MEDICINES IN DEVELOPMENT | 2020 REPORT

America's Biopharmaceutical Companies

CHILDREN

JUST THE FACTS

A CHILD BORN TODAY CAN EXPECT TO LIVE

27 YEARS LONGER

THAN A CHILD BORN A CENTURY AGO.[1]

INFANT MORTALITY DECLINED

15%

FROM 2005 TO 2014.[2]

THE DEATH RATE FROM CANCER DECLINED BY

2/3

IN CHILDREN AGES 0-14 YEARS FROM 1970 TO 2016.[3]

MORE THAN

800

APPROVED PEDIATRIC LABELING CHANGES HAVE BEEN MADE SINCE 1998.[4]

MEDICINES IN DEVELOPMENT | 2020 REPORT

CHILDREN

Nearly **600** Medicines in Development to Meet the Unique Needs of Pediatric Patients

Researching and developing innovative and therapeutically appropriate medicines for children and infants is an important priority for America's biopharmaceutical research companies. Because biopharmaceutical researchers know that children are not simply small adults and that medicines may work differently in children than in adults, researchers are studying, developing and testing medicines to meet the unique health needs of infants, children and adolescents. Additionally, pediatric diseases are often clinically different than the adult version, requiring different approaches to disease management. These medicines in development offer hope that the significant improvements achieved in children's health over the past few decades will continue and even accelerate.

The fact is that real progress has been made. Infant mortality has sunk to record lows. Vaccines protect children against many childhood diseases. Antibiotics prevent deaths from pneumonia and other infectious diseases that used to claim the lives of children. Thanks to new and improved treatment advances, 83% of children diagnosed with cancer from 2008 to 2014 will survive five years or longer, compared to 58% in the mid-1970s.[3]

Recently there has been tremendous growth in pediatric clinical research, resulting in critical advances in our understanding of pediatric illnesses and how to best treat them. The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) have worked together to foster pediatric drug development, creating a balanced approach that has incentivized and established requirements for the generation of important safety and efficacy information on the use of medicines in children. Together these laws enable biopharmaceutical companies to continue to make significant investments in pediatric drug research to advance children's medical care in the U.S.

In addition to developing new medicines specifically for children, biopharmaceutical research companies are testing many existing medicines currently approved for use in adults to determine safe and effective dosage levels and routes of administration for children. Today there are 580 medicines[5] in development for potential use in infants, children and adolescents. All of the medicines are in clinical trials or awaiting review by the U.S. Food and Drug Administration (FDA). The 580 medicines in the pipeline include:

- **125** for genetic diseases, including medicines for cystic fibrosis, which affects more than 30,000 American children and adults.[6]
- **86** for cancer which, despite significant progress, is still a leading cause of death by disease among American children between ages 1 and 19.[7]
- **75** for such infectious diseases as HIV/AIDS, ear infections, pneumonia and hepatitis.
- **55** for skin disorders, including atopic dermatitis, a chronic condition which affects about 20% of children in the U.S.[8]
- **37** for neurologic disorders, including potential new treatments for epilepsy, which affects about 470,000 children in the U.S.[9]
- **26** for diabetes, whose incidence is increasing for those under the age of 20. From 2002-2012 the incidence of type 1 diabetes increased 1.4% every year, while incidence of type 2 diabetes increased 7.1% every year.[10]
- **23** for mental illnesses, including serious mental illnesses which affect 22.2% of adolescents (age 13 to 18) in the U.S.[11]
- **23** for blood disorders, including sickle cell disease and iron deficiency anemia.
- **22** for cardiovascular disease, including hypertension, high cholesterol and congenital heart disease.
- **20** for respiratory disorders, including medicines for asthma, the most common chronic condition among children in the U.S., with more than 6 million children affected.[12]
- **19** for gastrointestinal disorders, including inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, which affect 140,000 Americans under the age of 18.[13]
- **14** for kidney diseases such as glomerulosclerosis (hardening of the kidney's blood vessels) and chronic kidney disease.
- **13** for allergies including peanut hypersensitivity.
- **12** for conditions related to transplantation such as graft-versus-host disease (when the donor's cells attack and damage the transplant recipient's healthy cells).
- Other areas of research include developmental disorders, eye disorders, and liver diseases, among others.

Medicines in Pediatric Clinical Trials

There are currently more than 2,100 industry sponsored pediatric clinical trials underway, involving more than 1.2 million pediatric patients across a variety of therapeutic areas, including diseases where there is significant unmet medical need, such as infectious diseases, neurologic conditions, genetic disorders, and several forms of cancer.[14] These clinical trials are testing 580 investigational medicines in infants, children and adolescents to understand their unique health needs, determine appropriate dosing levels and routes of administration, and establish safety and efficacy for use in these populations. The medicines in the pipeline include:

- A monoclonal antibody approved to treat **asthma** in adults and children age 12 years and older being tested in children ages 6 to 11. Asthma is the third-ranking cause of hospitalization among children younger than 15.[15] In eosinophilic asthma, eosinophils (a type of white blood cell) accumulate in lung tissue and cause damage to the lining of the passages. Interleukin-5 (IL-5) is essential for the production, activation and maturation of eosinophils. The antibody inhibits IL-5 resulting in a sustained reduction in the number of eosinophils accumulating in the lungs and stopping those already there from causing damage.

- The first DDP-4 inhibitor approved for adults with **type 2 diabetes** in the U.S. being tested in children ages 10 to 17. The medicine enhances a natural body system called the incretin system, which helps to regulate glucose by affecting the beta cells and alpha cells in the pancreas. Through DPP-4 inhibition, it works only when blood sugar is elevated to address diminished insulin due to beta-cell dysfunction and uncontrolled production of glucose by the liver due to alpha-cell and beta-cell dysfunction.

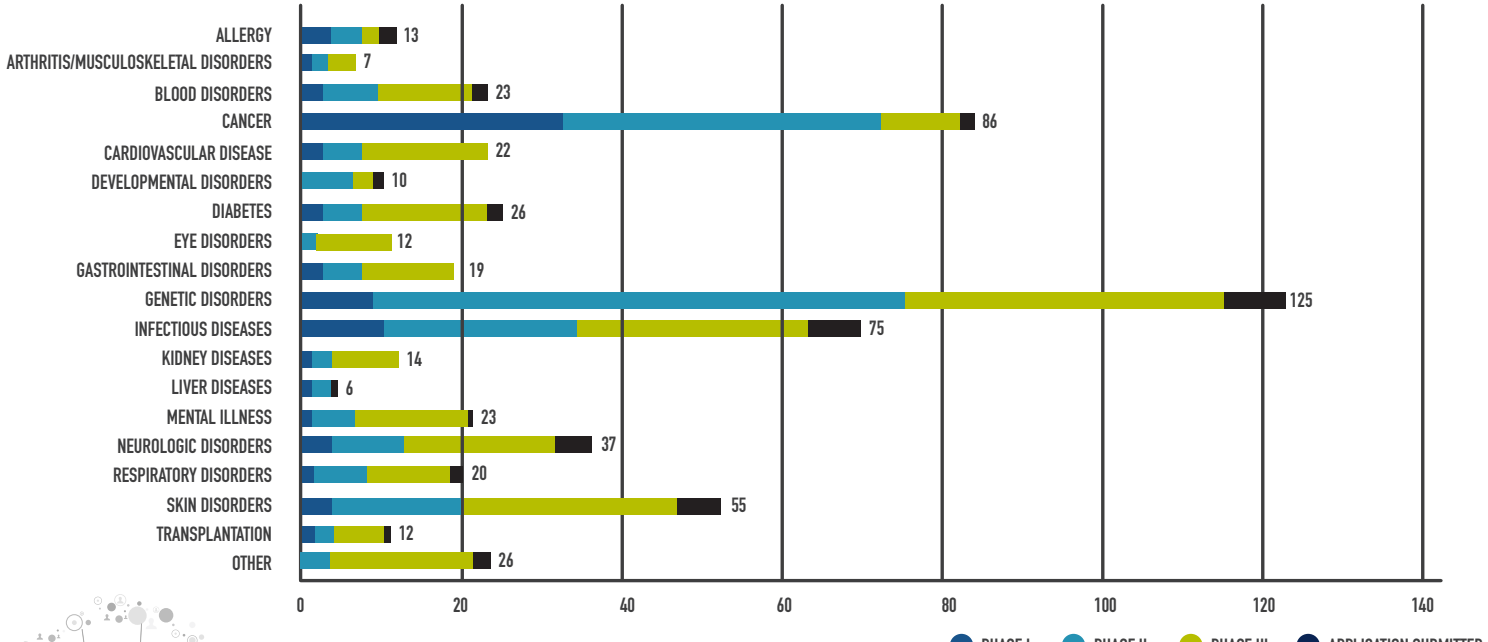
- A gene-edited cell therapy that could potentially be a one-time treatment for **sickle cell disease**, uses zinc finger nucleases (ZFNs), which consists of a protein with a DNA-cutting enzyme, to modify a patient's own hematopoietic stem cells to produce normal-shaped red blood cells using fetal hemoglobin. Normally, levels of fetal hemoglobin begin to decline after birth, while levels of adult hemoglobin increase. Since only adult hemoglobin contains the part of hemoglobin defective in patients with sickle cell disease, increasing fetal hemoglobin may be therapeutic for patients.

- A monoclonal antibody approved for the prevention of **migraine headaches** in adults being tested in clinical trials that include children ages 6 to 17. The antibody binds to and inhibits the activity of calcitonin gene-related peptide (CGRP). CGRP is expressed in the nervous system, where it plays a role in controlling the dilation of blood vessels and the transmission of neuropathic pain signals. Research suggests that CGRP pathways may be involved in the development of migraines. Anti-CGRP antibodies are thought to help inhibit the transmission of pain signals associated with migraines.

- A CAR-T (genetically modified chimeric antigen receptor T-cell) therapy in development for **leukemia and lymphoma** in patients up to 17 years old. CAR-T therapy utilizes a patient's own T-cells to uniquely recognize and kill cancerous tumor cells. To make the therapy, a patient's blood is filtered to remove T-cells, which are then altered in the lab by inserting a gene that codes for a receptor that targets a protein unique to cancer cells. The T-cells are then returned to the patient intravenously, where they can then bind to and kill the cancer cells.

- A dopamine/norepinephrine reuptake inhibitor in development for **attention-deficit/hyperactivity disorder** (ADHD) with an extended treatment window. This potential treatment showed significant improvement in both inattentive and hyperactivity/impulsivity ADHD symptoms in clinical trials. Clinical trials have included children ages 6 to 12.

Medicines in Development For Children



Note: Some medicines may be in more than one category.

Pediatric Clinical Research: Overcoming the Challenges

While there has been continued progress in pediatric drug development, biopharmaceutical companies still face unique scientific and operational challenges in pediatric drug research. Challenges include difficulty recruiting and enrolling young patients in clinical trials, identifying the optimal dosage, preparation, and delivery forms of medicines for young patients, and additional ethical, scientific and medical considerations. According to a 2016 survey[16] by Tufts University's Center for the Study of Drug Development, most of the biopharmaceutical companies who were surveyed reported a greater than 50% increase in pediatric study complexity since 2008. Reasons for an increase in complexity included lack of age-appropriate participants, validated endpoints, lack of sufficient safety information to start studies and differences in how disease may manifest differently in pediatric and adult populations.

One particular challenge in conducting pediatric research is the limited number of patients eligible for clinical research studies. This is a particular challenge in pediatric cancer research, where the potential use of biomarkers to identify the patients who are eligible for recruitment into trials can further segment the population into even smaller numbers.

Due to these challenges in pediatric research, data shows:

- It can take up to 15 years to complete a pediatric drug development program and nine years from adult approval for pediatric labeling to be made available.[17]
- Less than two pediatric patients are enrolled in trials, per site, per year and 30% of sites never enroll a single patient.[17]
- Pediatric drug development costs have increased by at least 25% between 2008 and 2016, for a majority of the companies, with close to half of the companies reporting an increase of more than 50%.[16]
- A report by FDA scientists showed that 42% of pediatric trials fail to demonstrate safety and efficacy necessary to establish new or expanded pediatric labeling.[18]

Improvements to pediatric drug research and development can stem from enhanced communication and collaboration between all stakeholders involved, including patients, researchers and regulatory decision-makers. Advances in science and technology, including new and powerful tools to determine how individual patients respond to specific treatments, novel clinical trial designs, and advanced statistical methods, as well as the use of real-world evidence, hold promise of advancing pediatric research and drug development.

Collaborative Initiatives Focusing on Pediatric Research

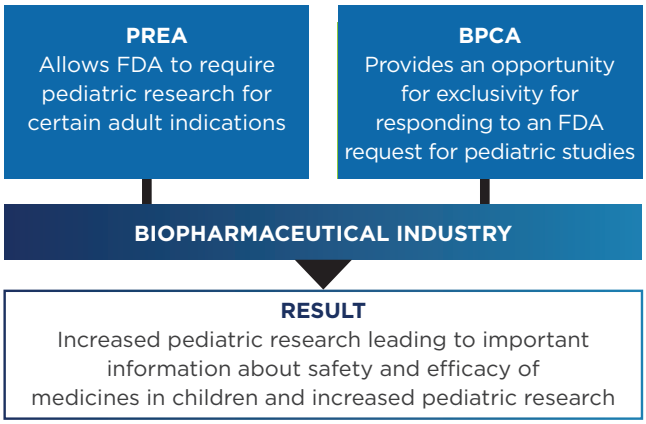
With all the challenges confronting children, their parents, doctors and biopharmaceutical research companies, new collaborative, pre-competitive initiatives have been created to help address some of the challenges. Collaborations to establish a robust clinical trial infrastructure have the potential to help overcome some of the enrollment and recruitment challenges inherent in conducting pediatric clinical trials.

PhRMA and our member companies are committed to improving the drug development process and addressing challenges in pediatric medicine development.

In October of 2016, the Children's Cause for Cancer Advocacy (CCCA), PhRMA, and Biotechnology Innovation Organization (BIO) convened a workshop that brought together, for the first time, the full spectrum of key pediatric oncology stakeholders to address some of the identified scientific and operational challenges in pediatric oncology medicine development. Participants included biopharmaceutical research companies, patient and provider advocacy groups, the FDA, National Cancer Institute/National Institutes of Health (NCI/NIH), and some of the country's leading pediatric oncologists.

Additionally, in 2017, the Institute for Advanced Clinical Trials for Children (I-ACT for Children) was launched to address challenges in bringing new therapies to children. I-ACT for Children, an independent nonprofit, seeks to foster public-private collaboration in finding solutions to barriers to pediatric medicine development, as well as improving the pediatric clinical trial process. Specifically, I-ACT for Children seeks to optimize pediatric study designs, protocols, best practices, training and engagement of patients and parents to advance clinical trials to improve children's health.

Regulatory Frameworks to Advance Pediatric Research



The need for pediatric-specific information prompted action by Congress and the FDA, leading to the passage of two laws that address the study of drugs in pediatric populations – Pediatric Research Equity Act (PREA) and The Best Pharmaceuticals for Children Act (BPCA). Permanently reauthorized by Congress in 2012, PREA and BPCA work together to foster pediatric drug development, providing previously unavailable information on dosing, safety, efficacy, and side effects.

Specifically, PREA requires that sponsors of certain new drug and biologic license applications or supplements, submit assessments regarding the drug's safety, effectiveness, dosing, administration and forms (e.g., liquid or chewable tablets) in pediatric populations. BPCA provides sponsors who conduct studies in response to a written request from FDA an opportunity to qualify for a six-month extension of existing statuary exclusivities and FDA's application of patent expiration dates for listed patents.

Today, pediatricians have more information than ever about which medicines are safe and effective for children and at what doses. Before BPCA/PREA, more than 80% of medicines used to treat children did not have pediatric dosing information.[19] That number has been reduced to 50% since BPCA/PREA.[19] Since 1998, BPCA and PREA have resulted in more than 800 pediatric labeling changes, according the FDA (as of October 15, 2019).[4]

"Before BPCA and PREA became law, more than 80% of the drugs approved for adult use were being used in children, even though the safety and effectiveness had not been established in children. Today that number has been reduced to about 50%."

—Dr. Lynne Yao, FDA

Recent Pediatric Labeling Approvals

BPCA and PREA are widely regarded as a success for patients, driving significant increases in pediatric research, product approvals, and approved labeling changes for the pediatric populations. Data from a 2016 Tufts Center for the Study of Drug Development showed that 46% of respondents agree that significant progress has been made in making pediatric studies a routine part of a drug development plan. Examples of recent approvals include:

- The first triple combination therapy for cystic fibrosis patients with at least one copy of the most common gene mutation was recently approved for patients 12 years and older. The F508del mutation in the cystic fibrosis transmembrane conductance regulator gene (CFTR) is present in about 80% of cystic fibrosis patients. The triple combination therapy is designed to increase the quantity and function of the defective CFTR protein at the cell surface.

- A medicine approved for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) in adults, received FDA approval to expand labeling to include children and infant patients three months and older after completing three pediatric clinical trials. This is the first FDA approval of a pediatric indication for cUTI and cIAI in more than a decade and addresses infections that post a significant health risk, particularly to the vulnerable and sensitive pediatric patient population with few treatment alternatives.

- The first autologous anti-CD19 CAR-T cell immunotherapy was approved for pediatric and young adult patients up to 25 years of age for B-cell cursor acute lymphoblastic leukemia (ALL). In CAR-T immunotherapy, the patient's own T-cells are genetically modified and are reintroduced back into their blood, where the cells can bind to the targeted cancer cells and destroy them while minimizing the effect on other non-cancerous cells.

- First approved in 1994, an anticoagulant was recently approved to treat pediatric patients one month of age and older with venous thromboembolism (VTE), which obstructs pulmonary circulation. VTEs are most common in children who are also receiving treatment for a primary illness, such as cancer or congenital heart disease or trauma/surgery and can be life threatening. It is the first anticoagulant approved for children with life-threatening blood clots.

- The first treatment for all six types of hepatitis C virus (HCV) was approved for use in children ages 12 to 17. The medicine was first approved in 2017 for use in adults and is part of the class of direct-acting antivirals that can reduce the amount of HCV in the body to undetectable levels by preventing the virus from multiplying. Approximately 23,000 to 46,000 children in the U.S. are infected with HCV.

- The first and only gene therapy for children with spinal muscular atrophy (SMA) was approved to treat pediatric patients less than two years of age. SMA is a rare genetic disease that leads to progressive muscle weakness, paralysis, and if left untreated, a leading cause of infant mortality. The treatment addresses the root cause of SMA by replacing the defective or missing gene responsible for the disease with a potential single, one-time infusion. It was developed exclusively for pediatric use.

While we celebrate the continued success that biopharmaceutical companies have made in pediatric research, more work remains to be done to develop treatments and cures for patients with unmet medical needs. America's biopharmaceutical researchers are committed to harnessing new scientific and technological advances to research and develop new medicines to allow children to live longer and healthier lives.

Sources:

1. National Vital Statistics Reports, United States Life Tables, Vol. 68, No. 4, May 7, 2019, National Center for Health Statistics (NCHS).
2. Trends in Infant Mortality in the United States, 2005–2014, Data Brief No. 279, March 2017, NCHS.
3. Cancer Facts & Figures 2019, American Cancer Society.
4. New Pediatric Labeling Information Database, U.S. Food and Drug Administration, Accessed October 15, 2019.
5. Number of medicines obtained through government and industry sources, and the Springer "Adis Insight" database. Current as of January 10, 2020.
6. Cystic Fibrosis Foundation
7. National Vital Statistics Reports, Deaths: Leading Causes for 2017, Vol. 68, No. 6, June 24, 2019, NCHS.
8. Atopic Dermatitis, Pediatric Clinics of North America, Vol. 61, Issue 2, April 2014.
9. National and State Estimates of the Numbers of Adults and Children with Active Epilepsy, United States, 2015, Morbidity and Mortality Weekly Report, U.S. Centers for Disease Control and Prevention (CDC), August 11, 2017.
10. Incidence Trends of Type 1 and Type 2 Diabetes Among Youth, 2002-2012, New England Journal of Medicine, 2017
11. National Institute of Mental Health – Statistics, 2001-2004
12. Asthma and Allergy Foundation of America
13. Crohn's and Colitis Foundation, Fact Sheet—Childhood IBD
14. Clinicaltrials.gov with search terms Recruiting, Not Yet Recruiting, Active, Not Recruiting, Interventional Studies, Child and Industry, Accessed June 7, 2019.
15. United States Environmental Protection Agency. Asthma Facts (May 2016)
16. Regulatory science, pediatric clinical trial networks hold promise for studies. Tufts Center for the Study of Drug Development Impact Report, Tufts University, Vol. 18, No. 6, November/December 2016
17. 2014 Pediatric Clinical Trials Forum, American Academy of Pediatrics
18. Momper JD, Mulugeta Y, Burckart GJ. Failed Pediatric Drug Development Trials. Clin Pharmacol Ther. 2015;98(3):245-51
19. Yao.L., FDA takes step to encourage pediatric drug studies. FDA Voice (August 2013)