

2015 profile

BIOPHARMACEUTICAL
RESEARCH INDUSTRY



PhARMA
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KEYFACTS 2015

RESEARCH AND DEVELOPMENT (R&D)¹

Average time to develop a drug = more than 10 years
Percentage of drugs entering clinical trials resulting in an approved medicine = less than 12%

DEVELOPMENT COSTS

Average cost to develop a drug (including the cost of failures):²

- 2000s–early 2010s = \$2.6 billion
- 1990s–early 2000s = \$1.0 billion*
- 1980s = \$413 million
- 1970s = \$179 million



R&D SPENDING

Year	PhRMA members ³
2014	\$51.2 billion (est.)
2013	\$51.6 billion
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:⁴
2000 = 49%
2013 = 88%



PERCENTAGE OF SALES THAT WENT TO R&D IN 2013⁵

Domestic R&D as a percentage of domestic sales = 23.4%
Total R&D as a percentage of total sales = 17.9%

ECONOMIC IMPACT OF THE BIOPHARMACEUTICAL SECTOR⁶

Direct jobs = more than 810,000
Total jobs (including indirect and induced jobs) = nearly 3.4 million

APPROVALS

- Medicines approved 2014 = 51^{7,8,9}
- Medicines approved since 2000 = more than 500^{10,11,12,13,14}
- In the 30 years since the Orphan Drug Act was established, more than 500 orphan drugs have been approved, with more than 230 approved in the last decade alone^{15,16}
- Only 2 of 10 marketed drugs return revenues that match or exceed R&D costs¹⁷

MEDICINES IN DEVELOPMENT

- Medicines in development around the world = 7,000¹⁸
- Potential first-in-class medicines** in clinical development globally = 70%¹⁹
- Medicines in development to treat rare disease = More than 450²⁰

VALUE OF MEDICINES

- **Cancer:** Since peaking in the 1990s, cancer death rates have declined nearly 22%.²¹ Approximately 83% of survival gains in cancer are attributable to new treatments, including medicines.²²
- **Hepatitis C:** Five years ago, treatment options available for hepatitis C cured just 41% of patients with the most common type of the disease, but with debilitating side effects.²³ Today, a range of treatment options are available to patients offering cure rates upwards of 90%, with few side effects, in as few as 8 weeks.^{24,25}
- **HIV/AIDS:** Since the introduction of highly active antiretroviral treatment (HAART) in 1995, the HIV/AIDS death rate has dropped nearly 85%.²⁶ As a result of HAART and all the medical innovations that followed, it is estimated that 862,000 premature deaths were avoided in the United States alone.²⁷

See inside back cover for references.

*Previous research by the same author estimated average R&D costs in the early 2000s at \$1.2 billion in constant 2000 dollars (see DiMasi JA, Grabowski, HG. The cost of biopharmaceutical R&D: is biotech different? *Manage Decis Econ.* 2007;28:469-479). That estimate was based on the same underlying survey as the author's estimates for the 1990s to early 2000s reported here (\$800 million in constant 2000 dollars), but updated for changes in the cost of capital.

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





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Letter from PhRMA's President and CEO

It's my pleasure to present the *2015 Biopharmaceutical Research Industry Profile*.

We publish at a dynamic time. Massive change continues across the United States and global health care systems driven by new health care policies, demographic shifts, changes in lifestyle, but—most of all—evolving, accelerating science.

The women and men working in America's biopharmaceutical companies wake up every day to ensure that patients derive the most benefit from such disruptive change.

Indeed, the very backbone of this 2015 Profile is the concept of "value"—how the scientific journey from hope to cures delivers profound value to:

Patients: Biomedical science breakthroughs are strengthening the arsenal of treatments against cancer, HIV/AIDS, and many other diseases. These and other treatments are driving down death rates across disease groups, and a number of previously fatal diagnoses have been transformed to manageable, chronic conditions. Research and development powers this scientific mission, and the biopharmaceutical sector continues its investment commitment, pouring an estimated \$51.2 billion into research and development in 2014 alone. The result: more than 7,000 potential treatments now swell the global drug development pipeline.

Our health system: New medicines deliver astonishing value to our health care system by helping avoid the need for hospitalizations and expensive surgeries. As you'll see in this Profile, medicines are perhaps where the health care dollar gains its best return on investment, which is why ensuring patient access to needed medicines is so critical.

The US economy: America's biopharmaceutical companies support the jobs of 3.4 million American women and men—more than 810,000 of them directly. The economic output of their work is valued at nearly \$800 billion every year, and the life-changing results of their work are exported to help patients around the world, helping sharpen America's competitive economic edge.

None of these accomplishments come easily, which is why our work never stops. But when we consider who we ultimately work for—patients—we know that every difficult question, every test, every re-test, every small success, every failure, and every new beginning is more than worthwhile. Because each one of those delivers hope.

Please join the conversation and let us know what you think by sending us a tweet to @PhRMA. We look forward to hearing from you.

John J. Castellani

President and Chief Executive Officer

Pharmaceutical Research and Manufacturers of America

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Biopharmaceutical Innovation: Benefiting Patients and the US Economy

Biopharmaceutical companies make the medicines that save and improve patients' lives every day. Patients often rely on medicines to keep their symptoms at bay and allow them to continue to work and live healthy, productive lives. Others rely on medicines to cure their disease or to prevent life-threatening complications that might keep them out of the hospital. These are just a few examples of how prescription medicines offer important benefits to patients. In 2014, the US Food and Drug

Administration approved a record number of new medicines, promising continued advancement in the treatment of a diverse range of diseases.

The ability of patients to access the medicines they need is not only essential to improve their health, but also to improve the quality and value of health care while managing costs. This is true because medicines have the potential to bring savings to other health care spending by preventing costly complications and care. Importantly, while

medicines provide such tremendous value, they consistently represent just 10% of overall health care spending in the United States.

Researchers in the biopharmaceutical industry are dedicated to discovering and developing new medicines to help many patients whose needs are not yet met. Our understanding of many diseases has grown in recent years, and the science has never been more promising. With more than 5,000 drugs in development today in the United States alone, researchers are working to turn this potential into medicines that will help patients.

This work not only benefits patients directly, but the US economy as a whole. The research enterprise touches communities across every state in the country, creating jobs and investments in local economies. Pharmaceutical Research and Manufacturers of America (PhRMA) members have invested more than half a trillion dollars in research and development (R&D) since 2000, including an estimated \$51.2 billion in 2014 alone.

This investment represents the largest of any business sector in the United States.

The *2015 Biopharmaceutical Research Industry Profile* provides an overview of the range of the value that new medicines and the biopharmaceutical industry bring to patients and society. Chapter 1 examines recent advances in medicines and the effect they have on 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 economic impact of biopharmaceutical companies on the local, state, and national level. Chapter 4 provides an overview of the R&D process as well as the challenges and opportunities related to drug discovery and development. And, finally, Chapter 5 explores the robust biopharmaceutical pipeline and the cutting edge science that researchers are exploring in their efforts to bring new medicines to patients.

Helping Patients Live Longer and Healthier Lives

“I was dying ... We’ve come so far in treatment and managing this disease.” -Jamie Pires, 13-year chronic myelogenous leukemia (CML) survivor and Florida representative of the National CML Society





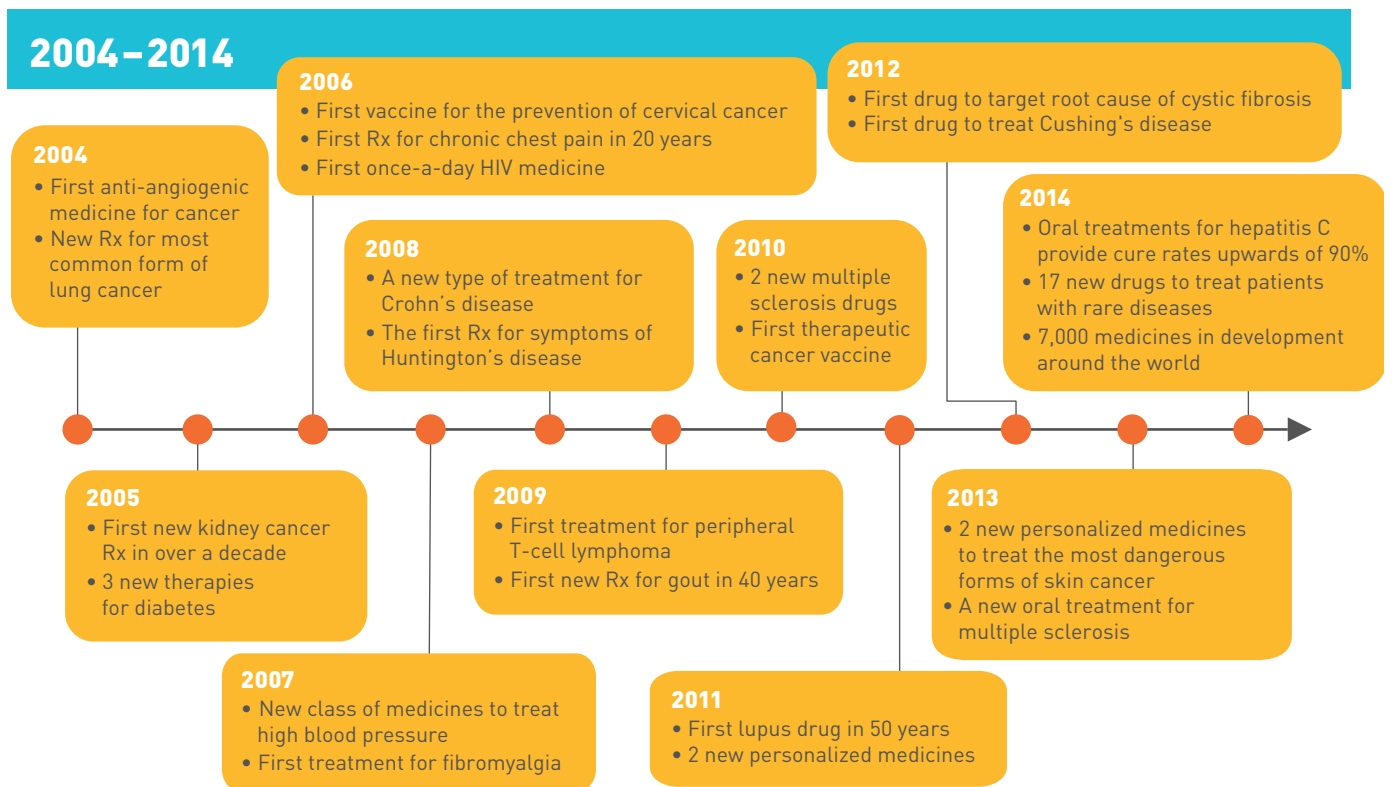
Helping Patients Live Longer and Healthier Lives

Patients benefit from new medicines every day. In recent years, prescription medicines have altered the trajectory of many debilitating diseases, resulting in decreased death rates for a number of conditions, improved health outcomes, and better quality of life (see Figure 1). For patients, access to new medicines can mean getting back to work, avoiding hospitalizations, feeling better, and living longer.

Recently approved medicines are delivering on unprecedented scientific advances in our under-

standing of disease. In 2014, the US Food and Drug Administration (FDA) approved 51 new medicines across a wide variety of disease areas.^{1,2} Forty-one of those approvals were by the Center for Drug Evaluation and Research (CDER) at the FDA, the highest number since 1996.^{3,4,5,6} Among CDER approvals, 41% were identified as first-in-class medicines, meaning they use a unique mechanism of action to treat a medical condition that is different from any other approved medicine.⁷ An additional 41% of these medicines were approved to treat rare diseases.⁸

FIGURE 1: A Decade of Advances



Sources: US Food and Drug Administration (FDA). Drugs@FDA: FDA approved drug products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Silver Spring, Md.: FDA. Accessed February 2014; Adis R&D Insight Database. Accessed February 2015.

The novel therapies approved in 2014 are offering important new treatment options for patients. For example:

- **Advanced Melanoma:** Two new medicines were approved to treat advanced melanoma, a disease that has historically been very difficult to treat. These medicines, known as immunotherapies, harness the immune system to fight melanoma by blocking a cellular pathway known as PD-1, which prevents the body's immune system from attacking melanoma cells. Seven new

drugs used to treat melanoma have been approved since 2011, including the 2 new medicines approved in 2014.^{9,10} (For more on immunotherapies see chapter 5).

- **Hepatitis C:** Two new antiviral combination therapies were approved to treat hepatitis C, a viral disease that affects 3.2 million Americans.¹¹ These combination therapies are oral medicines approved to treat patients with genotype 1 of the disease, and they provide cure rates of more than 90% in as few as 8 weeks.^{12,13}

"We are currently in a time of unprecedented progress in the development of effective treatments for melanoma."

- JEDD WOLCHOK, MD, MEMORIAL SLOAN KETTERING CANCER CENTER¹⁴



- **Rare Diseases:** A total of 17 new orphan drugs were approved in 2014 to treat diseases that each affect 200,000 or fewer people. For example:
 - *Morquio A syndrome* is an inherited enzyme pediatric disorder that causes problems with bone development, growth, and mobility. In 2014, the FDA approved the first-ever treatment for this rare disorder, which currently affects 800 patients in the United States.¹⁵
 - *Multicentric Castleman's disease (MCD)* is a rare disorder causing abnormal overgrowth of immune cells in lymph nodes, weakening the body's immune system. The FDA approved the first-ever treatment option for MCD in 2014. The new drug works by blocking a protein that leads to abnormal growth of immune cells.¹⁶
 - *Idiopathic pulmonary fibrosis (IPF)* is a debilitating disease that causes fibrotic scarring within the lungs and eventually leads to respiratory failure. Life expectancy after diagnosis with IPF is just 3 to 5 years. In 2014, the FDA approved 2 new treatment options for IPF, both of which significantly slow the progression of the disease.^{17,18,19}
- **Ovarian Cancer:** A new first-in-class treatment for ovarian cancer was approved for patients with a mutation in the BRCA gene. This medicine was approved along with a companion diagnostic, which detects the mutation in the gene. The drug is known as a poly ADP-ribose polymerase inhibitor. It works by blocking enzymes involved in repairing damaged DNA.²⁰
- **Diabetes:** Four new medicines were approved that offer new options for the 26 million Americans with type 2 diabetes. These medicines offer new tools—and in some cases an easier mode of administration—for patients to control their blood glucose levels, along with diet and exercise.²¹
- **Antibacterials:** The FDA approved 4 new antibiotics to treat serious infections, which is particularly important as bacteria continuously evolve to become resistant to existing antibiotics.^{22,23,24,25,26}

TRANSFORMING PATIENTS' LIVES

Medicines have a transformative effect on the health of Americans by curing diseases, extending lives, and improving quality of life and productivity. The following are just a few examples of the positive impact new and innovative therapies have on patient care.

I'm Not Average: Jamie Pires



Jamie Pires fainted in her doctor's office when she was told she has chronic myelogenous leukemia (CML), a cancer that starts inside the bone marrow. She only went to the doctor because she was experiencing hay fever symptoms. When Jamie was diagnosed, she found there was limited information on CML and few effective treatments. In many cases, CML patients faced grim prognoses. Jamie's situation was no different. However, thanks to recent advances in cancer medicines, CML is a manageable disease that no longer defines Jamie. She will always have CML, but because of these novel innovations Jamie is happy and healthy and able to live a full life.

For more on Jamie, see: <http://www.phrma.org/cancer#>.

"More important than the quantity of novel new drugs approved by CDER in 2014 is their quality and the important new roles they are serving to advance medical care."

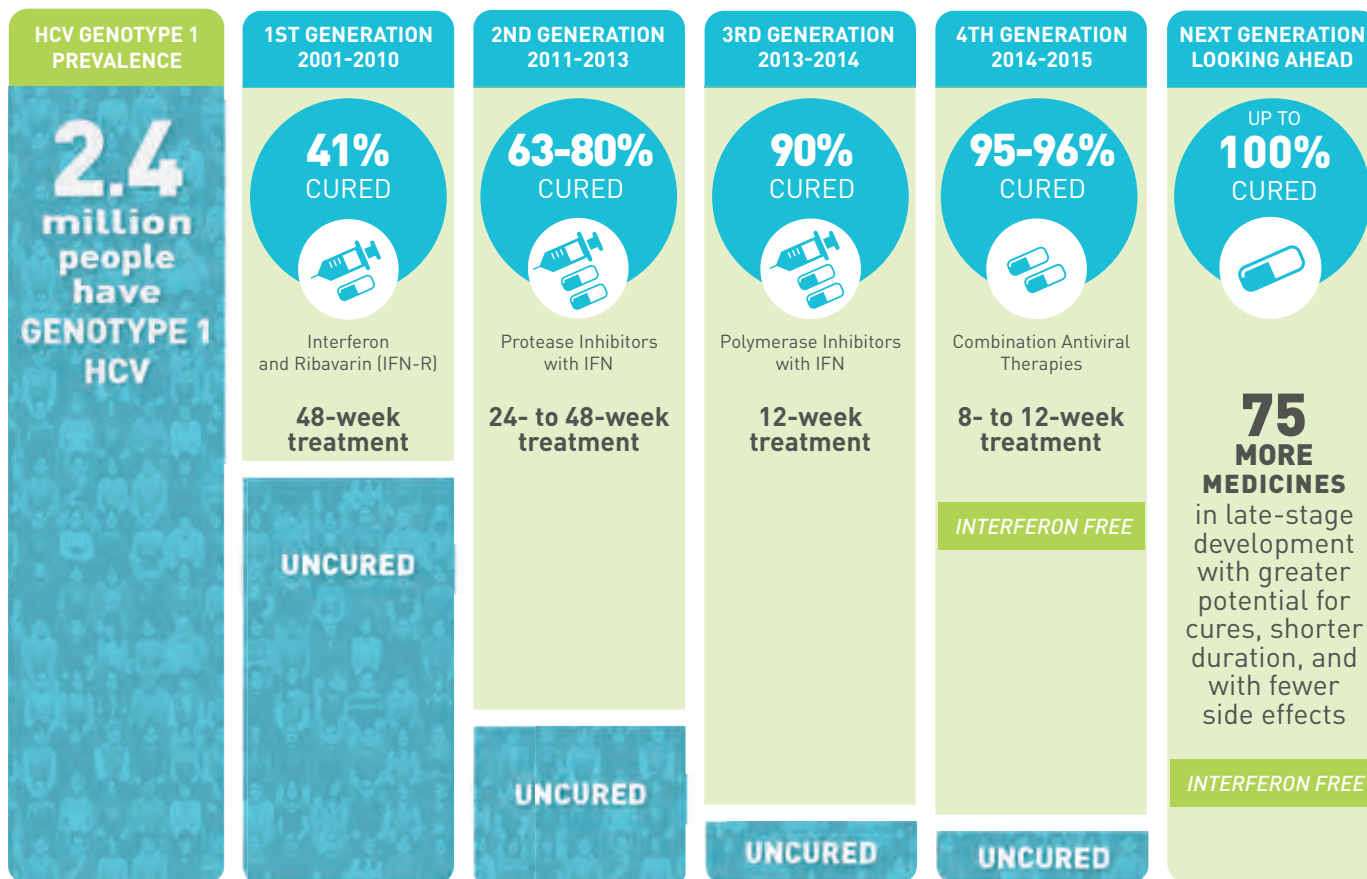
- FDA²⁷

Curing Disease

Hepatitis C: Until 5 years ago, treatment options for hepatitis C patients were limited to interferon and ribavirin, a combination that cured about 41% of patients with the most common type of the disease but resulted in debilitating side effects for many.²⁸ No alternative treatments existed, and

patients whose disease did not respond had to live with a chronic disease with serious and expensive complications, including liver cancer and liver transplantations. Now, several direct-acting, anti-viral, entirely oral medicines have been developed that offer cure rates greater than 90%, with few side effects, in as few as 8 weeks (see Figure 2).^{29,30}

FIGURE 2: Hepatitis C (HCV): Cure Rates Are Rising



Sources: Armstrong GL, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Int Med.* 2008;144:705-714; Elsevier Clinical Solutions. Viral hepatitis C. ClinicalKey. <https://www.clinicalkey.com/topics/gastroenterology/viral-hepatitis-c.html>. Accessed March 2015.; Cure rates based upon clinical trial results reported in FDA labels for: interferon; telaprevir; boceprevir; simeprevir; sofosbuvir; sofosbuvir and ledipasvir combination; and ombitasvir, paritaprevir, ritonavir, and dasabuvir combination. US Food and Drug Administration. Center for Drug Evaluation and Research. Drugs@FDA: FDA approved drug products. <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>. Silver Spring, Md.: FDA. Accessed March 2015.; Pharmaceutical Research and Manufacturers of America. Twenty-five years of progress against hepatitis C: setbacks and stepping stones. Washington, DC: PhRMA; December 2014. http://www.phrma.org/sites/default/files/pdf/Hep-C-Report-2014-Stepping-Stones_0.pdf. Accessed March 2015.

Extending Lives

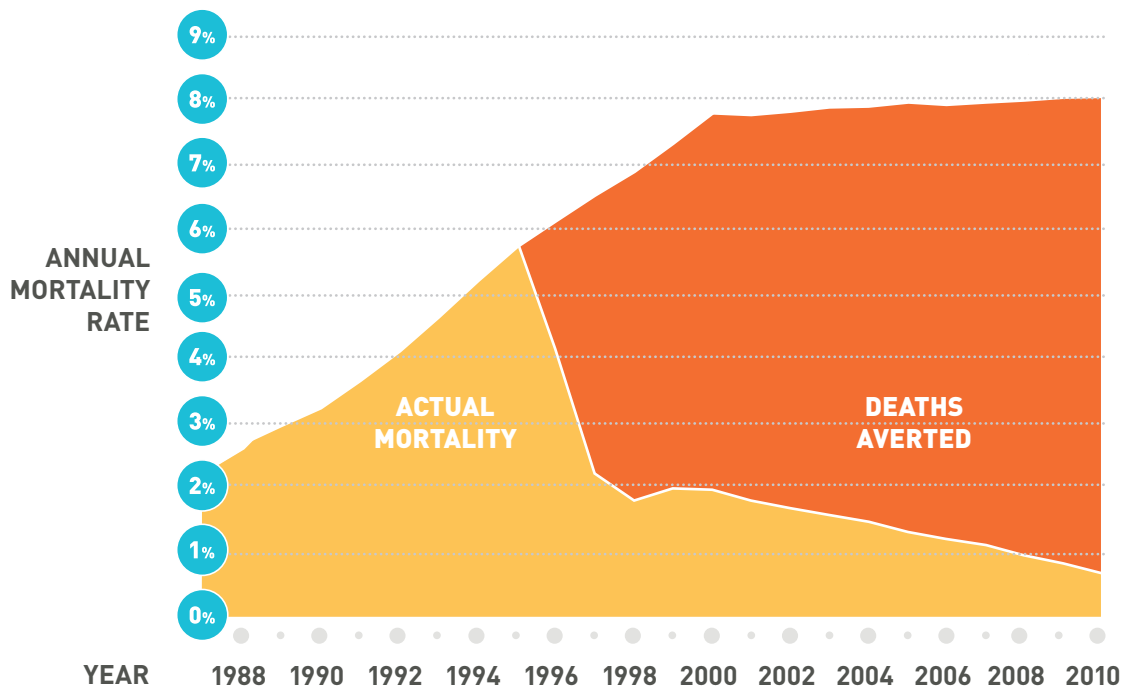
HIV/AIDS: Tremendous strides have been made over the past 25 years in the prevention and treatment of HIV/AIDS. Since peaking in 1995, death rates have fallen nearly 85% (see Figure 3).³¹ Treatment adherence among patients has improved because of reduced side effects, improved ease of use, and reduced pill burden, which has contributed significantly to improving and extending the lives of HIV patients. 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.³² A recent study found that

since the introduction of combination antiretroviral therapies in the mid-1990s, more than 862,000 premature deaths have been avoided and 27.7 million life years have been gained (see Figure 3).³³

Cancer: New medicines have been a driving force behind recent gains in the life expectancy of cancer patients. According to the American Cancer Society, the United States has seen a nearly 22% decline in cancer deaths since the early 1990s.³⁴ This translates into 1.5 million lives saved, thanks in large part to earlier diagnosis and treatment advances. Today, 2 out of 3 people diagnosed with

FIGURE 3: HIV/AIDS: Decline in Death Rates

ACTUAL vs PROJECTED Death Rates for HIV/AIDS in the United States



862,000 PREMATURE DEATHS AVOIDED

Sources: Lacey MJ, Hanna GJ, Miller JD, et al. Impact of pharmaceutical innovation in HIV/AIDS treatment during the highly active antiretroviral therapy (HAART) era in the US, 1987–2010: an epidemiologic and cost-impact modeling case study. <http://truvenhealth.com/Portals/0/Assets/Life-Sciences/White-Papers/pharma-innovation-hiv-aids-treatment.pdf>. Ann Arbor, Mich: Truven Health Analytics. Accessed February 2015; US Centers for Disease Control and Prevention. Health, United States, 2013, with special feature on prescription drugs. <http://www.cdc.gov/nchs/data/abus/abus13.pdf>. Atlanta, Ga.: CDC; 2014. Accessed February 2015.

cancer survive at least 5 years, up from only half in 1975.³⁵ A striking example of the advances made in cancer treatment is the survival rate for CML. In 1999, only 30% of patients with CML survived for 5 years. However, use of a new generation of targeted cancer medicines, known as tyrosine kinase inhibitors, has resulted in 90% of CML patients living at least 5 years.³⁶

Until the late 1990s, clinicians had 3 main treatment options available to fight cancer: surgery, radiation, and chemotherapy. In the last 2 decades, researchers have identified targeted therapies and immunotherapies, 2 additional tools for treating the disease.³⁷ Cancers such as metastatic melanoma are benefitting from these extraordinary advances (see sidebar: Metastatic Melanoma: Then and Now).

Improving Quality of Life

Multiple Sclerosis: Once faced with few treatment possibilities, the 400,000 Americans with multiple sclerosis (MS) now have a host of therapeutic

options that not only offer improved quality of life but also help facilitate improved treatment adherence as a result of reduced side effects. MS is a serious autoimmune disorder that affects the brain's ability to communicate with the rest of the body, causing a variety of symptoms. MS patients often have a high level of disability that disrupts normal activities and negatively impacts quality of life. Depression is also common among patients suffering from MS.³⁸

Ten years ago, treatment for MS was limited to a handful of injectable medications that often caused painful site reactions and other challenging side effects, making adherence to recommended therapy difficult. Today, patients have a wide range of treatment options—delivered via infusion or orally—that more effectively slow disease progression, prevent relapse, and improve symptom management. Side effects have been reduced, and patients can choose how and when to take their medication, which has

Metastatic Melanoma: Then and Now³⁹

2005: Then...

- The standard of care was surgery accompanied by adjuvant therapy, such as chemotherapy, radiation, and high-dose immunotherapy using interleukin 2.
- Patients often experienced severe side effects from treatment, such as flu-like symptoms, weakness and fatigue, low blood pressure, and loss of appetite.
- Life expectancy for patients following diagnosis was approximately 1 year.

2015: Now...

- The discovery of the BRAF gene mutation and the CTLA4 gene led to development of effective new medicines, including molecularly targeted therapies such as immunotherapies (for more on immunotherapies see chapter 5).
- Recently approved therapies are demonstrating incredible promise, with patient survival rates increasing dramatically through the use of these new medications and combination treatments.
- The severity of side effects associated with new medications has significantly decreased, improving patient adherence and quality of life.

For more on metastatic melanoma and other types of cancer, see: <http://www.phrma.org/sites/default/files/pdf/2014-cancer-setbacks-report.pdf>.



led to increased adherence to treatment, better outcomes, and improved quality of life.⁴⁰

The availability of medications that improve quality of life is particularly important for MS patients who suffer from work-related impairments. A study based on a registry surveying MS patients in North America found substantial numbers were not employed or in school due to their condition. Among those patients who were employed, substantial reductions in work productivity were reported, and nearly 45% of those younger than 65 years reported early retirement due to their illness.⁴¹ Advances in treatments over the past decade offer the potential to avoid some of this work-related burden for MS patients.

Rheumatoid Arthritis: Disease-modifying biological medicines have ushered in a new age of treatment for rheumatoid arthritis (RA). By targeting the cells involved in the progression of RA, these medicines have significantly slowed or even reversed the negative physical effects associated with the disease⁴² and made clinical remission possible for patients with severe RA.⁴³

Advances like these are especially important for RA patients among whom the costs of short-term disability and productivity loss are 3 times greater than the medical costs associated with RA.⁴⁴ The estimated costs of informal caregiving provided by family members of these patients are also

substantial—estimated at \$3.6 billion annually.⁴⁵ Disease-modifying biological medicines provide an important opportunity to reduce burdens on both RA patients and their families by affecting disease progression.

THE NATURE OF MEDICAL PROGRESS

We have made great progress in the fight against many diseases. Each step forward is the result of accumulated research and advances over time. The approval of a new medicine adds another important treatment option and is a tremendous milestone for patients and clinicians. But our understanding of a medicine does not stop there. Researchers and clinicians continue to learn even more about a new medicine once it reaches patients. Often, a medicine is found to provide additional benefit when it is used early in the development of the disease, used in combination with other medicines, or paired with a diagnostic test. In addition, through continued research, a medicine may prove to be effective in other disease areas. A full understanding of a medicine's benefits to patients evolves over time; examples include treatment advances against diseases like HIV/AIDS, cancer, and RA. The use of combination antiretroviral treatments earlier in the disease progression has revolutionized the outlook for many HIV/AIDS patients. For cancer patients, the identification of genetic mutations within tumors is increasingly allowing physicians to target treatment to the group of patients most likely to respond. And in RA, a growing understanding of the underlying molecular pathway of inflammatory disease has revealed that medicines used initially for RA are beneficial across a spectrum of autoimmune conditions. Because of the incremental and evolving nature of clinical research, it is important to recognize that the full value of a treatment is not completely understood at the time of approval but continues to grow over time.

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Improving the Quality and Value of Health Care

“My doctor told me I had 6 to 8 weeks—perhaps.”

-Warren Littrel, 5-year pancreatic cancer survivor and former foreign service officer





Improving the Quality and Value of Health Care

Improving the quality and value of health care while managing costs is critically important to both the health of Americans and the economy. Prescription medicines play a central role in achieving these goals, particularly given our aging population and the large number of people of all ages living with complex and chronic conditions.

Medicines help patients live healthier lives and reduce the need for costly health care services such as emergency department visits, hospital stays, surgeries, and long-term care, which can result in savings to the health system overall. Medicines also provide important benefits to patients and

society, including improved quality of life and better health outcomes, which lead to increased employee productivity as patients are able to delay or prevent disease progression.

Importantly, even as advances in medicine over the years have provided incredible value to patients and society, medicines continue to represent a small portion of total health care expenditures. This small share has remained consistent over the past 50 years and is projected to remain at similar levels over the next decade¹ (see sidebar: Medicines Bring Great Value to Patients).

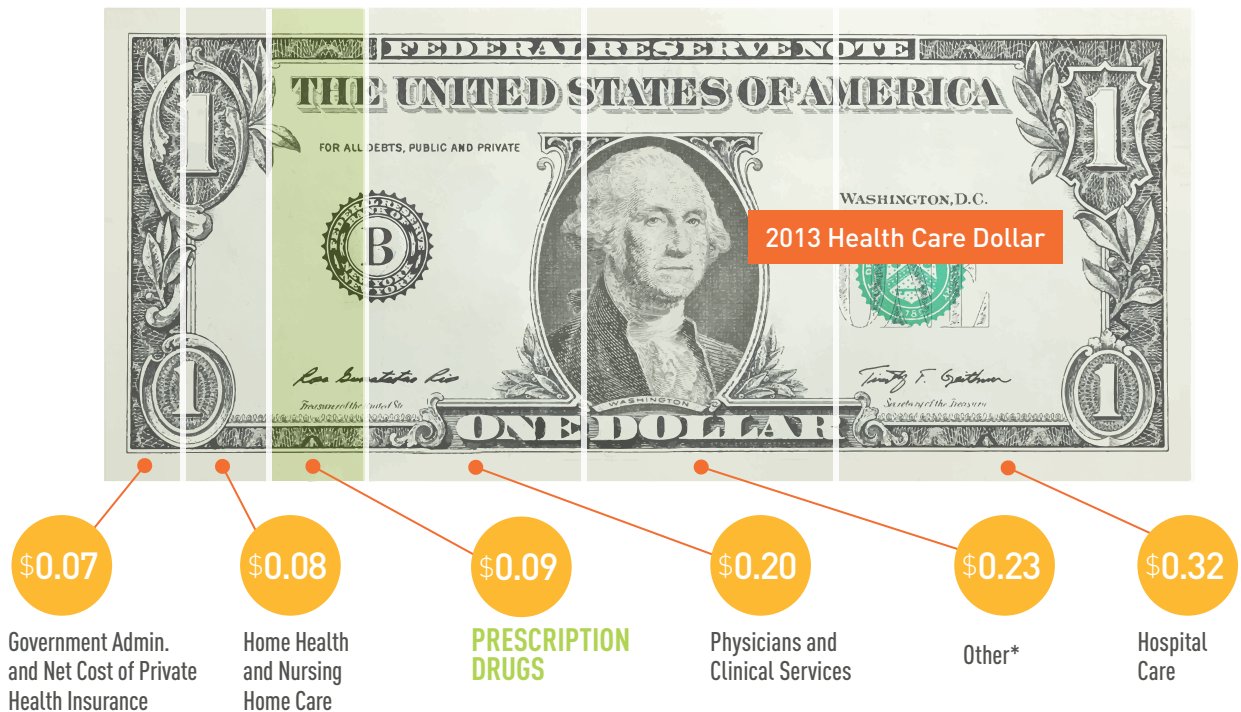
Medicines Bring Great Value to Patients While Remaining a Small Share of Overall Health Care Costs



Today, retail prescription medicines account for approximately 10% of total health care spending in the United States (see Figure 4)—the same percentage as in 1960 and roughly the same percentage projected a decade from now.^{2,3} Even as drugs have remained a steady share of national health spending, since 2000 alone, nearly 500 new medicines have become available to patients.^{4,5,6,7} Incredible advances such as these are possible because, unlike any other part of the health care system, cost containment is built into the prescription drug lifecycle. Innovative biopharmaceuticals eventually become lower cost generics and biosimilars that bring tremendous value to patients and society. However, lower cost generics and biosimilars would not be possible without the scientific work and large-scale investments of innovator companies. It takes at least 10 years and an average of \$2.6 billion to develop and bring a new FDA-approved medicine to market.⁸ It is as a result of these investments and the prescription drug lifecycle that we have been able to make progress against debilitating and costly diseases affecting patients today.

FIGURE 4: Retail Spending on Prescription Medicines Is a Small Share of Total US Health Care Spending

Prescription medicines today account for about 10% of health care spending in America, the same percentage as it was in 1960.



*Other includes dental, home health, and other professional services as well as durable medical equipment costs.

Source: PhRMA analysis of CMS data. National health expenditures by type of service and source of funds, CY 1960-2013. Baltimore, Md.: CMS; 2013. <http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/NHE2013.zip>. Accessed February 2015.



Despite the tremendous value medicines provide to patients, society, and the economy at large, suboptimal use of medicines and gaps in appropriate care remain significant challenges. As more Americans gain health care coverage in coming years, it is critically important that the care they receive provides them with adequate access to the medicines they need. Fortunately, improving the quality and efficiency of the health system overall and supporting the appropriate use of medicines go hand in hand.

THE HEALTH BENEFITS OF BETTER USE OF MEDICINE

When used appropriately, medicines play a central role in improving the health outcomes of patients. A large body of research demonstrates that better health outcomes are achieved among patients who are appropriately diagnosed, initiate

treatment promptly, and are adherent to prescribed medicines. Adherence to medicines not only prevents unnecessary hospitalizations and use of other costly health care services but also reduces risk of additional disease complications and even death. For example:

- **Preventing Unnecessary Use of Medical Services:** By taking medicines as prescribed, patients can avoid unnecessary and costly encounters with the health care system. Research has shown that poor adherence to prescribed medications is associated with an increase in medical expenditures and hospital visits.^{9,10,11} Researchers found that approximately one fourth of Medicare Part D enrollees with Parkinson's disease did not take their medicines as prescribed. Patients who did take their medicines as prescribed exhibited significantly lower rates of hospitalization, emergency department visits,

skilled nursing facility stays, home health agency visits, and physician appointments and substantially lower health care expenditures compared to those who did not.¹²

- **Preventing disease:** Taking medicine as prescribed has been shown to prevent and slow the progression of disease. As one example, researchers found that patients who did not take antihypertensive medicines as prescribed were, over 3 years, 7%, 13%, and 42% more likely to develop coronary artery disease, cerebrovascular disease, and chronic heart failure, respectively, than were patients who took the medicines as directed.¹³

- **Decreasing mortality:** Adherence to prescribed therapies can also reduce the risk of death. For example, a recent study found that patients who did not take statins as prescribed had a 1.2 to 5.3 times increase in risk of cardiovascular disease and a 1.3 to 2.5 times increase in risk of mortality compared with adherent patients.¹⁴

THE ECONOMIC BENEFITS OF BETTER USE OF MEDICINE

When used appropriately, medicines can keep patients healthy and reduce the need for medical services, producing savings for patients and the health care system. Conversely, poor adherence to medicines can result in unnecessary use of

New Medicines for Hepatitis C Provide Cures and Prevent Future Health Care Costs

Recent advances against hepatitis C are not only dramatically improving outcomes for patients, but they are offering to reduce the substantial economic burden associated with the disease. Hepatitis C is a devastating viral disease affecting 3.2 million Americans.¹⁵ It is also the leading cause of liver cancer and the most common reason for a liver transplant. Hepatitis C progresses slowly, meaning patients often remain asymptomatic, and unaware they are infected, until serious and often expensive complications emerge as a result of liver damage. Fortunately today, with the latest wave of treatments, 90% or more of patients can expect to be cured in as few as 8 weeks.¹⁶

As the vast majority of Americans with the disease are Baby Boomers, many are just now beginning to develop serious liver-related complications. Recent advances in treatment could not have come soon enough. Total nationwide hospitalization costs for hepatitis C patients with advanced liver disease increased 44% in the 6 years leading up to 2011. That year, nationwide annual hospitalization costs for this population had reached an average of nearly \$35 billion.¹⁷

Looking ahead, in the absence of newly available treatments, the burden of disease-related complications was projected to continue to grow at an alarming rate over the next decade. Annual health care costs associated with compensated cirrhosis had been projected to peak in 2022 at \$1.9 billion and decompensated cirrhosis in 2025 at \$4.2 billion. For patients with liver cancer, costs were expected to peak in 2025 at \$1.4 billion; for those requiring liver transplants, costs were anticipated to peak in 2025 at \$2.2 billion.¹⁸

Today, with the availability of new, effective treatments and more in the pipeline, these medicines can help patients live longer, healthier lives and avert the immense economic burden associated with this debilitating disease and its costly complications.

medical care and associated costs resulting in inefficient and costly care as well as poor patient outcomes.^{19,20,21} In fact, it is estimated that poor medication adherence, suboptimal prescribing, and medication errors result in \$213 billion in avoidable health care costs annually.²²

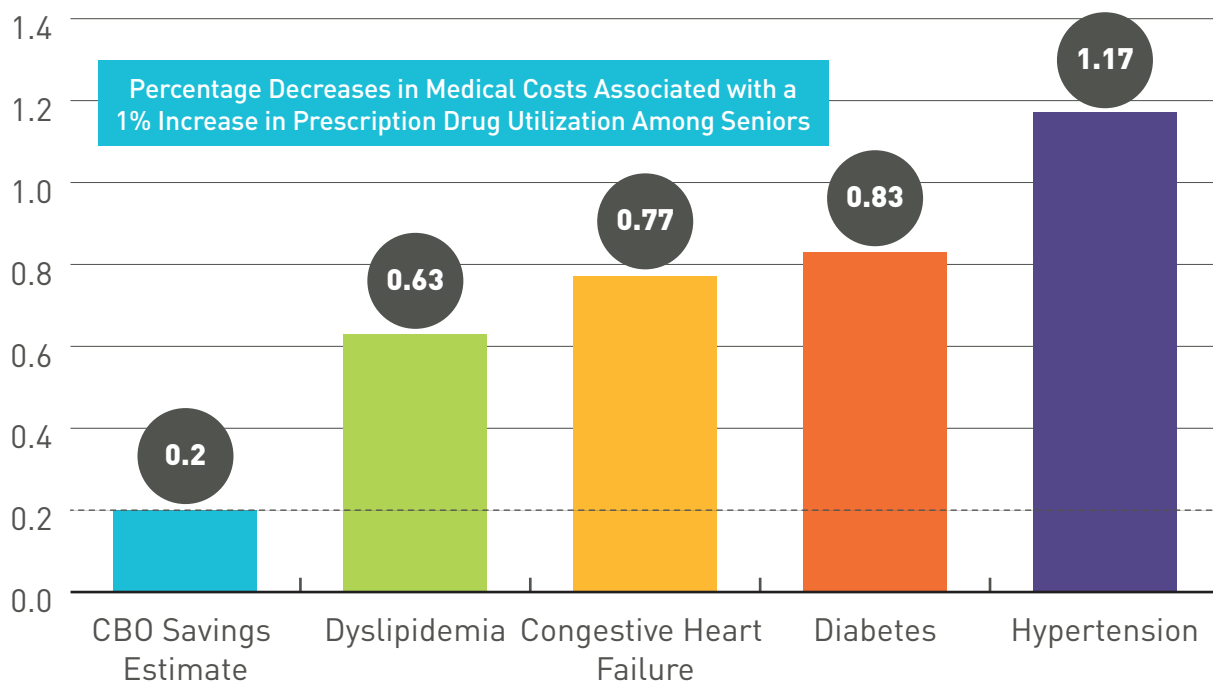
While improved adherence increases prescription drug spending, these costs are often more than offset by reductions in other health care spending. The cost offsets often associated with better use of prescription medicines have been widely demonstrated in a growing number of economic and epidemiological research studies. In recognition of this growing body of evidence, in 2012 the Congressional Budget Office (CBO) revised its methodology for estimating the federal budget impact of policy changes to reflect savings in

medical spending associated with increased use of medicines by patients in Medicare.²³ A more recent study suggests the CBO is likely underestimating the potential cost savings to Medicare resulting from appropriate use of medicines for specific chronic conditions. The recent study shows that increased use of medications to treat dyslipidemia, congestive heart failure, diabetes, and hypertension, which represent 40% of Medicare Part D utilization, may result in savings between 3 and 6 times greater than the CBO's current assumptions²⁴ (see Figure 5).

Several examples illustrate the *savings realized by patients and the health care system as a result of better use of medicines*:

FIGURE 5: Increased Use of Medicine Helps Reduce Spending on Other Medical Care

Medicare savings due to better use of medicines may be 3 to 6 times greater than estimated by the Congressional Budget Office for seniors with common chronic conditions.



Source: Roebuck MC. Medical cost offsets from prescription drug utilization among medicare beneficiaries. *J Manag Care Pharm.* 2014;20(10):994-995. <http://amcp.org/WorkArea/DownloadAsset.aspx?id=18569>. Accessed March 2015.



- **Chronic Conditions:** A recent study found that increased access to medicines due to Medicare prescription drug coverage resulted in an 8% decrease in hospital admissions for seniors, leading to \$41.5 billion in savings annually.²⁵
- **Diabetes:** Medicare Part D enrollees who adhered to their diabetes medicines saved the Medicare program between 15% and 20% per month in medical spending after 1 year of initiating treatment.²⁶ Improved and sustained adherence among diabetes patients has resulted in an estimated reduction of more than 1 million emergency department visits and hospitalizations annually, for an annual savings of up to \$8.3 billion.²⁷
- **High Cholesterol:** Research shows declines in adherence to prescribed medicines among patients with high cholesterol increases the likelihood of a cardiovascular event by 2.3 times.²⁸ Additionally, reductions in cholesterol associated with statin therapy are associated with about 40,000 fewer deaths, 60,000 fewer hospitalizations for heart attacks, and 22,000 fewer hospitalizations for strokes in 1 year.

Gross savings realized by avoided hospitalizations were nearly \$5 billion.²⁹

- **Chronic Obstructive Pulmonary Disease (COPD):** COPD patients who were more adherent to prescribed regimens had lower hospitalization rates and \$2,185 less in Medicare spending per patient than those who were not adherent. Similarly, those who adhered to their COPD maintenance medications over an extended period spent \$3,764 less in other health care costs relative to those who discontinued their COPD medications.³⁰

Medicines also result in improved health outcomes and quality of life for patients, which can lead to *increased employee productivity* through reduced absenteeism or disability leave.

- **Multiple Chronic Conditions:** Patients with diabetes, hypertension, high cholesterol, asthma, or COPD who consistently took medicines as prescribed missed fewer days of work and experienced less short-term disability than nonadherent patients. For example, adherent patients with COPD missed on average 9.8

fewer days of work and 3.6 fewer days of short-term disability per year than their nonadherent counterparts. This amounts to an average annual productivity enhancement of \$3,149 per worker (see Figure 6).³¹

- **Rheumatoid Arthritis (RA):** Evidence demonstrates the value provided by medicines in reducing work impairments, absenteeism, and lost work hours among patients with severe RA. One study found that continued use of a particular biologic medicine to treat RA was associated with a gain of 284.5 hours of productivity per year.^{32,33}
- **Crohn's Disease:** Those with Crohn's disease, an autoimmune disease that impairs the digestive system, suffer considerable work-related

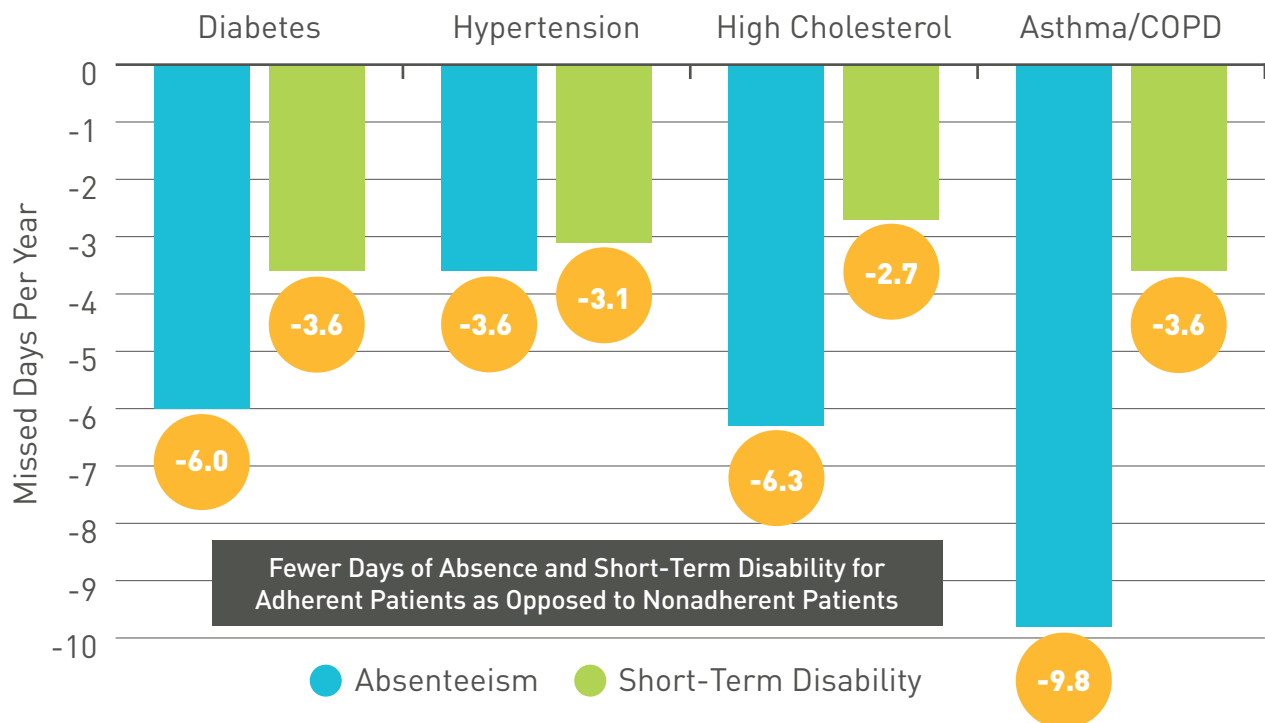
impairment due to its physical effects and the poor quality of life associated with the disease, suggesting an opportunity to improve outcomes and productivity for these patients. One study examining Crohn's patients treated by a particular medicine tested in clinical trials measured a number of work-related outcomes and found a 9% decrease in absenteeism and a 25% reduction in total work impairment.³⁴

GAPS IN APPROPRIATE USE OF MEDICINES

Despite the value provided to patients, gaps in appropriate use of medicines remain. A National Community Pharmacists Association survey showed that nearly 75% of adults do not follow

FIGURE 6: Improving Adherence to Treatment Increases Worker Productivity

Adherent patients miss fewer days of work and experience less short-term disability. For workers with asthma/COPD, better adherence results in more than \$3,100 in savings on average per worker annually.



Source: Carls GS, Roebuck C, Brennan TA, et al. Impact of medication adherence on absenteeism and short-term disability for five chronic diseases. *J Occup Environ Med.* 2012;54(7):792-805.

I'm Not Average: Warren Littrel



According to his doctor, Warren Littrel should have died several years ago. Instead, Warren recently celebrated the fifth anniversary of his diagnosis of stage IV pancreatic cancer. Before the diagnosis, Warren was active, ate the right things, and took care of himself. He ran marathons and hiked mountains. He did everything he was supposed to do to remain healthy. Due to the stage and location of his tumor, his treatment options were limited, and without medical care he was given 6 to 8 weeks to live. The most aggressive treatment option gave him an expected survival of just 14 months.

Five years later, Warren is thriving thanks to recent innovations in cancer care. New treatments have enabled Warren to manage his disease and to live a longer, healthier life. Since his diagnosis, Warren has remained on the move. He practices yoga, takes aerobics classes, and runs a ceramics business with his wife and children in Tunisia that employs over 50 local artists. "I now take the time to appreciate the little things in life," he said. "I've been fortunate that because of my treatment, I've been able to maintain a somewhat normal life, and this is what I'm most grateful for."

For more on Warren, see: <http://www.phrma.org/cancer#>.

their doctors' prescription orders, including not filling their prescriptions or taking less than the recommended dose.³⁵ A number of factors, such as complexity of treatment regimens and limited access to medicines, create barriers to the optimal use of medicines.

The complexity of treatment regimens and poor relationships or lack of communication between prescribers and patients can affect patients' ability to follow their doctors' instructions for their medications. Patients often do not understand their illness or the need for treatment. They may suffer from mental illness or cognitive or physical impairments that contribute to poor adherence to prescribed treatment. Patients with multiple chronic conditions often have trouble managing complicated treatment regimens. Additionally, underuse is a common problem among elderly patients; researchers report they are 17 times more likely to underuse prescribed medicines than to overuse them.³⁶

Limited access to, or coverage of, medicines may also contribute to gaps in appropriate use of medicines. A trend in recent years toward increased out-of-pocket costs for medicines has dramatically affected the use of medicines by patients who need them. Average per-capita out-of-pocket spending for medicines tripled between 2008 and 2012, increasing from \$326 in 2008 to \$1,146 in 2012.³⁷ Many studies have revealed that these increases in cost sharing have been associated with negative health and cost outcomes.³⁸ For example:

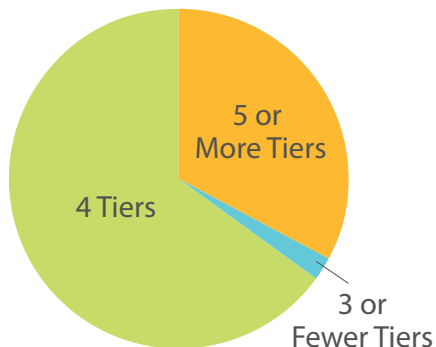
- **Out-of-pocket costs are increasing over time:** One in 9 employer plans use tiers in their drug benefit structure, with higher tiers subject to higher cost sharing. From 2000 to 2014, average copays for first-tier, or generic, drugs have risen about 38%, while cost sharing for second- and third-tier products has increased 107% and 83%, respectively. Over the past decade, plans have increasingly introduced 4 or more tiers for certain medicines (see Figure 7).³⁹

FIGURE 7: Plans Increasingly Subject Certain Medicines to Higher Cost-Sharing

Patients taking medicines placed on higher cost-sharing “tiers” can face higher out-of-pocket costs relative to lower tiers. Patients needing these medicines commonly face serious and chronic health conditions.

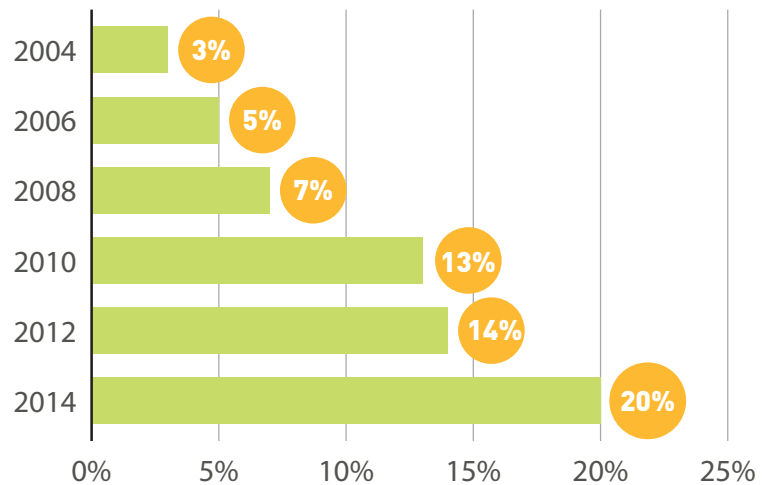
The use of 4 or more cost-sharing tiers is the norm for plans in Health Insurance Exchanges

Share of Silver Plans by Number of Tiers*



...and is becoming more common in employer plans

Share of Workers in Plans With 4 or More Tiers



*Silver Plans account for a majority of Health Insurance Exchange enrollment. “Tiers” refer to the different levels of cost sharing that plans require patients to pay for different groupings of medicines.

Source: Avalare PlanScape® Database. Accessed February 2015. Kaiser Family Foundation/Health Research & Educational Trust. Employer health benefits: 2014 annual survey. September 2014, 166.

- **Adherence decreases as out-of-pocket cost increases:** Research has shown that for every \$10 increase in out-of-pocket costs for prescription drugs, adherence decreases by approximately 4%, with the effect depending on therapeutic class and severity of condition.⁴⁰ One study found that doubling medication copayments for a variety of health conditions reduced medication adherence rates by 25% to 45%.⁴¹
- **Higher copays are linked to increased hospitalizations and spending:**⁴² For example, research shows that patients with acute coronary syndrome (ACS) who faced higher cost sharing were less likely to adopt—and more likely to discontinue—therapy within the first year following stent implantation. Subsequently, plans with high cost sharing had a \$2,180 increase in rehospitalization costs per patient with ACS in that time compared to lower cost-sharing plans.⁴³

Thus, high cost sharing for medications may limit patients’ access to needed treatments, reduce adherence, and lead to poor health outcomes. While there are many barriers to the optimal use of medicines among patients, there are also significant opportunities to improve patient health and the efficiency of the health care system by closing existing gaps in the use of medicines.

A large body of research supports the important role that appropriate use of medicines plays in improving health outcomes for patients and often in producing cost offsets in other areas of health care. Also critical to achieving these outcomes is access to quality drug coverage. Quality drug coverage is essential to ensuring patient access to the medicines they need to achieve better health outcomes and improved quality of life (see sidebar: ABCs of Health Coverage).

ABCs of Health Coverage

AccessBetterCoverage.org provides resources developed by PhRMA to help educate consumers about health insurance coverage and how their access to prescription medicines may be affected. The site features whiteboard videos on health insurance basics, a glossary of health care terms, news updates, and an interactive state map. It also includes the top 5 considerations when choosing health care insurance coverage:

1. Do the health care providers, hospitals, and pharmacies you prefer fall within the plan's network?
2. How much will you pay per month for coverage?
3. What is the amount you must pay out of pocket before your coverage kicks in?
4. Are you aware of other costs that you may be required to pay to access care?
5. Are your regular prescriptions covered by your insurance plan?

For more information, visit www.accessbettercoverage.org.

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Growing the US Economy

“I think it’s important that each patient be given the chance to survive longer.” -CJ Corneliussen-James,

8-year metastatic breast cancer survivor and co-founder of METAvivor





Growing the US Economy

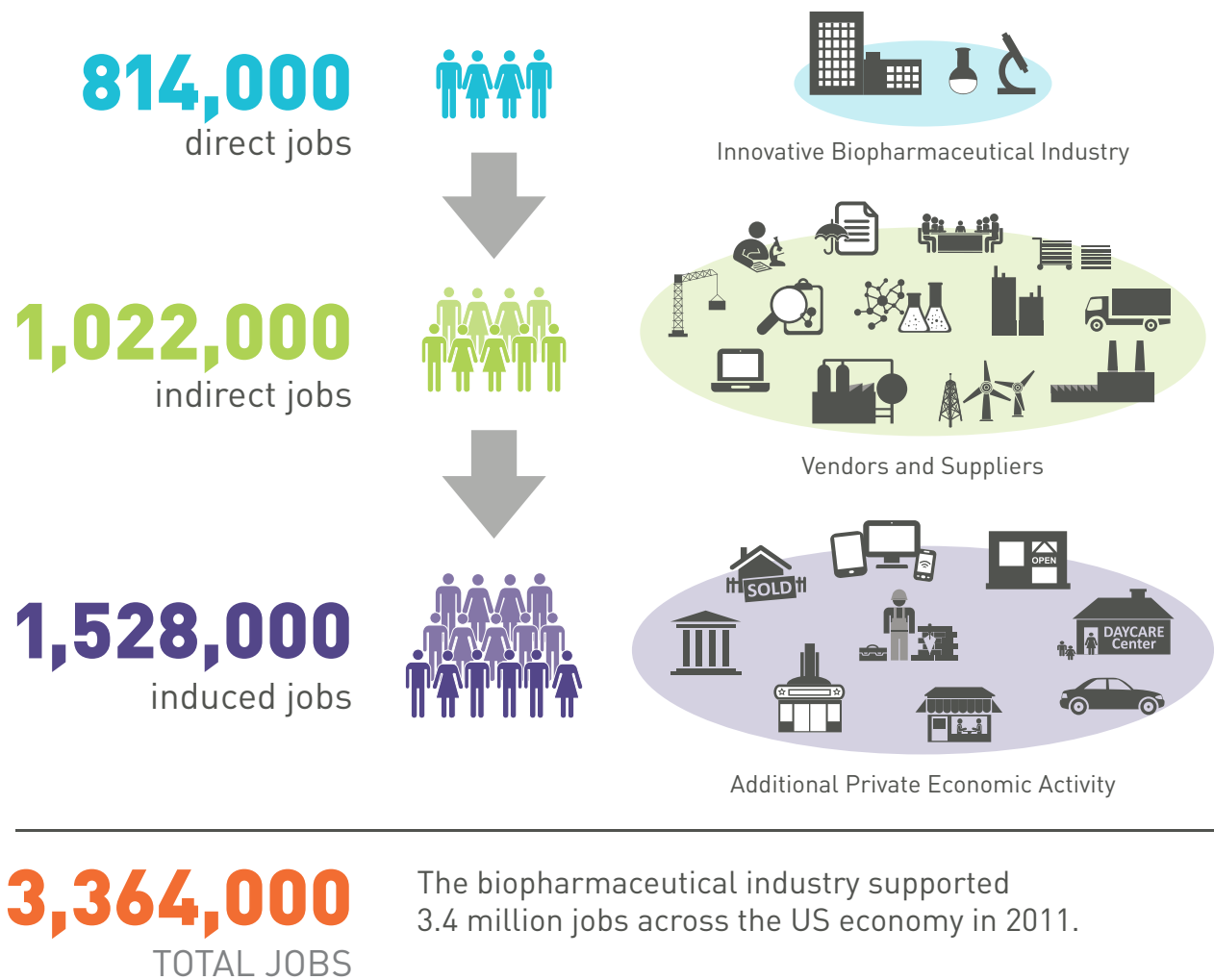
As the largest funder of drug research and development (R&D), the biopharmaceutical industry sits at the heart of a vibrant scientific and economic ecosystem that is vital to the economy and US global competitiveness. Innovative biopharmaceutical companies partner and collaborate with academic institutions, government agencies, nonprofit foundations, venture capital (VC), and patients in the pursuit of novel medicines.

These collaborative efforts not only drive medical research, they support local, state, and national economies. Biopharmaceutical companies put

down roots in communities across the country, generating high-quality jobs across a range of sectors, from suppliers to retail to personal services, which creates a ripple effect across the US economy. The industry employs more than 810,000 people, supports nearly 3.4 million jobs across the country, and contributes nearly \$790 billion in economic output on an annual basis when direct, indirect, and induced effects are considered (see Figure 8).¹

In 2011, each job in a biopharmaceutical research company supported a total of more than 4 jobs across the economy, ranging from

FIGURE 8: The Economic Reach of the US Biopharmaceutical Industry



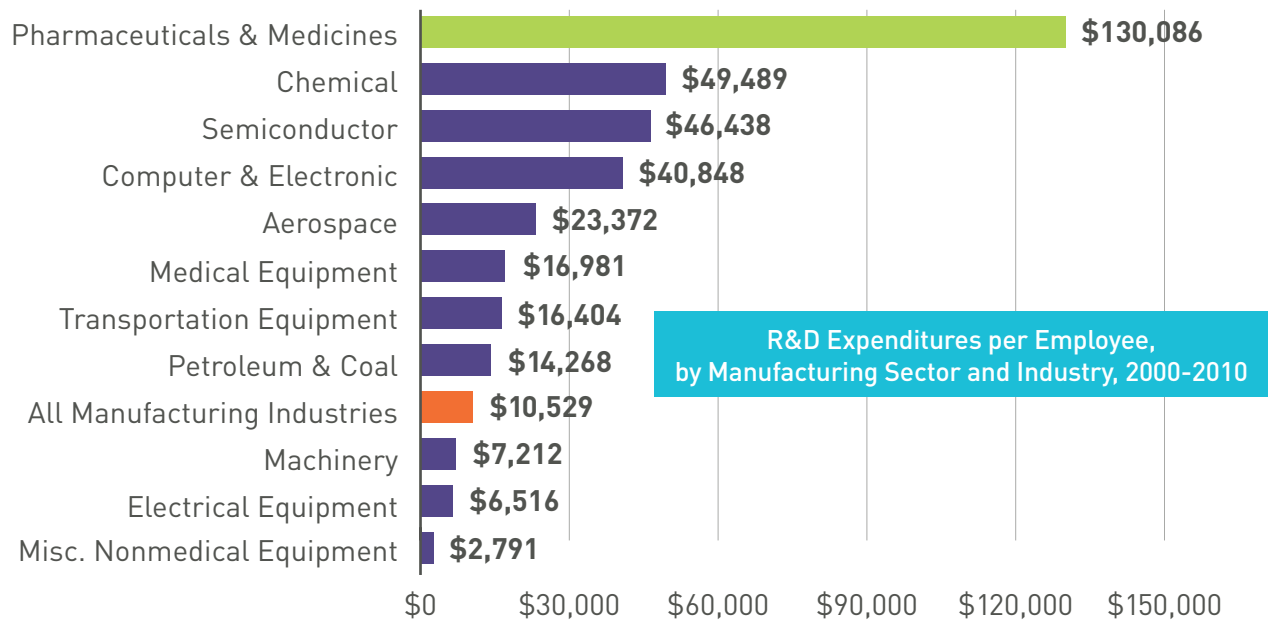
Source: Battelle Technology Partnership Practice. The US biopharmaceuticals sector: economic contribution to the nation. http://www.phrma.org/sites/default/files/pdf/2011_battelle_report_on_economic_impact.pdf. Report prepared for PhRMA. 2013. Accessed February 2015.

biopharmaceutical manufacturing jobs and construction to business services and childcare providers (see Figure 8).² The average wage of those employed by the biopharmaceutical sector is higher than the average wage across all other private sector industries. In 2011, the average total compensation per direct biopharmaceutical employee was \$110,490, twice the average compensation per US worker of \$54,455.³ The US biopharmaceutical industry helps support a vibrant scientific and economic ecosystem that is vital to the US economy and US global competitiveness.

The US biopharmaceutical industry is one of the most research-intensive industries in the United States (see Figure 9). Investing more than 13 times the amount of R&D per employee than manufacturing industries overall, the biopharmaceutical sector's significant investments in R&D drive its contributions to the US economy and allow it to be the world leader in the development of new medicines.⁴ According to the National Science Foundation, the US biopharmaceutical sector accounts for the single largest share of all US business R&D, representing about 1 in every 5 dollars spent on domestic R&D by US businesses.⁵

FIGURE 9: The Biopharmaceutical Sector Is the Most R&D Intensive in the United States

Biopharmaceutical companies invested more than 12 times the amount of R&D per employee than manufacturing industries overall.



Source: Pham N. IP-intensive manufacturing industries: driving US economic growth. Washington, DC: NDP Analytics; 2015. <http://www.ndpanalytics.com/ip-intensive-manufacturing-industries-driving-us-economic-growth-2015>. Accessed March 2015

ECONOMIC IMPACT OF CLINICAL TRIALS

Clinical trials, in which patients and healthy volunteers agree to participate in the testing of promising medicines, are an essential part of the drug development process (see Chapter 4). Of the billions of dollars spent on R&D each year by the biopharmaceutical industry, the majority is spent on clinical research. Because of their cost and length, clinical trials represent a large investment in communities across the country, helping to create jobs and boost local economies.

The biopharmaceutical industry accounts for roughly 90% of all spending on clinical trials of medicines and devices in the United States.⁶ 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. These collaborations between biopharmaceutical companies and local institutions benefit patients by providing new treatments and also benefit communities through jobs and investment.

In 2013, the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the United States, involving a total of 1.1 million volunteer participants.⁷ Biopharmaceutical company-sponsored clinical trials occurred in all 50 states and the District of Columbia. The industry spent nearly \$10 billion in these clinical trial locations in 2013.⁸ This is in addition to the significant resources invested in clinical trial-related activities such as management and data analysis functions occurring within companies and their contractors. Additionally, the research activities occurring in the field supported a total of \$25 billion in economic

activity in communities throughout the United States, after accounting for the economic ripple effect of expenditures by clinical trial vendors and contractors, as well as consumer spending by industry and vendor employees (see Figure 10).⁹

VENTURE CAPITAL (VC) INVESTMENTS

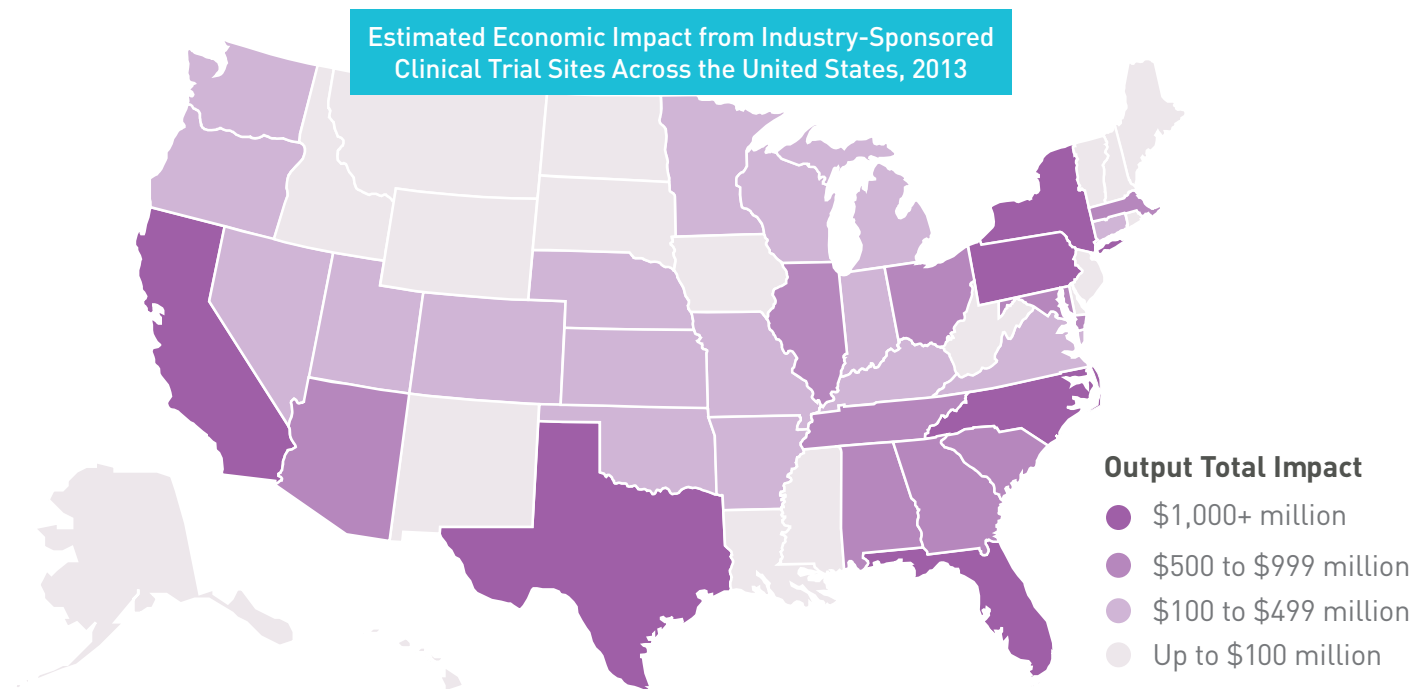
In addition to contributing immensely to the US economy, biopharmaceutical companies are dedicated to ensuring that the industry continues to innovate and produce much-needed medicines for patients. Emerging biopharmaceutical companies, which are important contributors to the creation of these new medicines, rely



on VC and other forms of private capital for financing. However, even with the recent uptick in VC investment—as biotechnology investment in 2014 returned to the record highs achieved in

FIGURE 10: Industry-Sponsored Clinical Trials Contribute Significant Value to the Communities in Which They Are Located

In 2013, the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the United States, involving a total of 1.1 million volunteer participants and supporting a total of \$25 billion in economic activity spread across all 50 states and the District of Columbia.*



*Estimates reflect only those activities occurring at clinical trial sites and exclude more centralized, cross-site functions such as coordination and data analysis. Also excludes nonclinical R&D such as basic and preclinical research and the significant economic contribution from non-R&D activities of the industry such as manufacturing and distribution.

Source: Battelle Technology Partnership Practice. Biopharmaceutical industry-sponsored clinical trials: impact on state economies. Report prepared for PhRMA. February 2015.

The Importance of Intellectual Property-Intensive Industries

Industries that are intellectual property (IP)-intensive, such as the biopharmaceutical industry, have a disproportionate impact on the economy, according to a recent study.¹⁰ In the report, IP-intensive manufacturing industries are defined as those industries that are more R&D-intensive than the average for all manufacturing sectors, and which rely heavily on patents to produce innovations. The authors found that these industries, including the biopharmaceutical sector, have an outsized impact on the economy based on a number of indicators, including wages per employee, output per employee, and exports per employee. This means that IP-intensive industries are contributing more to US economic sustainability and global competitiveness because they drive innovation, which has long been identified as a key determinant of economic growth in the increasingly knowledge-based global economy. Accordingly, policies related to IP rights should be crafted to encourage, rather than discourage, continued investment in future innovations. This is particularly true for the biopharmaceutical sector, for which IP was identified as the single most important policy factor driving industry growth in the United States, according to a recent survey of industry executives.¹¹

2007—the future of medical innovation remains uncertain as the number of deals have decreased over time, meaning fewer startups are able to receive funding.¹² Early stage companies are particularly affected by this trend, as they are often the ones most sensitive to uncertainties associated with biopharmaceutical R&D. This gap in early stage funding has grown due to several factors, including increasing regulatory

burdens, concerns about coverage and payment for new medical innovations, and uncertainties related to IP policies. As a recent report by Deloitte notes, “If these trends are sustained it will further encourage financiers to invest their capital elsewhere, and for an industry that heavily relies on small-cap firms and venture capital to fuel innovation, this could negatively impact the ecosystem in a permanent



Rx Response: Collaborating to Bring Medicines to Patients in Times of Disaster



During major disasters, maintaining access to medicines is critical. The breakdown of a single link in the biopharmaceutical supply chain can result in patients not being able to obtain their critically needed medicines.

Rx Response is a collaborative initiative that brings together the biopharmaceutical supply chain, including manufacturers, distributors, dispensers, and the American Red Cross, to help ensure that medicines are available during and after major disasters. In the 8 years since its inception, Rx Response has responded to 52 incidents and events, including natural disasters and emerging infectious diseases such as Ebola. In addition to fostering business continuity and information sharing to enhance community resilience, Rx Response offers Rx Open, an online resource that maps the location of open pharmacies in disaster-stricken areas. For more information about Rx Response, visit www.rxresponse.org.

way.”¹³ However, the corporate venture arms of established biopharmaceutical companies are stepping in to fill this gap. Corporate VC investments in early stage companies have steadily increased over time, with corporate venture arms participating in 35% of early stage deals in 2013, up from just 8% in 2005.¹⁴

RESPONDING TO SOCIETAL NEED

Patient Assistance

As an industry, biopharmaceutical companies are dedicated to ensuring patients are able to access the medicines they need. The industry participates in the Partnership for Prescription Assistance (PPA), a program that helps patients

FIGURE 11: Biopharmaceutical Companies Lead Corporate Giving

Biopharmaceutical companies led worldwide corporate giving* in 2013. Ninety percent of these contributions were in the form of in-kind product donations.

Average Corporate Giving by Sector	Total Giving as % of Pre-Tax Profit	Total Giving per Employee
All Companies	1.0%	\$644
Biopharmaceuticals	19.4%	\$24,453
Energy	0.8%	\$2,912
Utilities	1.2%	\$1,092
Information Technology	1.1%	\$666
Consumer Staples	1.1%	\$608
Industrials	0.8%	\$244

*Domestic giving makes up the largest portion of total corporate giving across all sectors surveyed. Domestic giving comprised 78% of total giving in 2013.

Source: Committee Encouraging Corporate Philanthropy (CECP). Giving in numbers: 2014 edition. New York: CECP; 2013. http://cecp.co/pdfs/giving_in_numbers/GIN2014_Web_Final.pdf. Accessed February 2015.

without prescription drug coverage access support for the medicines they need by matching them with the right assistance programs. The PPA has helped more than 9 million uninsured and financially struggling patients gain free and confidential access to 475 public and private patient assistance programs, including nearly 200 that are offered by pharmaceutical companies. PPA member programs offer more than 2,500 brand-name medicines and generic drugs.¹⁵ More than 1,300 major national, state, and local organizations have joined the PPA, including the American Academy of Family Physicians, American Cancer Society, American College of Emergency Physicians, Easter Seals, and United Way.¹⁶ Patients can learn about and apply to the PPA by visiting www.pparx.org.

Global Philanthropy

Biopharmaceutical companies are dedicated to important causes both in the United States and around the globe. In 2013, the industry led all other sectors in corporate giving, with nearly 90% of the contributions in the form of in-kind



product donations (see Figure 11).¹⁷ In addition, biopharmaceutical companies invested more than \$400 million in R&D for neglected diseases in 2013 alone, and much of this investment is showing incredible promise (see sidebar: Exciting Promise in the Fight to Prevent Dengue Fever).¹⁸ The biopharmaceutical industry is also working closely with colleagues around the world to help fight the Ebola epidemic through donations and research (see sidebar: Efforts of the Biopharmaceutical Industry to Fight Ebola).

Exciting Promise in the Fight to Prevent Dengue Fever



Dengue fever is a debilitating and often fatal virus that is transmitted by the *Aedes aegypti* mosquito. It is the fastest growing of all mosquito borne-illnesses, with half of the world's population at risk. Those infected with the disease generally experience high fever, rash, headaches, convulsions, joint and muscle pain, and in some cases, death. The disease causes an estimated 20,000 deaths each year and is known to be associated with a greater risk of death among children.¹⁹ Unfortunately, the complexity of the virus has challenged researchers for decades, and there is currently no cure for the disease.

Today, after 20 years of development, a vaccine in the late stages of clinical trials is showing incredible promise for protection against dengue fever. There are also several other vaccines in development that immunize across 4 different serotypes of the disease. The Cleveland Clinic, in naming these potential vaccines a top-10 medical innovation for 2015, noted these medicines could “translate into a huge benefit for countries plagued by the disease in terms of medical costs, work productivity, and human suffering.”²⁰

Efforts of the Biopharmaceutical Industry to Fight Ebola



Researchers around the world, across both public and private sectors, are working to develop new ways to prevent the spread of Ebola and to treat patients with the disease. Multiple factors, however, present challenges to the development of effective treatments:

- The near incapability of identifying an at-risk patient population for clinical trials due to the sporadic nature of the disease, which occurs in unpredictable outbreaks.²¹
- The fragmented and basic infrastructures and health systems in Western African countries currently affected by the outbreak create significant challenges for the recruitment, retention, and conduct of clinical trials.²²
- Outside of an epidemic setting, the efficacy of a medicine must be demonstrated in animal models.
- It is difficult to scale up manufacturing capacity, particularly in a crisis situation, due to the complexity of the process and the unpredictability of demand.

Despite these challenges, biopharmaceutical companies and other research organizations around the world are working together to advance promising new vaccines and treatments. Currently, there are 11 potential vaccines and treatments in clinical trials and at least 31 more moving through preclinical or earlier studies around the world.²³ Since 2000, at least 17 potential candidate medicines have either been discontinued or suspended in development. Although these setbacks are disappointing, they reinforce the tremendous scientific and other challenges associated with R&D in this area and have provided invaluable insights for researchers to build upon as they pursue new research tracks.

In addition to efforts to accelerate advances in prevention and treatment, numerous US biopharmaceutical companies are supporting humanitarian efforts to contain and treat the disease through organizations such as AmeriCares, Caritas International, Direct Relief International, International Federation of the Red Cross, International Rescue Committee, Project HOPE, Save the Children, and many others.

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R&D: Ushering in a New Era of Innovative Medicines for Patients

“This medication has now made my cancer something that I can live with.” -Marina Symcox, 17-year stomach cancer survivor, and co-founder of GIST Support International





R&D: Ushering in a New Era of Innovative Medicines for Patients

Emerging scientific advances are shaping our understanding of the causes of disease, creating new avenues of research, exploration, and discovery. Scientists are harnessing this knowledge and applying it to identify and develop new treatments for patients.

Despite advances in our scientific understanding of diseases, the research and development (R&D) process remains challenging and is often a long, complex, and expensive undertaking for

innovative biopharmaceutical companies. As the understanding of the science accelerates, so too does the complexity of each step of the process. Along the way, many medicines may not make it through the pipeline. Though these setbacks are frustrating, they provide invaluable knowledge for researchers to build on and use to inform the development of future medicines.

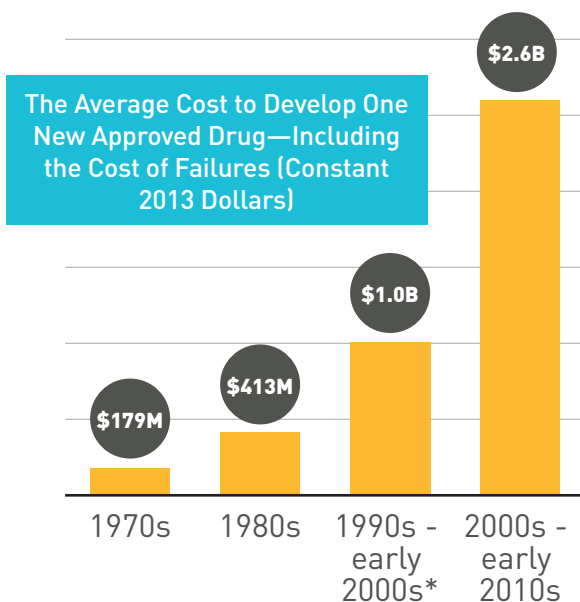
Some key facts give a sense of the challenges inherent in the process¹:

- On average, it takes more than 10 years for a new medicine to go through the entire R&D process, from the time the compound is identified to when it receives approval from the US Food and Drug Administration (FDA).
- The average cost to develop a new medicine is estimated to be \$2.6 billion. This number accounts for the cost of failures, as many of the initial investigate compounds that are developed will not make it through to FDA approval. Reflecting the growing complexity of the process, the total cost of development more than doubled in the last decade (see Figure 12).



FIGURE 12: Drug Development Costs Have Increased

According to a 2014 study, it costs an average of \$2.6 billion to develop one new drug. More recent studies estimate the costs to be even higher. Less than 12% of the candidate medicines that make it into phase I clinical trials will be approved by the FDA.



*Previous research by same author estimated average R&D costs in the early 2000s at \$1.2 billion in constant 2000 dollars (see DiMasi JA, Grabowski HG. The cost of biopharmaceutical R&D: is biotech different? Managerial and Decision Economics. 2007;28: 469-479). That estimate was based on the same underlying survey as the author's estimates for the 1990s to early 2000s reported here (\$800 million in constant 2000 dollars), but updated for changes in the cost of capital.

Source: Tufts Center for the Study of Drug Development (CSDD). Cost of developing a new drug. Briefing. Boston, Mass.: CSDD. Published November 2014. Accessed March 2015.

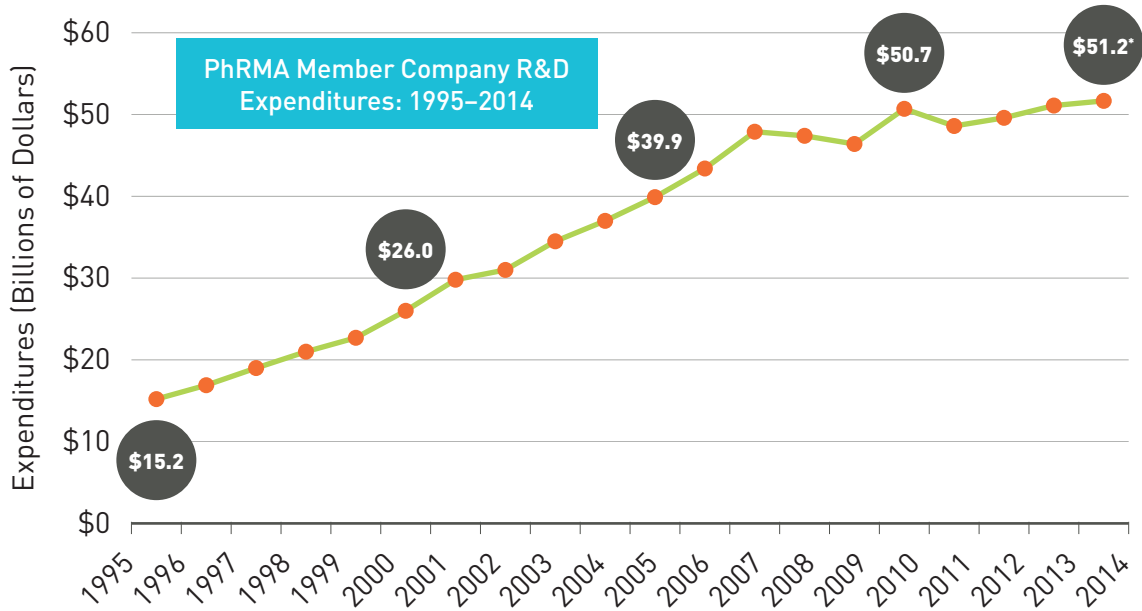
- Only 12% of the investigative medicines that enter phase I clinical trials will make it to FDA approval.

Despite the challenges, biopharmaceutical companies are dedicated to discovering new and better medicines to improve the lives of patients across the country. In 2014, Pharmaceutical Research and Manufacturers of America (PhRMA) members invested an estimated \$51.2 billion in R&D.² Since 2000, PhRMA members have spent more than half a trillion dollars on R&D (see Figure 13).

The dedication of researchers is reflected by the approximately 4,000 medicines currently in development in the United States alone.³ All of these medicines have the potential to benefit US patients, and each must undergo the same rigorous and time-consuming process to determine safety and efficacy for patients. (For more information about the scientific outlook and the many innovative medicines in the pipeline, see Chapter 5).

FIGURE 13: PhRMA Member Company R&D Investment

"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 US manufacturing firm." -CONGRESSIONAL BUDGET OFFICE



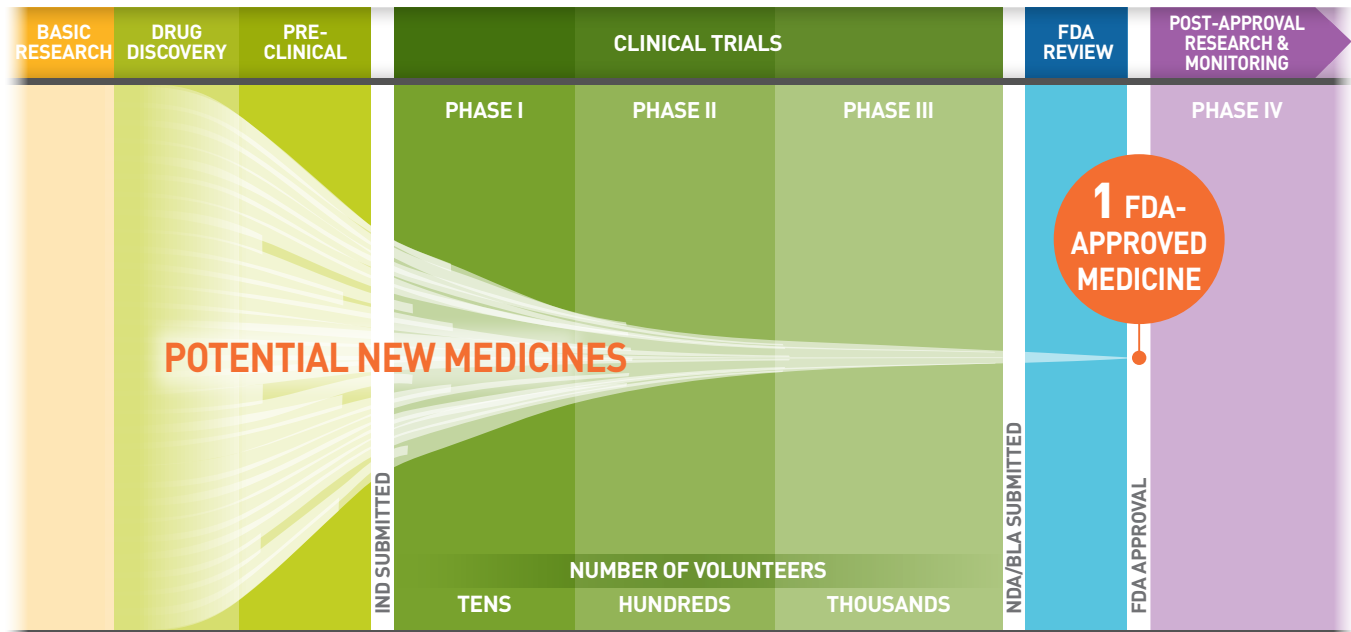
* Estimated FY 2014

Sources: Congressional Budget Office (CBO). Research and development in the pharmaceutical industry. www.cbo.gov/sites/default/files/cbofiles/ftpdocs/76xx/doc7615/10-02-drug-r-d.pdf. Washington, DC: CBO; October 2006. Accessed March 2014. Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA annual membership survey, 1996-2014. Washington, DC: PhRMA; 2015.



FIGURE 14: The Biopharmaceutical R&D Process

From drug discovery through FDA approval, developing a new medicine on average takes at least 10 years and costs \$2.6 billion.* Less than 12% of the candidate medicines that make it into phase I clinical trials will be approved by the FDA.



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Dimasi JA. Cost of developing a new drug. Tufts Center for the Study of Drug Development (CSDD). R&D Cost Study Briefing; November 18, 2014. http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18_2014.pdf. Boston Mass.: CSDD. Accessed February 2015; US Food and Drug Administration. Drug approval process. <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf>. Accessed January 2015.

OVERVIEW OF THE R&D PROCESS

A deeper understanding of the R&D process can help explain why so many compounds do not make it through. Candidate medicines move through a lengthy, complicated, multi-step process to deliver innovative new medicines to patients. The journey does not end with FDA approval, as research continues even after a medicine is approved (see Figure 14).

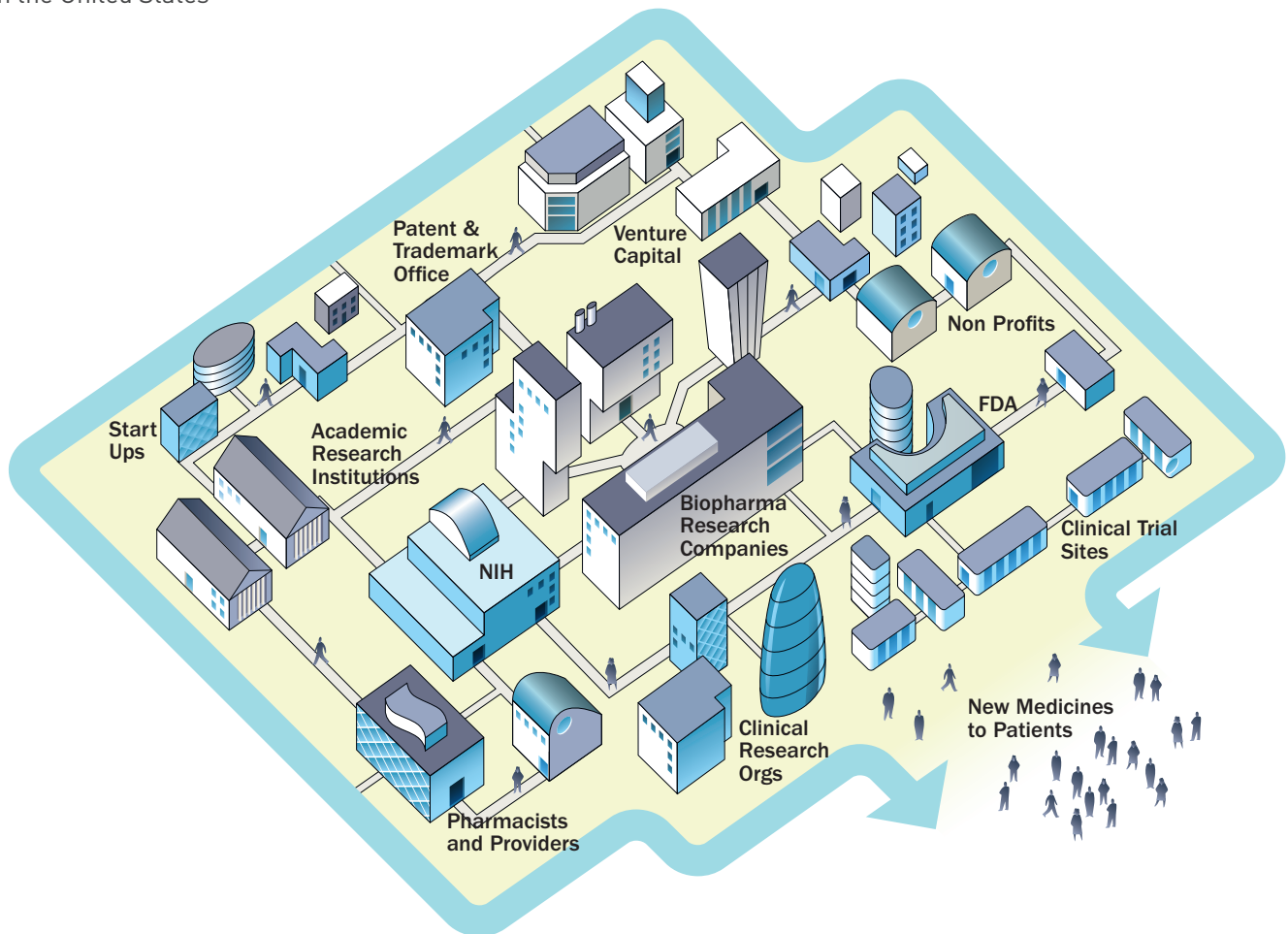
America’s biopharmaceutical companies are at the heart of a dynamic ecosystem that includes academic researchers, the National Institutes of Health (NIH), the FDA, nonprofit patient and disease groups, clinical research organizations, clinical trial centers, health care providers, and

venture and other private capital investors. These groups increasingly are working together to advance novel science and therapeutics. Collaboration and partnerships are crucial to moving potential new medicines through the pipeline to FDA approval (see Figure 15).

Drug Discovery

The first step in the biopharmaceutical R&D process is to identify potential biological targets for possible future medicines. Understanding the mechanisms of disease allows researchers to hone in on specific targets. They then look for a lead compound, meaning a promising candidate that could influence the target and potentially become a medicine. Even at this early stage,

FIGURE 15: Innovative Biopharmaceutical Companies Sit at the Heart of a Dynamic R&D Ecosystem in the United States



Source: Pharmaceutical Research and Manufacturers of America (PhRMA). 2014 PhRMA profile. <http://www.phrma.org/profiles-reports>. Washington, DC: PhRMA; 2014.

investigators already are thinking about the final product and how it will be manufactured and delivered to patients.

Preclinical Testing

To determine whether a compound is suitable for human testing, the most promising candidates are selected to undergo preclinical testing. Researchers conduct a series of laboratory and animal studies to test how the medicine works and determine its safety profile. At the end of this process, which spans several years, only a few compounds move to testing in humans.

Clinical Trials

After successfully completing preclinical studies, researchers file an Investigational New Drug application with the FDA to begin evaluating the candidate medicine in humans. Researchers conduct these studies, known as clinical trials, to demonstrate the safety and efficacy of the medicine. The sponsoring company works closely with an independent institutional review board (IRB) to design and monitor the clinical trials. The IRB, which is made up of physicians, researchers, and members of the community, ensures that the study is ethical and the rights and welfare of participants are protected. This review includes ensuring that

I'm Not Average: Marina Symcox



In her late 30s, Marina was diagnosed with a gastrointestinal stromal tumor. Existing chemotherapies were not effective at treating her cancer, and her prognosis was dire, giving her only a few weeks to live. Hope came into Marina's life when she learned of a clinical trial for an investigational medicine. "I had been sick for so long, not knowing that behind the scenes great science was occurring." By this point, Marina was so ill she could barely stand, let alone walk or play with her young children. She decided to enroll in the clinical trial and, as a result of the experimental medicine, her tumor began to shrink dramatically. Marina noted, "If you were to look at the clinical trial data, it would say the average time on the drug is 2 years. I have been on the same drug for 14 years...I was told initially that I had 3 to 5 months to live, and I beat the odds."

For more on Marina, see: <http://www.phrma.org/cancer#>.

research risks are minimized and are reasonable in relation to any potential benefits.⁴ Biopharmaceutical companies take great care to protect trial participants and ensure that they are thoroughly informed about the potential benefits and risks of participating in a clinical trial.

The clinical trials process occurs in several phases, and few candidate medicines that enter clinical trials make it to the FDA review and approval stage. A potential medicine must successfully complete each phase before undergoing review for FDA approval.⁵

- **Phase I** trials test the candidate medicine in a small group (eg, 20 to 80) of healthy volunteers to determine the safety of the compound and how it is best metabolized or processed in the body.
- **Phase II** trials are conducted in a somewhat larger group of patient volunteers (usually a few hundred) who have the disease or condition the compound is designed to treat. While primarily intended to examine safety and possible short-term side effects, phase II studies also

determine effectiveness of the compound and identify optimal dosing.

- **Phase III** trials test the compound in a much larger group (typically in the thousands) of patient participants. They are designed to generate statistically significant information about safety and efficacy. These studies help determine the overall benefit-risk ratio.

FDA Review and Approval

If the results of the clinical trials show that the compound is safe and effective, the sponsoring company submits a New Drug Application or Biologics License Application to the FDA requesting approval to market the drug. This application contains the results and data analysis from the entire clinical trial program as well as the earlier preclinical testing. It also includes proposals for manufacturing and labeling the new medicine.

FDA scientists carefully review all the data from all of the studies on the compound and, after weighing the benefits and risks of the potential medicine, decide whether to grant approval. Occasionally, the FDA will ask for additional research before

Clinical Trial Success Depends on Volunteers: What Clinical Trial Volunteers Can Expect



The most important component of a successful clinical trial is the volunteers who participate in the research studies; however, enrolling clinical trial participants is often challenging. This is partly due to a general lack of awareness about clinical trials and the fact that not all doctors discuss opportunities to participate in clinical trials with their patients. In early clinical studies, healthy volunteers are crucial so that researchers can confirm that the candidate medicine can be safely tolerated. In later clinical studies, the participation of patient volunteers who have the condition that the medicine is meant to address is

essential for evaluating the effectiveness of the medicine and understanding whether adjustments are needed that may make the medicine work more effectively for patients. Careful planning goes into the design and conduct of each clinical trial to ensure the safety of all participants. It is important for potential volunteers to understand what to expect, as the processes and procedures can be different for each clinical trial:

- **Informed consent.** Every trial has an ongoing informed consent process, which ensures that participants have all the information they need to fully understand the trial and make an educated decision about whether to begin or continue participating in a clinical trial. Informed consent documents describe the purpose of the trial, explain the visits and procedures to be done, and include easy-to-understand language about the possible risks and benefits of participation. Members of the research team discuss all known risks and benefits as well as answer any questions from potential participants. An independent IRB reviews, approves, and monitors the study design and the informed consent documents.
- **Costs of clinical trials.** Volunteers for clinical trials rarely have to pay any costs related to participating in the trial. Research costs are often covered by the sponsoring organization, and patient care costs are often covered by many insurance companies. Because clinical trials rely on voluntary participation, patients are free to leave a trial at any time, even after they have signed an informed consent and the study has begun.
- **Benefitting from a trial.** The decision about whether or not to use a placebo in a clinical trial is based on several important factors, including the severity of the disease, the availability of existing treatment options, and additional ethical considerations. Often, the best available treatment, called the “standard of care,” will be used instead of a placebo when the disease is serious or life-threatening.

Like all medical interventions, clinical trials have potential benefits and risks such as side effects or pain. Processes and procedures can be different for each clinical trial. Some, as in general medical care, may be unpleasant or carry risks. However, the doctor will talk to patients about what to expect, and the procedures and risks will be listed in the informed consent document for patients to consider when deciding whether to participate. See more at: <http://www.phrma.org/catalyst/debunking-common-myths-about-clinical-trials#sthash.7KVPNyBk.dpuf>.

granting approval or will 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 if there are any additional research requirements.

Manufacturing

In parallel with the clinical trial process, company scientists work to determine the best way to manufacture and package a new medicine for patients. A new medicine will usually be taken by a larger group of patients than were enrolled in the clinical trials, so careful planning must take place to scale-up production and ensure that enough medicine can be produced continuously and efficiently. Manufacturing facilities are designed and constructed to the highest standards to ensure that safety and quality are built into each step of the manufacturing process.⁶ Companies must adhere to FDA's Current Good Manufacturing Practices regulations. They also must constantly update, overhaul, or even rebuild facilities when new medicines are approved because each new medicine is manufactured differently. Many biopharmaceutical companies use the latest green manufacturing approaches.

These techniques streamline the process and reduce the use of resources such as energy and water, which can lower operating costs while protecting the environment.⁷

Advances in science have propelled biopharmaceutical manufacturing into a new realm of complexity in recent years. The emergence of biologics, which are larger than small molecule medicines and are often derived from living cells, has presented great challenges to manufacturers. These molecules require multiple steps that entail the use of robust technology to ensure purity, consistency, and quality. To keep pace with rapid advances in science and medicine, America's biopharmaceutical companies contribute to and use advanced manufacturing, which requires cutting-edge materials and emerging science capabilities to manufacture these complicated medicines (see sidebar: Advanced Biopharmaceutical Manufacturing in the United States).

Post-Approval Research and Monitoring

Research on a new medicine continues even after it has received FDA approval. The FDA often asks companies to conduct additional monitoring,

Advanced Biopharmaceutical Manufacturing in the United States

Rapid changes in molecular science have ushered in a new era of innovative biopharmaceuticals. The emergence of personalized or targeted therapies, the increased prevalence of large molecule medicines, and huge growth in the number of treatments for orphan diseases are just some of the factors that are having a significant impact on how medicines are created and manufactured on the large scale. To accommodate the ever-shifting global landscape, companies are investing in innovative manufacturing techniques. Biopharmaceutical manufacturers are innovating throughout the entire process, from raw material to finished drug products. These advances, including the use of continuous manufacturing, process analytical tools, and single-use systems, among other new technologies, are driving manufacturing flexibility and scalability while improving quality and efficiency. The implementation of innovative methods and techniques has an impact beyond the companies, as these new technologies require an increasingly specialized workforce and supply of materials. Using these advanced techniques efficiently delivers higher quality medicines to patients and increases the nation's standing as a global leader in innovation.⁸

including long-term studies to collect ongoing safety and efficacy data in specific patient subgroups.

Companies sometimes also conduct post-approval studies to assess the medicine's benefits in different populations or in other disease areas. Researchers study longer-term benefits and risks and assess whether possible adjustments may deliver even greater value to patients, including the development of improved delivery systems or dosage forms.

The FDA requires companies to monitor a medicine for as long as it stays on the market and to submit periodic reports on safety. Companies must report any adverse events that result from use of the medicine. The FDA may also require implementation of a risk evaluation and mitigation strategy (REMS) to accumulate additional information on the medicine's benefit-risk profile. REMS may require additional training and education of health care providers to properly prescribe, ship, or prepare the medicine and to ensure the correct reporting and monitoring of required safety factors.

THE EVOLVING R&D PROCESS

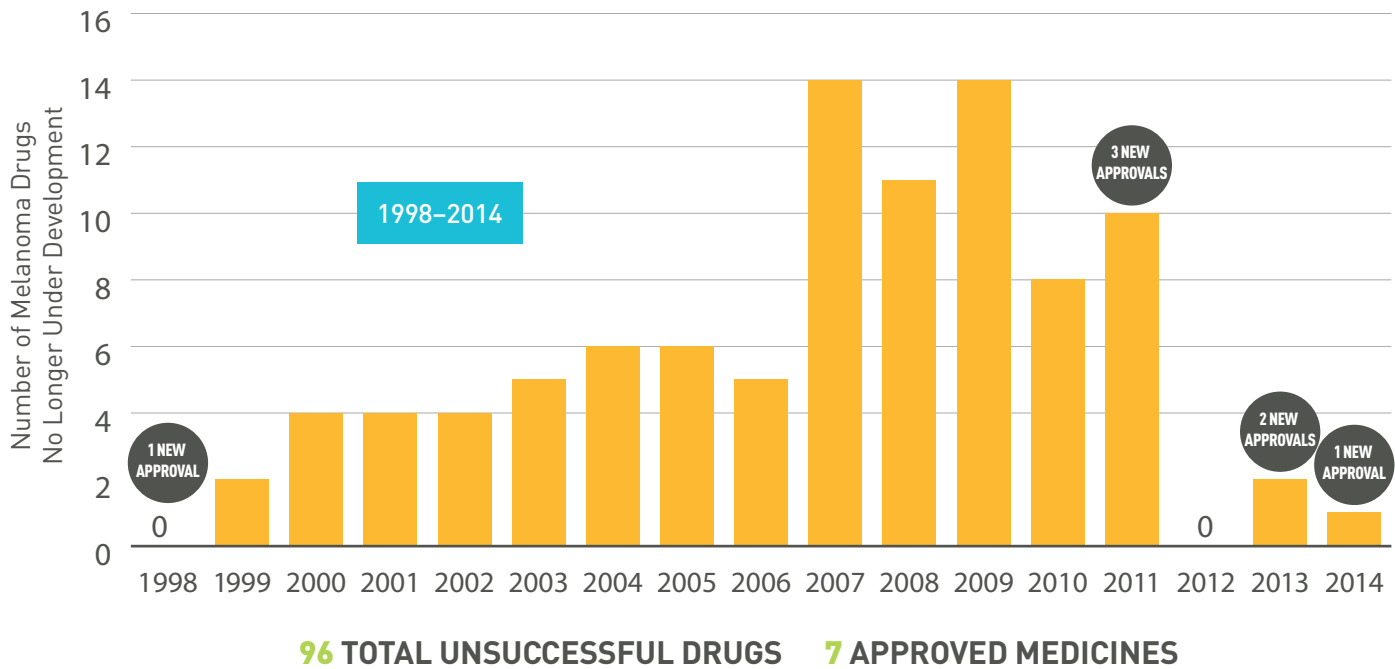
The R&D process is dynamic and changes as new science emerges and the regulatory, intellectual property, and coverage and payment environment shifts. New scientific advances bring greater promise but also increased complexity. In parallel, changes in clinical trial regulation, post-approval payment, and coverage standards create new challenges for innovative biopharmaceutical companies. Here are just a few examples of the forces that are changing the R&D process:

- **Complexity of science:** In recent years, scientists' deepening understanding of the biologic causes of disease has presented unprecedented

opportunities while simultaneously changing many aspects of drug development. For example, there is huge potential for personalized medicine to revolutionize the treatment paradigm for patients, but the development of these increasingly precise treatments is also highly complex, resulting in changes in the way medicines are identified, studied, and manufactured.

- **Research on complex diseases:** Increasingly, clinical investigators are exploring treatment options for more intricate 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 75 today.^{9,10} Although science has provided, and continues to provide, new areas for exploration, researchers face inevitable future failures and setbacks given the inherent nature of complex diseases.
- **Regulatory hurdles:** The burden of conducting a clinical trial is growing, with more numerous and complex eligibility criteria for study enrollment, increased site visits and procedures required, longer duration of the studies, and more data collected. In fact, the form used by researchers to collect data from each patient expanded in length by 227% between 2000 and 2011, reflecting the growing challenges of conducting clinical trials.¹¹
- **Reimbursement uncertainty:** Coverage and payment policies for new medicines, both in the United States and internationally, are affecting the availability of capital to invest in R&D. In addition, reimbursement hurdles create challenges in designing clinical trials, where selected trial endpoints may satisfy regulatory requirements

FIGURE 16: Unsuccessful Melanoma Drugs in Development



Source: PhRMA analysis of Adis R&D Insight Database. September 15, 2014.

Setbacks and Stepping Stones in Cancer Research



Although recent scientific advances have led to innovative and effective treatments for many patients, developing treatments for cancer is especially complex. This complexity is reflected in the drug development process:

- The National Cancer Institute estimates that more than 76,000 new cases of melanoma will have been diagnosed in 2014, and more than 10,000 people will die from this type of cancer. The disease is among the most common types of cancer diagnosed in adolescents and young adults in the United States.¹²
- The recent advances in treatment for melanoma resulted from many clinical trials and other research efforts that either never made it to, or failed in, clinical trials (see Figure 16). Since 1998, almost 100 investigational medicines in development for melanoma were “discontinued,” “suspended,” or had “no development reported.” These unsuccessful research efforts paved the way for the 7 medicines approved by the FDA over the same period, a nearly 14:1 ratio of “failures” to “successes.”¹³
- In 2014, 50 new melanoma medicines are in clinical development in the United States.¹⁴

but may not meet the standards put forth by a variety of public and private payers.

Novel medicines that target the underlying causes of diseases are improving the outlook for many patients. But behind every medicine that makes it to patients there are many that do not. The biopharmaceutical pipeline is littered with so-called “failures.” These setbacks are an inevitable part of the process, but researchers use the knowledge gained from them to better understand the disease and inform research on other medicines in development.

ADAPTING TO CHANGES AND CHALLENGES

Biopharmaceutical researchers are exploring ways to reduce development times and increase the odds of success using new research tools, novel

approaches to patient recruitment, and sophisticated methods of collecting and analyzing data. To address the most complex scientific and technological challenges, partnerships and collaborations are becoming increasingly common among researchers from biopharmaceutical companies, academic medical research centers, nonprofit organizations, patient advocacy groups, and others. In working together to address these challenges, partners share risks and are able to exchange intellectual, financial, and in-kind resources. Precompetitive partnerships and risk-sharing consortia are emerging as novel mechanisms of collaboration and information.¹⁵

Improving the clinical trials process is another area of active exploration. Innovative clinical trial designs and methodologies provide a more flexible framework for clinical development and hold promise for improving clinical trial success



Innovative Clinical Trial Designs Transform Drug Development: Lung-MAP

Biopharmaceutical companies are engaging in innovative partnerships to accelerate clinical trials and speed the development of medicines for patients. Lung-MAP is a first-of-its-kind clinical trial model that uses genetic information to assign patients to one of several different investigational medicines that treat second-line, recurrent squamous cell lung cancer. The FDA, National Cancer Institute, SWOG Cancer Research, Friends of Cancer Research, the Foundation for the NIH, Foundation Medicine, and several lung cancer advocacy groups are working hand-in-hand with industry to build the infrastructure necessary to drive this novel design. Patients undergo targeted screening that directs them to specific substudies, which each test a different investigational medicine. Importantly, these substudies all operate under one master study protocol, allowing for more efficient sharing of information and study conduct.¹⁶ “This is an entirely new way of looking at the development of cancer drugs. This is no longer business as usual. This approach changes the paradigm.” —David Gandara, Director, Thoracic Oncology Program, UC Davis¹⁷

rates. For example, adaptive clinical trials allow researchers to adjust elements of the trial (eg, dosing, number of people, patient population) while a trial is underway. This translates to more efficient use of resources.

The complexities of the R&D process and ecosystem are many, but America’s innovative biopharmaceutical companies are working

hard to accelerate innovation and deliver safe, effective medicines to patients. Increased collaboration across the research ecosystem and the use of advanced research and manufacturing tools will help propel the science forward, 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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The Promise of the Pipeline

“Because of the cancer treatment I’m receiving today, I’ve been able to experience many great days of life.”

-Matt Ellefson, advanced non-small cell lung cancer survivor and founder of SURVIVEit™





The Promise of the Pipeline

Our growing knowledge of the biologic basis of disease is yielding unprecedented promise in the biopharmaceutical pipeline. Today, researchers are employing scientific learnings and new technologies to target the most complex and challenging diseases. Recent medical advances have transformed the lives of many patients, and many more exciting advances are on the horizon. Potential medicines in clinical development today are poised to deliver on the promise of innovation and to meet the needs of patients struggling with a broad range of diseases and conditions.

Currently, there are about 7,000 medicines in development around the world, many of which offer the potential to provide new treatments or even cures for diseases or conditions for which there are currently few or no treatment options (see Figure 17).¹ In fact, one study found that 70% of medicines across the biopharmaceutical pipeline are potential first-in-class drugs, meaning they are a unique pharmacologic class using a mechanism of action distinct from any other marketed drugs.² For patients who have failed to respond to existing therapies and those for whom no existing

FIGURE 17: More than 7,000 Medicines in Development Globally

Biopharmaceutical researchers are working on new medicines for many diseases.

Selected Diseases	Medicines in Development*
Cancers	1,813
Cardiovascular disorders	599
Diabetes	475
HIV/AIDS	159
Immunological disorders	1,120
Infectious diseases	1,256
Mental health disorders	511
Neurological disorders	1,329

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

Source: Adis R&D Insight Database. Accessed February 2015.

treatment options are available, these potential new medicines offer the hope of a transformative or even life-saving result.

The promise of the pipeline depends on the dedication and hard work of scientists and a range of STEM (science, technology, engineering, and math) and non-STEM employees throughout innovative biopharmaceutical companies.

EXAMINING THE PIPELINE

Today’s scientific opportunities offer enormous potential for patients and society. Scientists continue

to delve deeper into the biologic basis of disease and are gaining a better understanding of genomics, proteomics, and other areas yielding promise for the development of medicines. The following are just a few examples of the many exciting approaches that researchers are exploring.

Cancer

Expanding knowledge of the mechanisms underlying cancer has uncovered the immense complexity of the many forms of this disease but has also revealed new possible ways to attack cancer cells. Many researchers are now focusing on how to better categorize different cancers. Historically, a particular type of cancer was identified based on the tissue in which the cancer cells began to develop; however, researchers today are increasingly able to define different types of cancer based on biologic characteristics. These advances are enabling researchers to better combat cancer by targeting the root causes of the disease.³

In the United States, approximately 1,200 cancer medicines and vaccines are either in clinical trials or in review by the US Food and Drug Administration (FDA).⁴ Cancer research has transformed dramatically over the past several decades, with advances in biology informing improved screening and the development of new personalized medicines. Through personalized medicines, specific pathways that cause cancer are targeted, potentially reducing patient side effects and improving quality of life. Other

"Scientifically, we have never been in a better position to advance cancer treatment. . . . We now understand many of the cellular pathways that can lead to cancer. We have learned how to develop drugs that block these pathways."

– RICHARD L. SCHILSKY, MD, PROFESSOR, UNIVERSITY OF CHICAGO; PAST PRESIDENT, AMERICAN SOCIETY OF CLINICAL ONCOLOGY; PROFESSOR EMERITUS, UNIVERSITY OF CHICAGO⁵



novel approaches include efforts to harness a patient's own immune system to combat cancer (see sidebar: Highlighting Immunotherapy in Cancer Care.) Examples of the many promising approaches in the oncology pipeline include:

- **Antibody drug conjugates:** Antibodies are immune system proteins that recognize specific targets for the immune system to attack, such as viruses, bacteria, or tumor cells. Antibody drug conjugates are particularly complex as they require the combination of antibody, linker, and a drug. The antibody targets and binds to particular proteins or receptors on the surface of a cancer cell and the chemotherapy is then directly delivered to the cancer cell. This delivery system ensures that the chemotherapy is only released when it reaches specific cancer cells, leaving

healthy cells unharmed.⁶ Two dozen medicines are in clinical trials for solid tumors and blood cancer, and 3 medicines that use this approach have already been approved.^{7,8}

- **Therapeutic cancer vaccines:** Unlike vaccines that prevent the development of disease, therapeutic vaccines are intended to treat an existing cancer by strengthening the body's natural defenses to fight cancer. In addition to the approval of a therapeutic vaccine in 2010 for the treatment of prostate cancer, there are currently cancer vaccines targeting 14 different types of cancer in clinical trials.⁹ One of the key challenges in the development of therapeutic vaccines has been finding ways to "teach" the immune system how to recognize and destroy "cancer" cells. The advances in therapeutic

Highlighting Immunotherapy in Cancer Care^{10,11}

For more than a century, researchers have hoped to use the immune system to fight cancer. Cancer cells often have sophisticated ways of evading the immune system by blending in with other cells or inhibiting immune response. The goal of immunotherapy research has been to enable the immune system to recognize, fight, destroy, and remember cancer cells in the same way that it does infectious agents. For many decades the research was plagued with setbacks, but in recent years the approach has become a reality.

A particularly exciting example of this progress is a new type of immunotherapy called "checkpoint inhibitors," first approved in 2011, with 2 more approved in 2014. These medicines work by blocking the action of certain proteins that have been found to inhibit the immune system from doing its job, thereby allowing immune cells to find and destroy cancer cells. This novel approach is allowing patients to live significantly longer than was previously possible, and the results are more profound when these medicines are combined with standard anticancer therapies. What is perhaps even more remarkable is that researchers are now hypothesizing that combining immunotherapy to boost the immune system, along with cancer-killing radiation or chemotherapy, will help to create immune cells that remain in the body over the long-term and serve to kill any returning cancer cells long after the initial treatment is completed.

The 3 checkpoint inhibitors that have been approved are producing tremendous results for patients with advanced melanoma (see Chapter 1). Researchers are now exploring these medicines against a broad range of cancers for which there is growing evidence of the effectiveness of these therapies, including lung, kidney, ovarian, and head and neck cancer. In fact, "some analysts predict that in the next ten years, immunotherapies will be used for 60% of people with advanced cancer."¹²

cancer vaccines have inspired research on how vaccines might be tailored for other diseases, including HIV and hepatitis.

Cardiovascular disease

Incredible progress has been made over the past 50 years to treat cardiovascular disease, thanks in large part to innovative medicines; however, the disease still remains a key public health challenge with substantial unmet need. Currently, more than 250 medicines are in development to treat cardiovascular disease.¹³ Many of these potential medicines use cutting-edge technologies and new scientific approaches, such as a gene therapy that uses a patient's own cells to treat heart failure, a medicine that blocks the transfer of good cholesterol (HDL) to bad cholesterol (LDL), and a genetically engineered medicine that dissolves clots to treat stroke (see more at: <http://www.phrma.org/more-than-200-innovative-medicines-development-heart-disease-stroke>). Additional examples include:

- **PCSK9 inhibitors:** Elevated levels of LDL cholesterol—sometimes known as “bad” cholesterol because it often collects in arteries—is a known risk factor for heart attack and stroke.¹⁴ Statin drugs are an important and effective tool for reducing LDL levels, but there are some patients who cannot obtain a sufficient reduction in cholesterol levels on these medicines. A new class of medicines in clinical development sharply lowers LDL levels in a completely new way. These medicines mimic a natural mutation that some people have in the PCSK9 gene that regulates LDL receptors in the body and reduces the risk of coronary heart disease.¹⁵ The medicines are self-injected once or twice a month and have been found to reduce LDL by as much as 75% when taken with a statin.¹⁶ Currently, there are several PCSK9 inhibitors in various stages of clinical development offering to fill a significant unmet need for patients with insufficient control of LDL levels.

I'm Not Average: Matt Ellefson



When Matt Ellefson developed a cough, he didn't think much of it. He assumed it was caused by the cold winter air, but as the weeks passed his cough lingered. Then he began coughing up blood. Within hours of going to the emergency room, Matt was diagnosed with advanced non-small cell lung cancer, and the prognosis was not good. With treatment, he faced a 5-year survival rate of less than 5%. His diagnosis in December 2009 was a complete shock. He was a nonsmoker who lived a healthy and fit lifestyle. Soon after being diagnosed, Matt enrolled in an aggressive clinical trial. After 5 months, his cancer went into remission. One year later, his cancer resurfaced and it had spread. Treatment options were limited. While waiting for his doctor to conduct follow-up testing, he learned about a targeted gene therapy that had been recently approved. However, the odds were still against him. Patients typically developed resistance to the medicine in 8 months. Three years later Matt is living an active, happy life, with his disease under control thanks to advances and innovations in cancer medicines. He runs marathons, participates in cycling competitions, and explores the world with his family. If he does become resistant to his current medicine, there are 3 new drugs that have been approved, so now he has other options. He has hope because of the progress made in cancer research.

For more on Matt, see: <http://www.phrma.org/cancer#>.

- **Angiotensin-receptor neprilysin inhibitor (ARNI):** Heart failure, which causes 55,000 deaths annually, is the most common diagnosis in Medicare patients. Fewer than 50% of patients are alive 5 years after a diagnosis of heart failure, and that number dips to 25% at 10 years after diagnosis. Although previous therapies in this area were able to decrease the workload of the heart and cut the risk of dying from heart failure in half, a number of drugs in development offer the potential to dramatically improve outcomes for heart failure patients.¹⁷ An international clinical trial involving more than 8,000 patients in 47 countries found that an investigational medicine in late stages of development reduced death or hospitalization rates due to heart failure by 20% compared with the current standard of care.¹⁸

HIV/AIDS

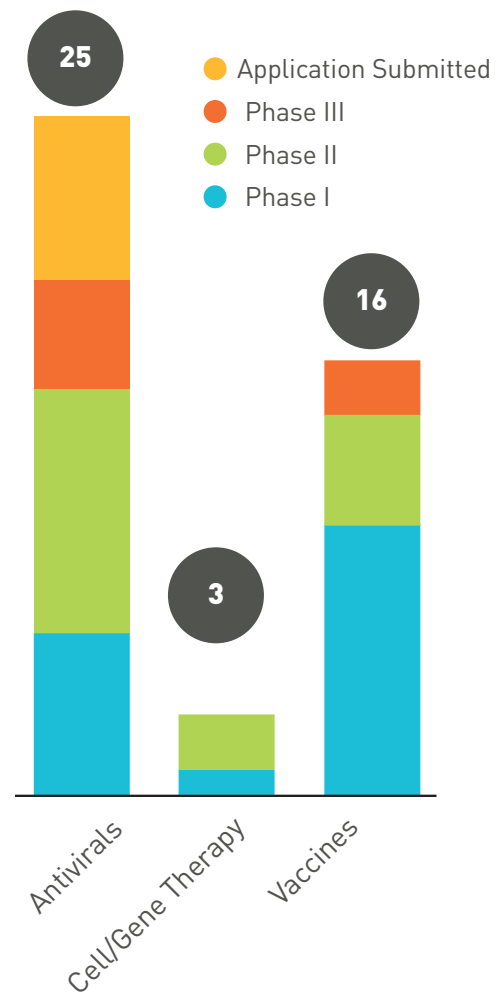
Since the early 1980s, when HIV was discovered, more than 2 dozen medicines have been approved for the treatment of HIV/AIDS.¹⁹ After the introduction of antiretroviral therapies in 1995, the HIV/AIDS-related death rate fell by nearly 85%.²⁰ Although medicines have made HIV infection a manageable chronic disease and helped to prolong the lives of patients, opportunities for even greater progress remain. Today, biopharmaceutical research companies have more than 44 medicines and vaccines in the pipeline to treat HIV infection (see Figure 18).²¹

- **Attachment inhibitor:** This investigational medicine has a potentially unique mechanism of action. The drug is intended to protect cells from HIV infection by preventing the virus from attaching to new cells and breaking through the cell membrane, which is the earliest stage of the viral lifecycle. One attachment inhibitor in development attaches to gp120, a part of the virus, and inhibits the entry of the virus into cells by

blocking the interaction between gp120 and the cell receptors. This could provide an important new treatment option, particularly for patients with resistance to current medications.

- **Gene modification:** CCR5 is a co-receptor on the surface of cells that allows HIV to enter and infect T cells. Without this receptor on the cell surface, it is more difficult for HIV to infect the cells. One gene therapy currently in clinical trials is designed to modify the DNA sequence encoding CCR5 to make the patient's own cells

FIGURE 18: 44 Medicines and Vaccines in Development for HIV/AIDS



Source: Pharmaceutical Research and Manufacturers of America. Medicines in development: HIV/AIDS. Washington, DC: PhRMA; 2014. <http://www.phrma.org/sites/default/files/pdf/2014-meds-in-dev-hiv-aids.pdf>. Accessed December 2014.

resistant to infection by HIV. The patient's cells are extracted, modified, and then reinserted into the patient. The goal of this therapy is to provide the patient with a population of cells that can fight HIV as well as the opportunistic infections from which patients with HIV often suffer.

- **Inducing T cell responses:** A therapeutic vaccine in development is designed to induce CD4+ T cell responses in HIV-infected people. CD4+ T cells play a key role in immune protection against viral infections. Deficits in CD4+ T cells are associated with virus reactivation, vulnerability to opportunistic infections, and poor vaccine efficacy. Therapeutic vaccines offer to strengthen

the body's natural anti-HIV immune response so that HIV-infected patients may no longer need to rely on antiviral therapies for the remainder of their lives.

The cutting-edge science and technologies being explored in today's biopharmaceutical pipeline not only represent unprecedented promise but many years of complex scientific work and the dedication of researchers to transform some of our most challenging diseases and conditions. Medicines in development targeting cancer, cardiovascular disease, and HIV/AIDS provide just a few exciting examples of the opportunities that await patients.

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Looking Ahead



Looking Ahead

Biopharmaceutical innovation has improved the lives of millions of people and is a source of hope for millions more. The challenges in developing life-saving and life-enhancing new medicines and bringing them to patients in an efficient and timely manner are significant, and addressing those challenges will require partnerships among all members of the biomedical innovation ecosystem, including the engagement and involvement of patients.

While there are substantial scientific opportunities, the nation's innovative biopharmaceutical companies face a range of challenges.

Researchers are tackling increasingly complex diseases, resulting in greater scientific setbacks as new approaches to target disease are explored. Regulatory hurdles are higher, and clinical trials are longer and more complex. These and other factors are contributing to increasing costs, time, and uncertainty related to drug development. In addition, coverage and payment policies must promote access for patients and recognize the role and value of prescription medicines in improving patient outcomes and reducing health care costs. Increasingly, public and private payers are placing coverage restrictions on new medicines and increasing cost sharing for patients, which impacts patient access to new medicines. At the same time, the percentage of generic prescriptions has never been greater, at 88%. As the US Food

and Drug Administration approves treatment advances, the health care delivery system needs to make them available to patients in a timely manner, promote informed choice from the range of treatment options, and provide appropriate incentives for continued progress against the most costly and challenging diseases. It is imperative that we maintain intellectual property protections that recognize the substantial time, financial investment, and intellectual capital involved in bringing medicines to patients.

Sustaining productivity in medical research is critical for the health of the economy as well as US competitiveness in the global marketplace. Biopharmaceutical companies are taking a variety of approaches to adapt to the changing scientific and business environments. For example, they are entering into innovative partnerships with academic and government researchers, and they continue to explore new approaches to improving the efficiency and effectiveness of the research and development and manufacturing processes to accelerate drug development.

Continued scientific and treatment progress is not guaranteed, but with thoughtful public policies and the commitment of the biopharmaceutical industry, patients will have new medicines to help them lead longer, healthier lives.

Appendix





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 \$51.2 billion in 2014 alone. This investment also helps drive the industry's significant contributions to the US 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, DC, 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 <http://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' US 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 United States. It 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. It 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 US-owned PhRMA member companies and R&D conducted abroad by the US divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies is excluded.

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.



List of Tables: Detailed Results from the PhRMA Annual Membership Survey

R&D, PhRMA Member Companies

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Table 3: Domestic R&D and R&D Abroad: 2013 **Available at <http://www.PhrMA.org>**

Table 4: R&D by Function: 2013 **Available at <http://www.PhrMA.org>**

Table 5: R&D by Geographic Area: 2013 **Available at <http://www.PhrMA.org>**

Sales, PhRMA Member Companies

Table 6: Domestic Sales and Sales Abroad: 1980-2014 **Available at <http://www.PhrMA.org>**

Table 7: Sales by Geographic Area: 2013 **Available at <http://www.PhrMA.org>**

TABLE 1**Domestic R&D and R&D Abroad, PhRMA Member Companies: 1980–2014**

(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2014**	\$41,104.4	1.7%	\$10,121.8	-9.8%	\$51,223.2	-0.8%
2013	\$40,396.0	7.7%	11,217.6	-7.1%	\$51,613.6	4.1%
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	29,722.7	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		10.5%		10.6%		10.5%

*R&D Abroad includes expenditures outside the United States by US-owned PhRMA member companies and R&D conducted abroad by the US 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, 2015.

TABLE 2**R&D as a Percentage of Sales, PhRMA Member Companies: 1980–2014**

(dollar figures in millions)

Year	Domestic R&D as a Percentage of Domestic Sales	Total R&D as a Percentage of Total Sales
2014*	23.4%	17.9%
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

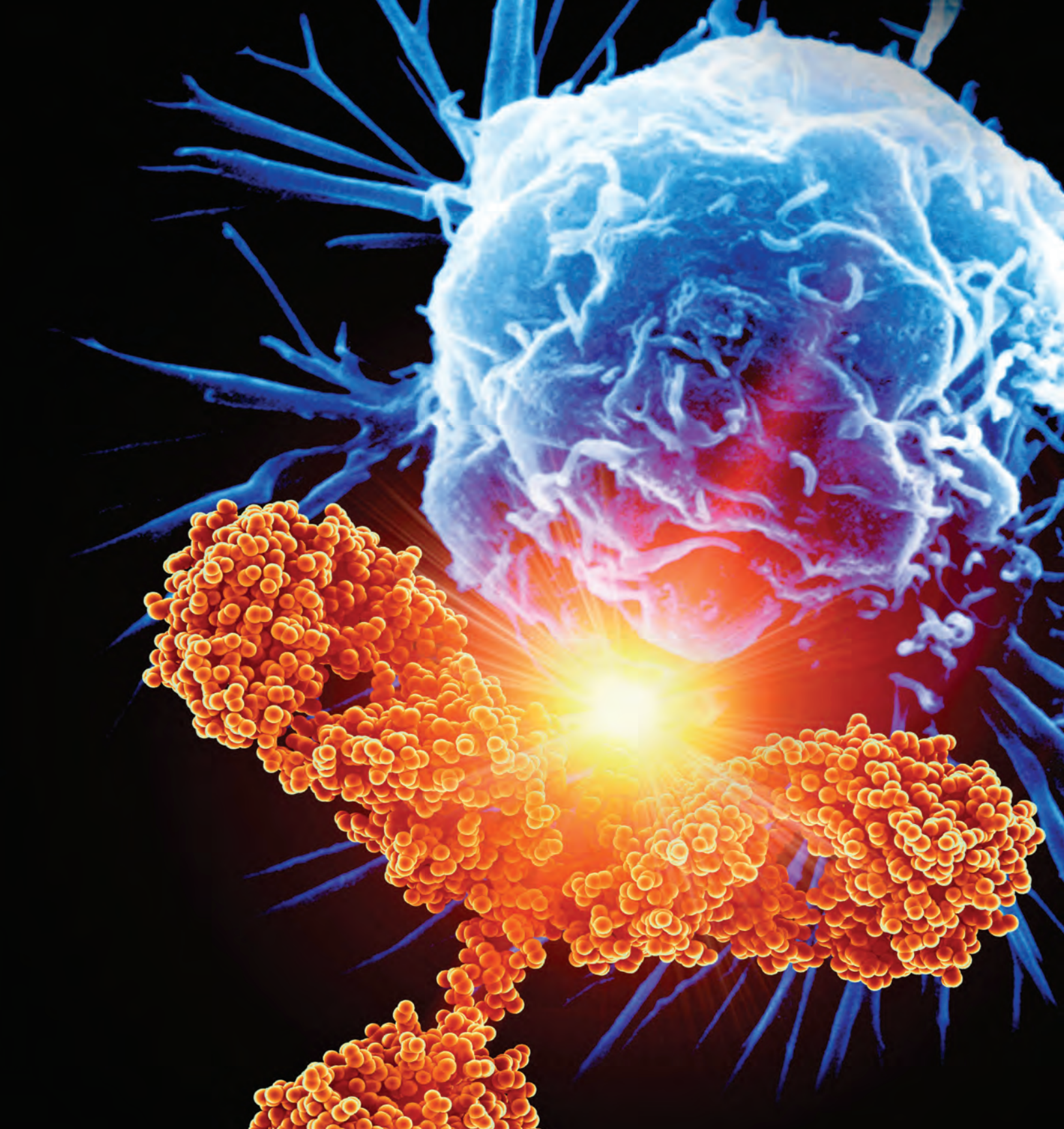
*Estimated.

**Revised in 2007 to reflect updated data.

Source: Pharmaceutical Research and Manufacturers of America, PhRMA Annual Membership Survey, 2015.

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