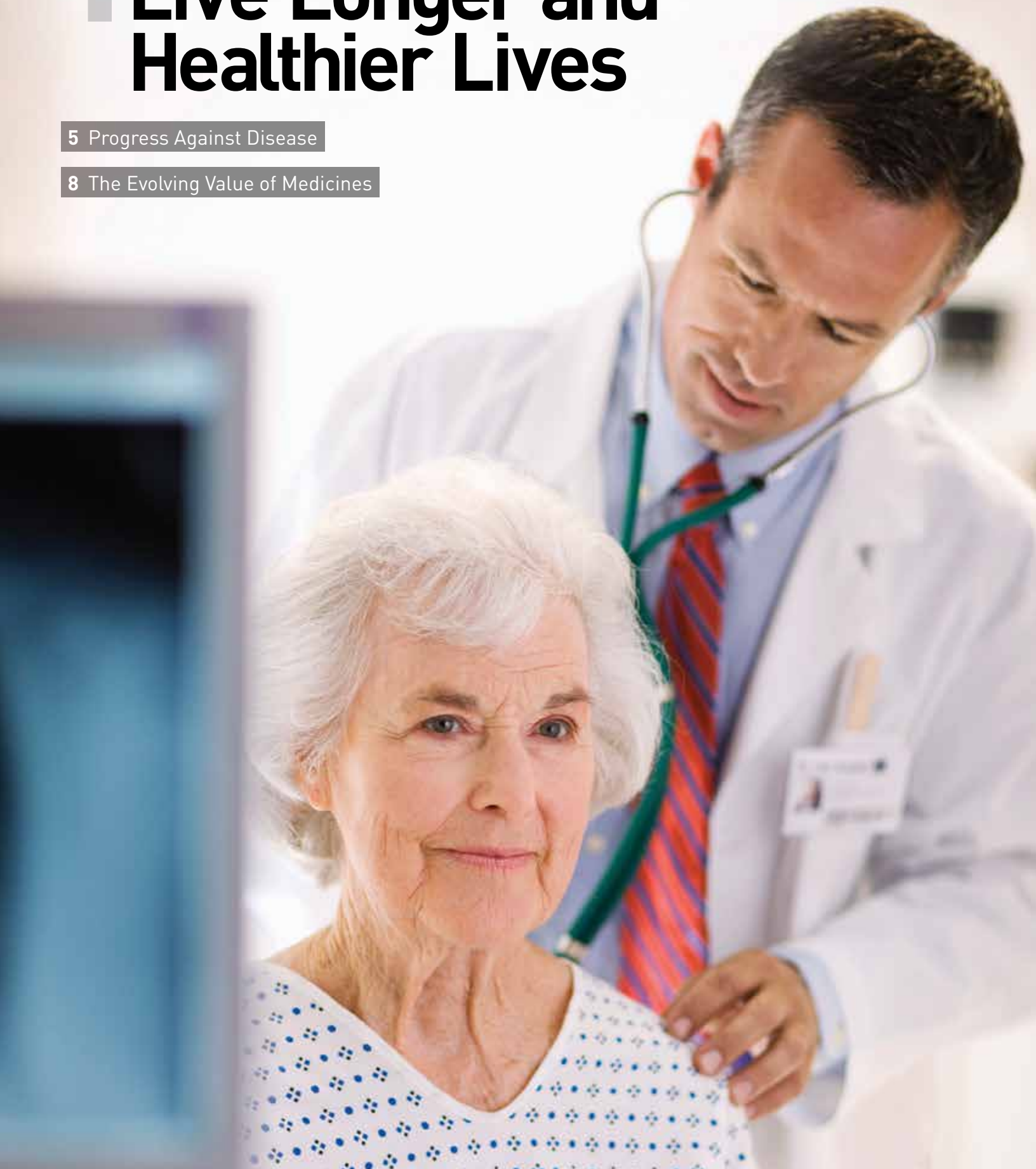
The biopharmaceutical research industry is a dynamic, knowledge-driven sector. The work of its scientists brings hope to millions of patients and benefits local, state and national economies. Biopharmaceutical companies invest heavily in research and development. Pharmaceutical Research and Manufacturers of America (PhRMA) members have invested more than half a trillion dollars in R&D since 2000, including an estimated $51 billion in 2013 alone. As discussed in the 2014 *Biopharmaceutical Research Industry Profile*, PhRMA's members represent a key driver of innovation in the U.S. health care system.

In addition to developing life-enhancing medicines, biopharmaceutical companies increasingly provide services and processes that:

- Improve health care quality and outcomes;
- Increase patient access to needed medicines;
- Help to control health care costs by reducing the need for hospital stays, surgeries and other costly interventions, ultimately improving quality of life and productivity;
- Develop and harness new technological and scientific breakthroughs in collaboration with others in the life sciences field, enhancing the efficiency and effectiveness of many complementary technologies; and
- Improve the R&D and manufacturing processes that help sustain and grow the U.S. economy.

The *2014 Biopharmaceutical Research Industry Profile* provides an overview of the range of contributions our nation's innovative biopharmaceutical companies make to the lives and health of people and to the U.S. economy. Chapter 1 examines the benefits new prescription medicines bring to patients. Chapter 2 discusses the critical role that medicines can play in improving the quality and value of health care and highlights how appropriate use of medicines can reduce costs elsewhere in the health care system. Chapter 3 describes the impact of the dynamic and collaborative biopharmaceutical industry on local, state and national economies, highlighting various ways in which the industry supports the broader life sciences ecosystem. Chapter 4 explores the robust biopharmaceutical pipeline and provides an overview of the R&D process as well as the challenges and opportunities related to drug discovery and development.

1 Helping Patients Live Longer and Healthier Lives



Helping Patients Live Longer and Healthier Lives

New medicines offer patients safe and effective treatment options, allowing people to carry out their daily activities and live longer and healthier lives. In recent years, medicines have resulted in significant progress against many diseases. With advances in personalized medicines and the application of novel scientific approaches in drug development, the science is proving more promising than ever.

In the past 5 years we have seen an upward trend in the number of medicines approved by the Food and Drug Administration (FDA). These approvals reflect breakthroughs treating many challenging diseases. In 2013, the FDA approved 34 new molecular entities (NMEs), of which 27 were approved by the Center for Drug Evaluation and Research (CDER).[1] One-third of CDER approvals were identified by the FDA as first-in-class, meaning drugs using a new and unique

> More important than the quantity of new drugs approved in 2013 is the quality of the new drugs the pharmaceutical industry has developed and the important new roles these drugs are serving to advance medical care." > FDA'S CENTER FOR DRUG EVALUATION AND RESEARCH[2]

mechanism of action for treating a medical condition that is distinct from any other approved medicine. Another third of the NMEs—many of which are also first-in-class—were approved to treat rare diseases.[3]

These novel therapies are providing important new treatments for patients in a range of disease areas. For example:

- **Blood Cancers:** Three new medicines were approved to treat various forms of rare blood cancers in 2013. One is a first-in-class medicine for treating multiple myeloma; it provides an important new option for patients who have not responded to other cancer drugs.[4] Another first-in-class medicine approved this year belongs to a promising group of medicines called B-cell receptor pathway inhibitors. These medicines target an important biological pathway found to be linked to the development of cancer cells. The new medicine treats a particularly aggressive form of blood cancer called mantle cell lymphoma.[5] (For more information about B-cell receptor pathway inhibitors, see Chapter 4.)
- **Hepatitis C:** Two new oral "direct-acting antiviral" medicines are changing the treatment of Hepatitis C. Both work by blocking a specific protein needed by the hepatitis C virus to replicate.[6] (For more information about direct-acting antivirals, see Chapter 4.)

Continuing Advances in Personalized Medicine

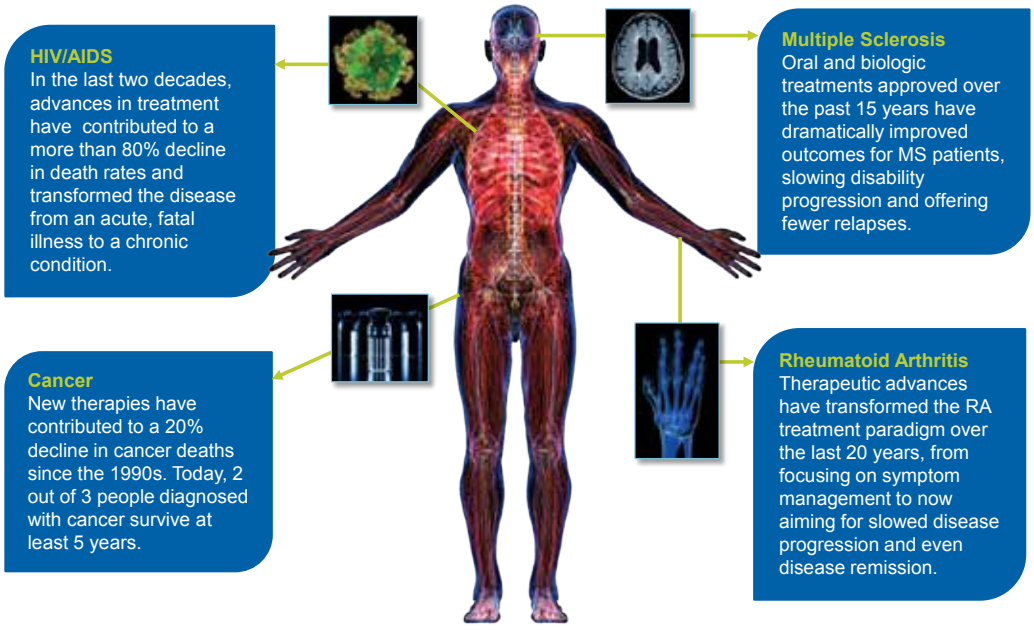
As our understanding of the genetic and molecular basis of disease grows, so too does our ability to effectively target disease with medicines. Personalized medicine advances are possible because of a growing understanding of how individual patients react differently to diseases and to their treatments, based upon their genetic makeup. This knowledge may help determine a person's risk of developing a particular medical condition and can inform not just potential treatment options but, increasingly, approaches to disease prevention and wellness. Moreover, by targeting treatments to patients most likely to benefit, personalized medicines represent an important tool, as they may reduce the use of unnecessary and often costly treatments or procedures.[7]

A 2010 study by the Tufts Center for the Study of Drug Development found that between 2005 and 2010, pharmaceutical companies increased their personalized medicine investment by roughly 75%. These companies also projected an additional 53% increase by 2015. The survey further found that 94% of pharmaceutical companies are investing in personalized medicine research, and 12% to 50% of the products in their pipelines are personalized medicines.[8]

> Now, with the advance of science and technology and the understanding of both the underlying mechanisms and the human response to disease, we have so many more opportunities to target therapies in exciting ways and really improve the care that we can offer and the effectiveness of treatments." > MARGARET HAMBURG, M.D., COMMISSIONER, FDA, 2013[9]

- **Skin Cancer:** Two personalized medicines with companion diagnostic tests are now approved to treat patients who have specific genetic mutations that are associated with the two most dangerous forms of skin cancer. About half of all melanoma cases express one of the two gene mutations targeted by these new medicines. One of these medicines is a first-in-class treatment.[10]
- **Multiple Sclerosis:** A new oral medication for adults with relapsing forms of MS has been proven to significantly reduce important measures of disease activity, including relapses and development of brain lesions. The medicine has also been shown to slow disability progression over time. While there is no cure for MS, this first-in-class medicine expands the options for treating this complex disease.[11]
- **Depression:** A novel therapy to treat a form of depression, commonly referred to as major depressive disorder, increases treatment options for patients and their doctors. Because different medications affect everyone differently, new

Figure 1: Medicines Are Transforming the Treatment of Many Difficult Diseases



SOURCE: The National Multiple Sclerosis Society, "The MS Disease-modifying Medications: General Information." Washington, DC: National Multiple Sclerosis Society, April 2013. Available at www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/12-3-7_DiseaseModifyingDrugs.pdf; C. Augustyn, B. Walker, and T.F. Goss. "Recognizing the Value of Innovation in the Treatment of Rheumatoid Arthritis." Boston, MA: Boston Healthcare Associates, March 2013. Available at www.phrma.org/sites/default/files/1888/rawhitepaperfinal2.pdf; National Center for Health Statistics. "Health, United States, 2010: with Special Feature on Death and Dying, table 35." Hyattsville, MD: NCHS, 2011. Available at www.cdc.gov/nchs/data/hus/hus10.pdf#045 (accessed February 2014); American Cancer Society. "Cancer Treatment and Survivorship Facts & Figures 2012-2013." Atlanta, GA: American Cancer Society, 2013.

The decline in cancer rates over the past two decades signifies "real progress in cancer control, reflecting a combination of primary prevention, early detection and treatment."[12] > NATIONAL CANCER INSTITUTE

options are especially important for the many people who suffer from major depressive disorder, which can be a very challenging disability. Access to a wide variety of treatment options is crucial to improving outcomes for these patients.[13]

PROGRESS AGAINST DISEASE

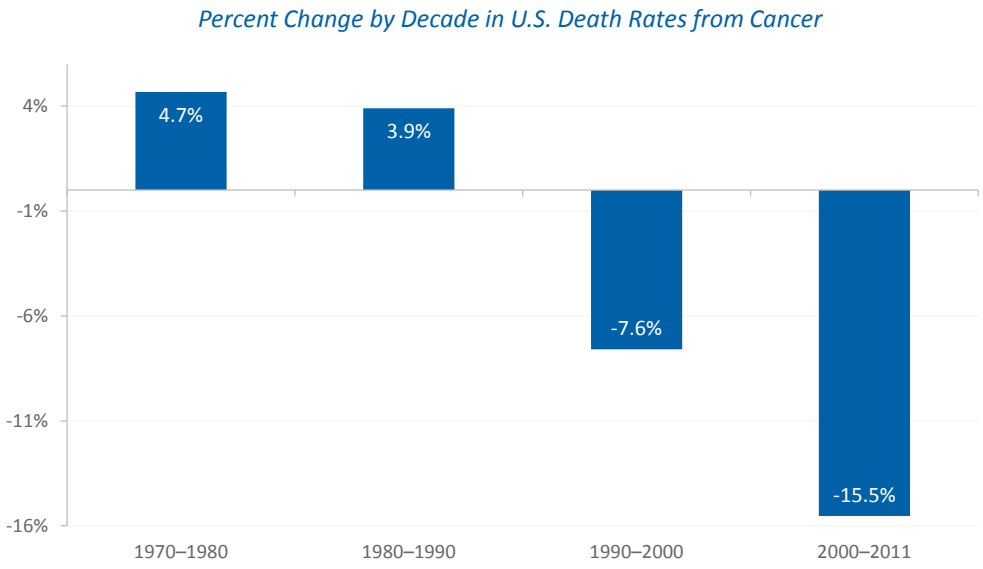
In addition to saving and extending lives, the development of innovative medicines has benefited the health and well-being of patients by halting or slowing disease progression, improving quality of life, preventing unnecessary hospitalizations, reducing side effects, and providing treatments for diseases where there were few or no treatments. New medicines have a transformative impact for patients across a broad range of disease areas.

Extending Lives

Cancer: New medicines for the treatment of various cancers have been a driving force behind recent life expectancy gains. According to the National Cancer Institute, the United States has seen a 20% decline in cancer deaths since the early 1990s[14] (see Figure 2). Five-year survival

Figure 2: Cancers: Decline in Death Rates

According to the American Cancer Society, improvements in treatment contributed to the increase in cancer survival.



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rates—meaning the chance that a cancer patient will live five years or more—are also on the rise. The survival rate increased from just 49% in the mid-1970s to 68% in the most recent time period (2002–2008)—representing a 39% increase across *all* types of cancer.[15] Research shows that 83% of the life expectancy gains for cancer patients seen over the past three decades are attributable to new treatments, including medicines.[16]

Cardiovascular disease: The appropriate use of medicines to treat cardiovascular disease has contributed greatly to declines in mortality. According to the American Heart Association (AHA), over the past 10 years overall death rates from cardiovascular disease have fallen by about 39%.[17] AHA also reports the stroke death rate has fallen by about 36% over the same period.[18] The U.S. Centers for Disease Control and Prevention cite new medicines among the factors contributing to these improving trends in cardiovascular disease.[19]

Slowing and Preventing Disease Progression

Leukemia: Cancer once was considered one monolithic disease. Today, we know cancer is at least 200 to 300 different diseases. As researchers gain a deeper understanding of these diseases on a molecular and genetic level, they are able to develop medicines targeting specific tumor pathways with greater success and efficacy.[20] In the case of chronic myeloid leukemia, greater understanding of the

Then and Now: Leukemia

- **Then:** A person diagnosed with chronic myeloid leukemia (CML) in 1999 would, in all likelihood, not be alive today: just three out of ten patients survived for even five years. Patients then had two daunting treatment options: a high-risk bone marrow transplant or daily injections of interferon, the side effects of which have been compared to "having a bad case of the flu every day of your life."[21]
- **Now:** A new generation of targeted cancer medicines, known as tyrosine kinase inhibitors (TKIs), is improving health outcomes for patients. Nearly 90% of CML patients taking the drug imatinib, for example, now live at least five years. This daily medicine has resulted in remission for many patients as well as helped normalize patients' blood counts. The medicine targets CML on a molecular level, so it affects only the enzyme responsible for the disease.[22] Since the approval of imatinib, five additional TKIs have been approved to treat CML. These medicines provide important options for patients who may have specific genetic mutations or for patients who do not respond to or cannot tolerate existing treatments.[23]

disease has led, over the past decade, to a number of new medicines that have for many halted the disease in its tracks, allowing for many patients to live close to normal life spans[24].

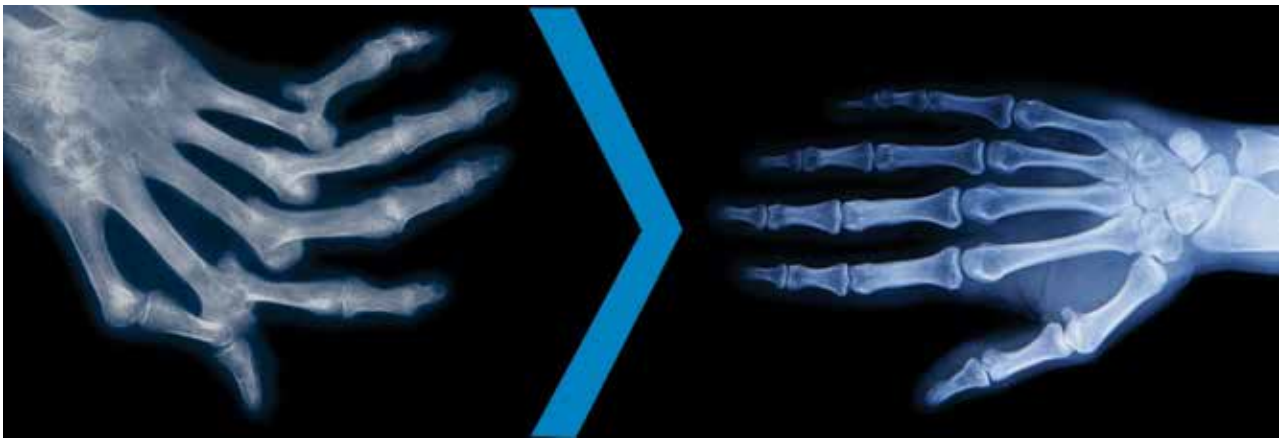
Preventing Unnecessary Hospitalizations

Diabetes: Many innovative medicines to treat diabetes have emerged in the past few years. These medicines have given patients new ways to effectively manage their disease with lower side effect profiles and more convenient dosing, thereby improving patients' health and quality of life. A 2012 study found that diabetes patients taking their medicines as directed were able to avoid unnecessary hospitalizations. The study showed that improved adherence to diabetes medications was associated with a lower likelihood of subsequent hospitalizations or emergency department visits. Similarly, a loss of adherence to these medicines was associated with a higher likelihood of the same outcomes. Based on these findings, the authors conclude that good adherence to medications offers substantial opportunity to prevent unnecessary hospitalizations for diabetes patients, projecting that 341,000 hospitalizations and 699,000 emergency department visits could be avoided annually.[25]

Improving Quality of Life

Rheumatoid Arthritis: Disease-modifying biological medicines have ushered in a new age of treatment for rheumatoid arthritis (RA) (see Figure 3). By targeting the cells involved in the progression of RA, these medicines have dramatically slowed or even

Figure 3: Rheumatoid Arthritis: Medicines Are Transforming the Lives of Patients



THEN:
Treatments for RA were effective at reducing joint inflammation but were limited to treating the symptoms of the disease, allowing for steady progression from disease onset to disability fairly rapidly.

NOW:
Biologic disease-modifying antirheumatic drugs (DMARDs) can target the underlying sources of inflammation, which improves physical functioning and prevents irreversible joint damage—making disease remission possible.

SOURCE: C. Augustyn, B. Walker, and T.F. Goss. "Recognizing the Value of Innovation in the Treatment of Rheumatoid Arthritis." Boston, MA: Boston Healthcare Associates, March 2013. Available at www.phrma.org/sites/default/files/1888/rawhitepaperfinal2.pdf.

reversed the negative physical effects associated with the disease[26] and made clinical remission possible for patients with severe RA.[27] A recent study found patients treated with combination therapy consisting of both a new and an older medicine had a 35% chance of complete clinical remission over the course of 5 years, compared with 14% for those taking only the older medicine—more than doubling remission rates for patients.[28]

Increasing Options for Patients with Rare Diseases

Researchers have made tremendous progress in recent years against rare diseases—those diseases affecting fewer than 200,000 patients in the United States.[29] In fact, the FDA notes that approximately one-third of all new medicines approved in the past 5 years have been designated as "orphan drugs"—the term used to refer to medicines that treat rare diseases. Although each of the nearly 7,000 identified rare diseases affects a small number of people, this collective impact on public health is anything but small: overall, rare diseases affect more than 30 million Americans.[30]

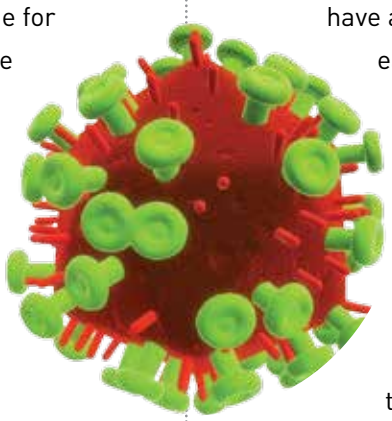
Because 85% to 90% of rare diseases are serious or life threatening, bringing new medicines to patients is especially important.[31] Just over 30 years ago, Congress passed the Orphan Drug Act. This critical piece of legislation created incentives for the development of new treatments for rare diseases and transformed the lives of millions of Americans. The success of the law is evident, with 450 medicines approved to treat rare diseases since 1983.[32] In the 1970s, the FDA had approved fewer than 10 orphan drugs.[33,34] Today, there are more than 450 in development.[35]

THE EVOLVING VALUE OF MEDICINES

Advances against disease such as those cited above are not typically driven by large, dramatic developments. More commonly, they result from a series of incremental gains in knowledge and understanding over time. This incremental, stepwise transformation in knowledge has led to increased survival rates, 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 into chronic, manageable conditions for patients.

Progress against HIV/AIDS, for example, did not happen through one single breakthrough, but rather through a series of stages, marked by both the introduction of new treatment options and constant learning about their optimal use and clinical value[36] (see Figure 4). FDA approval, which is based on

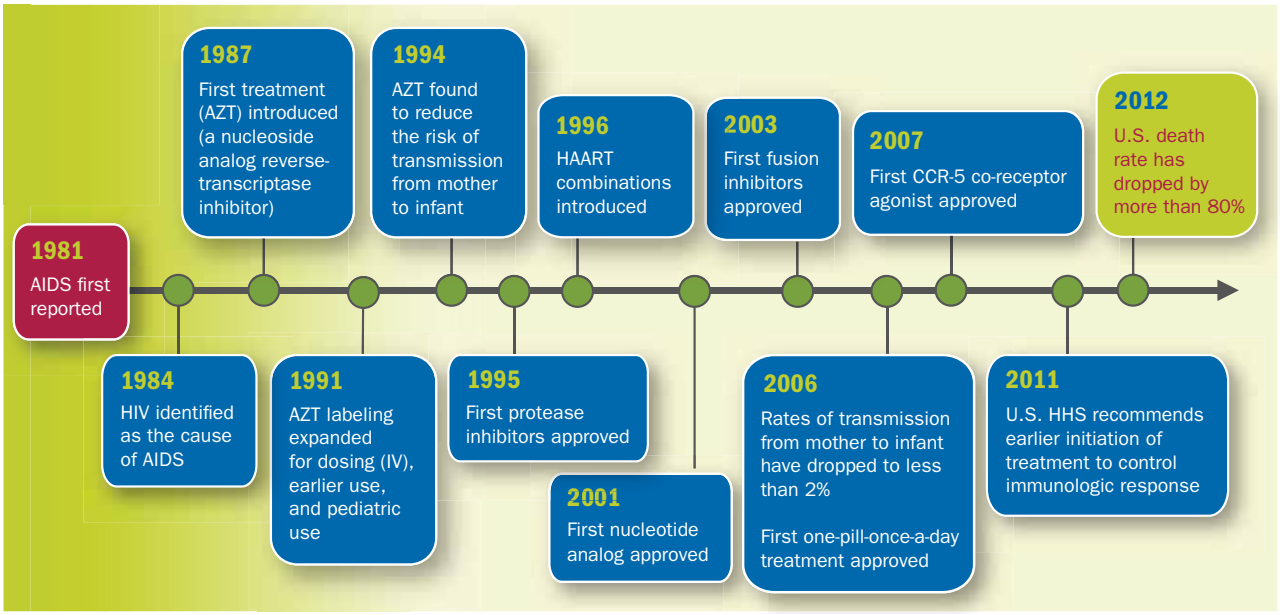
rigorous clinical trials in controlled settings, marks the starting point for the continuing evolution in our understanding of a treatment's full value for patients. As is the case for HIV/AIDS, the full value of new treatments is often not fully known at the time of FDA approval, but is realized over time as new treatments build on one another and real-world knowledge is accumulated. Since 1987, more than 30 treatment options for HIV have been developed, giving physicians a broad array of therapeutic options to increase survival and improve quality of life.[37]



The ongoing introduction of new HIV/AIDS therapies, and continuous research into their optimal use in patient care, has revealed additional value for treatments beyond what was known at the time they were introduced. Researchers and clinicians have found that many therapies are more effective when used in combination than when used alone; they have also found that initiating treatment earlier in the disease process leads to improved long-term outcomes and stronger immunologic responses. More recently, with improved understanding of how HIV evolves and progresses at the molecular level, researchers are finding ways that therapies can not only treat the disease, but also prevent its transmission. This has led to new uses and indications for many HIV/AIDS medicines.

Over the past 20 years, these research advances in HIV/AIDS have transformed the treatment standard for many patients. HIV/AIDS was once an acute, fatal illness and is now a manageable, chronic disease for those who have access to medications.

Figure 4: HIV/AIDS: Treatment Advances Build over Time

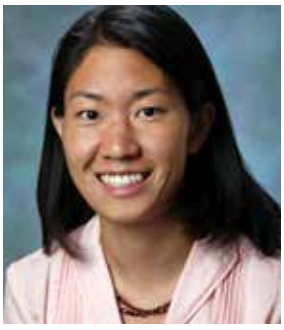


SOURCE: C. Augustyn, B. Walker, and T. F. Goss. "Recognizing the Value of Innovation in HIV/AIDS Therapy." Boston Healthcare Associates, December 2012.

In the United States alone, death rates have fallen more than 80 percent since 1995 as a result of the development of multiple drugs and their use in innovative combinations, known as highly active antiretroviral therapy (HAART).[38] Today, research shows that 20-year-olds diagnosed with HIV can expect to live into their early 70s—a life expectancy close to that of the general population and a 10-year increase in life expectancy from that seen just 10 years ago.[39]

For a personal look back at this extraordinary journey, watch an interview with author and activist David Mixner: http://www.youtube.com/watch?v=JgN2vgZeBKQ.

Protecting Children in Need with Immunizations



Dr. Linda Yu-Sing Fu is a general pediatrician at the Children's National Medical Center. She recently won a 2013 PhRMA Research and Hope Award for Patient and Community Health for her team's efforts to help parents understand why childhood immunizations are so important and to improve the quality of immunization delivery to an at-risk population in the District of Columbia. She has taken her work in the District and applied it on a national level to make sure that a generation of children is protected from a wide range of preventable diseases.[40] To learn more about Dr. Fu's work, watch http://www.youtube.com/watch?v=dx9GNZkaGOo.

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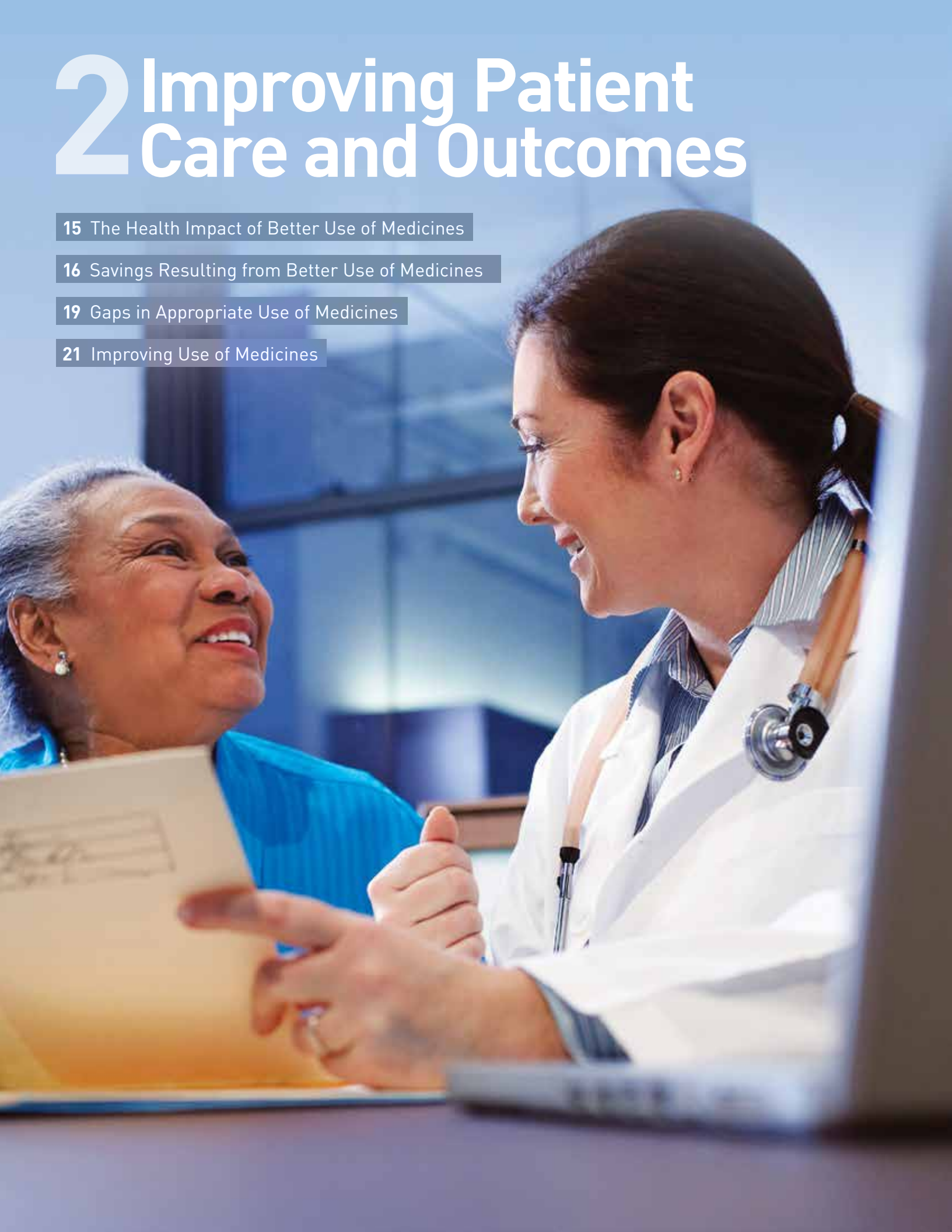
2 Improving Patient Care and Outcomes



Improving Patient Care and Outcomes

Today we face a growing aging population—many of whom are suffering from multiple chronic conditions. Given this reality, the health of Americans and our economy depend greatly on improving outcomes for patients. Working toward this imperative must come with the recognition of the role that prescription medicines play in achieving this goal, as well as the potential for medicines to reduce overall costs to the health care system.

Evidence demonstrates the ability of medicines to improve health outcomes and reduce the need for costly health care services such as emergency room admissions, hospitalizations, surgeries and long-term care. Such improvements in health are also shown to lead to gains in employee productivity. Recognizing this growing evidence, in 2012 the Congressional Budget Office (CBO) announced a revision to the methodology it uses to estimate the federal budget impact of policy changes related

> Pharmaceuticals have the effect of improving or maintaining an individual's health.... Adhering to a drug regimen for a chronic condition such as diabetes or high blood pressure may prevent complications.... Taking the medication may also avert hospital admissions and thus reduce the use of medical services."[1] > Congressional Budget Office

to Medicare. The CBO now incorporates into its estimates savings in medical spending associated with increased use of medicines among Medicare beneficiaries.[2]

As more Americans gain access to health care in the coming years, it is important to ensure they have access to the medicines they need. Appropriate medication use allows patients to live healthier lives and avoid unnecessary medical expenditures, yet suboptimal use of medicines and gaps in care remain significant challenges. Fortunately, patients and their health care providers can do much to improve the quality and efficiency of the health care system.

THE HEALTH IMPACT OF BETTER USE OF MEDICINES

In order for patients to derive the full value of their medicines, therapies must be taken appropriately and as recommended by a health care professional. This means appropriate and timely diagnosis and prescribing, prompt initiation of therapy and adherence to a prescribed therapy regimen, and should also involve periodic review by a health care professional to address any medication-related issues. Appropriate use of medicines can improve patient health outcomes and in many instances prevent disease progression and reduce unnecessary hospitalizations, especially for those with chronic conditions. Research shows that patients who take medicines appropriately and as prescribed achieve better health than patients who do not adhere to prescribed therapy regimens:

- **Hospitalizations:** Poor adherence to prescribed medicines is associated with increased use of medical services, such as hospital and emergency room (ER) visits, and medical expenditure.[3,4,5] One study showed, for example, 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.[6] Another study showed that children with low adherence to prescribed long-term control asthma medications experience a 21% greater likelihood of ER visits and a 70% greater likelihood of hospital admissions, compared to children who better adhered to prescribed treatment regimens.[7]

- **Development or Progression of Disease and Death:** Adherence can delay the development or progression of disease. For example, one study found that patients who did not take antihypertensive medicines as instructed were, over 3 years, 7%, 13%, and 42% more likely to develop coronary heart disease, cerebrovascular disease, and chronic heart failure, respectively, than were patients who took the medicines as directed.[8] Adherence to prescribed therapies can also reduce mortality risk. Poor adherence to statins was found to be associated not only with a 1.2 to 5.3 increase in risk of cardiovascular disease, but also with a 1.3 to 2.5 increase in mortality compared to adherent patients.[9]

SAVINGS RESULTING FROM BETTER USE OF MEDICINES

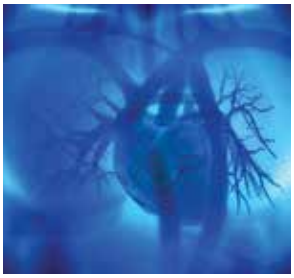
When used appropriately, medicines can not only result in better clinical outcomes, but can also reduce the use of medical services, leading to savings for patients and the health care system (see Figure 5). It is estimated that the cost of poor medication use, including nonadherence, undertreatment, administration errors, and underdiagnosis, is between $100 billion and $300 billion annually.[10,11,12,13]

The link between better use of prescription medicines and economic benefits has been demonstrated in a growing number of economic and epidemiological research studies. The CBO's recent methodological change supports this link, and emerging research continues to support the value of appropriate use of medicines in reducing medical expenditures. A 2013 study published in the *American Journal of Managed Care* examined patients with congestive heart failure (CHF) and found significant economic benefit associated with improved access to medicines. For CHF alone, the study reported that improved medication adherence associated with increased access to medicines under Medicare Part D reduced medical expenditures by nearly $2.6 billion among beneficiaries with prior limited or no drug coverage; approximately $2.3 billion of that amount was savings to Medicare. Further improvements in adherence were estimated to potentially save Medicare another $1.9 billion annually, generating upwards of $22.4 billion in federal savings over 10 years.[14]

Several examples illustrate the savings in medical spending that result from better use of medicines:

- **Chronic Conditions:** Improved adherence increases prescription drug spending, but these costs are often more than offset by reductions in other health care spending, as shown by one recent study of patients with diabetes, dyslipidemia, hypertension, and congestive heart failure (see Figure 5). For each additional dollar spent on prescriptions, patients who had better adherence to prescribed medicines experienced savings of $3 to $10 in nondrug spending. This represented a net savings of $1,200 to $7,800 per patient per year.[15]

Potential New Treatment for Congestive Heart Failure



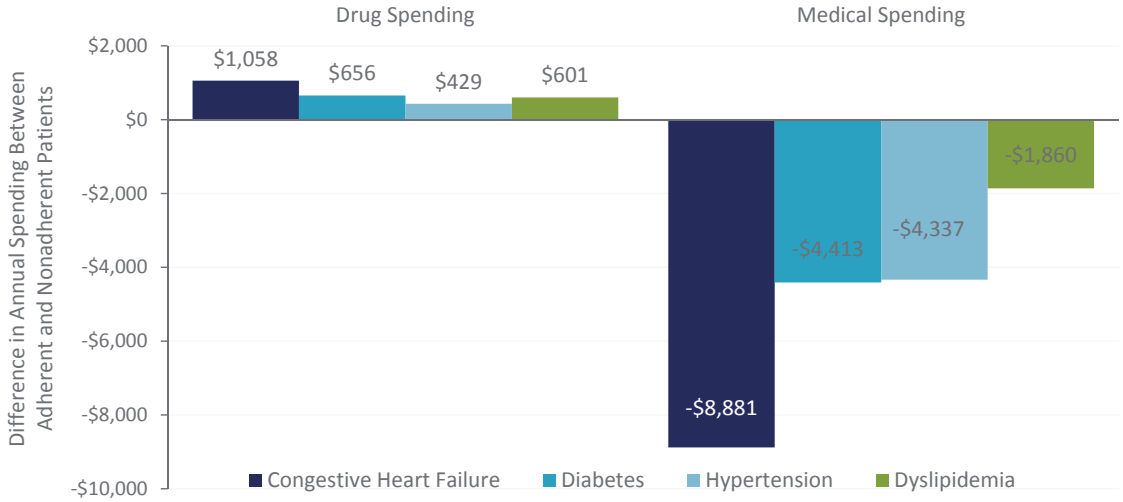
Congestive heart failure is the most common, and the most costly, diagnosis among elderly Medicare patients.[16] CHF patients represent 14% of the population and 43% of Medicare Parts A and B spending.[17] More than 3.5 million Part D enrollees were diagnosed with CHF in 2010, and the condition accounts for 55,000 deaths annually.[18] A new medicine now in the late stages of development can relieve symptoms and protect vital organs against damage during an acute heart failure episode.[19] Given the immense potential for reductions in medical expenditures associated with CHF,[20] this new medicine not only may improve outcomes for patients, but may also produce substantial savings for the health care system.

- **High Cholesterol:** Patients whose adherence declines from a high to a low level over one year experience a 2.3 greater likelihood of a cardiovascular event.[21] Studies have shown that statin therapy reduces low-density lipoprotein (LDL) cholesterol levels by an average of 19%. In the United States, over one year, this reduction in LDL levels was associated with about 40,000 fewer deaths, 60,000 fewer hospitalizations for heart attacks, and 22,000 fewer hospitalizations for strokes. These prevented hospitalizations represented gross savings of nearly $5 billion.[22]
- **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.[23]
- **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.[24]

In addition to improving health outcomes, the appropriate use of medicines also leads to improved productivity in the workplace through reduced

Figure 5: Prescription Medicines Are Part of the Solution to Reducing Medical Spending

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



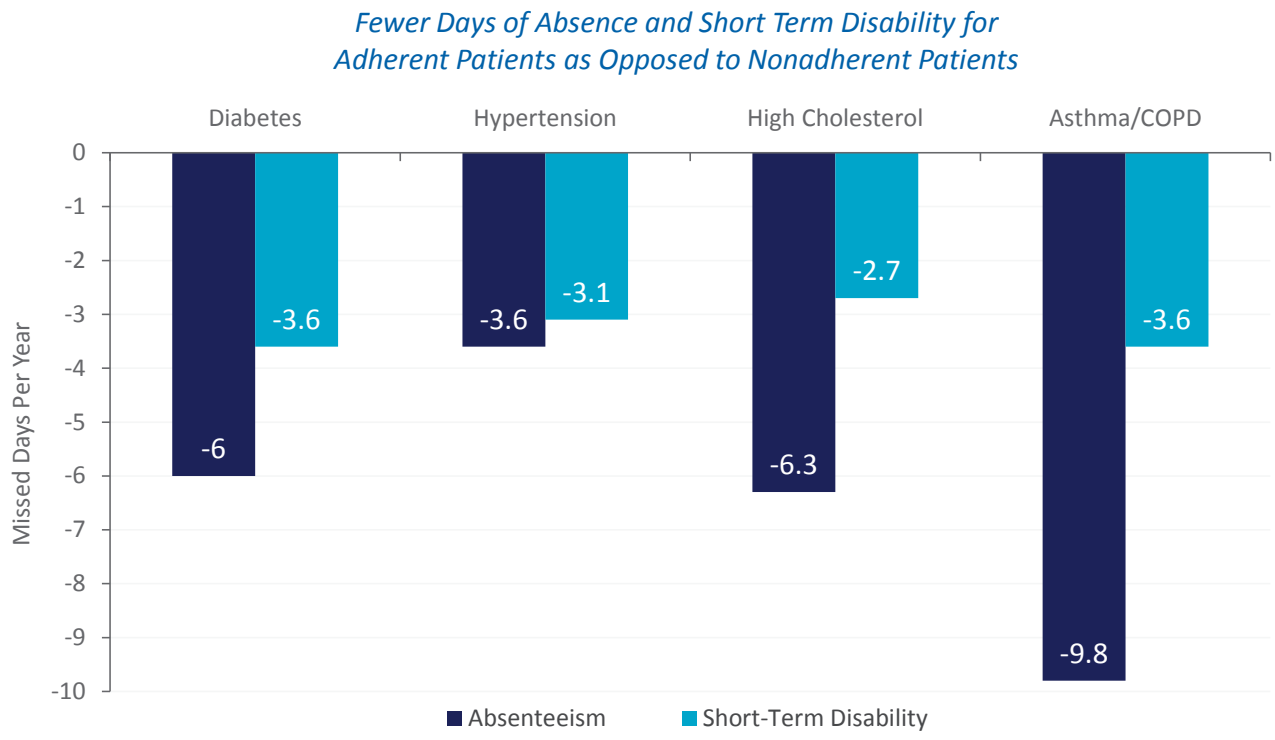
SOURCE: M.C. Roebuck, et al. "Medication Adherence Leads to Lower Health Care Use and Costs Despite Increased Drug Spending." *Health Affairs* 2011; 30(1): 91–99.

absenteeism and disability leave. These reductions benefit both the individual patient and society as a whole. For example:

- **Rheumatoid Arthritis:** Examining claims data across 17 employers, researchers at the Integrated Benefit Institute estimated that cost shifting to employees for rheumatoid arthritis (RA) medications decreased adherence and led to a higher incidence and longer duration of short-term disability, costing $17.2 million in lost productivity. The researchers demonstrated that with lower copayments and higher adherence to medicines, savings in productivity could be more than twice as large as increases in pharmacy costs.
- **Multiple Chronic Conditions:** One study found that patients with diabetes, hypertension, high cholesterol, asthma, or chronic obstructive pulmonary disease (COPD) who consistently took medicines as prescribed missed fewer days of work and experienced less short-term disability than nonadherent patients. For example, patients with asthma or COPD on average missed 9.8 fewer days from work and took 3.6 fewer days of short-term disability per year. For these patients, the productivity enhancement resulting from adhering to their medication regimen amounted to an annual average of $3,149 per worker[25] (see Figure 6).

Figure 6: Improving Adherence Increases Productivity

Adherent patients miss fewer days of work and experience less short-term disability.



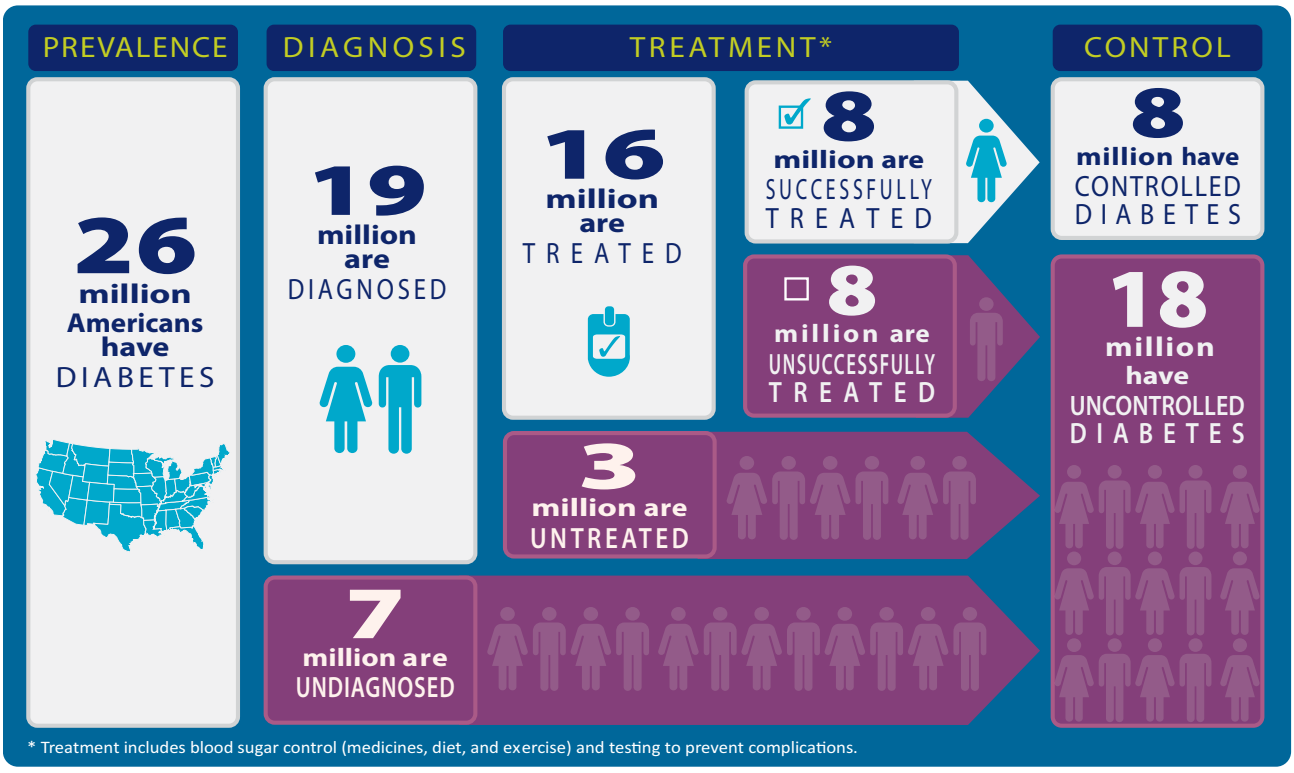
SOURCE: G.S. Carls, et al. "Impact of Medication Adherence on Absenteeism and Short-Term Disability for Five Chronic Diseases." *Journal of Occupational and Environmental Medicine* 2012; 54(7): 792–805.

GAPS IN APPROPRIATE USE OF MEDICINES

Undertreatment and poor use of prescription medicines is a significant problem throughout the health care system. 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.[26] Patients may fail to adhere to their doctor's instructions regarding their medications for a number of reasons. Sometimes patients do not understand their illness or do not comprehend their need for treatment. Often patients suffer from cognitive or physical impairments that can exacerbate this situation and result in poor adherence to treatment regimens. Complexity of treatment regimens, limited access to or poor coverage of medicines, and poor relationships between prescribers and patients may also contribute to gaps in appropriate use of medicines.

For example, patients with multiple chronic conditions often encounter difficulty in managing complicated treatment regimens. In fact, approximately 50 percent of medications for chronic diseases are not taken as prescribed.[27] Medication therapy management (MTM) programs are offered to Medicare Part D beneficiaries who have multiple

Figure 7: Diabetes: An Example of Underdiagnosis and Undertreatment



SOURCE: Centers for Disease Control and Prevention. "National Diabetes Fact Sheet: National Estimates and General Information on Diabetes and Prediabetes in the United States, 2011." Atlanta, GA: CDC, 2011. Available at www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf (accessed March 2014); IHS Global Insight Analysis based on 2010 National Health and Nutrition Examination Survey (NHANES).

chronic diseases and high drug costs to help manage their medication use. A recent *Health Affairs* study analyzed spending for Medicare Part D enrollees with chronic diseases and found that patients who adhered poorly to their medication regimens had higher health care costs—ranging from $49 to $840 per month for beneficiaries with diabetes, heart failure, and chronic obstructive pulmonary disease. Unfortunately, not all these patients were found to be uniformly more likely than others to be eligible for MTM services, which could have improved the quality of their care and reduced overall health care spending.[28] MTM services represent a significant opportunity for improving patient outcomes.

Similarly, certain vulnerable patient groups find it particularly challenging to adhere to their medicines—especially among elderly patients, where underuse of recommended medicines outweighs overuse by about 17 to 1.[29] Medication adherence among mental health patients is also difficult. A study examining health outcomes among patients with schizophrenia found that approximately 60 percent of patients were not adherent to medicines early in treatment, and were even less likely to be adherent several months later. For these patients, poor adherence resulted in more hospitalizations, with greater length of stay and cost of care.[30] While there are many barriers to the optimal use of medicines among patients, there are also many opportunities for improvement in patient care and outcomes.

IMPROVING USE OF MEDICINES

Health care stakeholders—health plans, pharmacists, biopharmaceutical companies, and others in the health care system—are pursuing a diverse array of strategies to improve the appropriate use of medicines and strengthen the health system overall. For example:

- Plans and providers offer medication therapy management to patients in order to improve the quality of chronic care management by providing counseling and reviewing drug regimens to improve adherence and detect adverse events.[31]
- Multiple medications in a treatment regimen can contribute to additional patient burden, leading to reduced adherence. Pharmacists are using advances in information technology to synchronize refills for patients who have multiple prescriptions. Some pharmacies now even send out reminders to patients when they need to pick up a prescription. This helps reduce the number of trips to the pharmacy, enabling patients to better manage their therapy regimens.
- Biopharmaceutical companies continue to develop new therapies, including subsequent-generation and combination products that simplify dosing regimens, provide more convenient routes of administration, or reduce side effects. These strategies make it easier for patients to take medicines.

In recent years, better access to medicines has improved health outcomes and provided savings to the health system by reducing spending on other nondrug medical expenses, such as for hospitalizations and skilled nursing home care. The introduction of the Medicare Part D program contributed greatly to these achievements. (See the accompanying sidebar on the 10th anniversary of Part D).

The 10th Anniversary of Medicare Part D

Ten years ago, Congress passed the law authorizing the Medicare prescription drug program (Part D). Today, more than 35 million people, or almost two-thirds of all Medicare beneficiaries, are enrolled in a Part D plan,[32] and the program's accomplishments are significant:

- The overwhelming majority of beneficiaries rate their coverage highly.[33] A recent survey reported that 96% of respondents were satisfied with their Medicare drug coverage, and 96% said their coverage worked well.
- Part D has improved access to medicines, leading to declines in costly hospitalizations and the need for skilled nursing care, providing an overall savings of $13.4 billion in the first full year of the program alone.[34]
- A 2011 study in *The Journal of the American Medical Association* found that beneficiaries with limited or no prior drug coverage who subsequently enrolled in Part D had an average savings of $1,200 in total nondrug medical costs in both 2006 and 2007.[35]
- The current estimates for total spending over the first 10 years of the program are $348 billion (45%) lower than initial projections.[36]

To learn more about the successes of Medicare's Part D program, visit www.phrma.org/issues/medicare.

Ensuring the appropriate use of medicines requires that patients are able to maintain access to those medicines. The Partnership for Prescription Assistance (PPA) serves as a single point of access to more than 475 public and private programs, including nearly 200 offered by biopharmaceutical companies, that help qualified patients get the medicines they need for free or nearly free. The PPA has helped nearly 8 million patients gain free and confidential access to these programs,[37] and PPA member programs are available for 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, the American Cancer Society, the American College of Emergency Physicians, Easter Seals, the National Association of Chain Drug Stores, United Way, and the Urban League. For more information about the PPA, please visit www.pparx.org.

Expansion of prescription drug coverage over the past two decades has improved access to medicines for many Americans. While more patients are expected to gain access to prescription medicines through the implementation of the Affordable Care Act, high cost sharing may mean that some patients will still be unable to afford the medicines they need. As patients gain insurance coverage through the implementation of the law, every effort needs to be made to ensure that this coverage provides access to a broad choice of medicines.

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3 Growing the U.S. Economy

Growing the U.S. Economy

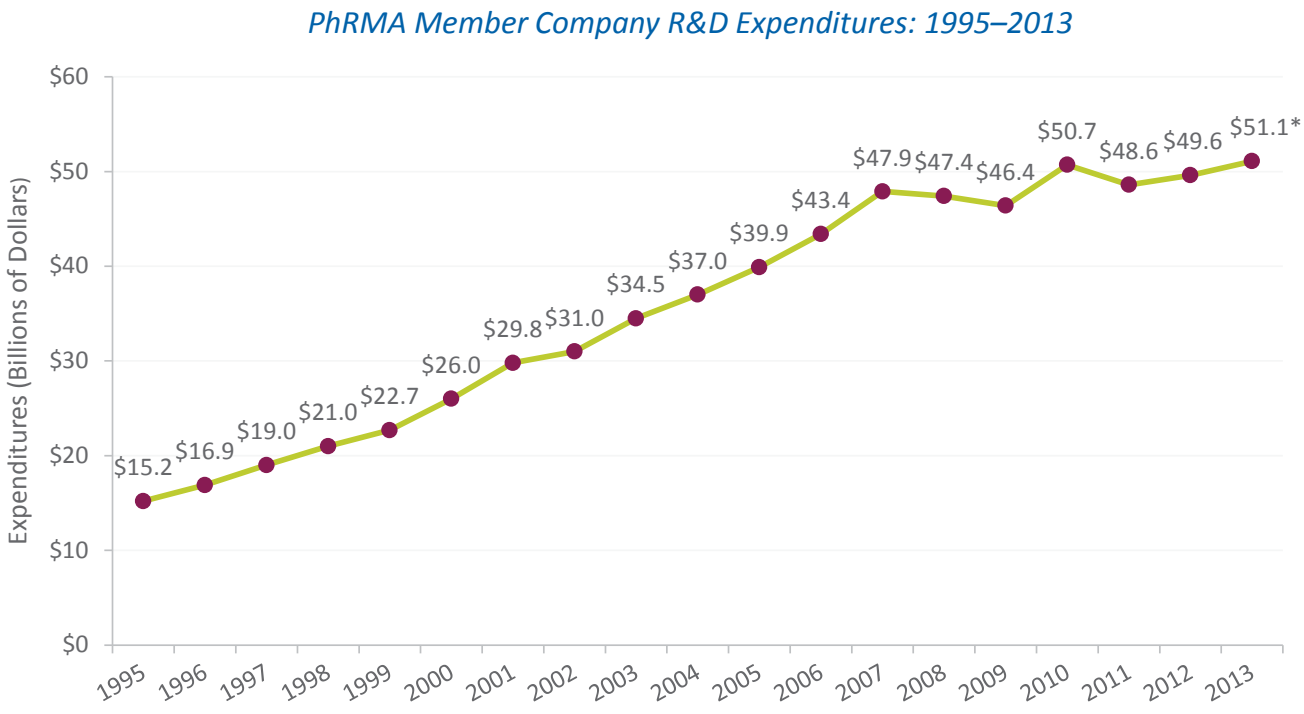
The innovative biopharmaceutical industry is recognized as a "dynamic and innovative business sector generating high-quality jobs as well as powering economic output and exports for the U.S. economy."[1] The sector supports nearly 3.4 million jobs across the economy, including more than 810,000 direct jobs, and contributes nearly $790 billion in economic output on an annual basis when direct, indirect, and induced effects are considered.[2] These outsized economic impacts are fueled by the industry's research and development (R&D) enterprises. As part of the industry's commitment to bringing new medicines to patients, the sector is the single largest funder of domestic business R&D, according to data from the National Science Foundation, accounting for more than 20% of all domestic R&D funded by U.S.

> The pharmaceutical industry is one of the most research-intensive industries in the United States. Pharmaceutical firms invest as much as five times more in research and development, relative to their sales, than the average U.S. manufacturing firm." > CONGRESSIONAL BUDGET OFFICE[3]

businesses.[4] The industry spends more than ten times the amount of R&D per employee as manufacturing industries overall.[5] In 2013 alone, PhRMA member companies invested an estimated $51.1 billion in R&D[6] (see Figure 8). This investment not only supports broad economic contributions, but also helps the U.S. lead the world in biopharmaceutical R&D, fueling competitiveness in an increasingly knowledge-based economy.

To support these R&D efforts, the biopharmaceutical industry employs a workforce with diverse skills and educational levels in a range of high-quality, high-wage jobs, particularly in science, technology, engineering and math (STEM). For all occupations involved in the biopharmaceutical sector, the average wage is higher than across all other private-sector industries. In 2011, the average total compensation per direct biopharmaceutical employee was

Figure 8: PhRMA Member Company R&D Investment



SOURCE: Pharmaceutical Research and Manufacturers of America. PhRMA Annual Membership Survey, 1996–2014.

$110,490, twice the average compensation per U.S. worker of $54,455.[7] The industry is a "jobs multiplier," meaning that each biopharmaceutical-sector job supports a total of more than four jobs across the economy, ranging from biopharmaceutical manufacturing jobs and construction to business services and child care providers.

Biopharmaceutical companies have roots in communities across the country, supporting a broad range of jobs directly related to clinical research and testing as well as manufacturing and distribution, and through vendors and suppliers. Companies and their corporate foundations also have established robust assistance programs and collaborations with public schools and others to improve STEM education and STEM teacher quality.

SUPPORTING STATE AND REGIONAL ECONOMIES

The R&D process, which includes clinical trials, can take between 10 and 15 years, at an average cost of $1.2 billion, to develop a new medicine—including the cost of failures—with recent estimates suggesting the costs are even higher.[8] Clinical trials are an essential part of the drug development process (see Chapter 4). Because of their cost and length, clinical trials represent a large investment in communities all across the country, helping to create jobs and boost local economies. Industry-funded clinical trials typically are conducted in collaboration with a range of local institutions—including academic medical research centers, contract research organizations, university medical and pharmacy schools, hospitals, and foundations.

To help raise awareness of the importance of participation in clinical trials and their contribution to local and state economies, PhRMA recently launched the "Research in Your Backyard" series. The program involves collaborative forums and the development of materials focused on various aspects of clinical trials within individual states. To date, more than 25 state reports have been developed that describe clinical trials targeting six of the nation's most debilitating diseases: asthma, cancer, diabetes, heart disease, mental illness and stroke. Since 1999, biopharmaceutical companies working with local research institutions have conducted, or are conducting:

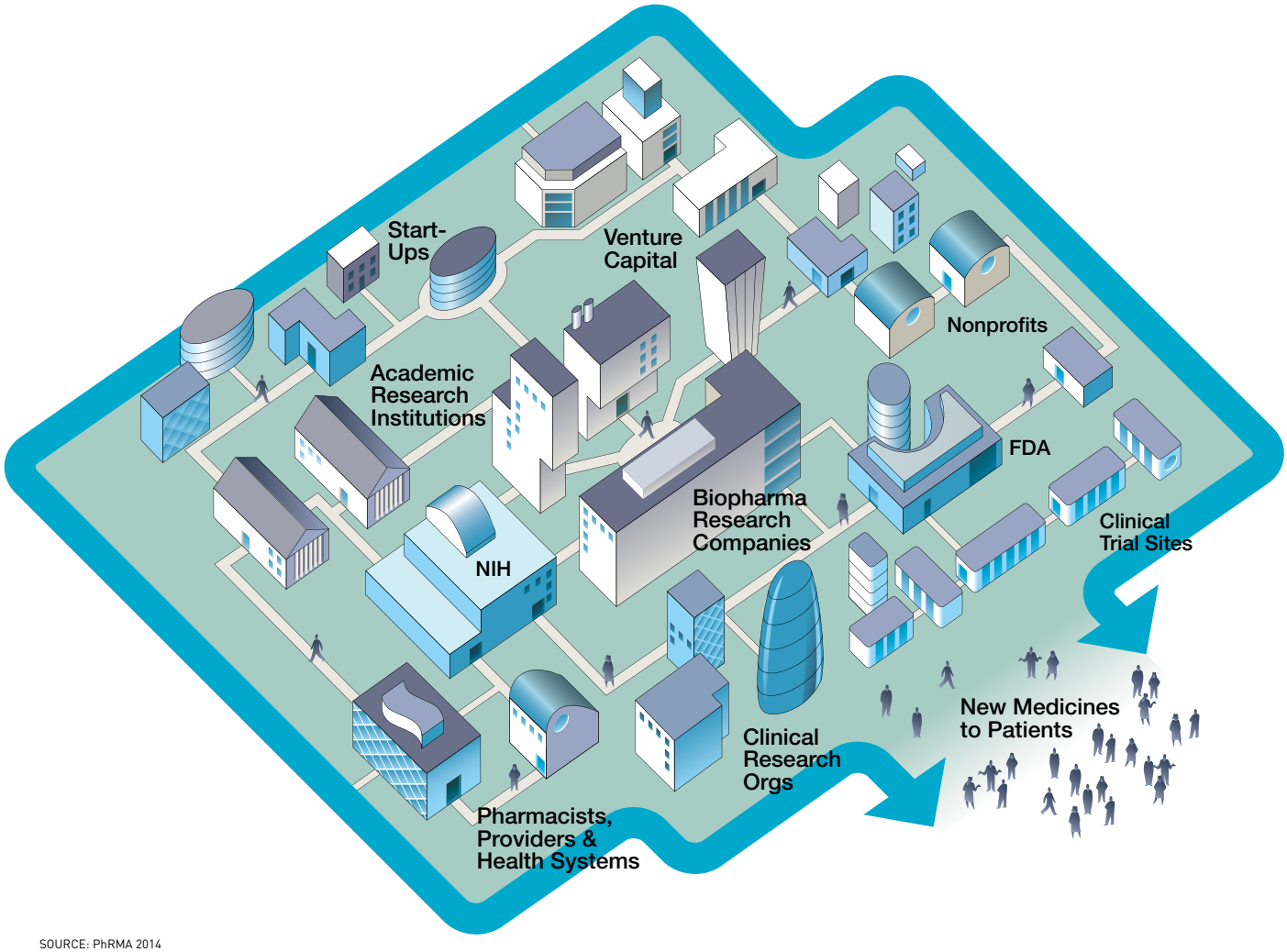
- Nearly 7,850 clinical trials in Florida, including 3,840 for six major chronic diseases.[9]
- More than 3,400 clinical trials in Michigan, including 1,725 for six major chronic diseases.[10]
- More than 3,700 clinical trials in Tennessee, including nearly 2,100 for six major chronic diseases.[11]
- Nearly 8,240 clinical trials in Texas, including almost 4,400 for six major chronic diseases.[12]

At the helm of each state's economic center is a governor squarely focused on job creation, economic development, and competitive advantage. While the task of educating elected officials on innovation has always been a challenge, the Research in Your Backyard program has been central to PhRMA's overall education effort, successfully combining important messages related to innovation, economic development and patient care. Last year alone, there were 19 Research in Your Backyard events in 17 different states, many of which were attended by governors, business leaders, patient advocacy organizations and university officials.

SUPPORTING THE BROADER LIFE SCIENCES ECOSYSTEM

The drug discovery and development enterprise is increasingly characterized by an ecosystem of partnerships and collaborations that bring together industry and academic institutions, government agencies, nonprofit foundations, venture capital, and patients into a support system for the pursuit of novel science and therapeutics (see Figure 9). As the largest funder and conductor of drug research and development, innovative biopharmaceutical companies play a central role in this ecosystem, dovetailing their core competencies with the strengths of these other stakeholders. These efforts are not only sustaining productivity in medical research, but benefiting local, state and national economies, sustaining productivity in medical research, and ensuring U.S. competitiveness in the global

Figure 9: Innovative Biopharmaceutical Companies Sit at the Heart of a Dynamic R&D Ecosystem in the U.S.



SOURCE: PhRMA 2014

> I've seen the lives of patients transformed as a result of new medicines we've discovered, developed and manufactured—and I've seen the unrelenting passion of scientists who work on those kinds of therapies. It's shown me how rewarding it can be to pursue science as a career—and the broad-based benefits that science, technology, engineering, and math (STEM) disciplines can provide. The danger we face today is the possibility that fewer people will enter highly technical fields in the decades ahead, at a time when demand for individuals with these kinds of skills is on the rise."[13] > ROBERT BRADWAY, CEO, AMGEN

marketplace. The industry is engaged in a broad range of efforts to support a thriving ecosystem—including, but not limited to, encouraging STEM education, pursuing precompetitive research collaborations and partnerships, and establishing corporate venture capital funds to support startup and emerging companies.

STEM Education

Continued scientific and technological innovations are critical to fostering sustained economic growth and global competitiveness and, most importantly, helping patients live longer, healthier, and more productive lives. The U.S. innovative biopharmaceutical industry is committed to building on new scientific discoveries and technological advances, relying on a workforce with education and skills in STEM. Around the world, an increasing number of countries have recognized that a robust, STEM-skilled workforce is needed to fuel continued economic growth. STEM workers have been shown to be key drivers of innovation, and thus to contribute significantly to economic productivity.

To maintain U.S. global competition in biopharmaceutical R&D, ensuring a supply of highly skilled STEM workers is critical to continued medical progress. STEM jobs range from production technicians with high school degrees to engineers, mathematicians, and scientists with advanced

degrees, who are involved in every stage of the R&D and manufacturing processes that result in new treatments and cures against our most costly and challenging diseases. Developing and maintaining a highly skilled STEM workforce is of particular concern for the innovative biopharmaceutical sector, as nearly one-third of workers in the industry's manufacturing component alone are employed in STEM-related occupations—roughly five times higher than the average share of STEM-related employment across the economy.[14] Biopharmaceutical companies are engaged in a broad range of initiatives throughout the United States to support STEM education, and in the process helping to pave the way for a globally competitive workforces (see sidebar, "Advancing STEM Education in the United States.")

Advancing STEM Education in the United States

According to a recent report by the President's Council of Advisors on Science and Technology, the United States will need to produce one million additional STEM graduates over the next decade to maintain its position as the world's leader in science and technology innovation.[15] But while the demand for STEM workers has increased for high-R&D industries, U.S. rankings on key STEM measures have experienced marked declines in recent years. Recent global rankings of high school student performance on science and math proficiency exams point to a growing gap in STEM talent: U.S. students now rank in the bottom half of 65 participating countries, while countries such as China and Singapore lead the world in both subjects.

The innovative biopharmaceutical industry is not sitting idly by, but rather is actively working with local school systems and others to improve STEM education and STEM teacher quality. A new report prepared for PhRMA by the Battelle Technology Partnership Practice[16] describes the range of efforts supported by PhRMA member companies and their corporate foundations to help improve STEM education in the United States. Among the key findings of the report:

- Over the past 5 years, the 24 PhRMA member companies responding to the survey funded more than 90 individual initiatives focused on students and/or teachers in STEM-related fields, impacting more than 1.6 million students and 17,500 teachers across the United States.
- In total, the 24 PhRMA member companies and their foundations have invested more than $100 million in STEM education–related initiatives since 2008, including awarding nearly 600 individual STEM education-related grants.
- Innovative biopharmaceutical companies and their corporate foundations are making significant contributions across the U.S. through a broad range of local-, state-, and national-level programs and initiatives aimed at elementary through postsecondary education, including 14 national-level programs and additional local-level programs being supported in 26 states, the District of Columbia, and Puerto Rico. (See Figure 10.)

In addition to financial contributions, the report found PhRMA member companies are making significant in-kind contributions by leveraging the talents of nearly 4,500 industry employees who have collectively volunteered almost 27,000 hours over the past 5 years. Other in-kind contributions include equipment donations and the use of company laboratory facilities, particularly at the K–12 levels, at a time when public school budgets are shrinking.

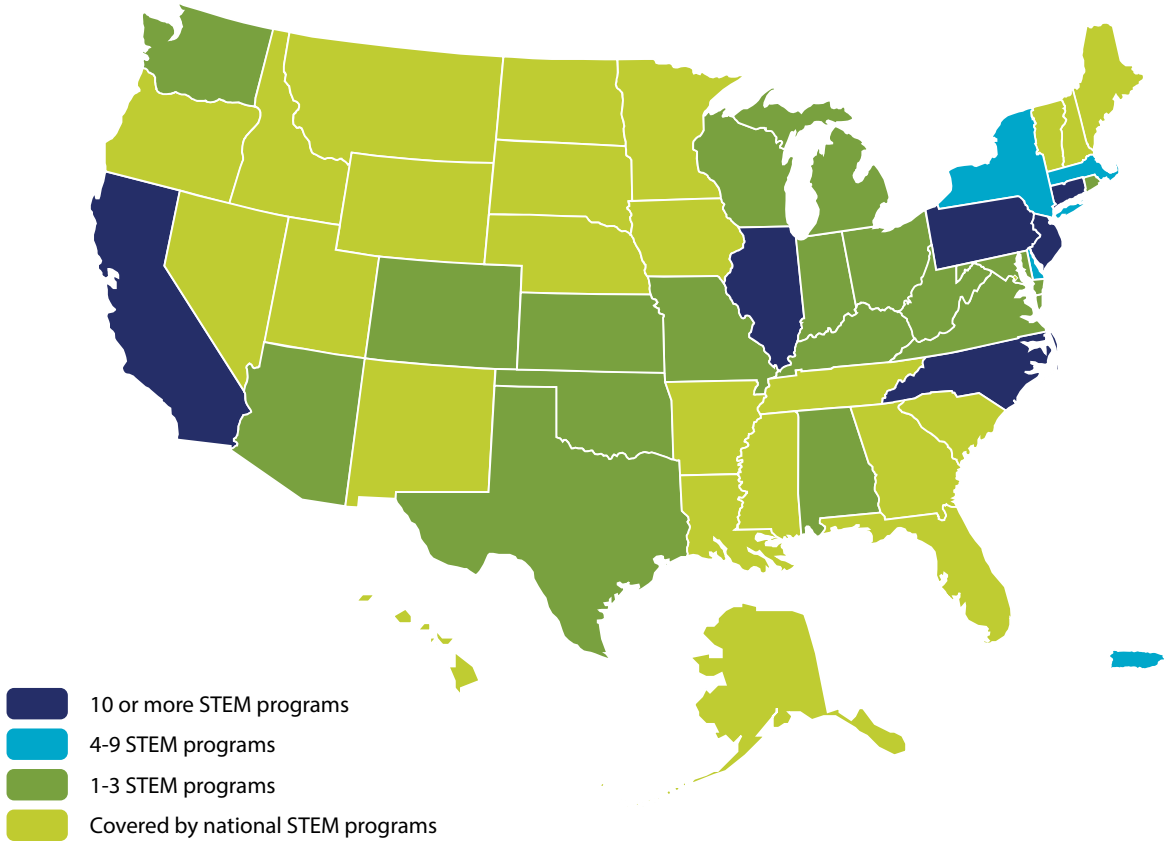
- A large majority (85%) of industry-supported STEM education programs focus on the K–12 levels and are aimed at improving the preparation of both students and teachers. This suggests that PhRMA member companies are focused on systemic changes in the way STEM education is taught in the United States, by engaging younger students and early education teachers.
- More than 30 PhRMA member programs are focusing on increasing diversity in STEM fields by providing students of all backgrounds, particularly women and minorities, experience with hands-on, inquiry-based scientific learning opportunities.

> All adults, especially teachers, parents and mentors, must foster excitement in young children about the wonders of science. All kids are naturally curious, and we should encourage them to explore and ask big questions.... We can't wait until kids are in high school to do this. We must start earlier, and that has guided much of our thinking on STEM related programming."[17] > JOHN LECHLEITER, Ph.D., CEO, ELI LILLY AND COMPANY

Collaboration Across the R&D Ecosystem

Effectively harnessing new scientific learnings and technological breakthroughs requires bringing together the best and the brightest across various components of the R&D ecosystem. Increasingly, biopharmaceutical companies are working in partnership with researchers in government, academia, smaller companies, and other sectors. According to a recent study of more than 3,000 such partnerships by the Tufts Center for the Study of Drug Development, collaborations between industry and academia benefit industry as well

Figure 10: Geographic Coverage of U.S. STEM Education Programs Supported by the Biopharmaceutical Industry[18]



SOURCE: PhRMA-Battelle "STEM: Building a 21st Century Workforce to Develop Tomorrow's New Medicines," January 2014.

as academia by providing opportunities for the sectors to explore promising new technologies together and to address tough scientific problems that may lead to advances against our most costly and challenging diseases.[19] These relationships vary significantly, and are continually evolving. Common partnership models include unrestricted research support; academic drug discovery centers; and precompetitive research centers, which bring together various institutions that ordinarily are commercial competitors to collaborate in early-stage research.

One exciting example of a precompetitive research collaboration is the Alzheimer's Disease Neuroimaging Initiative (ADNI). This initiative, which includes federal agencies, nonprofit organizations and industry members, aims to use neuroimaging to identify physical changes in the brain before the onset of Alzheimer's disease and then to track the progression of these changes. ADNI also will establish quality standards for imaging data collection and sharing, and will validate biomarkers to be used in clinical trials.[20] 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.[21]

Corporate Venture Capital Investments

In recent years, traditional venture capital investment in the biosciences has continued to decline. Biopharmaceutical companies are helping to fill this funding gap. Companies are developing their own corporate venture capital (CVC) funds and investing in venture capital funds, providing vital funding for promising R&D projects. Between 2010 and 2013, the corporate venture arms of large biopharmaceutical companies contributed more than $1.7 billion in support of biotech startups.[22]

In a recent analysis, the Boston Consulting Group found that participation in corporate venture capital investment by the 30 largest biopharmaceutical

Rx Response—Collaborating to Bring Medicines to Patients in Need

In times of major disaster, maintaining access to medicines is a critical priority for many people. The absence of even a single link in the biopharmaceutical supply chain can become a serious problem if it means that people cannot get their medicines.

Rx Response is a unique collaborative initiative that brings together biopharmaceutical companies, distributors, and dispensers, along with the American Red Cross, to help ensure that medicines continue to be available following a major disaster. In the 7 years since its inception, Rx Response has become an indispensable homeland security and public health asset. In 2013, Rx Response was recognized by the National Hurricane Conference and the National Lieutenant Governor's Association for their assistance to patients and federal, state, and local emergency responders. Among Rx Response's resources is Rx Open. This online resource maps the locations of open pharmacies in disaster-stricken areas. For additional disaster planning resources and more information, visit RxResponse at www.rxresponse.org.

> 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."> G. VON KROGH, ET AL. IN *NATURE BIOTECHNOLOGY*[23]

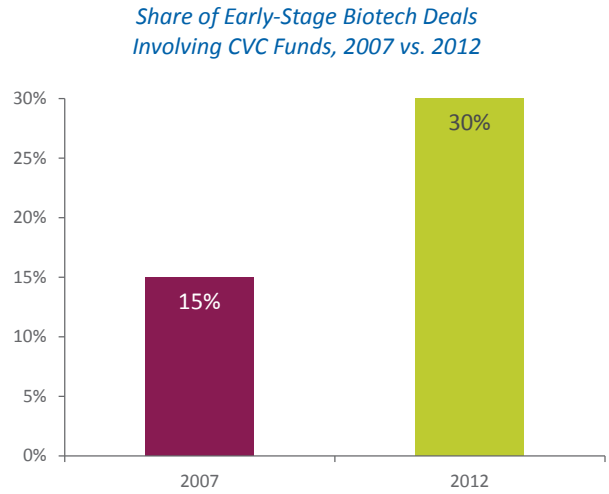
companies rose from 50% in 2007 to 63% in 2013.[24] Innovative biopharmaceutical companies are particularly focusing their investment efforts on early-stage startups, which have experienced the largest declines in funding. Since 2010, CVC investment in early-stage biotech startups has steadily increased, while traditional venture funds have moved investments toward later-stage companies. In fact, the share of early stage biotech companies receiving CVC investment has doubled since 2007 (see Figure 11).

LEADING THE WORLD IN MEDICAL RESEARCH: BRINGING NEW MEDICINES TO PATIENTS

The United States is the global leader in biopharmaceutical innovation. There are more than 5,000 medicines in clinical trials globally with the potential to aid U.S. patients.[25] This leadership continues even as emerging global economic competitors around the world are recognizing the economic and social benefits of biomedical research. An increasing number of countries are focused on attracting and growing innovative biopharmaceutical environment and related sectors as part of their

Figure 11: Corporate Venture Capital Helping to Fill Early-Stage Funding Gap

Venture capital investments in emerging biotech companies have dropped 22% from 2007 to 2013, with the most rapid declines seen in first-round deals. The corporate venture capital (CVC) arms of established biopharmaceutical companies are helping fill this growing gap.



SOURCE: PricewaterhouseCoopers and the National Venture Capital Association, 2013 MoneyTree™ National Data, 2014.

economic development plans.[26] Ensuring a favorable environment for innovation requires strong intellectual property protections to support the substantial time and R&D investments needed to develop tomorrow's new treatments. As the costs and complexities related to clinical trials continue to grow and the uncertainty regarding how new medicines will be used and valued increases, strong intellectual property rights are needed to recognize the substantial time, financial investments and intellectual capital involved in bringing medicines to patients.

Many of the recent treatment advances today, which are driven by lengthy and costly scientific research, would not have been possible without a system of laws that provide the structured and stable environment necessary to foster the investments needed to develop life-saving medicines.

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4 R&D: Bringing Hope to Patients

R&D: Bringing Hope to Patients

Novel scientific strategies, along with the mapping of the human genome, have opened up new understanding and expanded possibilities for treating disease. Over the past 20 years, advancements in our knowledge of the molecular and genetic basis of disease have led to the development of a vast array of scientific tools to target diseases more precisely. The application of these tools is resulting in a particularly robust pipeline, as there are more than 5,000 medicines in development globally with the potential to aid U.S. patients—many treating rare diseases or conditions for which there are currently few or no treatments available.[1] The immense potential in the pipeline represents not only an unprecedented opportunity to change the lives of patients, but also the tireless efforts of researchers to translate science into medicines.

Yet with incredible advancements in science comes greater complexity in research and development. The road to developing new medicines is a rigorous, long and costly one. In total, it takes about 10 to 15 years to develop a new medicine.[2,3,4] In many cases, the process begins with advanced screening of voluminous

compound libraries in order to identify a handful that have therapeutic potential. Despite advanced screening processes, only one viable candidate is likely to emerge and receive ultimate approval from the Food and Drug Administration (FDA). Between 1999 and 2004, the clinical approval success rate was estimated at 16%—or just one in six compounds.[5]

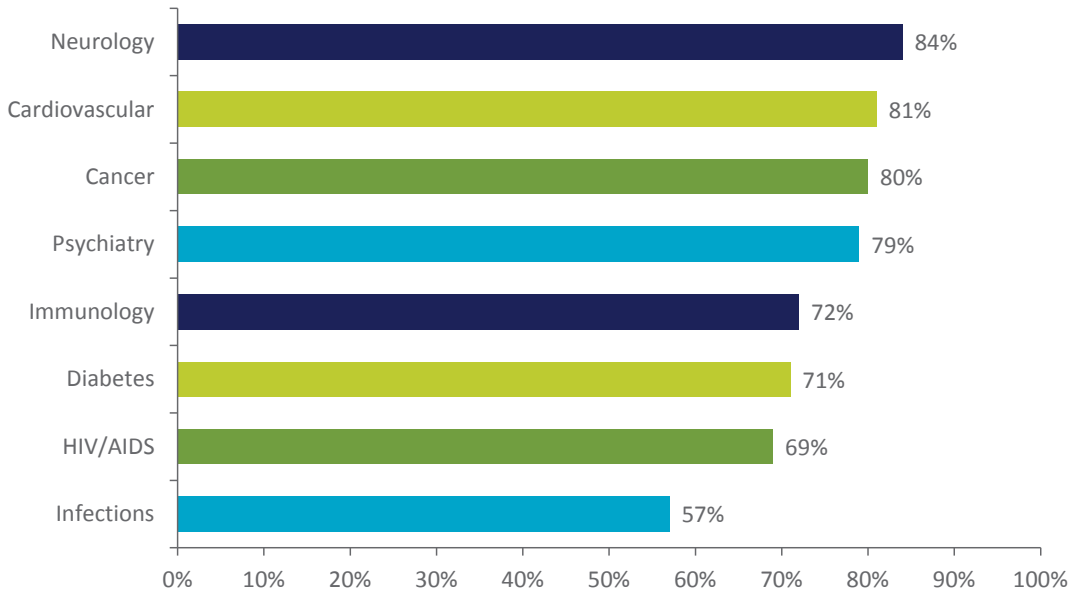
Despite these challenges, biopharmaceutical researchers are dedicated to their mission of advancing the science and bringing innovative new medicines to patients. Researchers are continuing to adapt to the growing complexity and rapidly evolving nature of the drug development enterprise, knowing that the work can result in new medicines that save lives, expand treatment options, and improve patients' quality of life. In service of this mission, in 2013 PhRMA launched the BioMedical Advisory Council, composed of heads of research and development (R&D) and chief medical officers from member companies to set the vision and provide direction to help promote a sustainable life sciences ecosystem and enable the industry to deliver on the promise of the biopharmaceutical enterprise.

EXAMINING THE PIPELINE

Recent advancements in science, combined with the commitment of biopharmaceutical researchers, is opening up immense opportunity in the development of new medicines.[6] A recent report examining innovation in the drug development pipeline found that 70% of the more than 5,000 new molecular entities being investigated are potential first-in-class medicines, or medicines that are in a unique pharmacologic class distinct from any other marketed drugs[7] (see Figure 12). First-in-class

Figure 12: Potential First-in-Class Medicines in the Pipeline

An average of 70% of drugs across the pipeline are potential first-in-class medicines.



SOURCE: G. Long and J. Works. "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 March 2014).

medicines offer new potential treatment options for patients, particularly for those who have not responded to existing therapies or for whom no treatment options are available. Increasingly, scientists are developing therapies to treat diseases for which no new medicines have been approved in the last 10 years. Researchers are currently investigating over 400 such medicines—including 158 to treat ovarian cancer, 41 to treat small-cell lung cancer, 28 to treat cervical cancer, 27 to treat anthrax, and 26 to treat septic shock.[8]

Rare diseases are another area that has seen significant progress in recent years, with FDA designations of orphan drugs in development showing a significant increase. An average of 140 drugs have been designated as orphan drugs each year over the past decade, compared with 64 in the previous 10 years.[9] Currently, America's biopharmaceutical research companies are developing 452 medicines and vaccines to treat rare diseases. In particular, researchers are focusing on rare cancers, genetic disorders, neurological conditions, infectious diseases, and autoimmune disorders.[10] Many of these diseases are serious or life threatening, and patients who have them frequently have few or no treatment options.

Unfortunately, while in recent years we have seen great progress in the development of medicines to treat rare diseases, fewer than 10 percent of patients with rare diseases have treatments available today, and the development of medicines in this area is particularly challenging.[11] Despite great progress, the development of medicines to provide treatment options for these patients remains critically important.

Innovation in Scientific Platforms

It often takes years, and sometimes decades, to translate scientific discoveries into new therapeutic approaches, but these discoveries provide a platform that allows researchers to pursue a range of never-before-possible options for treating a disease.[12] Innovative scientific platforms are often explored in the development of biologic medicines, which are complex medicines made by or from living cells to prevent, treat, diagnose, or cure disease in humans.[13] There are currently 907 biologic medicines in development, many of which are making use of a broad range of new technologies to harness scientific

> It's a long journey, very challenging, but at the end of the day once we get there, to have a new treatment for patients, it makes all the difference." > OLOF LARSSON, CHIEF SCIENTIFIC OFFICER, PAIN, ELI LILLY

Learn more about Dr. Larsson's work at: www.youtube.com/watch?v=PWxwGByHwrI.

A Look at the People Behind the Science

The biopharmaceutical industry's greatest strength is its scientific leadership, personified by the researchers who dedicate themselves to this endeavor, committing their lives and expertise to translate scientific and technological breakthroughs into new treatments for patients. Here are just a few of the researchers who are applying new knowledge to a range of different diseases and conditions and, as a result, opening new doors to improvements in human health around the world.

Dr. Pat Scannon leads a team of researchers who are searching for therapies that target cancer cells while leaving healthy cells undamaged. One of the most exciting parts of his work is watching his team members make progress individually as well as through dedicated teamwork. To learn more about the values that drive Dr. Scannon in his work and personal life, watch: www.youtube.com/watch?v=NO3HsCcskiI.

"We're looking for novel therapeutics for diseases that have no alternatives. What we're interested in is not just killing cancer cells... the idea is to kill the cancer cells without killing the other tissue so that person ultimately is able to get rid of the cancer and live a healthy life afterwards...There is a great amount of satisfaction and joy in taking your knowledge and using it to help other people."

"We're trying to understand how to reverse those changes in the biology [of the brain] to help people who are suffering from a range of different diseases, and chances are that you or someone you care about will develop one of these diseases. There are a lot of challenges, so it's more frustrating in that way, but it's also more rewarding."

Dr. Sean Pintchovski is fascinated by the brain in all its complexity. He is working on developing medicines that might slow or reverse the damage caused by neurodegenerative diseases such as Alzheimer's. Though unsuccessful attempts to find treatments far outnumber successes, the knowledge gained is invaluable, because it often points scientists in new and more fruitful directions. To learn more about Dr. Pintchovski's work, watch: www.youtube.com/watch?v=d0MxtyLyN38.

Dr. Sophie Biernaux, and her company's malaria vaccine team, were 2013 recipients of a PhRMA Research and Hope Award. Dr. Biernaux leads her company's R&D efforts to develop a malaria vaccine. She manages all of the phase III vaccine trials across sub-Saharan Africa and collaborates closely with governmental and nongovernmental organizations working to eradicate this devastating disease, which affects millions across the continent: more than 600,000 African children die of malaria each year. If the vaccine candidate is successful, it could be the first ever vaccine developed to prevent malaria or any parasitic disease.[14] To learn more about this work, watch: www.youtube.com/watch?v=CJTiKdOxfj8.

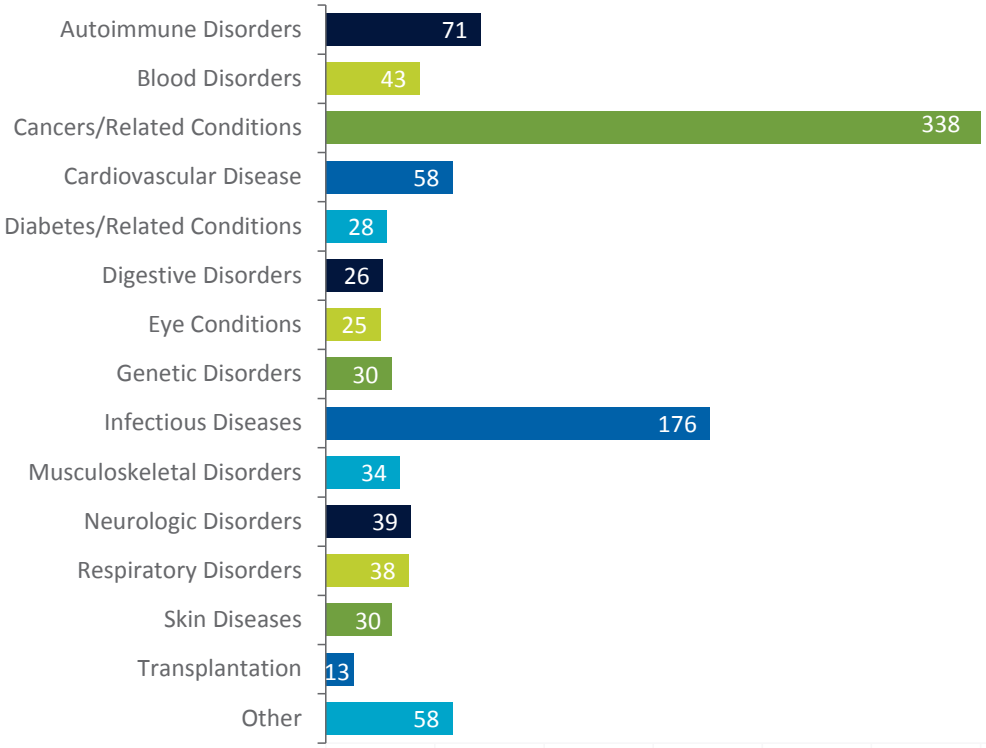
"I feel extremely honored on behalf of the team to get this award. Because for us that vaccine is really a great hope that we have for Africa and African children."

progress across a variety of disease areas (see Figure 13). Select examples include:

- **Antisense RNAi therapy**. Most drugs target proteins, such as enzymes and cellular receptors. RNAi therapy takes a different approach by targeting RNA, which carries genetic information to create proteins in the cell. RNA interference (RNAi) therapy can help silence harmful gene expression. In the past 20 years, this work has advanced from cutting-edge laboratory research to the development of actual treatment options for patients, with two RNAi therapies having been approved as of 2012, and over 127 more RNAi therapies in the pipeline.[15]
- **Therapeutic cancer vaccines**. In the late 1990s, scientists began experimenting with new vaccines that could harness the power of the immune system to fight cancer rather than to prevent it. The first therapeutic cancer vaccine was approved in 2010, and now there are more than 20 therapeutic vaccines for cancer in development.[16,17]
- **Cell Therapy**. This regenerative approach introduces new cells into tissue in order to treat a disease. Currently there are 245 cell therapies in the pipeline.[18]
- **Gene Therapy**. This strategy is designed to treat patients with a number of genetic diseases. It

Figure 13: More than 900 Biologic Medicines in Development in 2013

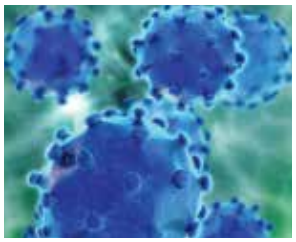
Biologic medicines—large, complex molecules derived from living cells—frequently represent novel strategies that have the potential to transform the clinical treatment of disease.



*Some medicines are being explored in more than one therapeutic category.

SOURCE: Pharmaceutical Research and Manufacturers of America. "Medicines in Development: Biologics—Overview." Washington, DC: PhRMA, 2013.

A Revolution in the Treatment of Hepatitis C



Hepatitis C is a devastating viral liver disease affecting five times as many people as HIV—amounting to more than 3 to 4 million people in the United States and approximately 180 million people worldwide.[19] The virus is a leading cause of liver transplantation and liver cancer and is directly linked to 15,000 deaths per year.[20,21] Hepatitis C will have an increasing impact on health care in the coming years, as baby boomers maintain the highest infection rates of hepatitis C. Because the symptoms of the disease are slow to appear, the aging of this population poses a growing threat to human health and to the health system.

Until recently, existing treatments for the disease were able to cure only about half of patients, and many discontinued treatment due to debilitating side effects.[22] A new era in the treatment of hepatitis C has begun with a new wave of medicines approved and in development that seek to act on targets in the virus lifecycle to directly inhibit viral production. These drugs—referred to as direct-acting antiviral (DAA) agents—are specifically targeted antiviral therapies for hepatitis C that act on virtually every stage in the viral lifecycle.[23]

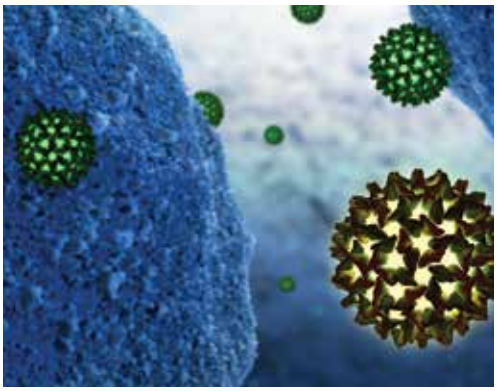
The first of these oral medicines was approved beginning in 2011 to treat patients with the most common form of the disease—those with genotype 1, accounting for more than 70 percent of patients. Up until this time, there were no proven medicines for patients who didn't respond to traditional hepatitis C therapy. These medicines not only provided much-needed treatment options for chronically ill patients, but marked a major advance toward the ultimate goal of providing more potent therapies with fewer side effects, and over a shorter course of treatment.

A second wave of oral DAAs, working through a different mechanism, is currently in the pipeline and expected to significantly reduce side effects and offer even higher cure rates. One of these medicines was already approved in 2013.[24] In addition to treating genotype 1, these medicines treat patients with genotypes 2 and 3 of the disease (which account for 20 to 25 percent of patients). Early evidence suggests improvements in cure rates reaching 90 percent or higher.[25,26]

In recognition of the progress made in cure rates, treatment duration, and the promising medicines in the pipeline, the Cleveland Clinic named the emerging DAAs for hepatitis C a Top 10 Medical Innovation for 2014 for its potential impact on patients.[27] As these new treatments are approved over the next several years, we will see expanded treatment options for various subpopulations, including increased potential for cures with shorter treatment times.

In consideration of the growing number of baby boomers infected with hepatitis C, Dr. Camilla Graham of Beth Israel Deaconness Medical Center in Boston points out, "We have a narrow window of time to find as many people as possible to cure them as quickly as possible, if we want to make a substantial impact on their disease progression, as well as on those very expensive complications in the future."[28] Dr. David Thomas, a liver specialist at Johns Hopkins University, seconds Dr. Graham's caution, adding: "If we fail to provide treatment to an expanding population of persons at risk of cirrhosis and liver cancer, then we'll have even greater costs...and they won't all be economic."[29]

Spotlight on B-Cell Receptor Pathway Inhibitors



A decade ago, a medicine known as imatinib produced a paradigm shift in the treatment of chronic myeloid leukemia (CML), taking it from a standard of chemotherapy treatment to an era of more targeted medicines designed to interfere with the underlying cellular processes causing a particular cancer—effectively treating the cancer while also minimizing side effects.[30]

In the years that followed, researchers learned that the B-cell receptor pathway tightly controls the growth of infection-fighting B cells; when this pathway becomes unregulated, it can contribute to the development of certain cancers. As a result, a number of novel therapies called B-cell receptor pathway inhibitors have been designed to inhibit this overactive pathway. In clinical trials over the past year, these agents have been found to be particularly effective in the treatment of low-grade B-cell lymphomas and leukemias over long periods of time, and with very few side effects.[31]

In particular, the B-cell pathway inhibitors in clinical trials are showing great success in the treatment of chronic lymphocytic leukemia (CLL)—so much so that experts are anticipating another major shift in treatment for these patients similar to that seen in CML. Dr. Richard Furman, director of the CLL Research Center at Weill Cornell Medical College, proclaimed at a 2013 meeting of the American Society of Hematology that these medicines "herald a dawn of a new age for CLL patients," noting that "people who should have died 5 years ago are alive and well and in complete remission. It's a huge paradigm shift."[32] Also this year, the Cleveland Clinic, at their annual medical innovation summit, named B-cell receptor pathway inhibitors a Top 10 Medical Innovation for these medicines' potential impact on health care in 2014—noting the impressive success seen with these agents in clinical trials for the treatment of CLL.

Describing the manner in which science builds upon previous advances, and how this process paves the way for future advances, experts at the Cleveland Clinic noted:

"The B-cell receptor pathway inhibitors are innovative because they help fulfill the initial promise of imatinib. They will help patients who are no longer responsive to chemotherapy live longer, provide an alternative to chemotherapy in the future, and will stimulate additional research to find similar advances for other cancers."[33]

To learn more, watch: www.clevelandclinic.org/innovations/summit/topten/2014.html.

A recent report found there are more than 240 medicines in development, including B-cell receptor pathway inhibitors, to treat a broad range of blood cancers—including 98 medicines to treat lymphomas, 97 to treat a variety of leukemias, and 52 to treat myelomas.[34] These potential medicines offer great hope for patients and families affected by these diseases.

involves the insertion, alteration, or removal of genes within cells and tissue—frequently to counteract genetic defects. There are 99 gene therapies in development.[35]

- **Conjugated Monoclonal Antibodies (mAbs)**. Conjugated mAbs utilize the selectivity of antibodies to deliver cytotoxic agents directly to tumor cells while sparing healthy cells. This approach offers to provide more targeted cancer therapies with reduced side effects. There are 102 conjugated mAbs in development.[36]

Many of these scientific strategies are showing particular promise in late-stage clinical trials and offer hope for patients who suffer from extremely difficult and complex diseases. A few examples of how biopharmaceutical researchers are applying these innovative scientific strategies to the development of new medicines are highlighted below.

- **RNAi Therapy to Treat Duchenne Muscular Dystrophy (DMD)**. DMD is a fatal muscle wasting disorder caused by mutations in the dystrophin gene. It is caused by deletions in the genetic code that encodes a protein found in normal muscle and causes muscle fibers to disintegrate faster than they can be regenerated. An RNAi therapy in development targets the restoration of this protein. In clinical trials, the medicine has shown improved protein expression as well as improvement in patients' ability to walk.[37]

- **Therapeutic Cancer Vaccine to Treat Melanoma**. A virus-based therapeutic vaccine in development for the treatment of melanoma is genetically modified to replicate selectively in tumor cells and express a gene for an immune-stimulating protein. The vaccine is injected directly into the tumor, where it replicates and spreads within the tumor, causing the death of cancer cells and stimulating the immune system to destroy cancer cells.[38]

OVERVIEW OF THE R&D PROCESS

The difficulty of drug development can be hard to grasp without an understanding of the length of time and the many steps involved in developing a medicine, the daunting odds that researchers face in producing a viable candidate, and the immense investment required to see the process through.

- On average, it takes about 10 to 15 years for a new medicine to complete the journey from initial discovery to patients.[39,40,41]
- Tens of thousands of compounds may be screened early in development, but only one ultimately receives approval. Even medicines that reach clinical trials have only a 16% chance of being approved.[42]
- The development process is costly and complex. The average R&D investment for each new medicine was estimated to average $1.2 billion, including the cost of failures, in 2007,[43] with more recent studies estimating the costs to be even higher[44] The requirements associated with the review and approval process have steadily increased over time, as have the uncertainties regarding whether the new medicines ultimately approved will be fully valued by payers and made available to patients.

The numerous lengthy steps each potential new medicine must take in order to make its way to patients are outlined in Figure 14. Despite these challenges, biopharmaceutical researchers are dedicated to the mission of advancing science and producing medicines that improve and save the lives of patients.

Drug Discovery

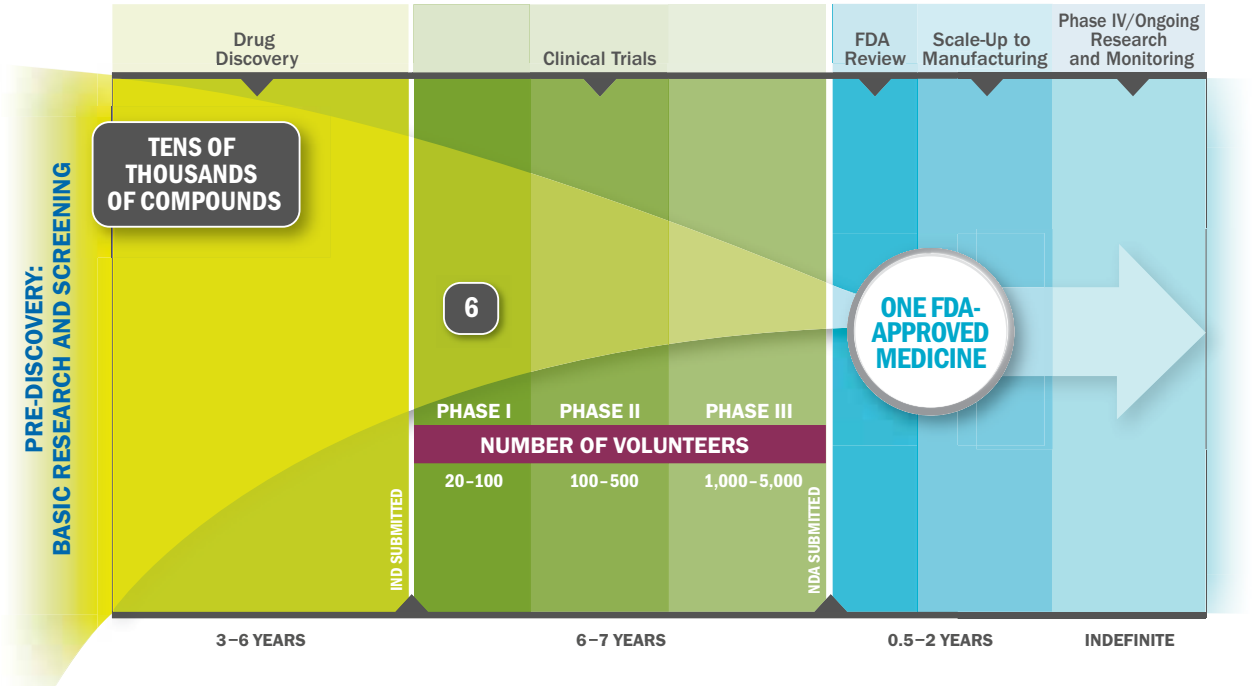
In the United States, we are fortunate to have a dynamic, collaborative research ecosystem that includes researchers from government, industry, academia, nonprofit organizations and patient advocacy groups that contribute to this body of knowledge (see Chapter 3). Even at these early stages of drug discovery, this collaborative ecosystem stands out as a great strength of the U.S. biomedical research system, and it enables the U.S. to stand out as a world leader in biopharmaceutical innovation.

Basic research provides clues that help researchers identify biological targets for a potential medicine. Researchers conduct studies in cells, tissues, and animal models to determine whether a particular target implicated in disease can be influenced by a compound being investigated.

Next, researchers look for a lead compound—a promising molecule that could influence the target and potentially become a medicine. Researchers do this in various ways, including creating a molecule, 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.

Figure 14: The Research and Development Process

Developing a new medicine takes an average of 10 to 15 years.



SOURCE: Pharmaceutical Research and Manufacturers of America. "Drug Discovery and Development: Understanding the R&D Process." Washington, DC: PhRMA, 2014.

Even this early on in the drug discovery process, investigators already are thinking about the final product. The formulation (or "recipe") for manufacturing a medicine, and the form in which it is delivered to patients (for example, whether it is taken in pill form, injected, or inhaled) are among the critical elements that need to be considered early on in the process.

Preclinical Testing

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

Clinical Trials

Upon reaching the clinical trial stage, a compound is tested in human volunteers. The clinical trials process occurs in several phases and takes many years. Before a medicine is submitted to the FDA for review, a potential medicine must successfully complete each phase. (See Chapter 3 for a discussion of the impacts of clinical trials on state and local economies.)

As this process involves a great deal of potential benefit but also inherent risks to clinical trial participants, companies are careful 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 trials are conducted with integrity and that clinical trial results are appropriately disclosed.

A study's design and informed consent process are reviewed, approved, and monitored by an Institutional Review Board (IRB). The IRB, which is made up of physicians, researchers, and members of the community, ensures that the study is ethical and that 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.[45]

Clinical trials have three main phases:

- **Phase I** trials test a compound in a small group (e.g., 20 to 100) of healthy volunteers to determine the safety of the compound.
- **Phase II** 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 the effectiveness of the compound, examine possible short-term side effects and risks, and identify optimal dose and schedule.
- **Phase III** 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

Upon completion of the clinical trials, providing the compound has demonstrated safety and efficacy, the company submits a New Drug Application or Biologics License Application to the FDA for approval to market the new medicine.

Upon careful review of all the data from all of the studies on the compound, and after weighing the benefits and risks of the potential medicine, FDA scientists 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

Medicines can be used by many millions of people or sometimes by a small, select population, and often they are on the market for many years. Consequently, manufacturing facilities must be carefully designed so that medicines can be consistently and efficiently produced at the highest level of quality and meet the needs of patients.

Accordingly, manufacturing facilities must be constructed to the highest of standards to ensure that safety and quality are built into each step of the manufacturing process.[46] 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, since each new medicine is manufactured differently.

Phase IV and Other Post-Approval Research and Monitoring

Research on a new medicine does not end upon approval, when a medicine reaches patients. On the contrary, companies conduct extensive post-approval research to monitor safety and long-term side effects in patients using the medicine, as well as phase IV clinical trials that evaluate long-term safety and efficacy in specific patient subgroups. Under certain circumstances, the FDA may also require companies to conduct risk evaluation and mitigation strategies to ensure that the benefits continue to outweigh the risks of a particular medicine.

Companies may also 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. Post-approval research is critical to improving researchers' and clinicians' understanding of a medicine's potential uses and full benefits to patients. In many cases, a medicine may reveal

itself over time to have an even greater impact on outcomes when used earlier in the progression of a disease, in combination with other medicines, in different disease indications, or in combination with specific biomarkers. The R&D process is a continuous, stepwise journey; additional research and clinical use provide new knowledge that can shape the way a product is used in future years (see the example of HIV/AIDS medicines in "The Evolving Value of Medicines" in Chapter 1, page 8).

THE PRESCRIPTION DRUG LIFECYCLE

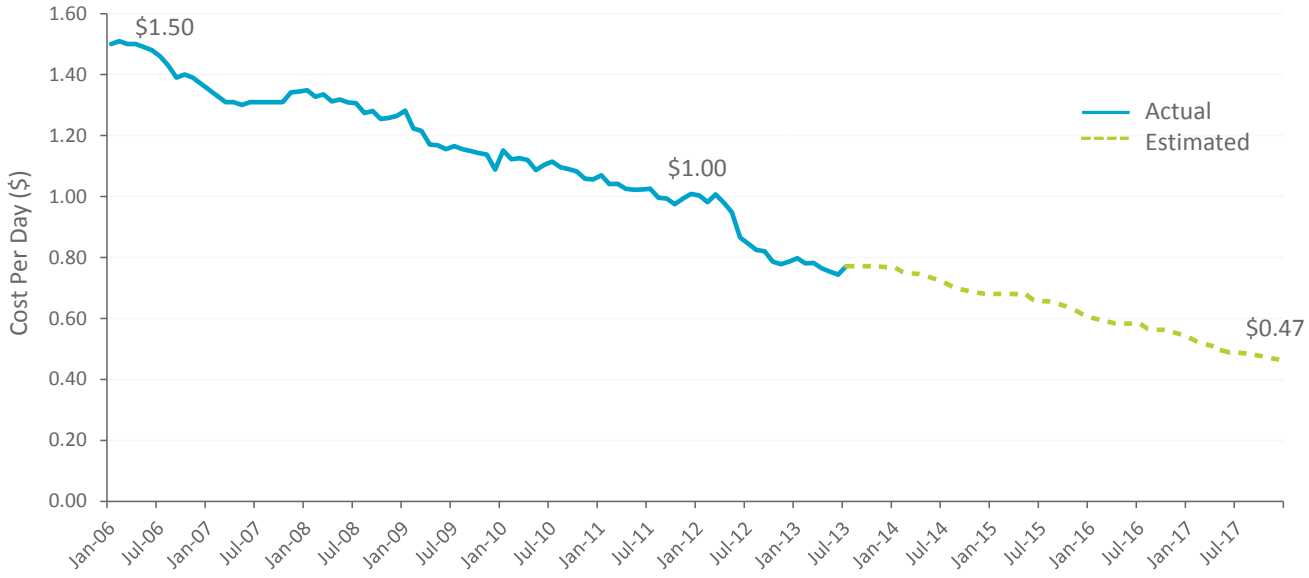
The R&D process is just one part of a larger prescription drug lifecycle in which innovative new medicines bring long-term savings to the health care system. This lifecycle begins with the initial development of a medicine, and it ends with a generic version of that medicine. Generics provide low-cost access to effective medicines for patients for many years to come 2000 (see Figure 15). But the benefits of generic medicines and, in the future, biosimilar medicines, would not be possible if innovator companies did not commit the incredible amount of time, resources, and investment to research and develop new, innovative medicines to save and improve the lives of patients.

After FDA approval, the average effective patent life of an innovative brand-name medicine is about 12.6

Figure 15: The U.S. Prescription Drug Lifecycle Promotes Innovation and Affordability

Innovator pharmaceutical companies produce medical advances through pioneering scientific work and large-scale investments. The innovators' work and investment lead both to new medicines and, over time, to generics that consumers use at low cost for many years.

Daily Cost of Top 10 Therapeutic Classes Most Commonly Used by Medicare Part D Enrollees*



*Ten therapeutic classes most commonly used by Part D enrollees in 2006 were: lipid regulators, ACE inhibitors, calcium channel blockers, beta blockers, proton pump inhibitors, thyroid hormone, angiotensin II, codeine and combination products, antidepressants, and seizure disorder medications.

SOURCE: M. Kleinrock. Daily Cost of Medicare Part D December 2013 Update. December 2013. IMS Institute for Healthcare Informatics.

years.[47] 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.[48] Patent challenges from generic manufacturers (Paragraph IV filings) also impact the ability to earn a return on investment, and research shows that patent challenges are increasing and being filed relatively early in the brand-name drug life cycle—within 7 years after brand launch, on average.[49]

Prior to the expiry of patent protection, innovator medicines face competition from other innovative medicines entering the class, expanding the treatment options for patients. After patent protection expires, generic versions of the innovator medicines quickly enter the market. In fact, the rate at which a generic medicine captures the market of a branded medicine has increased significantly over the past decade. For brand medicines facing generic entry in 2011–2012, generics captured an average of 84% percent of the market within a year of entry, compared with just 56% in 1999–2000.[50] In other words, brand medicines retained an average of only 16% of market share at 1 year post-generic entry in 2011–2012, compared with brand medicines maintaining a market share of 44% in 1999–2000.[51]

Today we estimate that 84% of all drug prescriptions are filled with a generic product,[52] yielding a savings of $1.1 billion over the past decade.[53] As biosimilars enter the market, increased competition is expected on both price and clinical effects.

As noted throughout this report, the R&D process is lengthy, costly, and complex; and harnessing the scientific challenges and opportunities to bring new treatments to patients requires the dedication of a range of stakeholders working collaboratively with biopharmaceutical companies over the course of the prescription drug lifecycle. The end result is medicines that save and improve patients' lives, reduce health care costs, and benefit local and national economies (see Chapter 3).

THE EVOLVING R&D PROCESS

The biopharmaceutical pipeline offers great hope for patients, but it also reflects increased complexity. The reality is that the biology of many diseases is complex, and the countless variables that must be considered make the process of discovering new medicines particularly challenging and uncertain. As science advances and provides new opportunities, the industry is continually innovating and adapting the R&D process in order to meet this challenge.

Here are a few examples of the forces that are contributing to the growing complexity of biopharmaceutical research:

Focusing on the molecular level: A deepening understanding of the molecular and genetic underpinnings of disease has brought unparalleled research opportunities and dramatically changed many aspects of drug development.

Researching increasingly complex diseases: Clinical investigators are increasingly exploring treatment options for complex diseases such as neurological disorders, cancer, and many rare diseases for which there are few or no treatments. For example, the number of medicines in development for Alzheimer's disease jumped from 26 in 2003 to 125 today.[54,55] New scientific opportunities make these avenues of exploration possible, but the complexities of these uncharted areas in the short term often mean an increased opportunity for failure.

> The science of drug discovery is hard. And it's just getting harder. In fact purely on a scientific level, taking a drug all the way from initial discovery to market is considered harder than putting a man on the moon."[56] > ASHUTOSH JOGALEKAR, SCIENTIFIC AMERICAN, 2014

Advancing personalized medicine: The emergence of personalized medicine has also made the R&D process more complex, as drug developers must now coordinate research on a new medicine with the development of a corresponding diagnostic that can help determine whether a patient will respond well to a medicine.

This increasingly complicated research scheme demands a greater understanding of how each patient may respond to a therapy, while also keeping pace with expanding regulatory requirements. As a result, 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,[57] (see Figure 16).

Patient recruitment for clinical trials also is an ongoing and growing challenge for researchers. On average, difficulty recruiting volunteers can nearly double the original timeline of phases I, II, III, and IV trials.[58]

The increased complexity of the research environment, combined with frequent failures

Figure 16: Complexity of Clinical Trials Has Increased

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	Increase in Complexity
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.

and setbacks, has contributed to the rising costs of clinical research.[59] In fact, the average cost of developing a drug—including the cost of failures—grew from $800 million in the late 1990s to about $1.2 billion in the early 2000s (see Figure 17). More recent studies have estimated the average costs to be much greater.

Adapting and Evolving

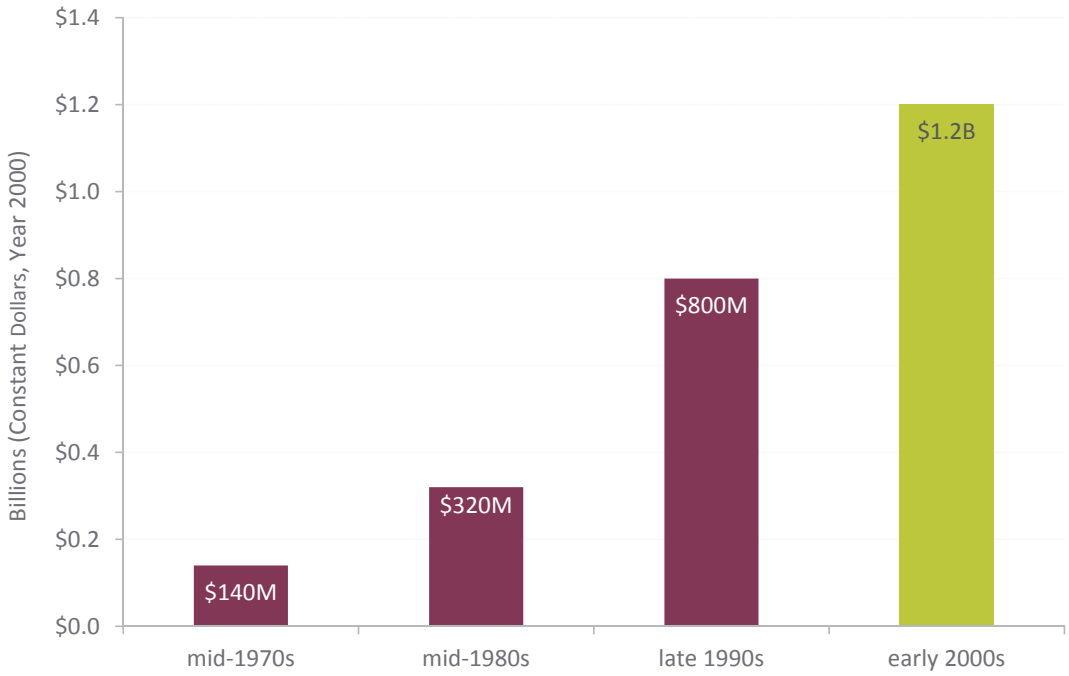
To produce innovative treatments more efficiently, biopharmaceutical companies must continually change, adapt, and build on prior knowledge to create new knowledge. Researchers are exploring new approaches that reduce development times and increase the odds of success, including adaptive designs which allow for modifications to trial and statistical procedures. Researchers are also developing and exploring new research tools, such as modeling and simulation, new approaches to patient recruitment—including the use of social media—and sophisticated methods of analyzing data to increase the efficiency and effectiveness of the R&D process.

Biopharmaceutical companies are looking to harness the potential of big data and real-world evidence

Figure 17: Drug Development Costs Have Increased

According to a 2007 study, it costs an average of $1.2 billion to develop one new drug. More recent studies estimate the costs to be even higher.

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



SOURCE: J.A. DiMasi and H.G. Grabowski. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 2007; 28: 469–479; More recent estimates range from $1.5 billion to more than $1.8 billion. See J. Mestre-Ferrandiz, J. Sussex, and A. Towse. "The R&D Cost of a New Medicine." London: 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; J.A. DiMasi, et al. "The Price of Innovation: New Estimates of Drug Development Costs." *Journal of Health Economics* 2003; 22: 151–185. Study findings originally reported in 2005 dollars. Based on correspondence with the study author, these figures were adjusted to 2000 dollars.

to better identify new potential drug candidates and develop them into effective, approved and reimbursed medicines more quickly.[60] To facilitate collaboration in this area, PhRMA collaborated this year with physicians and other experts through the Harvard Multi-Regional Clinical Trial Center to outline different models for responsible clinical trial data sharing. (For details regarding the models proposed, go to www.nejm.org/doi/full/10.1056/NEJMhle1309073.) Also this year, PhRMA and the European Federation of Pharmaceutical Industries and Associations demonstrated a commitment to advance clinical research and innovation by developing a governing set of principles on clinical data sharing amongst biopharmaceutical researchers. (For more on these principles, go to www.phrma.org/sites/default/files/pdf/PhRMAPrinciplesForResponsibleClinicalTrialDataSharing.pdf.) Partnerships and collaborative relationships with researchers in academia, government nonprofit organizations and other companies are also becoming increasingly important. Precompetitive partnerships, which seek to advance basic research, are a growing area of collaboration.[61] (For more

Accelerating R&D through Public-Private Partnerships

To address the most challenging scientific and technological challenges, partnerships and other forms of collaboration are becoming increasingly common among researchers from biopharmaceutical companies, academic medical research centers, nonprofit organizations, patient advocacy groups and others. Partners generally share certain risks and exchange intellectual, financial, and in-kind or human resources as mutually agreed upon. The close and synergistic relationships among these sectors is critical to ensuring a robust national biomedical research capacity in the United States. A recent study by the Tufts University Center for the Study of Drug Development found that these relationships frequently involve company and academic medical center scientists and other researchers working side by side on cutting-edge science with advanced tools and resources.[62] Collaborations like these enable researchers to tackle today's most challenging and complex diseases for which there are often few or no treatment options.

Precompetitive public-private partnerships to accelerate drug discovery and development are also an increasingly important approach to improve R&D efficiency and effectiveness and bring new medicine to patients. As just one example, in 2014 a groundbreaking new partnership was announced called the Accelerating Medicines Partnership (AMP). The collaboration among the National Institutes of Health, several nonprofit disease foundations, 10 biopharmaceutical companies and PhRMA aims to transform the current model for developing new diagnostics and treatments by joining forces to identify and validate promising biological targets of disease. AMP represents a new, integrated approach to treatment discovery and seeks to increase the number of new diagnostics and therapies for patients while reducing the time and cost associated with their development. The initiative will begin with three- to five-year pilot projects focused on three disease areas: Alzheimer's; type 2 diabetes; and autoimmune disorders, including rheumatoid arthritis and lupus.

details on these partnerships see "Accelerating R&D Through Public-Private Partnerships.")

Although initial approval by the FDA is a crucial step, the approval of a new medicine is not the end of a medicine's journey through the R&D process. 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 Evolving Value of Medicines" in Chapter 1). The complexities of the R&D process and ecosystem are many, and increased collaboration among various elements of the ecosystem have become the norm rather than the exception, providing increased hope for patients that the promise of potential new treatments in the pipeline will continue to revolutionize the treatment of disease.

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Conclusion

The Outlook for Innovation

The *2014 Biopharmaceutical Research Industry Profile* provides just a glimpse of the tremendous potential in the pipeline. Fully realizing this potential and the ability for new prescription medicines to transform the treatment of disease will require increased collaboration and convergence across a range of sectors and fields, such as biology, computer science and the physical sciences, to harness novel scientific approaches.

These new approaches include gene and cell therapies, increased understanding of human genomics, leveraging massive amounts of data and computational capabilities, and a range of new technologies. Encouragingly, the scope of scientific and technological challenges and opportunities is heralding a new era of precompetitive partnerships across a range of stakeholders.

Despite the promising pipeline, the policy and regulatory environment in the United States has become increasingly difficult at a time when other countries are increasingly recognizing the economic and other benefits of an innovative biopharmaceutical sector and are making substantial investments to increase their global competitiveness. The benefits that a strong, innovative biopharmaceutical research sector brings to patients and the U.S. economy can be lost to competition, overregulation, and a failure to take the long-term view required to foster a favorable environment for innovation.

OPPORTUNITIES FOR FOSTERING CONTINUED INNOVATION

Strengthen the science base to meet 21st-century challenges. 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 chronic diseases such as arthritis, cancer, diabetes and neurodegenerative disorders—and the scientific opportunities that are leading researchers to focus on new, targeted approaches such as personalized medicine. This sophisticated science requires equally sophisticated tools, technologies and expertise as well as a regulatory process that is timely, science-based, and transparent and that appropriately balances benefits and risks.

Encourage access to new medicines. Coverage and payment policies must recognize the role and value of prescription medicines in improving patient outcomes and reducing health care costs, as evidenced by the Congressional Budget Office's recognition of the beneficial impact medicines have on reducing other health care spending. Medicines can play a key role, not only in the treatment

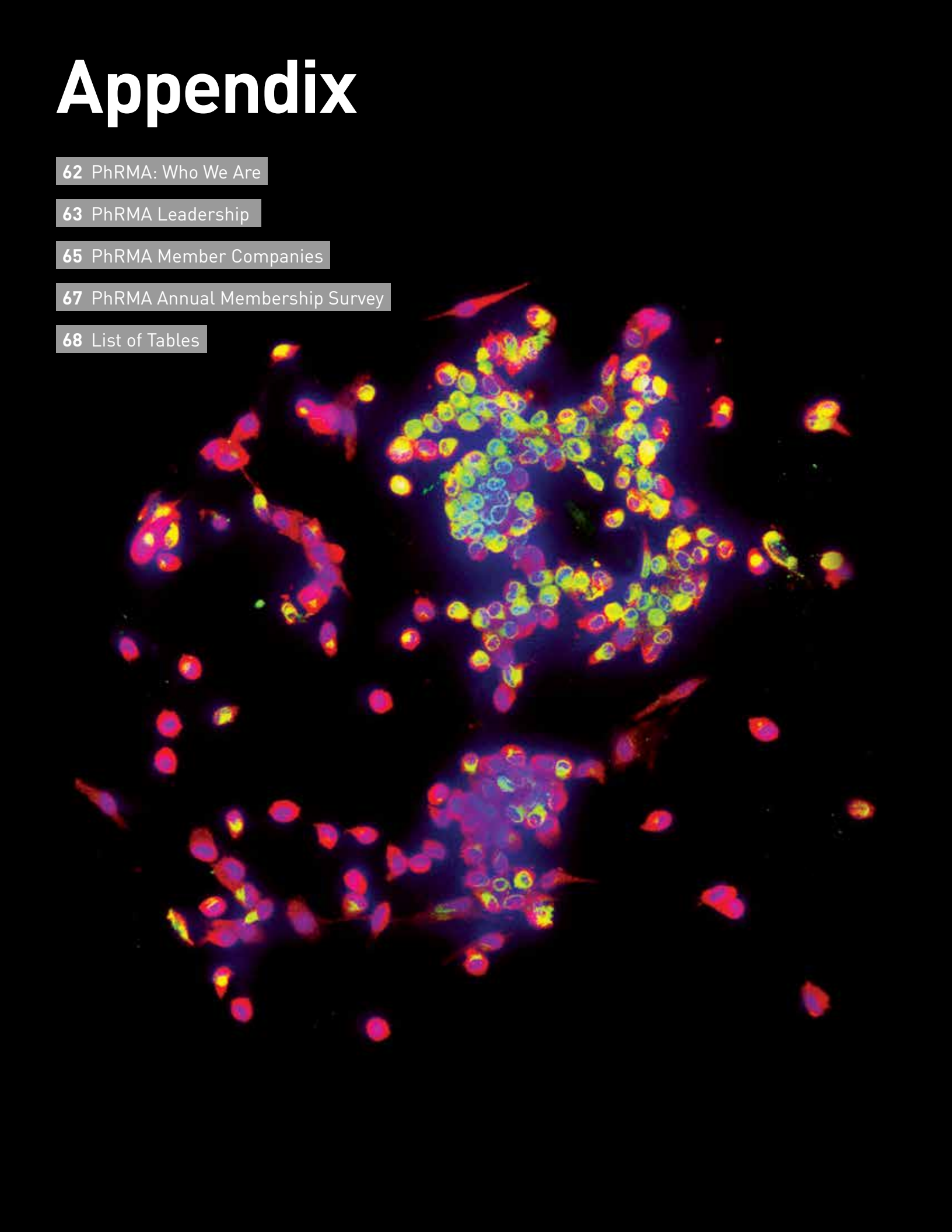
of disease, but also in prevention and early intervention, resulting in substantial improvements in patient outcomes. No nation, no matter how wealthy, can provide innovative health care for its citizens unless it values wellness, prevention and disease management at least as much as it values acute care—we cannot afford to disincentivize investment in the new medicines that can help reduce those costs.

Maintain intellectual property protections that provide incentives for continued medical innovation. Substantial resource and time investments are necessary to bring the promise of the pipeline to patients. A company's decision to make these costly investments hinges on the availability of strong intellectual property rights such as patents and data protection. As other countries are implementing industrial and other policies to attract and grow biopharmaceutical R&D investment, the United States needs to embrace forward-looking policies that recognize the economic contributions and value of knowledge-based industries like the innovative biopharmaceutical industry. Such a policy mindset is paramount to preserving U.S. global leadership in biopharmaceutical R&D.

America's biopharmaceutical companies are adapting and seeking creative solutions to meet 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, as well as with nonprofits and academic research institutions, to advance regulatory science and to foster the integration of real-word evidence and emerging technologies into the development and review of new medicines.

The nation's innovative biopharmaceutical industry is committed to the ongoing search for disease solutions that work best for patients. However, the industry's ability to succeed requires a scientific, regulatory, investment, and economic ecosystem that fosters collaborative innovation and provides broad patient access to new medicines.

Appendix



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 $51.1 billion in 2013 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.

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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 I/II/III 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 IV 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: 1980–2013

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2013**	$40,087.4	6.9%	$10,972.7	-9.1%	$51,060.1	3.0%
2012	37,510.2	3.1	12,077.4	-1.6	49,587.6	1.9
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
Average		**10.6%**		**13.6%**		**10.9%**

*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, 2014.

Table 2

R&D as a Percentage of Sales, PhRMA Member Companies: 1980–2013

(dollar figures in millions)

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2013*	22.7%	17.8%
2012	21.0	17.3
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

*Estimated.

**Revised in 2007 to reflect updated data.

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2014.

Table 3

Domestic R&D and R&D Abroad, PhRMA Member Companies: 2012

(dollar figures in millions)

R&D Expenditures for Human-use Pharmaceuticals	Dollars	Share
Domestic	$37,058.0	74.7%
Abroad*	$11,800.1	23.8%
Total Human-use R&D	**$48,858.2**	**98.5%**
R&D Expenditures for Veterinary-use Pharmaceuticals		
Domestic	$452.1	0.9%
Abroad*	$277.3	0.6%
Total Vet-use R&D	**$729.4**	**1.5%**
TOTAL R&D	**$49,587.6**	**100.0%**

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

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

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2014.

Table 4

R&D by Function, PhRMA Member Companies: 2012

(dollar figures in millions)

Function	Dollars	Share
Prehuman/Preclinical	$11,816.3	23.8%
Phase I	3,823.3	7.7
Phase II	5,756.2	11.6
Phase III	15,926.8	32.1
Approval	3,834.6	7.7
Phase IV	6,776.5	13.7
Uncategorized	1,653.8	3.3
TOTAL R&D	**$49,587.6**	**100.0%**

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

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2014.

Table 5

R&D by Geographic Area, PhRMA Member Companies: 2012

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$6.4	0.0%
South Africa	56.3	0.1
Other Africa	7.9	0.0
Americas		
United States	$37,510.2	75.6%
Canada	696.1	1.4
Mexico	124.8	0.3
Brazil	155.4	0.3
Argentina	135.3	0.3
Venezuela	11.3	0.0
Columbia	33.8	0.1
Chile	21.9	0.0
Peru	15.9	0.0
Other Latin America (Other South America, Central America, and all Caribbean nations)	80.6	0.2
Asia-Pacific		
Japan	$1,127.1	2.3%
China	387.3	0.8
India	59.7	0.1
Taiwan	58.1	0.1
South Korea	55.4	0.1
Other Asia-Pacific	158.8	0.3
Australia		
Australia and New Zealand	$300.3	0.6%
Europe		
France	$406.9	0.8%
Germany	721.3	1.5
Italy	225.5	0.5
Spain	232.0	0.5
United Kingdom	1,850.9	3.7
Other Western European	4,458.9	9.0
Czech Republic	64.7	0.1
Hungary	41.6	0.1
Poland	93.7	0.2
Turkey	34.5	0.1
Russia	92.4	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)	289.7	0.6
Middle East		
Saudi Arabia	$3.3	0.0%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	69.8	0.1
Uncategorized	—	0.0%
TOTAL R&D	**$49,587.6**	**100.0%**

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

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

SOURCE: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2014.

Table 6

Domestic Sales and Sales Abroad, PhRMA Member Companies: 1980–2013

(dollar figures in millions)

Year	Domestic Sales	Annual Percentage Change	Sales Abroad*	Annual Percentage Change	Total Sales	Annual Percentage Change
2013**	$176,839.4	-0.9%	$110,699.7	2.8%	$287,539.1	0.5%
2012	178,437.6	-5.0	107,677.8	-8.1	286,115.4	-6.2
2011	187,870.7	1.7	117,138.5	9.9	305,009.2	4.7
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
Average		**9.0%**		**9.6%**		**9.1%**

*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, 2014.

Table 7

Sales by Geographic Area, PhRMA Member Companies: 2012

(dollar figures in millions)

Geographic Area*	Dollars	Share
Africa		
Egypt	$384.7	0.1%
South Africa	771.6	0.3
Other Africa	1,346.1	0.5
Americas		
United States	$178,437.6	62.4%
Canada	6,564.0	2.3
Mexico	2,294.1	0.8
Brazil	3,864.2	1.4
Argentina	1,046.0	0.4
Venezuela	1,646.2	0.6
Columbia	852.5	0.3
Chile	335.3	0.1
Peru	161.2	0.1
Other Latin America (Other South America, Central America, and all Caribbean nations)	1,118.7	0.4
Asia-Pacific		
Japan	$16,828.4	5.9%
China	4,839.8	1.7
India	794.4	0.3
Taiwan	1,043.1	0.4
South Korea	1,579.0	0.6
Other Asia-Pacific	3,191.3	1.1
Australia		
Australia and New Zealand	$3,587.6	1.3%
Europe		
France	$8,778.4	3.1%
Germany	8,100.7	2.8
Italy	5,542.3	1.9
Spain	4,973.7	1.7
United Kingdom	5,650.8	2.0
Other Western European	10,215.1	3.6
Czech Republic	576.2	0.2
Hungary	390.6	0.1
Poland	730.9	0.3
Turkey	1,366.8	0.5
Russia	1,674.1	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)	5,243.9	1.8
Middle East		
Saudi Arabia	$756.6	0.3%
Middle East (Yemen, United Arab Emirates, Iraq, Iran, Kuwait, Israel, Jordan, Syria, Afghanistan, and Qatar)	1,429.4	0.5
Uncategorized	–	0.0%
TOTAL SALES	**$286,115.4**	**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.

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(continued from inside front cover)

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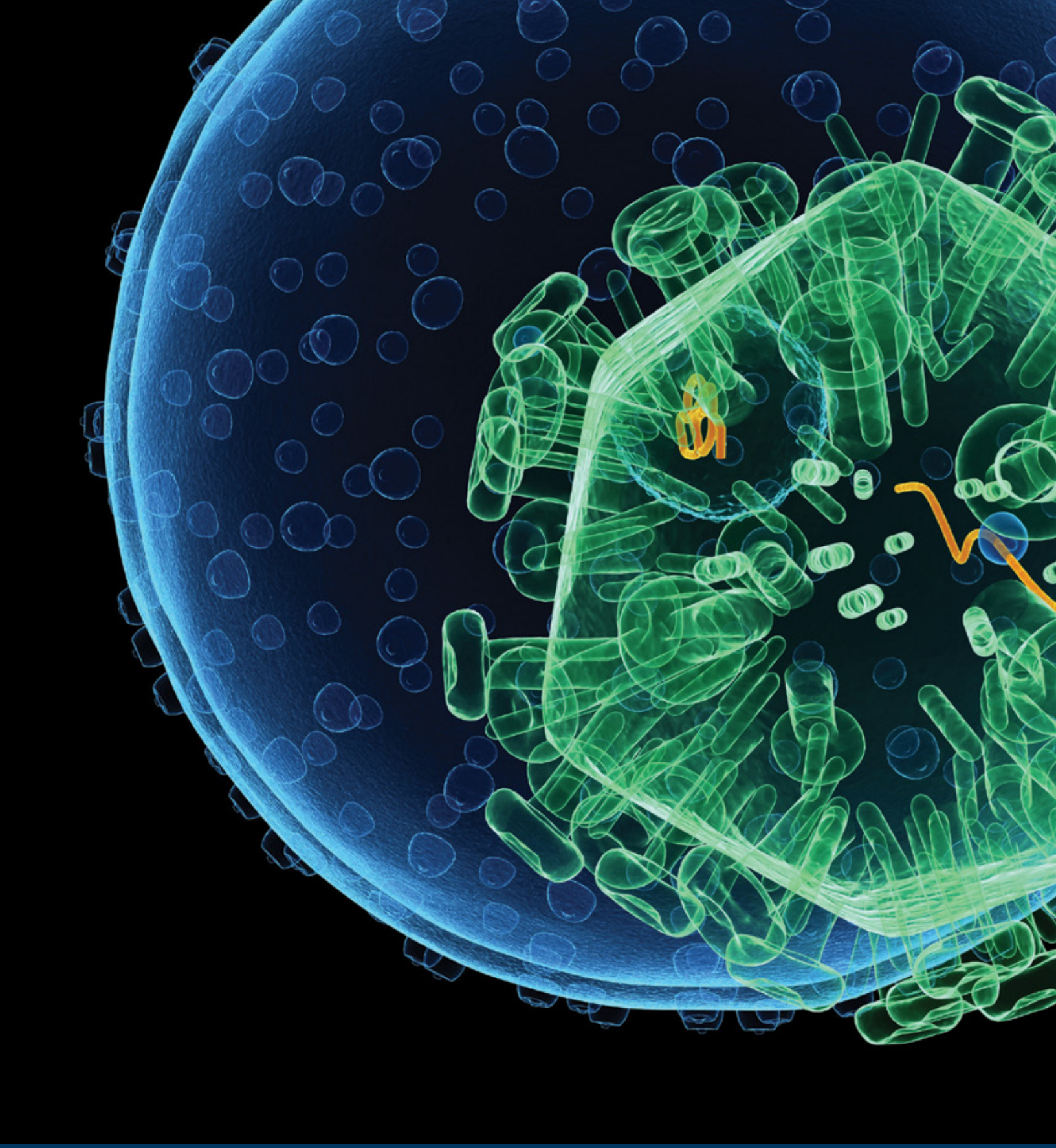

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