U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVANCING HEALTH THROUGH INNOVATION

2018 NEW DRUG THERAPY APPROVALS

Impact | Innovation | Predictability | Access

January 2019

www.fda.gov

Table of Contents

Introduction

Welcome to the FDA's Center for Drug Evaluation and Research's (CDER) annual report, Advancing Health Through Innovation: New Drug Therapy Approvals.

This report helps illustrate CDER's role in bringing innovative new drug therapies that are safe and effective to patients in need.

Many of this year's new drug therapies are novel drugs --- those never before approved or marketed in the United States. Novel drugs often represent important new therapies for advancing patient care.

Our report also highlights medically significant approvals for existing drugs. As in past years, many important advances in 2018 use an already FDA-approved drug to treat a new disease or a new population of patients, such as children.

Our report emphasizes some of the many innovative ways we were able to evaluate safety and efficacy for these new therapies, as well as key regulatory tools we used to enhance our efficiency and expedite the review and approval of applications.

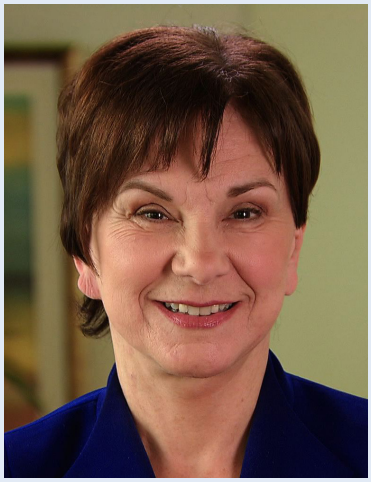
This report also highlights the year's biosimilar approvals. Biosimilars have great potential for both patients and the entire health care system. As patents and exclusivity protections for biologics expire in the United States, we can expect many more biosimilars to be submitted for approval. More products on the market means greater competition that can lead to increased access to therapies and lower costs to patients.

The decisions we made on these approvals were generally completed by or before their goal dates as defined by Congressionally-approved agreements with industry (referred to as user fee programs). Most were approved in the United States before any other country in the world.

Throughout all of our approval evaluations, safety remains our top priority. Our annual Drug Safety Priorities report provides a valuable overview of the many ways we work to ensure safety for all of our approvals.

Keep in mind that this report focuses on CDER approvals. FDA's Center for Biologics Evaluation and Research (CBER) also approves many important therapies to advance and protect the health of the American public. For more information, please visit CBER's web page for 2018 Biological Approvals.

We trust this report will continue to promote greater understanding of the many ways CDER works to support innovation and improve treatments for patients.



Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

2018: Another Strong Year for Innovation and Advances

CDER approved many new treatment options for patients in need.

In 2018, FDA's Center for Drug Evaluation and Research's (CDER's) new drug therapy approvals helped a wide range of patients suffering from many different medical conditions gain new hope for improved quality of life, and in some cases, improved chances of surviving life-threatening illnesses.

Rare Diseases

Among 34 novel approvals to help patients with rare diseases, CDER approved the first drug to treat patients with a rare, inherited form of **rickets,** a condition that leads to impaired bone growth and development. Also, CDER approved the first orally-administered drug to treat **Fabry disease**, a rare and serious disorder that can cause many adverse symptoms, including pain and burning in the hands and feet, and damage to the kidneys and heart. We also approved a new drug to treat patients with **phenylketonuria** (PKU), a rare dietary condition in which patients are born with an inability to break down protein-containing foods and certain sweeteners, and which can lead to brain and nerve damage.

Infectious Diseases

CDER approved the first drug ever to treat **smallpox** and therefore help in the event of a bioterror attack with this virus. We also approved the first of a new class of drugs to treat patients with **HIV-1** infection who have failed other therapy. Additionally, CDER approved two new versions of the same drug for **malaria**: one to prevent relapse of a certain form, and one to protect travelers to endemic areas from contracting it. CDER also approved a new single dose treatment for **influenza** (flu). CDER also approved a new formulation of an antibiotic to treat certain patients with **nontuberculous mycobacterial lung disease**. This is the first antibacterial drug product approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway, which is designed to streamline development and approval of antibacterial drugs to treat serious or life-threatening infections in a limited population of patients with unmet need.

Neurological Disorders

CDER approved a new drug to treat seizures in patients with the rare diseases **Lennox-Gastaut syndrome** and **Dravet syndrome**. We also approved a second drug to treat seizures in patients with Dravet syndrome. Previously there had been no FDA-approved therapy for use in **Dravet syndrome**. We approved three new drugs --- all in a new drug class --- to treat patients with **migraine**. We also approved two new drugs to treat polyneuropathy (nerve damage) in patients with hereditary **transthyretin-mediated amyloidosis**, a severely disabling condition that can cause symptoms such as muscle weakness and loss of sensation. Additionally, CDER approved the first therapy to treat **multiple sclerosis** in children.

Heart, Lung, and Circulatory Diseases

CDER approved a new drug for the treatment of patients with **hereditary angioedema**, a disorder that results in recurrent attacks of severe swelling --- most commonly affecting the arms, legs, face, intestinal tract, and airway.

Women's Health

CDER approved the first new treatment in more than 10 years for patients with pain caused by **endometriosis**, a common condition that affects as many as one in 10 women of child-bearing age, in which the tissue that lines the uterus grows in other parts of the body. Many times, this pain occurs during menstruation. We also approved the first vaginal ring **contraceptive** that can be used for an entire year.

Cancer and Blood Disorders

2018 was another strong year for making new cancer and blood therapies available to patients in need. We approved new advances for certain patients with **breast cancer**, a new drug to treat certain patients with **prostate cancer**, and a new drug for patients with a certain type of **lung cancer**. We also approved:

- Two previously-approved melanoma (skin cancer) drugs, which are given together to treat patients with a highly aggressive form of **thyroid cancer**;
- A new drug to treat patients with an unusual type of **cancer that may occur in the pancreas or gastrointestinal tract** (neuroendocrine tumors) that is no longer responding to hormone treatment;
- The first FDA-approved drug for the treatment of patients with p**heochromocytoma or paraganglioma** (rare tumors of the adrenal gland);

Cancer and Blood Disorders (Cont.)

- Another new cancer therapy that can be used to treat any kind of tumor that has a **specific genetic marker**, as opposed to where in the body the tumor originated --- only the second cancer therapy approved by the FDA to target treatment based on a specific characteristic of a tumor instead of its site of origin;
- Two new drugs to treat certain adult patients with **relapsed or refractory acute myeloid leukemia** (a type of cancer of the blood and bone narrow), each to treat patients who have a specific genetic mutation that enables them to be a candidate for treatment with the drug;
- A new front-line treatment (prior to a relapse or failed treatment with another drug) for patients with **acute myeloid leukemia** (AML);
- A new therapy to treat patients with **classical Hodgkin lymphoma** (a type of cancer of a part of the immune system called the lymphatic system);
- A new therapy for certain patients with a form of **acute lymphoblastic leukemia**;
- A new treatment for adult patients with relapsed or refractory **mycosis fungoides** (MF) or **Sézary syndrome** (SS), both a type of non-Hodgkin lymphoma in which a type of white blood cell in the body becomes cancerous and affect the skin, and;
- The first two therapies for **thrombocytopenia** (a deficiency of platelets in the blood) in patients with chronic liver disease scheduled to undergo a medical or dental procedure.

CDER's drug therapy approvals of 2018 will help advance patient care in many new areas.

Other Advances

CDER approved the first non-opioid drug product approved to help adult patients suffering from **opioid withdrawal symptoms**. We also approved a new indication for a **non-opioid nerve block therapy** to help adult patients with pain management for 48 hours after shoulder surgery. Additionally, CDER approved a drug originally approved to treat rheumatoid arthritis to now also treat patients with **ulcerative colitis**. CDER also approved a new drug therapy for patients suffering from a rare disease affecting the cornea of the eye, called **neurotrophic keratitis**. It provides a drug therapy alternative to surgery and is considered an important advance because it offers complete corneal healing for many patients with the condition. We also approved seven new **biosimilars**, which will further help to create competition, increase patient access, and potentially reduce the cost of important biological drug therapies.

CDER's Drug Therapy Approvals of 2018

In 2018, CDER approved a wide variety of drug therapies to improve the health of the American public, including:

- Novel drugs, which are often among the more innovative products in the marketplace, and help advance clinical care by providing therapies never before marketed in the United States;
- New and expanded uses for already FDA-approved drugs;
- Biosimilars, which are highly similar to already FDA-approved therapeutic biological products. These approvals add consumer choice and spur marketplace competition;
- New formulations or new manufacturers of already FDA-approved products that can provide advantages over original products, such as being able to take the drug on an empty stomach instead of with food, and;
- New dosage forms that can add value to already FDA-approved drugs, such as chewable tablets for patients unable to swallow pills.

This report summarizes these approvals and highlights examples, emphasizing those approvals that offer new and innovative treatments to patients in need.

As with all FDA-approved products, the new drug therapies discussed in this report are associated with risks. For more information about these drugs and for complete risk information, see the drugs' approval letters and FDA-approved labeling at Drugs@FDA.

Novel Drugs

Novel drugs are often innovative products that serve previously unmet medical needs or otherwtise significantly help to advance patient treatments. The active ingredient or ingredients in a novel drug have never before been approved in the United States. This report lists all of CDER's novel drug approvals of 2018 and also discusses those that CDER considers notable advances. In 2018, CDER approved 59 novel drugs, either as new molecular entities (NMEs) under New Drug Applications (NDAs), or as new therapeutic biologics under Biologics License Applications (BLAs).

CDER's Novel Drug Approvals of 2018

CDER's novel drug approvals for 2018 are listed alphabetically below by trade name.* See **Appendix A** in this report or visit online, CDER's Novel Drug Approvals for 2018 for the non-proprietary names, dosage forms, and what each drug is used for.

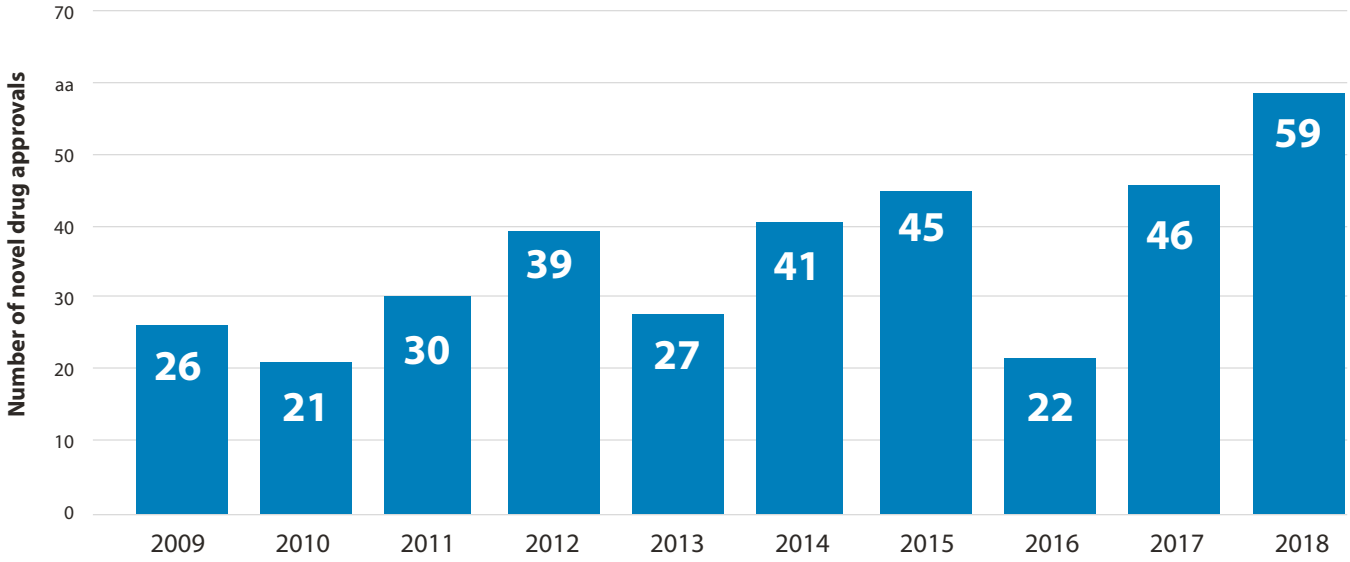
Aemcolo	Daurismo	Ilumya	moxidectin**	Poteligeo	Trogarzo
Aimovig	Diacomit	Krintafel	Mulpleta	Revcovi	Ultomiris
Ajovy	Doptelet	Libtayo	Nuzyra	Seysara	Vitrakvi
Akynzeo,	Elzonris	Lokelma	Olumiant	Symdeko	Vizimpro
Annovera	Emgality	Lorbrena	Omegaven	Takhzyro	Xerava
Asparlas	Epidiolex	Lucemyra	Onpattro	Talzenna	Xofluza
Biktarvy	Erleada	Lumoxiti	Orilissa	Tavalisse	Xospata
Braftovi	Firdapse	Lutathera	Oxervate	Tegsedi	Yupelri
Copiktra	Galafold	Mektovi	Palynziq	Tibsovo	Zemdri
Crysvita	Gamifant	Motegrity	Pifeltro	Tpoxx	

* This information is accurate as of December 31, 2018. In rare instances, it may be necessary for FDA to change a drug's NME designation or the status of its application as a novel BLA. For instance, new information may become available which could lead to a reconsideration of the original designation or status. If changes must be made to a drug's designation or the status of an application as a novel BLA, the agency intends to communicate the nature of, and the reason for, any revisions as appropriate.

** Product approved with no trade name

CDER's Annual Novel Drug Approvals: 2009 - 2018

In 2018, CDER approved 59 novel drugs. The 10-year graph below shows that from 2009 through 2017, CDER has averaged about 33 novel drug approvals per year.



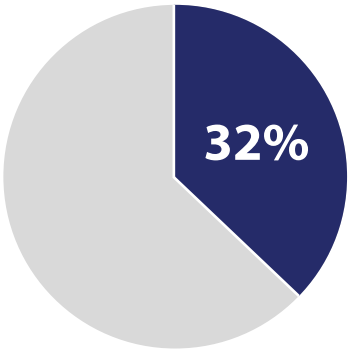
Impact of Novel Drug Approvals

Many of the novel drugs CDER approved in 2018 are notable for their potential positive impact and unique contributions to quality medical care and patient treatment.

CDER identified
19 of the 59
novel drugs approved in 2018 (32%) as first-in-class.

First-in-Class

CDER identified 19 of the 59 novel drugs approved in 2018 (32%) as first-in-class, which is one indicator of the drug's potential for strong positive impact on the health of the American people. These drugs often have mechanisms of action different from those of existing therapies. Novel drugs approved in 2018 that FDA identified as first-in-class were: Aimovig, Crysvita, Elzonris, Galafold, Gamifant, Lucemyra, Lutathera, Onpattro, Orilissa, Oxervate, Palynziq, Poteligeo, Tavalisse, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Vitrakvi, and Xofluza.



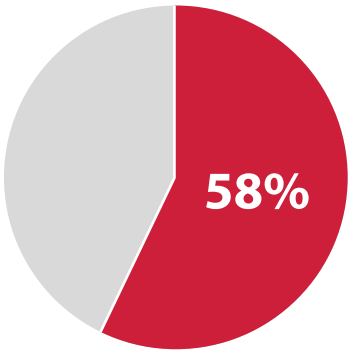
Examples of notable First-in-Class novel approvals for 2018 include:

- **Galafold (migalastat)** (under accelerated approval, see p. 19), for adults with **Fabry disease**, a rare and serious disorder that results from the buildup of a type of fat, called globotriaosylceramide, in the body's cells, including in the kidneys and the heart. This is the first oral medication approved for this indication. A previously FDA-approved treatment for Fabry disease must be administered via subcutaneous injection. Thus far, treatment of Fabry disease has involved replacing the missing enzyme that causes the particular type of fat buildup in this disease. Migalastat differs from enzyme replacement in that it increases the activity of the body's deficient enzyme.
- **Lucemyra (lofexidine hydrochloride)**, the first non-opioid drug product approved to help reduce **opioid withdrawal symptoms** and to facilitate abrupt discontinuation of opioids in adults. It may lessen the severity of withdrawal symptoms but may not completely prevent them and is only approved for treatment for up to 14 days. Lucemyra is not a treatment for opioid use disorder (OUD), but can be used as part of a broader, long-term treatment plan for managing OUD.
- **Trogarzo (ibalizumab-uiyk)**, a new type of antiretroviral medication for adult patients living with HIV-1 who have tried multiple **HIV-1** medications in the past and whose HIV-1 infection cannot be successfully treated with other available therapies (multidrug resistant HIV-1, or MDR HIV-1). This drug is administered intravenously once every 14 days by a trained medical professional and used in combination with other antiretroviral medications. While most patients living with HIV-1 can be successfully treated using a combination of two or more antiretroviral drugs, a small percentage of patients who have taken many HIV-1 drugs in the past have MDR HIV-1, limiting their treatment options and putting them at a high risk of HIV-1-related complications and progression to death. This drug is the first in a new class of antiretroviral medications --- a monoclonal antibody --- that can provide significant benefit to patients who have run out of HIV-1 treatment options and may be able to improve outcomes for these patients.

CDER approved the first monoclonal antibody to treat certain patients with HIV-1.

Drugs for Rare Diseases

34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases.



In 2018, 34 of CDER's 59 novel drugs (58%) were approved to treat rare or "orphan" diseases that affect 200,000 or fewer Americans. Patients with rare diseases often have few or no drugs available to treat their conditions. Novel drugs approved in 2018 with the orphan drug designation were: Asparlas, Braftovi, Copiktra, Crysvita, Daurismo, Diacomit, Elzonris, Epidiolex, Firdapse, Galafold, Gamifant, Krintafel, Lorbrena, Lumoxiti, Lutathera, Mektovi, moxidectin, Omegaven, Onpattro, Oxervate, Palynziq, Poteligeo, Revcovi, Symdeko, Takhzyro, Tavalisse, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Ultomiris, Vitrakvi, Vizimpro, and Xospata.

Notable examples of novel approvals of 2018 that advance the care of patients with rare diseases approved in 2018 include:

- **Crysvita (burosumab-twza)**, the first FDA-approved drug to treat adults and children ages one year and older with **x-linked hypophosphatemia (XLH)**, a rare, inherited form of rickets. XLH causes low levels of phosphorus in the blood and leads to impaired bone growth and development in children and adolescents, and problems with bone mineralization throughout a patient's life. XLH differs from other forms of rickets in that vitamin D therapy is not effective. This approval represents an important advance for those living with this serious disease.
- **Epidiolex (cannabidiol) [CBD]**, approved for the treatment of seizures associated with two rare and severe forms of epilepsy, **Lennox-Gastaut syndrome and Dravet syndrome**, in patients two years of age and older. It is also the first FDA approval of a drug for the treatment of seizures in patients with Dravet syndrome. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the "high") that comes from tetrahydrocannabinol (THC). THC (not CBD) is the primary psychoactive component of marijuana.
- **Palynziq (pegvaliase-pqpz)**, approved for adults with a rare and serious genetic disease known as phenylketonuria (PKU). Patients with PKU are born with an inability to break down **phenylalanine** (Phe), an amino acid present in protein-containing foods and high-intensity sweeteners used in a variety of foods and beverages. Left untreated, the condition can cause brain and nerve damage. This drug is a novel enzyme therapy for adult PKU patients who have uncontrolled blood Phe concentrations while on current treatment. This approval helps address a significant unmet need in PKU patients who have been unable to control their blood Phe levels with current treatment options.

In 2018, CDER approved the first FDA-approved drug derived from marijuana.

Other Notable Novel Drug Approvals: Advances in Patient Care Across a Broad Range of Diseases

In addition to the noteworthy first-in-class and orphan-designated drugs mentioned above, the 2018 novel drug field also includes these notable examples --- approved for the first time in the United States, and likely to significantly improve the care of patients with the conditions noted below:

- **Aimovig (erenumab-aooe)**, **Ajovy (fremanezumab–vfrm)** and **Emgality (galcanezumab-gnlm)**, all approved this year for adult patients for the prevention of **migraine**. These drugs are self-injected under the skin. Each belongs to a new class of drugs called calcitonin gene-related peptide receptor (CGRP-R) antagonists. They offer patients new options for reducing their number of days with migraine.

CDER approved three new drugs for the prevention of migraine.

- **Annovera (segesterone acetate; ethinyl estradiol)**, a combined hormonal contraceptive for women of reproductive age used to prevent pregnancy. It is the first vaginal ring **contraceptive** that can be used for an entire year.
- **Copiktra (duvelisib)** (under accelerated approval, see p. 19), to treat patients with **chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)**, a single disease that goes by these two names depending on where it is in the body. It is a type of cancer that starts in cells of the bone marrow and then moves to the blood, whereby it reaches the lymph nodes and eventually other organs. When most of the cancer cells are in the bloodstream and the bone marrow, the disease is called CLL; When the cancer cells are located mostly in the lymph nodes, the disease is called SLL. This condition is the most common form of leukemia. It progresses slowly, and many patients have no symptoms for years after the cancer begins growing.
- **Daurismo (glasdegib)**, to be used in combination with low-dose cytarabine, a type of chemotherapy, for the treatment of newly-diagnosed **acute myeloid leukemia** (AML) in adults who are 75 years of age or older or who have other chronic health conditions or diseases that may preclude the use of intensive chemotherapy. Intensive chemotherapy is usually used to control AML, but many adults with AML are unable to have intensive chemotherapy because of its toxicities.
- **Diacomit (stiripentol)**, to treat seizures in patients with **Dravet syndrome**, a rare, severe, lifelong form of epilepsy that begins in the first year of life with frequent and/or prolonged seizures. This drug and the newly approved Epidiolex (see above) are the only FDA-approved treatments for patients with Dravet syndrome.

CDER approved the first two drugs to treat a rare and serious form of epilepsy called Dravet syndrome.

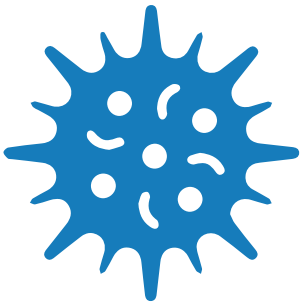
- **Doptelet (avatrombopag)** and **Mulpleta (lusutrombopag)**. CDER approved Doptelet as the first new therapy to treat **thrombocytopenia** (low blood platelet count) in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure. Patients with chronic liver disease who have low platelet counts and require a procedure are at increased risk of bleeding. This drug was demonstrated to safely increase the platelet count and may decrease or eliminate the need for platelet transfusions, which are associated with risk of infection and other adverse reactions. CDER subsequently approved Mulpleta, which is approved to treat the same patient population approved for treatment with Doptelet. The two drugs are in a class called platelet thrombopoietin receptor agonists and are the only two drugs approved by the FDA to treat thrombocytopenia in the patient population described above. This new drug class offers important new therapy options.

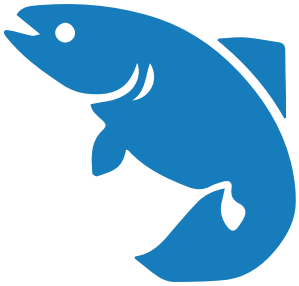
CDER approved the first drug approved based on the use of the endpoint of metastasis-free survival, which measures the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment.

- **Elzonris (tagraxofusp-erzs)**, to treat patients with **blastic plasmacytoid dendritic cell neoplasm**, an aggressive and severely life-threatening form of blood cancer from which patients often develop skin lesions. Until this approval, there was no FDA-approved treatment for this condition.
- **Erleada (apalutamide)**, for the treatment of patients with prostate cancer that has not spread (non-metastatic), but that continues to grow despite treatment with hormone therapy (cancer is castration-resistant). This is the first FDA-approved treatment for non-metastatic, castration-resistant prostate cancer. The FDA evaluates a variety of methods that measure a drug's effect, called endpoints, in the approval of oncology drugs. This approval is the first to use the endpoint of metastasis-free survival, which measures the length of time that tumors did not spread to other parts of the body or that death occurred after starting treatment. In the trial supporting approval, this drug had a strong effect on metastasis-free survival. The drug's approval is an example of the importance of using novel endpoints to expedite important therapies to market.
- **Firdapse (amifampridine phosphate)**, to treat symptoms of **Lambert-Eaton myasthenic syndrome** (LEMS), a rare autoimmune disorder that causes gradual muscle weakness, especially of the pelvic and thigh muscles. Approximately 60 percent of LEMS cases are associated with small cell lung cancer, and the onset of symptoms often comes before the cancer is detected. LEMS patients with cancer tend to be older and nearly always have a long history of smoking. In cases where there is no associated cancer, disease onset can be at any age.
- **Gamifant (emapalumab-lzsg)**, for the treatment of patients with primary (hereditary) **hemophagocytic lymphohistiocytosis** (HLH), a life-threatening condition in which cells of the immune system that usually destroy infected cells become overactive and instead damage the patient's own tissues and organs, including the liver, brain, and bone marrow.
- **Krintafel (tafenoquine)**, a one-dose treatment to prevent relapses of vivax **malaria**. Antimalarial drugs can provide an initial cure, but the infection can hide in a dormant form in the patient's liver and cause recurrences months or years later. A second drug is needed to help prevent these relapses. Before tafenoquine, the standard second-drug treatment to prevent relapses was a two-

week course of therapy taken daily. (See also **Arakoda** under New Formulations, for another new approval of tafenoquine to treat patients with malaria).

- **Libtayo (cemiplimab-rwlc)**, for the treatment of patients with metastatic **cutaneous squamous cell carcinoma** (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. This is the first FDA approval of a drug specifically for advanced CSCC, a potentially deadly type of skin cancer.
- **Lokelma (sodium zirconium cyclosilicate)**, for the treatment of adults with **hyperkalemia** (excess potassium in the blood). Risk of hyperkalemia increases significantly for patients with chronic kidney disease (CKD) and for those who take certain medications for heart failure, such as renin-angiotensin-aldosterone system (RAAS) inhibitors. Severe hyperkalemia may lead to cardiac arrest and death if not treated rapidly.
- **Lorbrena (lorlatinib)** (under accelerated approval, see p. 19), a drug in a class known as ALK tyrosine kinases inhibitors (TKIs) --- to treat patients with a type of lung cancer called **ALK+ non-small cell lung cancer** (NSCLC) whose cancer has progressed despite treatment with one or more previously-approved TKIs. Treatment resistance to TKIs resulting in disease progression is a challenge for patients with ALK-positive metastatic NSCLC. Lorlatinib offers a new option for overcoming resistance to previously-approved TKIs.
- **Lumoxiti (moxetumomab pasudotox-tdfk)**, for the treatment of adult patients with relapsed or refractory **hairy cell leukemia** (HCL) who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog. HCL is a rare, slow-growing cancer of the blood in which the bone marrow makes too many B cells (lymphocytes), a type of white blood cell that fights infection. HCL is named after these extra B cells, which look "hairy" when viewed under a microscope. This drug is a CD22-directed cytotoxin and is the first of this type of treatment for patients with HCL.
- **Lutathera (lutetium Lu 177 dotatate)**, for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. It is indicated for adult patients with **somatostatin receptor-positive GEP-NETs**, a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing. FDA approved this drug, in part,





based on safety and efficacy data from an expanded access program --- a program in which patients use an experimental drug because there is no FDA-approved therapy to treat their life-threatening condition. This use of data represents an innovative way to establish safety and efficacy to approve a needed therapy.

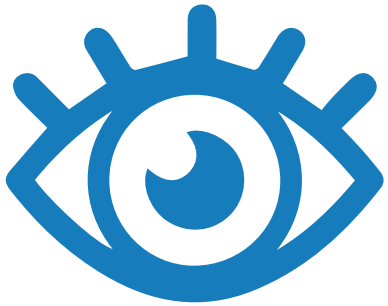
- **Moxidectin**, for the treatment of the tropical parasitic disease, **onchocerciasis**, also called river blindness, in patients aged 12 years and older. Symptoms of the disease include severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness.
- **Omegaven (fish oil triglycerides)**, the first injectable fish oil triglyceride product for pediatric patients. The injectable fish oil provides a source of calories and fatty acids for pediatric patients with **parenteral nutrition-associated cholestasis** (PNAC), a significant life-threatening complication in children receiving parenteral nutrition ((intravenous feeding for patients unable to eat).

CDER approved two drugs that interfere with the production of an abnormal disease-producing protein, targeting a disease at its root cause.

- **Onpattro (patisiran)** and **Tegsedi (inotersen)**. These are the first drugs approved to treat patients with polyneuropathy (peripheral nerve damage) caused by **hereditary transthyretin amyloidosis** (hTTR). Hereditary transthyretin amyloidosis is a genetic disease caused by the build-up of an abnormal protein in the nerves, heart, and/or gastrointestinal tract. Onpattro is the first of a promising and entirely new class of drugs called a small interfering ribonucleic acid (siRNA). RNA acts as a messenger within the body's cells, carrying instructions from the genes to the manufacturing site of proteins. When there is a mutation in a gene, the RNA "message" contains incorrect instructions that lead to the production of an abnormal protein. siRNAs work by interacting with this RNA, inhibiting production of the abnormal protein. Tegesdi works through a somewhat different mechanism. Tegesdi is an "antisense" RNA, which is designed to bind specifically to the abnormal RNA, again reducing production of the abnormal protein. These drugs offer important new treatment options for patients with hTTR. These approvals are also part of a broader wave of advances that reflect our greater scientific understanding of various conditions. They enable disease treatment by targeting its root cause, which hold the potential to arrest or reverse a condition, rather than just slowing its progression, or treatment of only the disease's symptoms.

- **Orilissa (elagolix)**, for the treatment of patients with pain caused by **endometriosis**, a common condition that affects approximately one in 10 women of reproductive age, in which the tissue that lines the uterus grows in other parts of the body. Many times, this pain occurs during menstruation. It is the first new treatment for this condition in more than 10 years.
- **Oxervate (cenegermin-bkbj)**, for the treatment of neurotrophic keratitis, a rare and serious disease affecting the cornea of the eye. This condition affects fewer than five in 10,000 people, but its impact on an individual patient can be devastating. In the past, surgery has often been necessary. This approval provides a drug therapy alternative to surgery as an advance that offers complete corneal healing for many patients with the condition.
- **Poteligeo (mogamulizumab–kpkc)**, for the treatment of adult patients with **relapsed or refractory mycosis fungoides** (MF) or **Sézary syndrome** (SS). (Relapsed means the condition returned after an initial treatment with a different drug. Refractory means an initial treatment with a different drug was unsuccessful.) These diseases are **types of non-Hodgkin lymphoma** in which lymphocytes (a type of white blood cell) become cancerous and affect the skin. This approval provides a new treatment option for patients with MF and is the first FDA-approved drug specifically for SS.
- **Revcovi (elapegademase–lvlr)** (under accelerated approval, see p. 19), to treat **adenosine deaminase deficiency** in patients with severe combined immunodeficiency (ADA deficiency or ADA-SCID) a rare metabolic disorder that causes severe immunodeficiency and is life-threatening without treatment. The main symptoms of ADA deficiency are frequent or severe infections. Affected children also grow slower than healthy children and some may have developmental delay. Most individuals with ADA deficiency are diagnosed with SCID in the first six months of life.
- **Symdeko (tezacaftor and ivacaftor)**, to treat patients ages 12 years and older with **cystic fibrosis** who have a certain type of genetic "F508del" mutation.

In 2018, CDER approved a drug therapy alternative to surgery for patients with a serious eye disease.



- **Takhzyro (lanadelumab–flyo)**, the first monoclonal antibody approved in the United States to treat patients 12 years and older with **hereditary angioedema (HAE)**, a rare and serious genetic disease that affects people with low levels and poorly functioning C1-INH proteins in the body. This results in recurrent, unpredictable episodes of severe swelling in specific parts of the body, including the stomach, limbs, face and throat. The product is used to prevent angioedema attacks from occurring.
- **Talzenna (talazoparib)**, for the treatment of patients with a type of breast cancer called **germline BRCA-mutated HER2-negative breast cancer** that is locally advanced or has spread to other parts of the body.
- **Tavalisse (fostamatinib)**, to treat adult patients with chronic **immune thrombocytopenic purpura** (ITP), an autoimmune blood disorder in which the body destroys its own blood platelets and, in some cases, the cells that produce them, causing a decrease in platelets that can result in excessive bruising and/or bleeding. Although there are other drugs approved by FDA to treat patients with this condition, chronic ITP is difficult to treat because there are many variations of the disease, and it is unclear how an individual patient will respond to available therapies. Fostamatinib works via a mechanism unlike those of other FDA-approved drugs for patients with ITP, and therefore provides another option for patients who do not respond to other available treatments.
- **Tibsovo (ivosidenib)** and **Xospata (gilteritinib)**. CDER approved Tibsovo in July 2018 for the treatment of adult patients with **relapsed or refractory acute myeloid leukemia** (AML), (a type of cancer of the blood and bone marrow). (Relapsed means the AML returned after an initial treatment with a different drug. Refractory means an initial treatment with a different drug was unsuccessful.) Tibsovo is approved for patients who have a specific "IDH1" genetic mutation. This drug is a targeted therapy that fills an unmet need for patients with relapsed or refractory AML who have an IDH1 mutation. Its use is associated with a complete remission in some patients and a reduction in the need for both red cell and platelet transfusions. In November 2018, CDER approved Xospata, also to treat adult patients with AML. Like Tibsovo, Xospata is a targeted therapy, but it targets the "FLT3" mutation --- also filling an important unmet medical need for certain patients with AML.

- **Tpoxx (tecovirimat)**, the first drug with an indication for treatment of patients with **smallpox**, a contagious and sometimes fatal disease. Although the World Health Organization declared smallpox to be eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon. Because smallpox no longer occurs, the drug could not be tested on humans with the disease. Instead, this drug was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.

CDER approved the first new drug to treat smallpox, helping to protect the U.S. from bioterrorism.

- **Ultomiris (ravulizumab-cwvz)**, to treat patients with **paroxysmal nocturnal hemoglobinuria**, a sometimes-life-threatening disease that varies in intensity by individual. It is caused by an acquired genetic mutation (the patient is not born with it and it is not hereditary), which causes the body's immune system to attack its own red blood cells and break them down. The disease is characterized by blood in the patient's urine, primarily at night.

- **Vitrakvi (larotrectinib)** (under accelerated approval, see p. 19), for the treatment of patients with **locally advanced or metastatic solid tumors** with a genetic characteristic known as a biomarker, called an "NTRK gene fusion." In 2017, CDER approved Keytruda (pembrolizumab) to treat patients whose cancers have a specific characteristic, a biomarker called MSI-H. This was the first time the FDA approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated. Larotrectinib marks another example of a drug approval for treating cancer based on the tumor's characteristics rather than its site of origin in the body.

CDER approved a second new cancer therapy that can be used for treatment of any kind of tumor that has a specific characteristic, as opposed to where in the body the tumor originated.

- **Xofluza (baloxavir marboxil)**, for the treatment of patients with uncomplicated **influenza** (flu). It is approved to be given as a single dose.

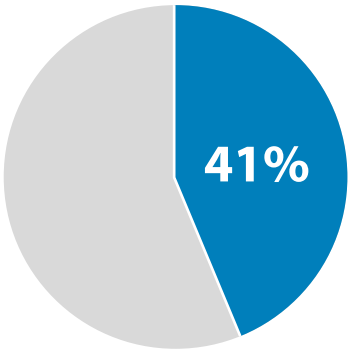
In 2018, CDER approved a new single dose treatment for patients with influenza (flu).

- **Zemdri (plazomicin)**, a once-daily antibiotic for the treatment of **complicated urinary tract infections** (cUTI). A "complicated UTI," as opposed to "simple UTI," is one in which the patient has structural abnormalities in his or her body, or other diseases that make the infection more difficult to treat. This approval is an important advance for patients with such complications.

Innovation: Frequent Use of Expedited Development and Review Pathways

CDER used several regulatory pathways to enhance efficiency and expedite the development and approval of novel drugs in 2018. These pathways use a range of approaches, including more interactions between CDER staff and drug developers, greater program design flexibility, and shortened timelines for review of applications.

CDER designated **24 of the 59** novel drugs (41%) in 2018 as Fast Track

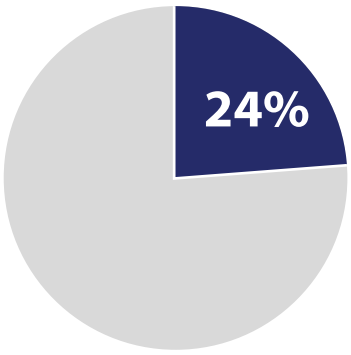


Fast Track

Fast Track-designated drugs have the potential to address unmet medical needs. CDER designated 24 of the 59 novel drugs (41%) in 2018 as Fast Track. Fast Track speeds new drug development and review by increasing the level of communication between FDA and drug developers, and by enabling CDER to review portions of a drug application ahead of the submission of the complete application.

Drugs designated with Fast Track status were: Aemcolo, Copiktra, Crysvita, Epidiolex, Erleada, Galafold, Lucemyra, Lumoxiti, Lutathera, Mulpleta, Nuzyra, Omegaven, Onpattro, Oxervate, Palynziq, Revcovi, Symdeko, Takhzyro, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Xerava, and Xospata.

CDER designated **14 of the 59** novel drugs (24%) in 2018 as breakthrough therapies



Breakthrough Therapy

Breakthrough therapies are drugs for serious or life-threatening diseases for which there is unmet medical need and for which there is preliminary clinical evidence demonstrating that the drug may result in substantial improvement on a clinically significant endpoint (usually an endpoint that reflects how the patient feels, functions or survives) over other available therapies. CDER designated 14 of the 59 novel drugs (24%) in 2018 as breakthrough therapies. A breakthrough therapy designation includes all the Fast Track program features, as well as more intensive FDA guidance on an efficient drug development program. Breakthrough therapy designation is designed to help shorten the development time of a potential new therapy.

Drugs designated with Breakthrough therapy status were: Crysvita, Elzonris, Firdapse, Gamifant, Krintafel, Libtayo, Lorbrena, Onpattro, Oxervate, Poteligeo, Symdeko, Takhzyro, Trogarzo, and Vitrakvi.

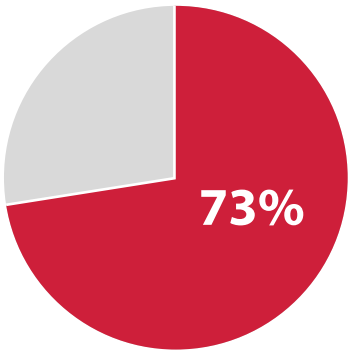
Priority Review

A drug receives a Priority Review if CDER determines that the drug could potentially provide a significant advance in medical care. The drug is reviewed in an expedited time line: within eight months instead of the standard 12 months. Forty-three of the 59 novel drugs approved in 2018 (73%) were designated Priority Review. Note, in some instances, priority review is assigned as a result of the sponsor redeeming a voucher for priority review under CDER's Priority Review Voucher program, which may mean the drug does not potentially provide a significant advance. Such drugs are not included in the list below.

Drugs designated Priority Review were: Aemcolo*, Ajovy, Biktarvy, Copiktra, Crysvita, Daurismo, Diacomit, Doptelet, Elzonris, Epidiolex, Erleada, Firdapse, Galafold, Gamifant, Krintafel, Libtayo, Lorbrena, Lucemyra, Lumoxiti, Lutathera, moxidectin, Mulpleta, Nuzyra*, Omegaven, Onpattro, Orilissa, Oxervate, Palynziq, Poteligeo, Revcovi, Symdeko, Takhzyro, Talzenna , Tegsedi, Tibsovo, Tpoxx, Trogarzo, Vitrakvi, Vizimpro, Xerava*, Xofluza, Xospata, and Zemdri.*

* Aemcolo, Nuzyra, Xerava, and Zemdri received Priority Review as Qualified Infectious Disease Products (QIDPs) as authorized by the Generating Antibiotics Incentives Now Act (GAIN Act), which provides incentives to help bring new antibiotics and other antimicrobials to market. These products may or may not have otherwise received the priority review designation.

43 of the 59 novel drugs approved in 2018 (73%) were designated Priority Review

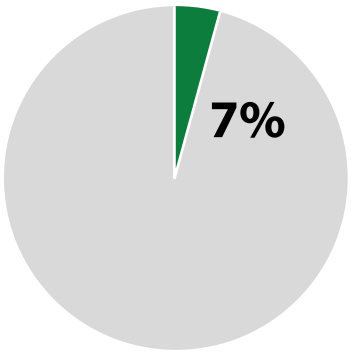


Accelerated Approval

The Accelerated Approval program allows FDA more flexibility in what endpoints can be used to approve a drug that offers a benefit over current treatments for a serious or life-threatening illness. These accelerated approval endpoints may include ones that show benefits over a shorter duration of treatment (where longer term demonstration of benefit is needed for full approval) or are considered as "reasonably likely" to predict that an important clinical benefit will be seen. Subsequent confirmatory trials must be conducted to support full approval. CDER approved four of the 59 novel drugs (7%) in 2018 under the Accelerated Approval program. The application of accelerated approval brings drugs that can provide important advances to patients sooner than with traditional approvals.

Novel drugs approved in 2018 that received the Accelerated Approval designation were: Copiktra, Galafold, Lorbrena, and Vitrakvi.

CDER approved **4 of the 59** novel drugs (7%) in 2018 under the Accelerated Approval program



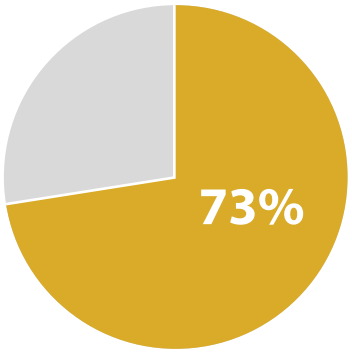
See Appendix B for a summary chart of designations for CDER's novel drug approvals.

Overall Use of Expedited Development and Review Methods

Forty-three of the 59 novel drug approvals of 2018 (73%) were designated in one or more expedited categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval.

Novel drugs approved in 2018 using at least one expedited approval method were: Aemcolo, Ajovy, Biktarvy, Copiktra, Crysvita, Daurismo, Diacomit, Doptelet, Elzonris, Epidiolex, Erleada, Firdapse, Galafold, Gamifant, Krintafel, Libtayo, Lorbrena, Lucemyra, Lumoxiti, Lutathera, moxidectin, Mulpleta, Nuzyra, Omegaven, Onpattro, Orilissa, Oxervate, Palynziq, Poteligeo, Revcovi, Symdeko, Takhzyro, Talzenna, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Vitrakvi, Vizimpro, Xerava, Xofluza, Xospata, and Zemdri.

43 of the 59 novel drug approvals of 2018 (73%) were designated in one or more expedited categories of Fast Track, Breakthrough, Priority Review, and/or Accelerated Approval



Predictability: Meeting PDUFA Goals

Under the Prescription Drug User Fee Act (PDUFA), sponsors are assessed user fees that provide FDA with the additional resources needed to maintain an efficient and effective review process. Throughout the year, CDER met or exceeded every PDUFA goal date for application review agreed to with the pharmaceutical industry and approved by Congress. In 2018, **CDER met its PDUFA goal dates for 100% of the novel drugs approved (59 of 59).**

Access: First Cycle Approval and Approvals Compared to Other Countries

First Cycle Approval

CDER approved 56 of the 59 novel drugs of 2018 (95%) on the "first cycle" of review, meaning without a "complete response" letter from FDA that requires re-submission with additional information, resulting in more time before the drug can be approved. From 2011 through 2017, CDER approved 250 novel drugs, of which 205 (82%) were approved on the first cycle. This high proportion of first-cycle approval reflects the extent to which CDER staff and drug developers work together to ensure that the application contains the information CDER needs to be able to fully review, and if appropriate, approve an application.

Novel drugs approved in 2018 on the first cycle were: Aemcolo, Aimovig, Ajovy, Akynzeo, Annovera, Asparlas, Biktarvy, Braftovi, Copiktra, Crysvita, Daurismo, Diacomit, Doptelet, Elzonris, Emgality, Epidiolex, Erleada, Firdapse, Galafold, Gamifant, Ilumya, Krintafel, Libtayo, Lorbrena, Lucemyra, Lumoxiti, Mektovi, Motegrity, moxidectin, Mulpleta, Nuzyra, Omegaven, Onpattro, Orilissa, Oxervate, Palynziq, Pifeltro, Poteligeo, Revcovi, Seysara, Symdeko, Takhzyro, Talzenna, Tavalisse, Tegsedi, Tibsovo, Tpoxx, Trogarzo, Ultomiris, Vitrakvi, Vizimpro, Xerava, Xofluza, Xospata, Yupelri, and Zemdri.

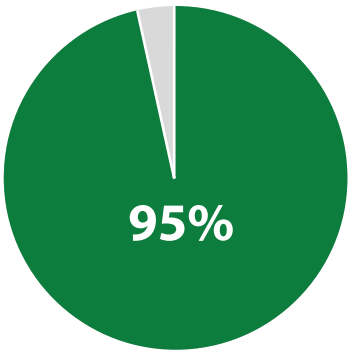
First cycle approval prevents delays in bringing valuable new therapies to market.

Approval in the United States Before Other Countries

Although regulatory processes differ widely between FDA and those of regulatory agencies in other countries, 42 of the 59 novel drugs approved in 2018 (71%) were approved in the United States before receiving approval in any other country.

Novel drugs of 2018 approved first in the United States were: Aemcolo, Aimovig, Ajovy, Akynzeo, Annovera, Asparlas, Biktarvy, Braftovi, Copiktra, Daurismo, Doptelet, Elzonris, Emgality, Epidiolex, Erleada, Gamifant, Ilumya, Krintafel, Libtayo, Lumoxiti, Mektovi, moxidectin, Nuzyra, Onpattro, Orilissa, Palynziq, Pifeltro, Revcovi, Seysara, Symdeko, Takhzyro, Talzenna, Tavalisse, Tibsovo, Tpoxx, Trogarzo, Ultomiris, Vitrakvi, Vizimpro, Xerava, Yupelri, and Zemdri.

CDER approved **56 of the 59** novel drugs of 2018 (95%) on the "first cycle" of review



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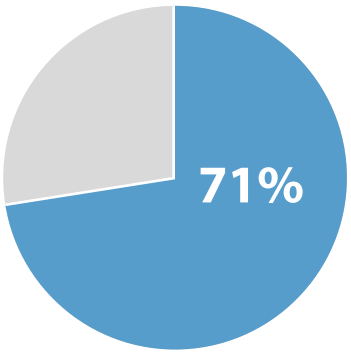


See Appendix B for a summary chart of designations for CDER's novel drug approvals.

New and Expanded Uses of Already FDA-Approved Drugs

After CDER approves a new drug, it is not uncommon for a manufacturer to submit an application with new data that demonstrate safety and effectiveness of the same product for an additional purpose or for use in a different population of patients. Applications to modify the use of an already-approved drug or to expand its use to other patients are in a category of supplemental applications known as "efficacy supplements."

New Uses

The products below are some notable approvals of 2018 for new uses of an already-FDA-approved drug:

- **Adcetris (brentuximab vedotin)**, originally approved in 2011 to treat patients with certain forms of Hodgkin lymphoma only after failure of other treatments. It was approved in March 2018 to treat adult patients with previously untreated stage III or IV **classical Hodgkin lymphoma** (a type of cancer of a part of the immune system called the lymphatic system) in combination with chemotherapy. This approval represents a significant improvement in the initial treatment regimens of advanced Hodgkin lymphoma that were introduced into clinical practice more than 40 years ago. In November 2018 CDER also expanded approval of Adcetris to include treatment, in combination with chemotherapy, for adult patients with certain types of **peripheral T-cell lymphoma** (PTCL). This is the first FDA approval for treatment of newly diagnosed PTCL, a rare, fast-growing form of non-Hodgkin lymphoma, a type of cancer involving white blood cells. The review to approve Adcetris for this PTCL indication was conducted under the Real-Time Oncology Review (RTOR) Pilot Program, a method of review that can lead to faster approval (see also Kisqali below).
- **Avycaz (ceftazidime and avibactam)**, originally approved in 2015 for the treatment of patients with complicated urinary tract infections. In 2018, this drug's approval was expanded to include the treatment of patients with **hospital-acquired bacterial pneumonia** and **ventilator-associated bacterial pneumonia** (HABP/VABP) caused by a variety of microorganisms.

- **Blincyto (blinatumomab)**, first approved in 2014 to treat patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia, a type of cancer of the blood and bone marrow. It was approved in 2018 to treat adults and children with B-cell precursor **acute lymphoblastic leukemia** (ALL) who are in remission but still have minimal residual disease (MRD). MRD refers to the presence of cancer cells below a level that can be seen under the microscope. In patients who have achieved remission after initial treatment for this type of ALL, the presence of MRD means they have an increased risk of relapse. This is the first FDA-approved treatment for patients with MRD-positive ALL. Because patients who have MRD are more likely to relapse, having a treatment option that eliminates even very low amounts of residual leukemia cells may help keep the cancer in remission longer.
- **Exparel (bupivacaine liposome injectable suspension)**, approved in 2011 for single use injection into a surgical site to produce postsurgical analgesia (pain relief). It was approved in 2018 for use as a nerve block to help adult patients with **pain management** for 48 hours after shoulder surgery. This approval helps to fill a need for additional nonaddictive pain management tools by providing a new option for certain patients. However, its new use is limited to individuals who have had shoulder surgery.
- **Hemlibra (emicizumab)**, originally approved in 2017 as a new drug for the prevention of bleeding or to reduce the frequency of bleeding episodes only in patients with hemophilia A who have developed antibodies called Factor VIII inhibitors. In 2018, this drug's approval was expanded to include a new indication for routine prevention of bleeding or to reduce the frequency of bleeding episodes in adults and children with **hemophilia A** with or without factor VIII inhibitors.
- **Invokana (canagliflozin)**, originally approved in 2013 as an adjunct to diet and exercise to improve glycemic (blood sugar) control in adults with type 2 diabetes mellitus. It was approved in 2018 to reduce the risk of **major adverse cardiovascular (CV) event**s in adults with type 2 diabetes who have or are at risk for CV disease.
- **Kisqali (ribociclib)**, first approved in 2017 for use in combination with an aromatase inhibitor for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic **breast cancer**, as

Expanding approval of an already-FDA approved drug can be much less costly, and just as effective, as developing a completely new drug.

2018 saw CDER's first approval granted as a part of two new pilot programs that aim to make the development and review of cancer drugs more efficient, while improving FDA's rigorous standard for evaluating efficacy and safety.

initial endocrine-based therapy. It was approved in 2018 in the same combination and for the same condition as its 2017 approval but also for **women who have not been through menopause**. It was also approved in 2018 for use in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine-based therapy or following disease progression on endocrine therapy. This is the first approval that FDA has granted as a part of two new pilot programs announced earlier this year that collectively aim to make the development and review of cancer drugs more efficient, while maintaining FDA's rigorous standard for evaluating efficacy and safety. Using these pilots, FDA exercised real-time review in which our reviewers could start evaluating the clinical data as soon as the trial results became available. In this way, FDA was ready to approve the new use of this drug soon after filing the sponsor's application.

- **Lynparza (olaparib tablets)**, first approved in 2017 to treat certain patients with specific types of epithelial ovarian, fallopian tube, or peritoneal cancers. The use of Lynparza tablets was approved in 2018 for the treatment of patients with certain types of **breast cancer** that have spread (metastasized) and whose tumors have a specific inherited (germline) genetic mutation, making this the first drug in its class (poly ADP ribose polymerase, or "PARP" inhibitor) approved to treat breast cancer. It is also the first time any drug has been approved to treat certain patients with metastatic breast cancer who have a "BRCA" gene mutation. Patients are selected for treatment with Lynparza tablets based on an FDA-approved genetic test, called the BRACAnalysis CDx.

- **Mekinist (trametinib)** and **Tafinlar (dabrafenib)**, administered together, for the treatment of **anaplastic thyroid cancer** (ATC) that cannot be removed by surgery or has spread to other parts of the body, and has a type of abnormal gene, BRAF V600E (BRAF V600E mutation-positive). Anaplastic is a term used to describe cancer cells that divide rapidly and have little or no resemblance to normal cells. This is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer, and the third cancer with this specific gene mutation that this drug combination has been approved to treat. The other two are BRAF V600 mutation-positive metastatic melanoma and BRAF V600E mutation-positive, metastatic non-small cell lung cancer. This approval demonstrates that targeting the same molecular pathway in diverse diseases is an effective way to expedite the development of treatments that may help more patients. Mekinist was also originally approved in 2013 for treatment of certain patients with melanoma (skin cancer). Separately, Tafinlar was originally approved in 2013 to treat certain patients with melanoma.

- **Trisenox (arsenic trioxide)** approved in 2000 for the treatment of certain adult patients with low-risk **acute promyelocytic leukemia (APL)**, a sub-type of acute myeloid leukemia (AML), whose initial treatment with another drug was unsuccessful. It was approved in 2018 to also treat certain patients who are newly-diagnosed with the condition.

- **Venclexta (venetoclax)** for a new indication of treatment of the blood cancer, **acute myeloid leukemia** (AML) in combination with certain other medications in newly-diagnosed patients who are ineligible for intensive chemotherapy. This drug received accelerated approval in 2016 and then regular approval in June 2018 for treating certain patients with chronic lymphocytic leukemia and small lymphocytic leukemia.

- **Xeljanz (tofacitinib)**, first approved in 2012 to treat certain patients with rheumatoid arthritis. It was approved in 2018 to treat adults with moderately to severely active **ulcerative colitis**, a chronic, inflammatory bowel disease affecting the colon. This is the first oral medication approved for chronic use in this indication. Other FDA-approved treatments for the chronic treatment of moderately to severely active ulcerative colitis must be administered through an intravenous infusion or subcutaneous injection.

- **Xeomin (incobotulinumtoxinA)**, approved in 2009 for treatment of cervical dystonia (painful and involuntary neck muscle contraction) and blepharospasm (involuntary closing of the eyelids). This drug's approval was expanded in 2018 to include treatment of adult patients with **chronic sialorrhea** (excessive drooling), a common condition in a variety of neurological diseases.

New Populations

The products listed below are notable approvals in 2018 of an already-approved drug for use in an expanded population of patients:

- **Astagraf XL (tacrolimus extended-release capsules)**, approved in 2018 with an expanded indication to help prevent kidney transplant rejection in children who can swallow capsules intact. It was originally approved in 2013 only for adult kidney transplant patients. This drug is a long-acting formulation of the drug tacrolimus. Tacrolimus was first approved by the FDA in 1994 to prevent liver transplant rejection and subsequently expanded over the years to include kidney and heart transplants.
- **Gilenya (fingolimod)**, first approved in 2010 to treat adults with **relapsing multiple sclerosis** (MS). In 2018, it was approved to treat children and adolescents age 10 years and older with relapsing MS. This is the first FDA approval of a drug to treat MS in pediatric patients.
- **Latuda (lurasidone)**, originally approved in 2010 to treat patients with schizophrenia --- and subsequently approved in 2013 with a new indication to treat adult patients with depressive episodes associated with **bipolar I disorder** (bipolar depression). In 2018, it was approved to treat children and adolescents with major depressive episodes with bipolar I disorder.
- **Lithium**, for the treatment of pediatric patients with **bipolar I disorder**. Lithium was approved by FDA in 1980 and has been used to treat a wide variety of illnesses in adults, including bipolar disorder; depression; schizophrenia. eating disorders including anorexia and bulimia; and blood disorders, including anemia and low white-cell count. The National Institutes of Health (NIH) conducted two adequate and well controlled studies in pediatric patients with bipolar I disorder. The NIH study results enabled FDA to approve this new use for children.
- **Tasigna (nilotinib)** originally approved in 2007 to treat adults with certain forms of **chronic myeloid leukemia** in patients resistant to prior therapy with other treatments. It was approved in 2018 to treat pediatric patients one year of age or older with the same conditions.

In 2018, CDER approved the first therapy to treat multiple sclerosis in children.

Additional Approvals

In addition to the many notable novel drug and efficacy supplement approvals of 2018, CDER approved a variety of other therapies. Among these are biosimilars, and new formulations, manufacturers, combinations, or dosage forms of already FDA-approved drugs, as well as others. Below are notable examples of these various types of approvals.

Biosimilars expand treatment options and bring competition to the U.S. marketplace.

Biosimilars

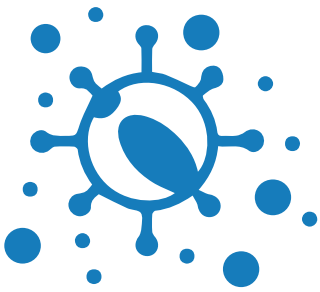
An FDA-approved biosimilar is highly similar to and has no clinically meaningful differences in terms of safety, purity and potency (safety and effectiveness) from an already FDA-approved biological product, called the reference product. Biological products are highly complex, and often used to treat patients with serious and life-threatening conditions. The law allowing FDA to approve biosimilars was designed to create competition, increase patient access, and potentially reduce cost of important therapies.

In 2018, CDER approved seven new biosimilars:

- **Fulphila (pegfilgrastim-jmdb)**, and **Udenyca (pegfilgrastim-cbqv)**, respectively the first and second biosimilars to Neulasta (pegfilgrastim), approved to **decrease the chance of infection** as suggested by febrile neutropenia (fever, often with other signs of infection, associated with an abnormally low number of infection-fighting white blood cells), in patients with non-myeloid (non-bone marrow) cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia. Myelosupression is reduced bone marrow activity leading to low production of red blood cells, white blood cells, and platelets.
- **Herzuma (trastuzumab-abtr)**, the second biosimilar to Herceptin (trastuzumab), to treat patients with breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma) whose tumors overexpress the HER2 gene. CDER approved the first Herceptin biosimilar, Ogivri (trastuzumab – dkst) in 2017.
- **Hyrimoz (adalimumab-adaz)**, the third biosimilar to Humira, approved to treat patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. CDER approved Amjevita (adalimumab – atto), first biosimilar to Humira, in 2016. The second, Cyltezo (adalimumab–adbm), was approved in 2017.

- **Nivestym (filgrastim-aafi)**, the second biosimilar to Neupogen (filgrastim). It is approved to d**ecrease the chance of infection** for certain patients receiving myelosuppressive anti-cancer drugs (those that reduce bone marrow production of platelets, and red and white blood cells); reducing the time to restore white blood cells and recovery from fever, following certain chemotherapy treatment of patients with acute myeloid leukemia; reducing the duration of low white blood cell count episodes and their adverse effects, such as fever and infections, in certain patients undergoing chemotherapy followed by bone marrow transplantation; to enhance the process of leukapheresis (a laboratory procedure in which white blood cells are separated from a sample of blood); and chronic administration to reduce the incidence and duration of the adverse effects of low white blood cell count. CDER approved the first Neupogen biosimilar, Zarxio (filgrastim – sndz) in 2015.
- **Retacrit (epoetin alfa-epbx)**, the first biosimilar to Epogen/Procrit (epoetin alfa), approved for the treatment of patients with **anemia** caused by chronic kidney disease, chemotherapy, or use of zidovudine in patients with HIV-1 infection. Retacrit is also approved for use before and after surgery to reduce the chance that red blood cell transfusions will be needed because of blood loss during surgery.
- **Truxima (rituximab-abbs)**, the first biosimilar to Rituxan (rituximab), is approved for use in previously untreated follicular, CD20-positive, B-cell Non-Hodgkin Lymphoma (NHL) in combination with first-line chemotherapy or as single-agent maintenance therapy in patients that have achieved a complete or partial response to Rituxan in combination with chemotherapy. Truxima is also approved for relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL and for non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.

CDER has now approved a total of 16 biosimilars for 9 different reference products since 2015. This includes at least one biosimilar for each of these top selling biological drugs in the United States: Humira, Rituxan, Enbrel, Herceptin, Avastin, Remicade, and Neulasta. Two biological reference products (Humira and Remicade) now have three biosimilars each, three reference products (Herceptin, Neulasta, and Neupogen) have two biosimilars each, and four reference products (Avastin, Enbrel, Epogen/Procrit, and Rituxan) currently each have one biosimilar. Multiple biosimilars for an FDA-approved reference product can strengthen market competition. An increase in market competition may lead to significantly reduced costs for both patients and our healthcare system.



New Formulations and Other Notable Approvals

A new formulation of a drug is one in which the product's active ingredient is already FDA-approved. New formulations of already-approved drugs can offer significant advances in therapy. Below are notable new formulations as well as other notable non-novel drug approvals of 2018, including, but not limited to, those with a new combination of active ingredients or a new manufacturer of an already FDA-approved drug.

- **Arakoda (tafenoquine)** for the prevention of **malaria** in adults for up to six months of continuous dosing. After a loading regimen (multiple doses to reach the intended blood level), the drug is taken once weekly. (see also, Krintafel under Other Notable Novel Drug Approvals).
- **Aristada Initio (aripiprazole lauroxil)**, a new formulation of the drug, Aristada (aripiprazole), approved in 2015 to treat patients with **schizophrenia**. This new formulation is to be used as an intramuscular injection in combination with oral aripiprazole to initiate therapy. Prior to approval of Aristada Initio, dosing for aripiprazole needed to be gradual, starting at a low dose and gradually increasing to an effective dose. This new formulation enables immediate dosing to therapeutic levels --- an important feature to help treat symptoms of schizophrenia as soon as possible.
- **Atropine autoinjector**, for emergency use in the initial treatment of **muscarinic symptoms of poisoning by certain insecticides, or nerve agents**, including those that can be used in bioterrorism attacks. Muscarinic symptoms include excessive salivation, sweating, watering of the eyes, urination, diarrhea, vomiting, and abnormal heart rhythms, and can be fatal. The autoinjector can be used for adults and for children who weigh more than 90 pounds (usually about 10 years of age or older). It can be injected through clothing and is a valuable addition to our country's efforts to protect against terror attacks. This is a new formulation of the drug, atropine, which has been approved by FDA for many years and in many other dosage forms.
- **Azedra (iobenguane I 131)** for the treatment of patients 12 and older with **pheochromocytoma or paraganglioma** (rare tumors of the adrenal gland) that cannot be surgically removed (unresectable), have spread beyond the original tumor site, and require systemic anticancer therapy. This is the first FDA-approved drug for this use. Prior to this approval, iobenguane I 131 was approved in 1994 as a diagnostic agent used to help find tumors but not treat them, and was subsequently discontinued by the manufacturer.

CDER approved a discontinued diagnostic drug to treat rare tumors of the adrenal gland --- **the first FDA-approved drug for this use.**

- **RadioGenix System (Technetium Tc-99 sodium pertechnetate generator)**, to produce Technetium-99m (Tc-99m), a **radioactive imaging** product used to detect potentially life-threatening diseases like coronary artery disease and cancer, as well as evaluating lung, liver, kidney and brain function. Every day, tens of thousands of people in the United States undergo a nuclear medical imaging procedure that depends on Tc-99m, yet health care professionals have faced challenges with adequate supply due to a complex supply chain that has sometimes resulted in shortages. Before this approval, production of Tc-99m depended on the use of enriched uranium that had to be shipped from the United States to foreign facilities to make Molybdenum-99, or Mo-99, the source of Tc-99m. The RadioGenix System does not require the use of enriched uranium. Its approval marks the first non-uranium process to produce Mo-99 to prepare Tc-99m and the first time in 30 years that patients in the United States have a domestic source of this important diagnostic agent.
- **Jynarque (tolvaptan)**, approved to **slow kidney function decline** in patients with autosomal-dominant polycystic kidney disease, the first product approved for this use. It is a new formulation of the drug tolvaptan, which was originally approved in 2009 under the trade name Samsca to treat patients with hyponatremia (not enough sodium in the blood).

CDER approved a new technology to produce Tc-99 for a wide range of imaging studies to diagnose illness --- ensuring adequate supplies without having to depend on foreign sources.

As with all FDA-approved products, **the new drug therapies approved by CDER discussed in this report are associated with risks**. For more information about these drugs and for complete risk information, see the drugs' approval letters and FDA-approved labeling at Drugs@FDA.

New Dosage Forms

New dosage forms for already FDA-approved drugs can improve patient health by helping to increase patient adherence to therapy, ensure a proper dose is taken, and improve quality of life for patients who must use the medication on a prolonged basis. Notable approvals in this category include:

- **Arikayce (amikacin liposome inhalation suspension)** a new inhaled formulation of the injectable antibiotic amikacin, which has been approved by FDA for more than 30 years and used to treat patients with a variety of very serious infections. Arikayce was approved for adults who have limited or no alternative treatment options for the treatment of **Nontuberculous Mycobacterial (NTM) lung disease** caused by Mycobacterium avium Complex (MAC) as part of a combination antibiotic regimen. NTM is an uncommon organism, often present in the environment. Susceptible patients, with underlying chronic lung disease, can develop a lung infection. This is the first antibacterial drug product approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway, established by Congress under the 21st Century Cures Act. LPAD is designed to streamline development and approval of antibacterial drugs to treat serious or life-threatening infections in a limited population of patients with unmet need.

CDER approved the first antibiotic approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) pathway, which helps to ensure that new antibiotics are used only for certain patients with certain conditions --- to prevent over-use and development of bacterial resistance to the drug.

- **Dsuvia (sufentanil)**, a sublingual (under the tongue) opioid analgesic tablet delivered through a disposable, pre-filled, single-dose applicator. It is approved for use in adults in a certified medically supervised healthcare setting, such as hospitals, surgical centers, and emergency departments for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Dsuvia was approved with a Risk Evaluation and Mitigation Strategy (REMS) to ensure that it is dispensed only to patients in certified medically supervised healthcare settings to mitigate the risk of respiratory depression resulting from accidental exposure. Because of the REMS constraints, Dsuvia may not be dispensed by pharmacies directly to patients for home use. Dsuvia is the first orally administered sufentanil product approved by the FDA. Sufentanil for intravenous administration was first approved by the FDA under the trade name Sufenta in 1984 and has been used for decades as an injectable opioid analgesic, primarily in surgical and critical care settings where pain relief is required for a short period of time
- **Perseris (risperidone)**, the first FDA-approved antipsychotic with a subcutaneous (SQ) route of administration. SQ means it is injected under the skin. Risperidone oral tablets were originally approved in 1993. There have since been a variety of new dosage forms, such as oral solutions and intramuscular injections. This new SQ dosage form is long-acting and administered once per month.
- **Prograf Granules (tacrolimus for oral suspension)**, a new dosage form of tacrolimus, which has been available in oral capsules and injectable forms since 1994. Tacrolimus is an **anti-rejection medication** following kidney, liver, or heart transplant. The granules are mixed with water by the patient or caregiver before it is administered. This new dosage form helps patients who cannot swallow pills.
- **Qbrexza (glycopyrronium)**, a new dosage form of glycopyrronium with the medication available in a cloth for applying to the skin. It is approved to treat patients nine years of age and older who have **primary axillary hyperhidrosis** (excessive underarm sweating).

Conclusion

CDER's staff consists of individuals with a range of different areas of expertise, including physicians, safety evaluators, chemists, biologists, biostatisticians, nurses, pharmacists, pharmacologists, epidemiologists, legal and regulatory experts, and many more. They work together to bring safe and effective drug therapies to the American public as efficiently as possible.

These therapies come in the form of novel drugs never before marketed in the United States, other new drugs that add important medical value, already FDA-approved products approved for new uses and for administration to new populations of patients, and new dosage forms of products designed to offer advantages over earlier versions.

More important than the quantity of the new therapies is their medical value and the important new roles these drugs are serving to advance patient care.

Also noteworthy is the efficiency with which these drugs were reviewed and approved. CDER used a variety of expedited development and regulatory review tools to help speed these drugs to market.

In all cases, while striving for efficiency of review of applications for new drug therapies, CDER maintains its rigorous standards for demonstration of safety and efficacy.

Our drug therapy approvals of 2018 will help many patients in need for years to come. However, CDER's mission goes well beyond critically reviewing the safety and efficacy of drug applications we receive from industry. We also look to advance the science and technology that can lead to future innovative drugs --- many of which may not yet even be conceived. We are working to develop more efficient and innovative approaches for evaluating the safety and efficacy of the drug therapies that will come from these new advances.

Although not a comprehensive compilation of all our approvals for the year, this report serves to provide a wide variety of valuable examples of the many ways CDER approves new drug therapies to enhance patient health.

Although our regulatory work extends to many scientific, clinical, and technological areas, we cannot accomplish all that is necessary on our own. CDER works collaboratively with a wide range of stakeholders across the medical community, including academia, industry, patients and their caregivers, patient advocacy groups, state and other federal agencies, and more. Listening has become an important component of this work. We strive to ensure that we understand the needs of our key constituencies and that we are providing the most benefit for patients and the strongest possibilities for improved public health in America.

Appendix A: CDER's Novel Approvals of 2018 (In alphabetical order)

For information about vaccines, allergenic products, blood and blood products, cellular and gene therapy products go to 2018 Biological License Application Approvals.

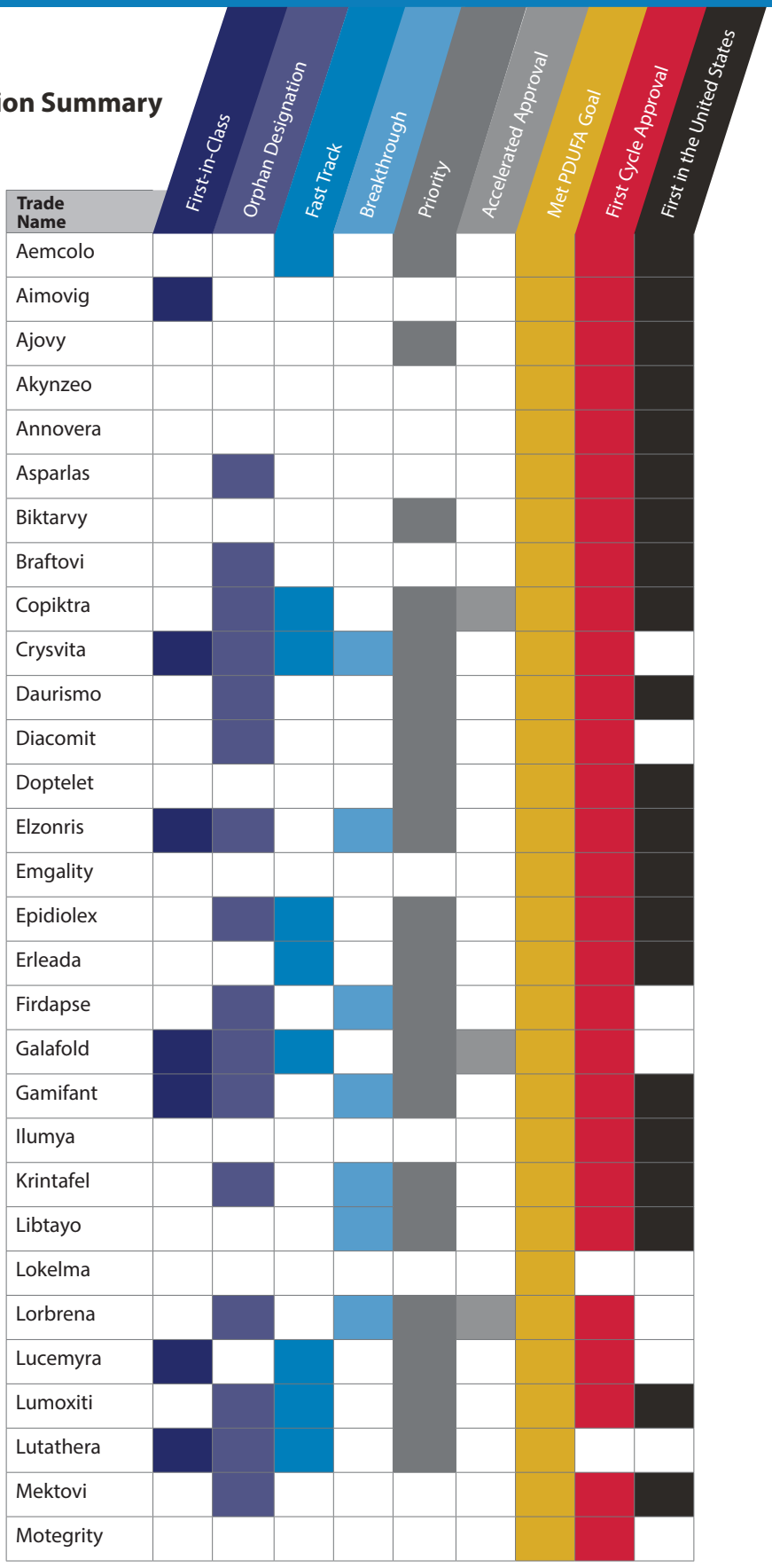
Trade Name	Active Ingredient	Summary of FDA-approved use on approval date (See Drugs@FDA for complete indication)	Dosage Form
Aemcolo	Rifamycin SV MMX	Traveller's diarrhea	Tablet
Aimovig	erenumab-aooe	Preventive treatment for migraine	Injection
Ajovy	fremanezumab-vfrm	Preventive treatment for migraine	Injection
Akynzeo	fosnetupitant and palonosetron	Prevent acute and delayed nausea and vomiting for certain patients using cancer chemotherapy	Injection
Annovera	segesterone acetate and ethinyl estradiol	Vaginal ring used to prevent pregnancy	Vaginal Ring
Asparlas	calaspargase pegol-mknl	Acute lymphoblastic leukemia	Injection
Biktarvy	bictegravir, embitcitabine, tenofovir alafenamide	HIV-1 infection	Tablet
Braftovi	encorafenib	Unresectable or metastatic melanoma	Capsule
Copiktra	duvelisib	Relapsed or refractory chronic lymphocytic leukemia, small lymphocytic lymphoma and follicular lymphoma	Capsule
Crysvita	burosumab-twza	X-linked hypophosphatemia	Injection
Daurismo	glasdegib	Acute myeloid leukemia or high-risk myelodysplastic syndrome	Tablet
Diacomit	stiripentol	Dravet syndrome	Capsule
Doptelet	avatrombopag	Thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure	Tablet
Elzonris	tagraxofusp-erzs	Blastic plasmacytoid dendritic cell neoplasm	Injection
Emgality	galcanezumab-gnlm	Preventive treatment for migraine	Injection
Epidiolex	cannabidiol	Lennox-Gastaut syndrome and Dravet syndrome	Oral Solution
Erleada	apalutamide	Prostate cancer	Tablet
Firdapse	amifampridine phosphate	Lambert-Eaton Myasthenic Syndrome	Tablet
Galafold	migalastat	Fabry disease	Capsule
Gamifant	emapalumab-lzsg	Primary hemophagocytic lymphohistiocytosis	Injection
Ilumya	tildrakizumab-asmn	Moderate-to-severe plaque psoriasis	Injection
Krintafel	tafenoquine	Radical cure of Plasmodium vivax malaria	Tablet
Libtayo	cemiplimab-rwlc	Cutaneous squamous cell carcinoma	Injection
Lokelma	sodium zirconium cyclosilicate	Hyperkalemia	Powder for Suspension
Lorbrena	lorlatinib	Anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer	Tablet
Lucemyra	lofexidine hydrochloride	Non-opioid treatment of opioid withdrawal symptoms	Tablet
Lumoxiti	moxetumomab pasudotox-tdfk	Hairy cell leukemia	Injection

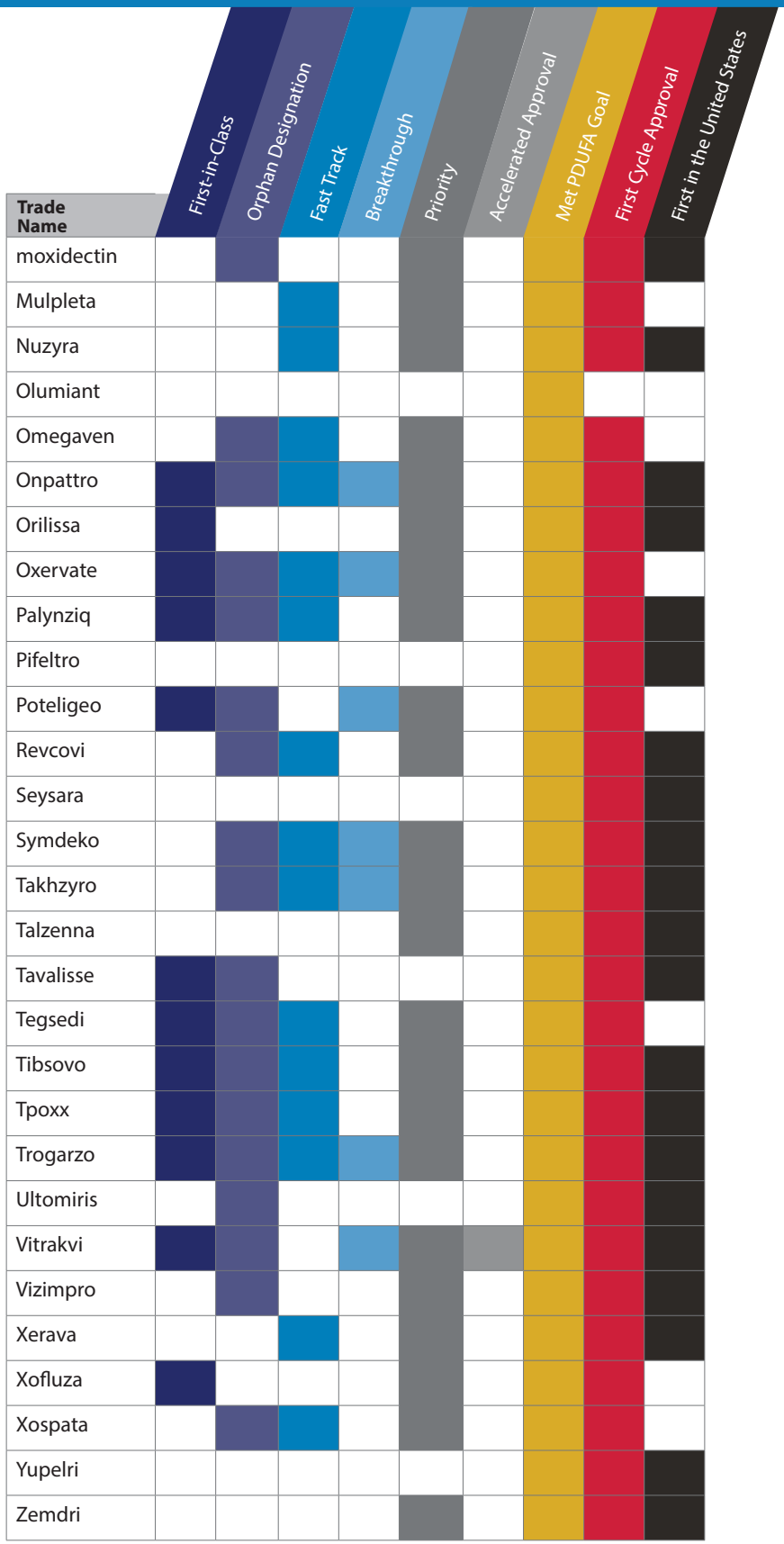
Trade Name	Active Ingredient	Summary of FDA-approved use on approval date (See Drugs@FDA for complete indication)	Dosage Form
Lutathera	lutetium Lu 177 dotatate	Gastroenteropancreatic neuroendocrine tumors	Injection
Mektovi	binimetinib	Unresectable or metastatic melanoma	Tablet
Motegrity	prucalopride succinate	Chronic idiopathic constipation	Tablet
Moxidectin	moxidectin	Onchocerciasis due to onchocerca volvulus	Tablet
Mulpleta	lusutrombopag	Thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure	Tablet
Nuzyra	omadacycline	Community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections	Tablet
Olumiant	baricitinib	Moderately to severely active rheumatoid arthritis	Tablet
Omegaven	fish oil triglycerides	A source of calories and fatty acids in pediatric parenteral nutrition-associated cholestasis	Injection
Onpattro	patisiran	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Injection
Orilissa	elagolix sodium	Pain associated with endometriosis	Tablet
Oxervate	cenegermin-bkbj	Neurotrophic keratitis	Ophthalmic solution
Palynziq	pegvaliase-pqpz	Phenylketonuria	Injection
Pifeltro	doravirine	HIV-1 infection in adult patients	Tablet
Poteligeo	mogamulizumab-kpkc	Relapsed or refractory mycosis fungoides or Sézary syndrome	Injection
Revcovi	elapegademase-lvlr	Adenosine deaminase-severe combined immunodeficiency	Injection
Seysara	sarecycline	Severe acne vulgaris	Tablet
Symdeko	tezacaftor; ivacaftor	Cystic fibrosis	Tablet
Takhzyro	lanadelumab	Types I and II hereditary angioedema	Injection
Talzenna	talazoparib	Metastatic breast cancer	Capsule
Tavalisse	fostamatinib	Thrombocytopenia	Tablet
Tegsedi	inotersen	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Injection
Tibsovo	ivosidenib	Relapsed or refractory acute myeloid leukemia	Tablet
Tpoxx	tecovirimat	Smallpox	Capsule
Trogarzo	ibalizumab-uiyk	HIV-1 infection	Injection
Ultomiris	ravulizumab-cwvz	Paroxysmal nocturnal hemoglobinuria	Injection
Vitrakvi	larotrectinib	Metastatic solid tumors with NTRK-fusion proteins	Capsule
Vizimpro	dacomitinib	Metastatic non-small-cell lung cancer	Tablet
Xerava	eravacycline	Complicated intra-abdominal infections	Injection
Xofluza	baloxavir marboxil	Acute uncomplicated influenza	Tablet
Xospata	gilteritinib	Acute myeloid leukemia	Tablet
Yupelri	revefenacin	Chronic obstructive pulmonary disease	Inhalation Solution
Zemdri	plazomicin	Complicated urinary tract infections	Injection

Appendix B:

Novel Drug Designation Summary

(In alphabetical order)




Trade Name
First-in-Class
Orphan Designation
Fast Track
Breakthrough
Priority
Accelerated Approval
Met PDUFA Goal
First Cycle Approval
First in the United States
moxidectin
Mulpleta
Nuzyra
Olumiant
Omegaven
Onpattro
Orilissa
Oxervate
Palynziq
Pifeltro
Poteligeo
Revcovi
Seysara
Symdeko
Takhzyro
Talzenna
Tavalisse
Tegsedi
Tibsovo
Tpoxx
Trogarzo
Ultomiris
Vitrakvi
Vizimpro
Xerava
Xofluza
Xospata
Yupelri
Zemdri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