MEDICINES IN DEVELOPMENT

Heart Disease and Stroke

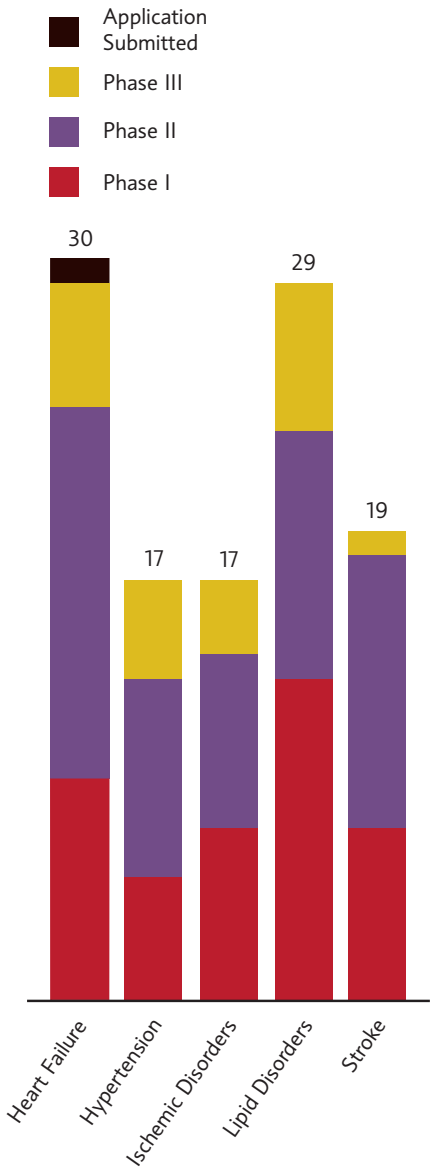
A Report on Cardiovascular Disease

PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

2013 REPORT

OVERVIEW

Medicines in Development For Heart Disease and Stroke



More Than 200 Medicines in Development for Cardiovascular Disease—Leading Cause of Death in the United States

Biopharmaceutical research companies are developing 215 medicines for two of the leading causes of death in Americans—heart disease and stroke. These therapies promise to build on the progress made by existing treatments, which have helped cut deaths from heart disease by a third between 2001 and 2011, according to the Centers for Disease Control and Prevention (CDC).

According to the CDC's National Center for Health Statistics, heart disease has topped the list of deadly diseases every year since 1921. Thanks in large part to new drug treatments, death rates from heart disease and stroke are falling. In 2008, stroke dropped to the fourth leading cause of death after being the third for more than 50 years. Much of the progress is due to the development of effective medicines to control both blood pressure and cholesterol, according to the National Heart, Lung and Blood Institute (NHLBI).

Despite this progress, heart disease and stroke persist as key public health challenges. According to the American Heart Association, every 39 seconds an American dies from cardiovascular disease, and more than 83 million Americans have at least one form of the disease. Many people who survive heart attacks still develop heart failure, a chronic disease that affects 5.7 million Americans. These diseases cost society more than $312 billion a year.

The medicines in development include: 30 for heart failure, 29 for lipid disorders (such as high cholesterol), 19 for stroke and 17 each for high blood pressure and ischemic disorders. Many of the 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 (HDL) cholesterol to bad (LDL).
- A genetically-engineered medicine that dissolves clots to treat stroke.

These new medicines—all in either human clinical trials or awaiting review by the Food and Drug Administration—promise to continue the already remarkable progress against heart disease and stroke and to raise the quality of life for patients suffering from these diseases.

This overview highlights some of the innovative medicines listed in the *report*, recent scientific advances in treating cardiovascular disease, and the value of medicines for patients and our healthcare system.

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Innovative Medicines in the Pipeline

Long-term Treatment for Chronic Heart Disease—Atherosclerosis, an inflammatory disease characterized by the building-up of plaque within the walls of the arteries, is the underlying cause of most heart attacks and strokes. One novel medicine is a selective inhibitor of an enzyme found in blood and atherosclerotic plaque, Lp-PLA2. Elevated levels of the enzyme are involved in the development and progression of atherosclerosis.

Stem Cell Therapy—A potential treatment for ischemic heart failure uses adult stem cells to target damaged tissue in the heart. The cells are inserted using an investigational catheter that enables local delivery of cell and gene therapies.

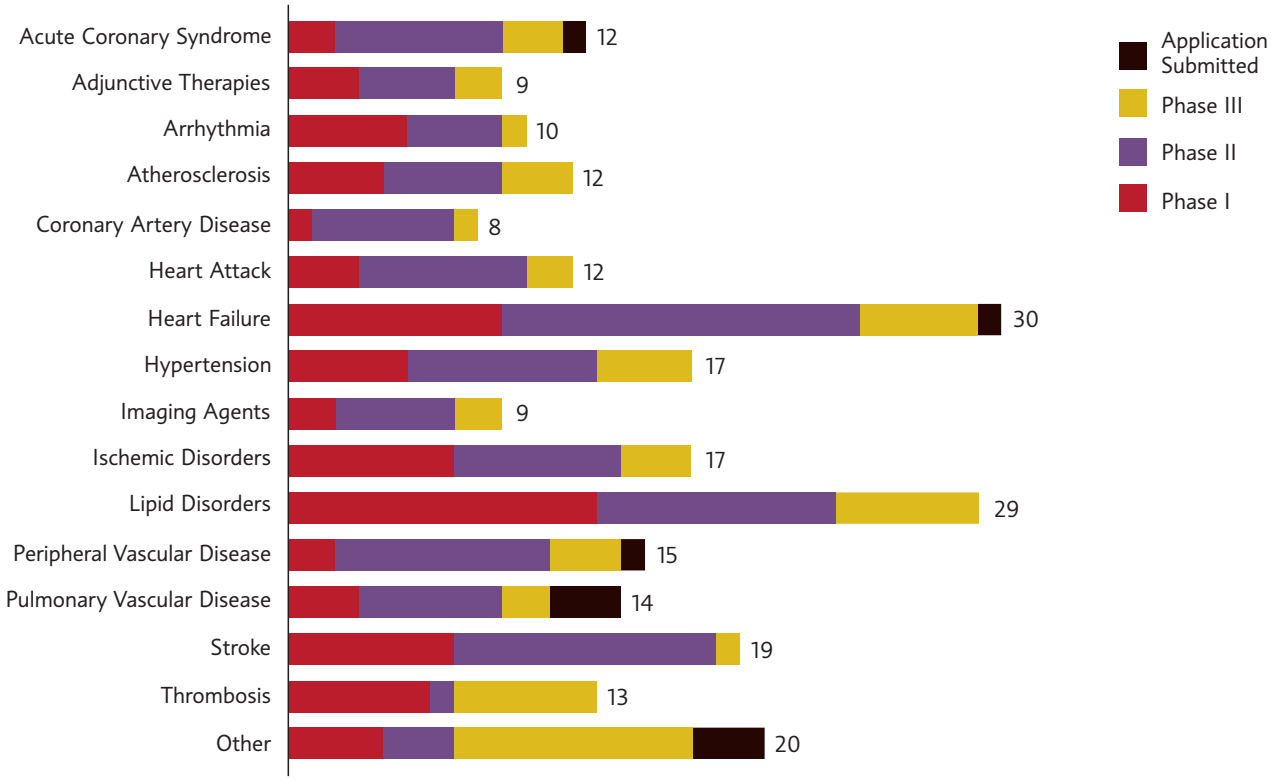
Lowering Blood Lipids—A potential medicine in development is a selective inhibitor of a protein that plays a major role in transferring high-density cholesterol lipoprotein (HDL, or good cholesterol) to low-density lipoprotein cholesterol (LDL, or bad cholesterol). High HDL levels can help decrease the risk of cardiovascular disease. The CDC estimates that a 10 percent decrease in total cholesterol levels population-wide could result in a 30 percent reduction in the incidence of coronary artery disease.

Gene Therapy for Heart Failure—A genetically-targeted enzyme replacement therapy for congestive heart failure is being tested to restore levels of a specific gene to promote a failing heart to pump better and minimize the severity of heart failure. In all forms of late-stage heart failure, levels of the gene decline resulting in deficient heart function.

Recombinant Fibrin for Stroke—A genetically-engineered clot-dissolving protein derived from the saliva of the vampire bat, *Desmodus rotundus*, is being developed for the treatment of ischemic stroke. The protein—fibrin-specific plasminogen activator—is structurally similar to human tissue-type plasminogen activator (tPA)—a medicine approved to treat stroke. TPA treatment must take place within three hours from when a stroke takes place. About 80 percent of strokes are not diagnosed until after three hours. The potential medicine is being tested to lengthen the treatment window up to nine hours.

Medicines in Development for Cardiovascular Disease By Type and Phase of Development

Some medicines are listed in more than one category



Treatment Advances—Lives Saved, Costs Reduced, Improved Treatments

In the late 1950s, cardiovascular deaths were on the rise and doctors had few tools to treat their patients. Today, doctors have many new ways to treat cardiovascular disease. These new tools have helped reduce the number of deaths since the 1960s.

Advances in medicine helped cut deaths from heart disease by 30 percent between 2001 and 2011, according to the CDC. The CDC said the factors contributing to the ongoing decline are better control of risk factors, early detection, and better treatment and care, including new drugs and expanded use of existing drugs.

Progress against cardiovascular disease has had a profound impact on helping to control health care costs. According to a study published in *Health Affairs*, every additional dollar spent on medicines for adherent patients with congestive heart failure, high blood pressure, diabetes and high cholesterol generated $3 to $10 dollars in savings on emergency room visits and inpatient hospitalizations.

Atrial Fibrillation and Stroke Risk

Patients with atrial fibrillation (AFib)—the most common form of arrhythmia—are five times more at risk for a stroke than people without AFib. For more than 50 years, patients with AFib have relied on the anticoagulant warfarin to thin their blood and reduce their risk of a stroke. The use of warfarin requires frequent blood monitoring, dosage adjustments and food restrictions. Two new medicines approved for the reduction of the risk of stroke and blood clots in patients with AFib, do not require frequent blood monitoring, dosage adjustments or food restrictions. While the new drugs use different mechanisms of action—both have an easy treatment regimen—with one or two dosages daily.

Lipid Disorders—High Cholesterol

The CDC reported in 2007 that U.S. adults reached an average cholesterol level in the ideal range (below 200) for the first time in 50 years. Authors of the report attribute the drop to the increased use of cholesterol-lowering medicines in the over-60 population. Also, research has shown that statin therapy reduces low-density lipoprotein cholesterol levels by

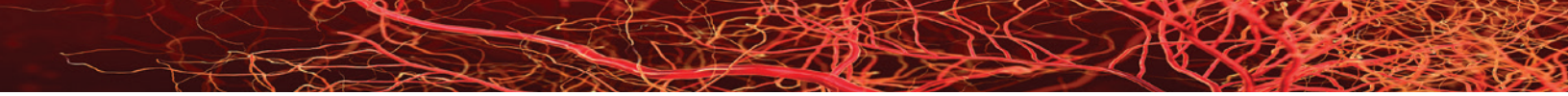
FRAMINGHAM HEART STUDY

In 1961, a huge milestone in cardiovascular research was achieved: data from the Framingham Heart Study, a joint project between the National Heart, Lung and Blood Institute and Boston University, definitively revealed a link between high blood cholesterol levels and heart disease. These findings helped focus research that led to new medicines.

Following subsequent public/private research and published studies, the development and launch of the first statin in the U.S. occurred in 1987 resulting in better control of cholesterol levels among U.S. adults, and falling death rates from cardiovascular disease.

Death rates from cardiovascular disease declined more than 30% from 1998 to 2008, the American Heart Association recently reported. A 2007 study in JAMA *showed that between 1999 and 2005, death rates for heart failure and heart attack decreased by nearly half—thanks to greater use of cholesterol medicines, blood thinners and angioplasty.*

While there were many research milestones that led to a better understanding of the role of cholesterol and the eventual discovery of statins, the Framingham Heart Study's pioneering work was a pivotal moment.



an average of 19 percent. Over one year, this reduction in bad cholesterol was associated with roughly 40,000 fewer deaths, 60,000 fewer hospitalizations for heart attacks, and 22,000 fewer hospitalizations for strokes in the U.S. From an economic perspective, those prevented hospitalizations translated into gross savings of nearly $5 billion.

Congestive Heart Failure

Patients with CHF are among the most expensive to treat in the entire health care system. Several studies have found key savings: hospitalizations, surgeries, and ER use are all key drivers of the high costs of CHF, with hospitalizations for a typical CHF patient costing up to $21,868 (in 2010 USD). Consistent use of medicines, however, which might cost $3,468 per year (in 2010 USD), can prevent complications and slow the progression of the disease. Patients who take their medications as prescribed can reduce their healthcare costs by up to $9,161 (in 2010 USD) compared to patients who do not take their medication as recommended by their doctor. Certain medications have been shown to improve symptoms and decrease hospital readmission rates. In addition, if used early, these medicines also play an important role in preventing CHF from developing in the first place. Medication therapy leading to well controlled hypertension, for example, can reduce the risk of CHF by 40 percent to 50 percent, potentially leading to even greater savings.

Hypertension—High Blood Pressure

According to a study published in *Health Affairs,* treating patients with high blood pressure in accordance with clinical guidelines would result in fewer strokes and heart attacks, preventing up to 89,000 deaths and 420,000 hospitalizations annually and saving $15.6 billion a year.

Growing New Heart Muscle

Two studies published in *Nature*, showed that a new approach called myogenesis (growing new heart muscle) shows promise in replacing damaged or lost heart muscle after a heart attack. These studies revealed that by reprogramming non-beating heart muscle cells (non-cardiomyocytes) into beating heart muscle cells (cardiomyocytes) could replace damaged heart cells and repair scarring.

Results of two human trials using different types of cardiac cells showed that cells from heart biopsies could be purified and replaced into the patient's own heart, improving heart function and reducing scarring. The studies were published in *The Lancet*.

CARDIOVASCULAR DISEASE RISK FACTORS

Studies published last year, found lifestyle factors have a huge impact on lowering the risk of heart disease and stroke, and in helping people extend their lives. People with "ideal cardiovascular health," measured by ***health behaviors*** *(not smoking, regular exercise and healthy diet) and* ***health factors*** *(ideal body mass index, cholesterol, blood pressure and blood glucose) had the lowest risk.*

Even with adequate cardiac care, prevention is still the most important factor in reducing cardiovascular disease. Major risk factors include:

- *Family history and genetics*
- *Smoking*
- *High Blood Cholesterol and Other Lipids*
- *Physical Inactivity*
- *Overweight/Obesity*
- *Diabetes*

Medicare Part D Providing Economic Value and Improved Adherence

The American Heart Association estimates that heart failure (congestive heart failure) costs will double in the next 20 years as prevalence rates rise and the U.S. population ages. By 2030, direct and indirect costs to treat heart failure could more than double from $31 billion in 2012 to $70 billion in 2030. And, the number of people with heart failure could increase by 46 percent from 5 million in 2012 to 8 million in 2030.

As the prevalence and cost of heart failure is rising, a new study supported by PhRMA and published in *The American Journal of Managed Care*, found that improved adherence to medication following the expansion of drug coverage under Medicare Part D, led to nearly $2.6 billion in savings in medical expenditures annually among beneficiaries with congestive heart failure (CHF). Despite the improvements in adherence following Part D, medication use remains sub-optimal. The study also found that improving adherence to recommended levels could save Medicare another $1.9 billion annually, leading to $22.4 billion over 10 years.

A recent report by the Congressional Budget Office (CBO) explicitly recognized the beneficial impact prescription medicines have on reducing other health care spending. Specifically, the CBO changed its scoring methodology to reflect savings in medical spending associated with policies that increased use of medicines in Medicare. Savings estimates may even be conservative and underestimate the magnitude of effect for many beneficiaries with chronic conditions, for whom cost offsets are likely to be greater and more sensitive to drug use than the broader population.

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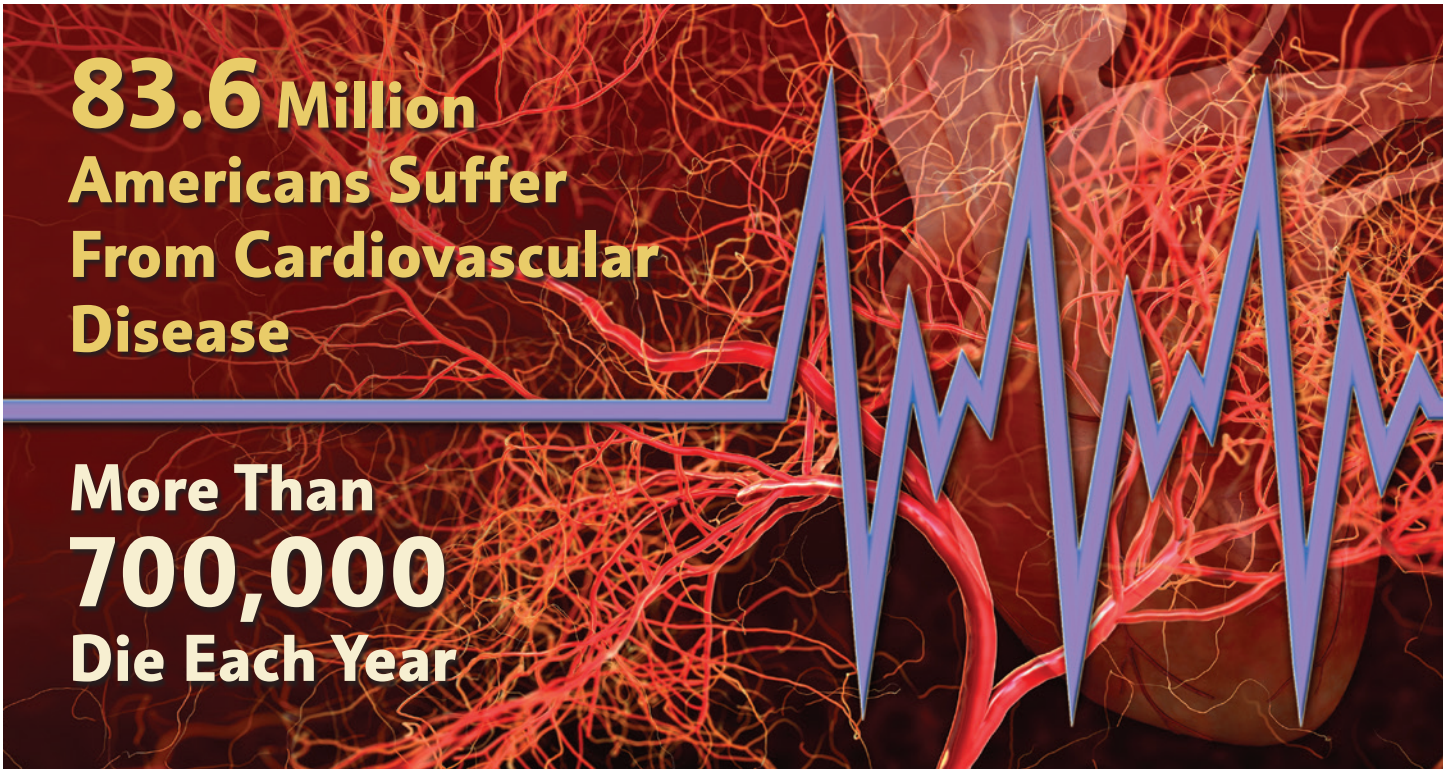
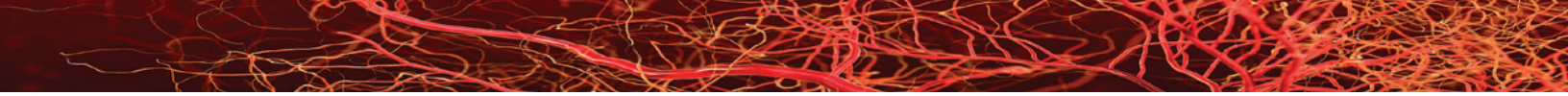




Facts About Heart Disease and Stroke in the United States

Cardiovascular Diseases (CVD)

- Approximately 83.6 million American adults—greater than one in three—have one or more types of **CVD**. Of that total, 42.2 million are estimated to be age 60 and older.[1]
- On average, 2,150 Americans die of **CVD** each day, about one death every 40 seconds. CVD claims more lives each year than cancer and chronic lower respiratory diseases combined.[1]
- In 2010, **CVD** accounted for 727,165 of all 2,468,435 deaths from all causes—29.5 percent.[2]
- The estimated direct and indirect costs of **CVD** were $312.6 billion in 2009.[1]

Major Cardiovascular Diseases[1]

Condition	Prevalence	Deaths
Angina Pectoris	7.8 million	n/a
Atrial Fibrillation	2.7 million – 6.1 million	15,434
Coronary Heart Disease	15.4 million	386,324
Heart Attack (Myocardial Infarction)	7.6 million	125,464
Heart Failure	5.1 million	56,410
Hypertension	77.9 million	61,672
Stroke	6.8 million	128,842

Atherosclerosis[2]

- **Atherosclerosis** of the coronary arteries is the leading cause of death for both men and women in the United States. In men, the risk increases after age 45; in women, the risk increases after age 55.
- In 2009, **atherosclerosis** accounted for 7,377 deaths.

Coronary Heart Disease (CHD)[1]

- Each year, an estimated 915,000 new and recurrent cases of **CHD** and 715,000 new and recurrent cases of **myocardial infraction** occur.
- There are 500,000 new cases of **stable angina** each year.

Lipid Disorders[1]

- The 2010 estimated prevalence of total **cholesterol** in adults age 20 and older at or above 200 mg/dL was 98.9 million.

Stroke[1]

- On average, someone in this country has a **stroke** every 40 seconds. An estimated 6.8 million Americans have suffered a stroke, and each year about 795,000 people experience a new or recurrent stroke.
- On average, someone dies from a stroke every four minutes in the United States.
- Eighty-seven percent of all strokes are ischemic, 10 percent are intracerebral and 3 percent are subarachnoid hemorrhage.

Thrombosis[1]

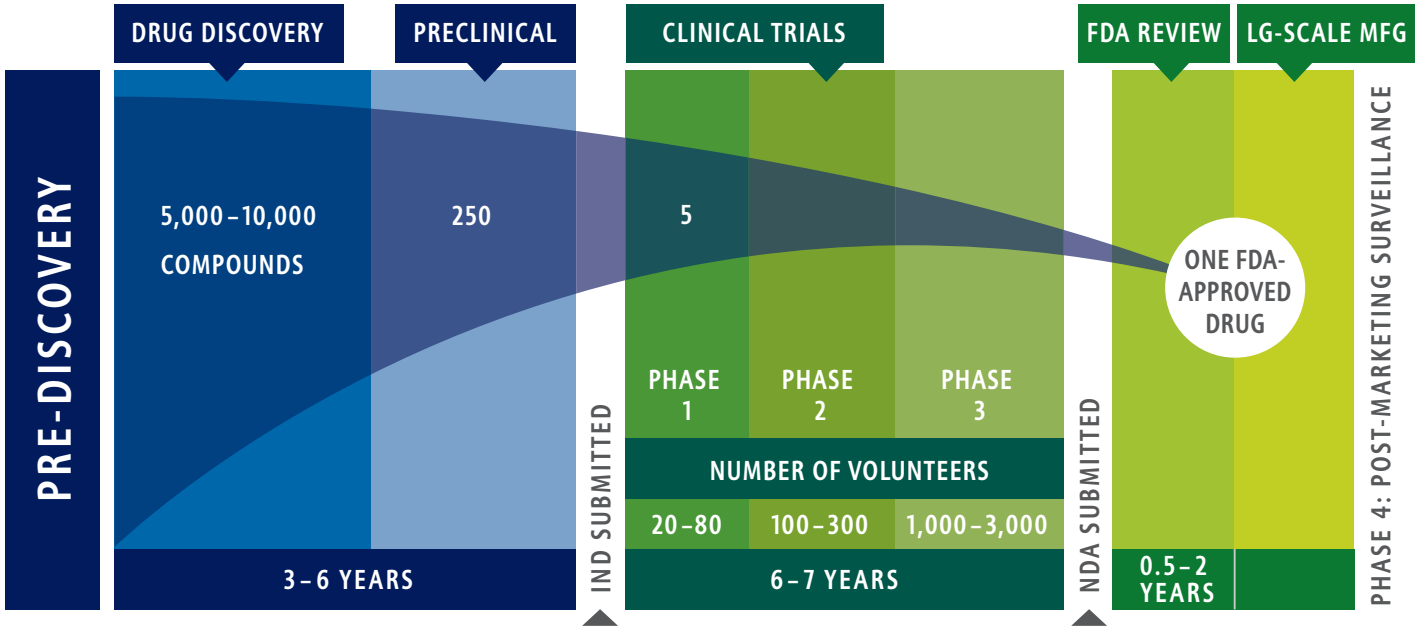
- **Pulmonary embolism (PE)** accounted for 7,040 deaths in 2009 in the United States and accounted for 186,000 hospital discharges that same year.
- In 2009, 2,452 Americans died from **deep vein thrombosis (DVT)**.

Sources:

1. *Heart Disease and Stroke Statistics—2010 Update*, American Heart Association, *www.heart.org*
2. National Heart, Lung and Blood Institute, *www.nhlbi.nih.gov*

Developing a new medicine takes an average of 10-15 years;
For every 5,000-10,000 compounds in the pipeline, only 1 is approved.

Drug Discovery and Development: A LONG, RISKY ROAD



The Drug Development and Approval Process

The U.S. system of new drug approvals is perhaps the most rigorous in the world.

It takes 10-15 years, on average, for an experimental drug to travel from lab to U.S. patients, according to the Tufts Center for the Study of Drug Development. Only five in 5,000 compounds that enter preclinical testing make it to human testing. And only one of those five is approved for sale.

On average, it costs a company $1.2 billion, including the cost of failures, to get one new medicine from the laboratory to U.S. patients, according to a recent study by the Tufts Center for the Study of Drug Development.

Once a new compound has been identified in the laboratory, medicines are usually developed as follows:

Preclinical Testing. A pharmaceutical company conducts laboratory and animal studies to show biological activity of the compound against the targeted disease, and the compound is evaluated for safety.

Investigational New Drug Application (IND). After completing preclinical testing, a company files an IND with the U.S. Food and Drug Administration (FDA) to begin to test the drug in people. The IND shows results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. All clinical trials must be reviewed and approved by the Institutional Review Board (IRB) where the trials will be conducted. Progress reports on clinical trials must be submitted at least annually to FDA and the IRB.

Clinical Trials, Phase I—Researchers test the drug in a small group of people, usually between 20 and 80 healthy adult volunteers, to evaluate its initial safety and tolerability profile, determine a safe dosage range, and identify potential side effects.

Clinical Trials, Phase II—The drug is given to volunteer patients, usually between 100 and 300, to see if it is effective, identify an optimal dose, and to further evaluate its short-term safety.

Clinical Trials, Phase III—The drug is given to a larger, more diverse patient population, often involving between 1,000 and 3,000 patients (but sometime many more thousands), to generate statistically significant evidence to confirm its safety and effectiveness. They are the longest studies, and usually take place in multiple sites around the world.

New Drug Application (NDA)/Biologic License Application (BLA). Following the completion of all three phases of clinical trials, a company analyzes all of the data and files an NDA or BLA with FDA if the data successfully demonstrate both safety and effectiveness. The applications contain all of the scientific information that the company has gathered. Applications typically run 100,000 pages or more.

Approval. Once FDA approves an NDA or BLA, the new medicine becomes available for physicians to prescribe. A company must continue to submit periodic reports to FDA, including any cases of adverse reactions and appropriate quality-control records. For some medicines, FDA requires additional trials (Phase IV) to evaluate long-term effects.

Discovering and developing safe and effective new medicines is a long, difficult, and expensive process. PhRMA member companies invested an estimated $48.5 billion in research and development in 2012.

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