Medicines in Development

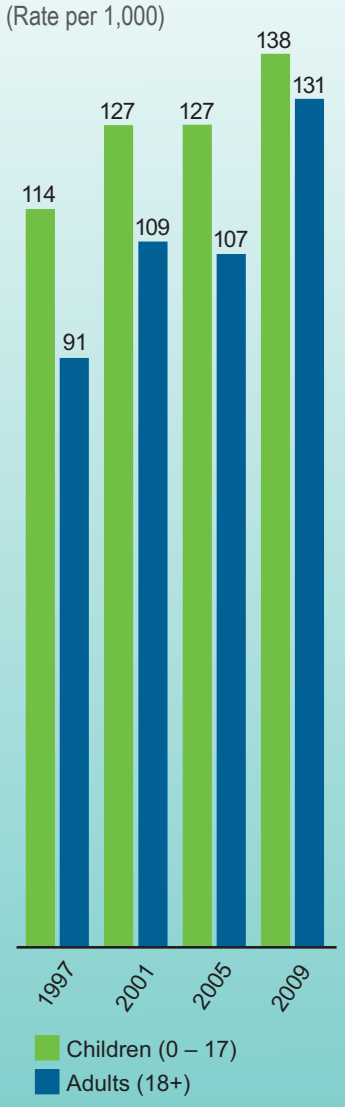
ASTHMA

PRESENTED BY AMERICA'S BIOPHARMACEUTICAL RESEARCH COMPANIES

2012 REPORT

Biopharmaceutical Research Companies Are Studying More Than 70 Medicines for Asthma

Asthma Prevalence in the United States



Source: U.S. Centers for Disease Control and Prevention, National Center for Health Statistics.

24 million American adults and children suffer from **asthma;** each day **40,000** Americans miss school or work due to **asthma**

More than 24 million Americans are affected by asthma, with prevalence increasing 12 percent in the last decade. Asthma is a narrowing of the airways to the lungs caused by inflammation in the air passages resulting from both genetic and environmental influences. It is the most common chronic condition in children and costs the U.S. economy an estimated $56 billion each year in direct and indirect costs.

America's biopharmaceutical research companies are developing 74 medicines to treat or prevent asthma. All of the medicines are either in clinical trials or awaiting review by the U.S. Food and Drug Administration.

New medicines today in the pipeline offer hope of reducing the human and economic costs of asthma. Examples of some medicines now being tested to treat the disease include:

- A monoclonal antibody that inhibits eosinophils from accumulating in the lungs.
- A new inhalation therapy that harnesses the body's natural defenses in the airway against asthma.
- A medicine that blocks the pro-inflammatory effect of prostaglandin in allergic asthma.

The quest for new medicines is intense and financially risky. Each new medicine costs, on average, more than $1 billion and takes 10 to 15 years to develop. But new scientific advances are increasing our knowledge, and researchers are using every tool at their disposal.

Advances in our understanding of diseases and how to treat them have allowed America's biopharmaceutical research companies to conduct the cutting-edge research needed to reduce the destructive toll of asthma.

PhRMA

Asthma

Product Name	Sponsor	Indication	Development Status*
ABT-308 (IL-13 modulator)	Abbott Laboratories *Abbott Park, IL*	asthma	Phase I (847) 937-6100
AM211 (CRTH2 antagonist)	Panmira Pharmaceuticals *San Diego, CA*	asthma	Phase I completed (858) 875-4810
AMG 157 (mAb)	Amgen *Thousand Oaks, CA*	asthma	Phase I (800) 772-6436
AMG 761 (mAb)	Amgen *Thousand Oaks, CA*	asthma	Phase I (800) 772-6436
AMG 827 (brodalumab)	Amgen *Thousand Oaks, CA*	asthma	Phase II (800) 772-6436
AMG 853 (CRTH2/D-prostanoid receptor)	Amgen *Thousand Oaks, CA*	asthma	Phase III (800) 772-6436
Arcapta® Neohaler® indacaterol	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase III (888) 669-6682
ARRY-502 (CRTH2 antagonist)	Array BioPharma *Boulder, CO*	allergic asthma	Phase I (877) 633-2436
ASM8	Pharmaxis *Exton, PA*	allergic asthma	Phase II (610) 363-5120
AZD1981	AstraZeneca *Wilmington, DE*	asthma	Phase II (800) 236-9933
benralizumab (MEDI-563)	MedImmune *Gaithersburg, MD*	asthma	Phase II (301) 398-0000
BI-54903	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	asthma	Phase II (800) 243-0127
BI-54903/olodaterol fixed-dose combination	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	asthma	Phase II (800) 243-0127
BI-144807	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	asthma	Phase I (800) 243-0127

* For more information about a specific medicine in this report, please call the telephone number listed.

Asthma

Product Name	Sponsor	Indication	Development Status
BI-671800	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	asthma	Phase II (800) 243-0127
Bosatria™ mepolizumab	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249
CNTO 3157 (mAb)	Janssen Biotech *Horsham, PA*	asthma	Phase I (800) 526-7736
CNTO 5825 (mAb)	Janssen Biotech *Horsham, PA*	allergic asthma	Phase I (800) 526-7736
Dulera® mometasone furoate/ formoterol fumarate	Merck *Whitehouse Station, NJ*	asthma (children under 12 years) ---------- allergic asthma (adults and adolescents)	Phase III (800) 672-6372 ---------- Phase II (800) 672-6372
E004 (epinephrine inhalation aerosol)	Amphastar Pharmaceuticals *Rancho Cucamonga, CA*	asthma	Phase III (800) 423-4136
fluticasone furoate/ fluticasone propionate	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase III (888) 825-5249
Flutiform™ formoterol/fluticasone propionate	SkyePharma *London, England*	asthma	application submitted www.skyepharma.com
GSK1440115	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase I completed (888) 825-5249
GSK2190914	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249
GSK2190915 (fiboflapon)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249
GSK2239633 (CCR4 receptor antagonist)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase I (888) 825-5249
GSK2269557	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase I (888) 825-5249
GSK256066 (PDE-IV inhibitor)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249

Asthma

Product Name	Sponsor	Indication	Development Status
GSK679586 (mAb)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II completed (888) 825-5249
GSK870086 (glucocortoid agonist)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249
GW766994 (CCR3 antagonist)	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase II (888) 825-5249
house dust mite allergy vaccine tablet (MK-8237)	ALK-Abello *Horsholm, Denmark* Merck *Whitehouse Station, NJ*	allergic asthma	Phase II (800) 672-6372
ibudilast (MN-166)	MediciNova *San Diego, CA*	asthma	Phase II (858) 373-1500
IMO-2134	Idera Pharmaceuticals *Cambridge, MA*	asthma	Phase I (617) 679-5500
indacaterol/mometasone (QMF149 Twisthaler®)	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase II (888) 669-6682
INV102 (oral nadolol)	Inverseon *San Francisco, CA*	asthma	Phase II www.inverseon.com
JNJ-39758979	Janssen Research & Development *Raritan, NJ*	asthma	Phase II completed (800) 526-7736
JNJ-40929837	Janssen Research & Development *Raritan, NJ*	asthma	Phase II (800) 526-7736
LAS 100977 (LABA)	Almirall *Barcelona, Spain* Forest Laboratories *New York, NY*	asthma	Phase II (800) 678-1605
lebrikizumab (RG3637)	Genentech *South San Francisco, CA*	allergic asthma, asthma	Phase II (800) 626-3553
masitinib	AB Science *Short Hills, NJ*	asthma	Phase III (973) 218-2437
MK-1029	Merck *Whitehouse Station, NJ*	mild to moderate asthma	Phase I (800) 672-6372

Asthma

Product Name	Sponsor	Indication	Development Status
MN-221	MediciNova *San Diego, CA*	exacerbations of acute asthma	Phase II (858) 373-1500
montelukast/mometasone (MK-0476C)	Merck *Whitehouse Station, NJ*	asthma	Phase II (800) 672-6372
N6022	N30 Pharma *Boulder, CO*	acute asthma	Phase I/II (920) 945-7700
olodaterol (BI-1744)	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT*	asthma	Phase II (800) 243-0127
ONO-6950	Ono Pharma USA *Trenton, NJ*	asthma	Phase I (609) 219-1010
OPK-0018	OPKO Health *Miami, FL*	asthma	Phase I (305) 575-4100
PUR003 (liquid iCALM)	Pulmatrix *Lexington, MA*	asthma	Phase I (781) 357-2333
QAV680	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase II (888) 669-6682
QAW039	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase II (888) 669-6682
QAX576	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase II (888) 669-6682
QGE031	Novartis Pharmaceuticals *East Hanover, NJ*	asthma	Phase I (888) 669-6682
R343	Rigel Pharmaceuticals *South San Francisco, CA*	allergic asthma	Phase I completed (650) 624-1100
R(+) zileuton	Cornerstone Therapeutics *Cary, NC*	asthma	Phase I (888) 466-6505
Relovair™ vinanterol inhalation/ fluticasone furoate powder	GlaxoSmithKline *Rsch. Triangle Park, NC* Theravance *South San Francisco, CA*	asthma ---------- asthma (children 5 – 11 years)	Phase III (888) 825-5249 (877) 275-8479 ---------- Phase II (888) 825-5249 (877) 275-8479

Asthma

Product Name	Sponsor	Indication	Development Status
reslizumab	Cephalon *Frazer, PA*	eosinophilic asthma	Phase III (610) 344-0200
RG7185 (CRTH2-antagonist)	Genentech *South San Francisco, CA*	asthma	Phase I (800) 626-3553
RG7449 (anti-M1 prime mAb)	Genentech *South San Francisco, CA*	allergic asthma	Phase II (800) 626-3553
RNS60	Revalesio *Tacoma, WA*	asthma	Phase II www.revalesio.com
RX-10001	Resolvyx Pharmaceuticals *Cambridge, MA*	asthma	Phase I (781) 541-5045
salbutamol dry-powder inhalation	Teva North America *North Wales, PA*	asthma	Phase III (888) 838-2872
SAR231893 (REGN668)	Regeneron Pharmaceuticals *Tarrytown, NY* sanofi-aventis *Bridgewater, NJ*	asthma	Phase II (914) 345-7400 (800) 981-2491
setipiprant (ACT-129968)	Actelion Pharmaceuticals *South San Francisco, CA*	asthma	Phase II (650) 624-6900
Singulair® montelukast	Merck *Whitehouse Station, NJ*	exercise-induced asthma (children 4-14 years)	Phase III completed (800) 672-6372
Syk kinase silencer (Excellair™)	ZaBeCor Pharmaceuticals *Bala Cynwyd, PA*	asthma	Phase II (610) 660-7733
Spiriva® HandiHaler® tiotropium bromide	Boehringer Ingelheim Pharmaceuticals *Ridgefield, CT* Pfizer *New York, NY*	moderate to severe asthma	Phase III (800) 243-0127 (860) 732-5156
Symbicort® formoterol/budesonide inhalation	AstraZeneca *Wilmington, DE*	asthma (children 6-11 years)	Phase III (800) 236-9933
Symbicort® SMART® formoterol/budesonide	AstraZeneca *Wilmington, DE*	asthma	Phase III (800) 236-9933
TC-6987	Targacept *Winston-Salem, NC*	asthma	Phase II (336) 480-2100

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Product Name	Sponsor	Indication	Development Status
tralokinumab (CAT-354)	MedImmune *Gaithersburg, MD*	asthma	Phase II (301) 398-0000
Veramyst® fluticasone furoate	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase III (888) 825-5249
		asthma (in children 5 – 11 years)	Phase II (888) 825-5249
vilanterol	GlaxoSmithKline *Rsch. Triangle Park, NC*	asthma	Phase III (888) 825-5249
VR506	Vectura *Wiltshire, United Kingdom*	asthma	Phase II/III www.vectura.com

The content of this report has been obtained through public, government and industry sources, and the Adis "R&D Insight" database based on the latest information. ***Report current as of February 3, 2012.*** *The information in this report may not be comprehensive. For more specific information about a particular product, contact the individual company directly or go to www.clinicaltrials.gov. The entire series of* Medicines in Development *is available on PhRMA's web site.*

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application submitted—Application for marketing has been submitted to the Food and Drug Administration (FDA).

asthma—A disorder that causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing. Asthma is caused by inflammation in the airways. An **asthma attack** occurs when the muscles surrounding the airways become tight and the lining of the air passages swells, thus reducing the amount of air that can pass through. Most people with asthma have attacks separated by symptom-free periods Some people have long-term shortness of breath with episodes of increased shortness of breath. Either wheezing or a cough may be the main symptom. Asthma attacks can last for minutes to days, and can become dangerous if the airflow is severely restricted. In sensitive people, asthma symptoms can be triggered by breathing in allergy-causing substances (called allergens or triggers). Some common asthma triggers include pet hair or dander, dust, changes in the weather, chemicals in the air or in food, mold, pollen, and tobacco smoke.

eosinophilic asthma—Eosinophils are a type of white blood cell that tends to increase with worsening asthma and other allergic conditions. Eosinophils normally help protect the body from foreign invaders such as bacteria, viruses, and parasites, but in asthma eosinophils release chemicals that lead to inflammation. Eosinophils are produced in the bone marrow, but travel to other organs in the body when exposed to an asthma trigger. Re-exposure to a trigger (an allergen) leads to the release of chemicals like histamine that cause bronchoconstriction and asthma symptoms such as wheezing, chest tightness, shortness of breath, and chronic cough.

Phase I—Safety testing and pharmacological profiling in humans.

Phase II—Effectiveness and safety testing in humans.

Phase III—Extensive clinical trials to demonstrate safety and efficacy in humans.

Selected Facts about Asthma in the United States*

Overview

- Approximately 24.6 million Americans (including 7.1 million children) had **asthma** in 2009. That was a rate of 81.5 per 1,000 population. The highest **prevalence rate** was seen in those 5-17 years of age (109.3 per 1,000 population). Overall, the rate in those under 18 (96.1 per 1,000) was significantly greater than those over 18 (76.8 per 1,000).
- In 2009, an estimated 12.8 million Americans (including 4.1 million children under 18) had an **asthma attack**. That represents 48 percent of the 24.6 million people who currently have asthma. The asthma attack rate was 42.6 per 1,000 population.
- The **overall percentage of asthma sufferers** tends to be highest in the South, in non-Hispanic whites, in 18-44 year olds, and in females.
- The **hospital discharge rate for asthma** increased dramatically from 1979 to 1988, remained stable in the early 1990s, and peaked at 511,000 discharges (19.5 per 10,000 population) in 1995. During 2006, 444,000 discharges (14.9 per 10,000 population) were attributed to asthma. Between 2003 and 2006, there was a 25 percent decrease in the hospitalization discharge rate for asthma in the United States.
- In 2006, **asthma** caused 10.6 million **physician office visits**, 1.2 million **hospital outpatient department visits**, and almost 1.7 million **emergency room visits**.
- In 2008, **asthma** accounted for an estimated 14.4 million **lost school days** for children and 14.2 million **lost work days** for adults.
- In 2007, 3,447 people died of asthma. The number of **asthma deaths** has decreased by 26 percent since 1999.
- From 2002 to 2007, the **annual economic cost of asthma** in the United States was $56 billion; direct health care costs consisted of $50.1 billion with indirect costs (lost productivity) contributing an additional $5.9 billion.

Asthma in Females and Males

- **Females** traditionally have consistently **higher rates of asthma than males**. In 2009, females were about 11.1 percent more likely than males to ever have been diagnosed with asthma.
- In 2009, 10.3 million males and 14.2 million females had **asthma**. The overall **prevalence rate** in females (92.7 per 1,000 people) was 33 percent greater than the rate in males (69.9 per 1,000 people). Among adults over 18 years, females were 76 percent more likely than males to have asthma (97.0 per 1,000 vs. 55.1 per 1,000). However, this pattern is reversed among children. The current asthma prevalence rate for boys under 18 (112.8 per 1,000) was 44 percent higher than the rate among girls (78.6 per 1,000). The difference in rates between sexes is statistically significant in both children and adults.
- Females tend to have consistently higher **asthma attack prevalence rates** than males. In 2009, 7.6 million females (49.6 per 1,000) had an asthma attack compared to 5.2 million males (35.2 per 1,000). The difference in attack prevalence rates between sexes has been significant each year since 1999.
- Between 1995 and 2006, the number of **hospital discharges due to asthma** decreased 13 percent overall, 16 percent in males, and 12 percent in females. In 2006, a total of 266,000 discharges were reported in females and 177,000 were reported in males.
- In 2007, the age-adjusted **death rate for asthma** was 1.1 per 100,000 population. That year, the female age-adjusted death rate was 33 percent greater than the rate seen in males. Of the 3,447 people who died of asthma in 2007, approximately 63 percent of them were women.

Selected Facts about Asthma in the United States*

Asthma in Children

- Since 1999, **children** ages 5-17 have had the **highest asthma prevalence**. In 2009, 8.5 million children ages 5-17 had been diagnosed with asthma in their lifetime.
- For the past 10 years, 5- to 17-year-olds had the highest **asthma attack prevalence rates** while those over 65 had the lowest every year until 2009, when those 18-44 had the highest rates. Since 1999, the asthma attack prevalence rate in those under age 18 has been significantly greater than among those over 18; in 2009, those rates were 54.8 versus 28.8 per 1,000, respectively.
- **Hospital discharges due to asthma** are very common among the pediatric population. Approximately 33 percent of the asthma discharges in 2006 were in those under age 15, although only 20.2 percent of the U.S. population was under age 15.
- **Asthma deaths** are rare among children and increase with age. In 2007, 152 children under age 15 died from asthma (0.2 per 100,000 population) compared to 659 adults over 85. (The death rate in those 85 and over was 173 percent greater than the second highest mortality rate, seen among those 75-84 years of age [12.0 per 100,000 versus 4.4 per 100,000]).

Asthma in African Americans

- **African Americans** are more likely to be diagnosed with asthma over their lifetime. In 2009, the current **asthma prevalence** was 43 percent higher in blacks than in whites (111.5 per 1,000 people versus 78 per 1,000 people, respectively). The difference between races is statistically significant. The highest prevalence for whites and blacks were among the 5-17 age group. Whites under age 5 and blacks age 65 and older had the lowest prevalence rates compared to other age groups within each race.
- In 2009, the **asthma attack prevalence** in blacks was 40 percent higher than in whites. The asthma attack prevalence in whites and blacks were highest among the 5-17 age group and lowest in those 65 years and older.
- The 2006 **hospital discharge rate** for African Americans with asthma (29.3 per 10,000 people) was more than 3 times higher than that seen in whites and 4.4 times higher than that seen in other races (9.6 and 6.7 per 10,000, respectively).
- In 2007, the age-adjusted **death rate for asthma** was 2.8 times higher among the black population than among the white population (2.5 versus 0.9 per 100,000, respectively). Black women had the highest age-adjusted mortality rate due to asthma (2.2 per 100,000).

Asthma in Hispanics

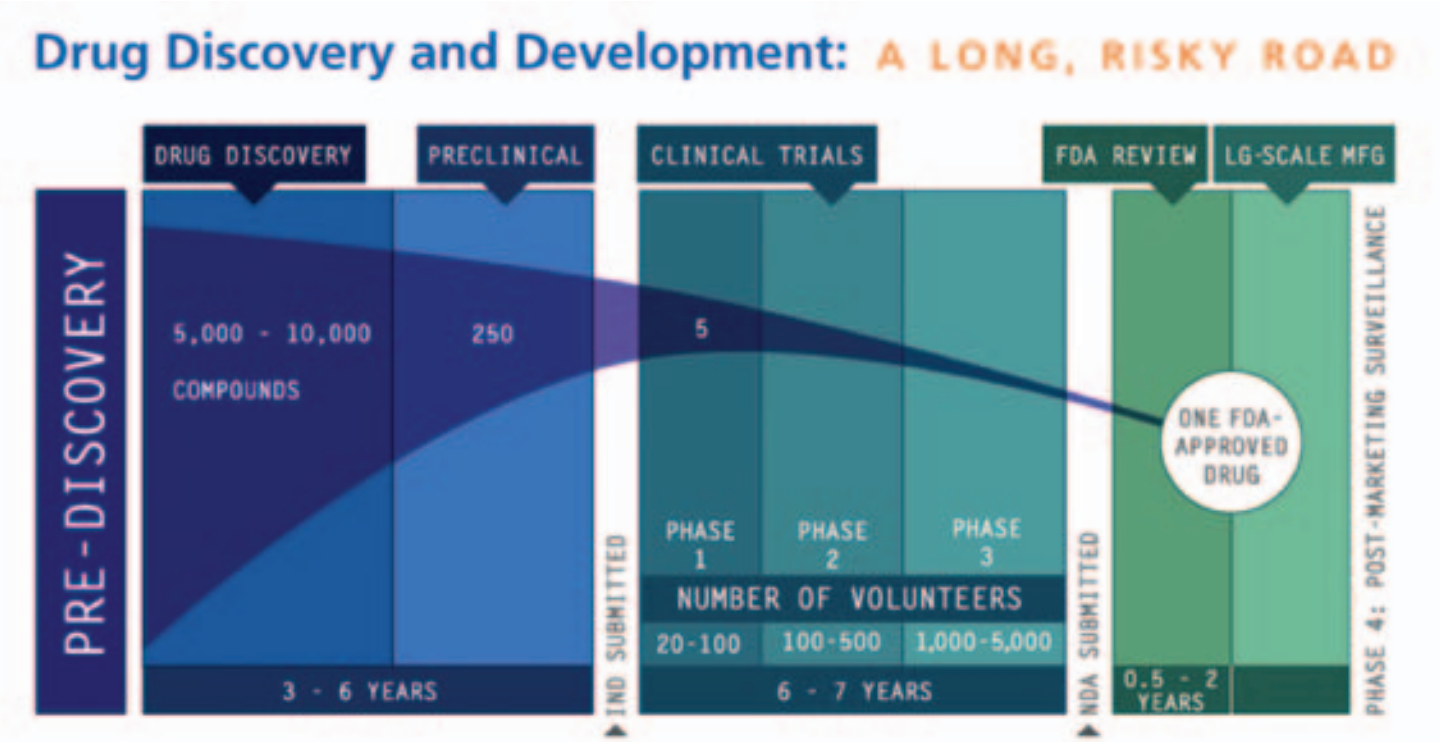
- In 2009, 5.3 million **Hispanics** had been diagnosed with **asthma** in their lifetime; 3 million reported that they still have the disease; and 1.6 million of those experienced an **asthma attack** in the past year. Lifetime, current and attack prevalence in Hispanics were significantly lower than non-Hispanic blacks and non-Hispanic whites in 2009. Studies have suggested that within Hispanic subgroups, Puerto Ricans may have higher rates of asthma than other Hispanic subgroups and non-Hispanic whites.
- In 2007, 239 Hispanics died of asthma—an age-adjusted **death rate** of 0.8 per 100,000 population. Age-adjusted death rates in Hispanics were 69 percent lower than in non-Hispanic blacks and 11 percent higher than non-Hispanic whites. However, studies have suggested that Puerto Ricans have higher age-adjusted death rates than all other Hispanic subgroups and non-Hispanic whites and blacks.

Source:

* American Lung Association, *Trends in Asthma Morbidity and Mortality,* July 2011 *www.lungusa.org*

The Drug Discovery, Development and Approval Process

It takes 10-15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.



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 2007 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. These tests usually involve about 20 to 100 healthy volunteers. The tests study a drug's safety profile, including the safe dosage range. The studies also determine how a drug is absorbed, distributed, metabolized, and excreted as well as the duration of its action.

Clinical Trials, Phase II. In this phase, controlled trials of approximately 100 to 500 volunteer patients (people with the disease) assess a drug's effectiveness and determine the early side effect profile.

Clinical Trials, Phase III. This phase usually involves 1,000 to 5,000 patients in clinics and hospitals. Physicians monitor patients closely to confirm efficacy and identify adverse events.

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. Biopharmaceutical companies invested an estimated $67.4 billion in research and development in 2010.