2018 FDA drug approvals

The FDA approved a record 59 drugs last year, but the commercial potential of these drugs is lacklustre.

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The FDA's Center for Drug Evaluation and Research (CDER) approved 59 novel drugs in 2018, breaking its record of 53 drugs in 1996 (FIG. 1; TABLE 1). This bumper approval crop follows on the heels of a few fruitful years for drug developers. The FDA's 5-year annual average is now 43 drugs per year, nearly twice its nadir in 2009.

As in previous years, US regulators approved a high proportion of orphan drugs and cancer drugs (FIG. 2). The 34 orphan drugs approved in 2018 accounted for 58% of the total — higher than the 5-year average of 45%. Cancer drugs make up 27% of the total, in keeping with a 5-year average of 25%. 13 of the 16 cancer drugs were for orphan indications, representing 38% of the orphan cohort.

Other therapeutic areas with high approval counts included infectious diseases and neurology (FIG. 3). Both of these therapeutic areas also scored multiple approvals in 2017 and 2016.

The agency approved 14 drugs with breakthrough therapy designation, 24% of the cohort. This is down from the 5-year running average of 29%. Breakthrough designation is intended for drugs that promise substantial improvements over existing therapies in serious or life-threatening diseases.

However, the commercial potential of the class of 2018 is lacklustre. Only two of the newly approved products are expected to achieve annual sales of US$2 billion or more by 2024 or sooner, suggest consensus sales forecasts collected by Clarivate Analytics's Cortellis platform. Another 11 products should reach peak sales of more than $1 billion (FIG. 4). In 2017, by contrast, 7 of the newly approved products were on track for multibillion-dollar annual sales and another 9 had billion-dollar sales potential.

The combined and average projected peak sales of the newly approved drugs is also on the decline, shows an annual analysis by Boston Consulting Group. These analysts forecast combined peak sales of $45 billion for this year's newly approved drugs, corresponding to average peak sales of only $720 million per drug. This is down from a high point of $84 billion in 2014, when average peak sales potential was $1.6 billion per drug. The low point was 2008, with cumulative sales of $13 billion and average peak sales of $500 million.

Sales forecasts are notoriously unreliable, however, and can miss actual revenue numbers by more than 40%.

The agency's Center for Biologics Evaluation and Research (CBER) approved only a few notable new products in 2018 (TABLE 2). FDA rejections were also down last year (TABLE 3).

Notable approvals

The new approval with the greatest commercial potential is Gilead Sciences' combination product Biktarvy, for the treatment of HIV.

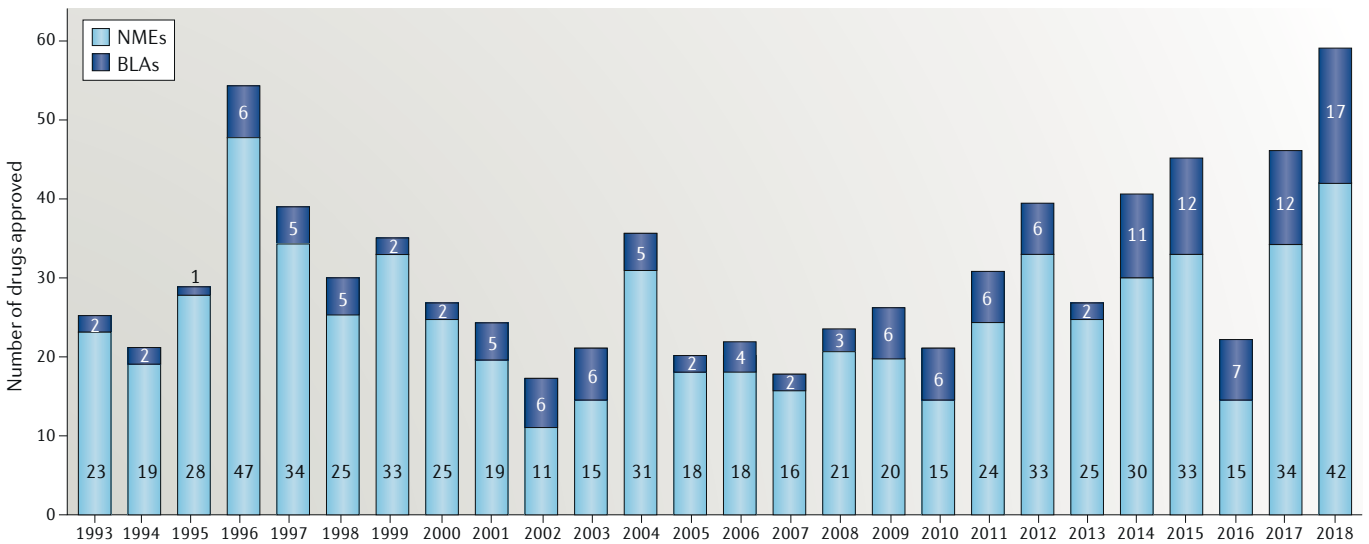

Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2018. Approvals of products such as vaccines by the Center for Biologics Evaluation and Research (CBER) are not included in this drug count (see Table 2). Source: Drugs@FDA.

Table 1 | **CDER approvals in 2018**

Drug (brand name)	Sponsor	Properties	Indication	Review type
Lutetium Lu 177 dotatate (Lutathera)	Advanced Accelerator Applications/Novartis	Somatostatin receptor-targeted radiopharmaceutical	GEP-NETs	P, O
Bictegravir, emtricitabine and tenofovir alafenamide (Biktarvy)	Gilead Sciences	HIV-1 integrase inhibitor and HIV-1 nucleoside/nucleotide reverse transcriptase inhibitors	HIV	P
Tezacaftor and ivacaftor (Symdeko)	Vertex Pharmaceuticals	CFTR corrector and CFTR potentiator	Cystic fibrosis	P, O, B
Apalutamide (Erleada)	Johnson & Johnson	Androgen receptor inhibitor	Prostate cancer	P
Ibalizumab (Trogarzo)[a]	TaiMed Biologics/ Theratechnologies	CD4 antibody	HIV	P, O, B
Tildrakizumab (Ilumya)[a]	Sun Pharma	IL-23 antibody	Plaque psoriasis	S
Fostamatinib (Tavalisse)	Rigel Pharmaceuticals	SYK inhibitor	Immune thrombocytopenic purpura	S, O
Burosumab (Crysvita)[a]	Ultragenyx Pharmaceutical/Kyowa Hakko Kirin	FGF23 antibody	X-linked hypophosphataemia	P, O, B
Palonosetron and fosnetupitant (Akynzeo IV)	Helsinn Group	5-HT_3 receptor antagonist and NK_1 receptor antagonist	Chemotherapy-induced emesis	S
Lofexidine (Lucemyra)	US WorldMeds	α_2-adrenoceptor agonist	Opioid withdrawal	P
Erenumab (Aimovig)[a]	Amgen/Novartis	CGRP receptor antibody	Migraine	S
Sodium zirconium cyclosilicate (Lokelma)	AstraZeneca	Potassium binder	Hyperkalaemia	S
Avatrombopag (Doptelet)	Dova Pharmaceuticals	Thrombopoietin receptor agonist	Thrombocytopenia	P
Pegvaliase (Palynziq)[a]	BioMarin Pharmaceutical	PAL replacement therapy	Phenylketonuria	P, O
Baricitinib (Olumiant)	Incyte/Eli Lilly	JAK inhibitor	Rheumatoid arthritis	S
Moxidectin (NA)	Medicines Development for Global Health	Antihelmintic GABA receptor and glutamate channel modulator	River blindness	P, O
Cannabidiol (Epidiolex)	GW Pharmaceuticals	Cannabinoid	Dravet syndrome and Lennox–Gastaut syndrome	P, O
Plazomicin (Zemdri)	Achaogen	Aminoglycoside antibacterial	Urinary tract infections	P
Binimetinib (Mektovi)	Array BioPharma	MEK inhibitor	BRAF-mutated melanoma	S, O
Encorafenib (Braftovi)	Array BioPharma	BRAF inhibitor	BRAF-mutated melanoma	S, O
Tecovirimat (TPOXX)	SIGA Technologies	Viral p37 protein inhibitor	Smallpox	P, O
Ivosidenib (Tibsovo)	Agios Pharmaceuticals	IDH1 inhibitor	IDH1-mutated AML	P, O
Tafenoquine (Krintafel)	Medicines for Malaria Venture/GlaxoSmithKline	8-Aminoquinoline antimalarial	*Plasmodium vivax* malaria	P, O, B
Elagolix sodium (Orilissa)	AbbVie	GnRH receptor antagonist	Pain associated with endometriosis	P
Fish oil triglycerides (Omegaven)	Fresenius	Mixture of fatty acids	Parenteral nutrition-associated cholestasis	P, O
Lusutrombopag (Mulpleta)	Shionogi	Thrombopoietin receptor agonist	Thrombocytopenia	P
Mogamulizumab (Poteligeo)[a]	Kyowa Hakko Kirin	CCR4 antibody	Mycosis fungoides and Sézary syndrome	P, O, B
Patisiran (Onpattro)	Alnylam Pharmaceuticals	TTR-directed small interfering RNA	Hereditary TTR-mediated amyloidosis	P, O, B
Segesterone acetate and ethinyl estradiol vaginal system (Annovera)	TherapeuticsMD	Progestin and estrogen combined hormonal contraceptive	Female contraception	S
Migalastat (Galafold)	Amicus Therapeutics	α-galactosidase regulator	Fabry disease	P, O, A

Table 1 (cont.) | **CDER approvals in 2018**

Drug (brand name)	Sponsor	Properties	Indication	Review type
Stiripentol (Diacomit)	Biocodex	GABA reuptake inhibitor	Dravet syndrome	P, O
Cenegermin (Oxervate)[a]	Dompé	Recombinant NGF	Neurotrophic keratitis	P, O, B
Lanadelumab (Takhzyro)[a]	Dyax/Shire	Kallikrein antibody	Hereditary angioedema	P, O, B
Eravacycline (Xerava)	Tetraphase Pharmaceuticals	Tetracycline antibiotic	Complicated intra-abdominal infections	P
Doravirine (Pifeltro)	Merck & Co.	NNRTI	HIV	S
Moxetumomab pasudotox (Lumoxiti)[a]	AstraZeneca	CD22-directed antibody–drug conjugate	Hairy cell leukaemia	P, O
Fremanezumab (Ajovy)[a]	Teva	CGRP antibody	Migraine	P
Duvelisib (Copiktra)	Verastem	PI3K inhibitor	CLL, FL and SLL	P, O, A
Galcanezumab (Emgality)[a]	Eli Lilly	CGRP antibody	Migraine	S
Dacomitinib (Vizimpro)	Pfizer	EGFR inhibitor	EGFR-mutated NSCLC	P, O
Cemiplimab (Libtayo)[a]	Regeneron/Sanofi	PD1 antibody	CSCC	P, B
Sarecycline (Seysara)	Allergan	Tetracycline antibiotic	Severe acne vulgaris	S
Omadacycline (Nuzyra)	Paratek Pharmaceuticals	Tetracycline antibiotic	CABP and ABSSSI	P
Elapegademase (Revcovi)[a]	Leadiant Biosciences	Recombinant adenosine deaminase	ADA-SCID	P, O
Inotersen (Tegsedi)	Ionis Pharmaceuticals	TTR-directed antisense oligonucleotide	Hereditary TTR-mediated amyloidosis	P, O
Talazoparib (Talzenna)	Pfizer	PARP inhibitor	BRCA-mutated HER2-negative breast cancer	P
Baloxavir marboxil (Xofluza)	Shionogi/Roche	Polymerase acidic endonuclease inhibitor	Acute uncomplicated influenza	P
Lorlatinib (Lorbrena)	Pfizer	ALK and ROS1 inhibitor	ALK-positive NSCLC	P, O, B, A
Revefenacin (Yupelri)	Theravance Biopharma/ Mylan	Long-acting muscarinic receptor antagonist	COPD	S
Rifamycin (Aemcolo)	Cosmo Technologies	Ansamycin antibacterial	Travellers' diarrhoea	P
Emapalumab (Gamifant)[a]	Novimmune	Interferon-γ-blocking antibody	Primary haemophagocytic lymphohistiocytosis	P, O, B
Glasdegib (Daurismo)	Pfizer	Hedgehog pathway inhibitor	AML	P, O
Larotrectinib (Vitrakvi)	Loxo Oncology/Bayer	TRKA, TRKB and TRKC inhibitor	NTRK-positive solid cancers	P, O, B, A
Gilteritinib (Xospata)	Astellas	FLT3 inhibitor	FLT3-positive AML	P, O, B
Amifampridine (Firdapse)	Catalyst Pharmaceuticals	Potassium channel blocker	Lambert–Eaton myasthenic syndrome	P, O
Prucalopride (Motegrity)	Shire/Takeda	5-HT_4 receptor agonist	Chronic idiopathic constipation	S
Calaspargase pegol (Asparlas)[a]	Servier	Asparagine specific enzyme	ALL	S, O
Ravulizumab (Ultomiris)[a]	Alexion	Complement inhibitor	Paroxysmal nocturnal haemoglobinuria	S, O
Tagraxofusp (Elzonris)[a]	Stemline Therapeutics	IL-3 and diphtheria toxin fusion protein	Blastic plasmacytoid dendritic cell neoplasm	P, O, B

A, accelerated; ABSSSI, acute bacterial skin and skin structure infection; ADA-SCID, adenosine deaminase severe combined immunodeficiency; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; B, breakthrough; CABP, community-acquired bacterial pneumonia; CLL, chronic lymphocytic leukaemia; COPD, chronic obstructive pulmonary disease; CSCC, cutaneous squamous cell carcinoma; FL, follicular lymphoma; GEP-NETs, gastroenteropancreatic neuroendocrine tumours; NA, not applicable; NNRTI, non-nucleoside reverse transcriptase inhibitor; NSCLC, non-small-cell lung cancer; O, orphan; P, priority; PAL, phenylalanine ammonia lyase; S, standard; SLL, small lymphocytic lymphoma; TTR, transthyretin. [a]Biologic therapy. Source: Drugs@FDA.

This once-daily drug combines the newly approved integrase inhibitor bictegravir with the nucleoside/nucleotide reverse transcriptase inhibitors emtricitabine and tenofovir. Gilead says it is the smallest three-drug integrase-inhibitor-containing tablet on the market. It is approved for adults who are new to antiretroviral treatment and for those who want to replace their current antiretroviral regimen with a more convenient option. Analysts expect the drug to achieve annual sales of $6.7 billion by 2024.

Vertex's cystic fibrosis combination therapy Symdeko is also set to achieve multi-billion-dollar peak sales. The product is for patients who have two copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or who have at least one mutation that is responsive to the therapy. It combines the novel CFTR corrector tezacaftor with the established CFTR potentiator ivacaftor. Symdeko's improved efficacy and tolerability over Vertex's Orkambi — which combines the CFTR corrector

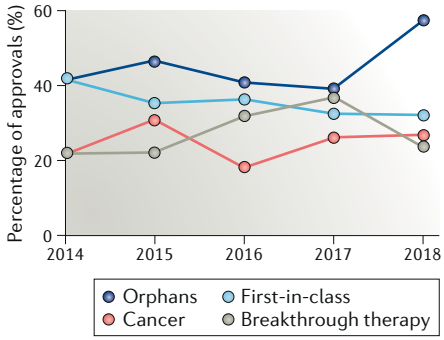

Fig. 2 | **CDER approval trends.** Source: *Nature Reviews Drug Discovery*, FDA.

lumacaftor and ivacaftor — are expected to drive uptake of the new combination, and analysts forecast annual sales of $2 billion by 2024. Vertex is also working on triple-agent combinations that could further expand the treatable patient population and the expected commercial potential.

From a scientific novelty perspective, 2018 saw the landmark approval of Alnylam's patisiran as the first small interfering RNA (siRNA) drug, which uses RNA interference (RNAi) to downregulate protein expression.

Researchers first discovered the RNAi pathway in 1998, and a Nobel prize was awarded for this work in 2006. RNAi-based drugs harness the RNA-induced silencing complex to neutralize the expression of mRNA transcripts. Alnylam's patisiran is a double-stranded siRNA oligonucleotide that downregulates the expression of transthyretin (TTR), a transport protein that can misfold and aggregate to cause hereditary TTR-mediated amyloidosis.

At least six other RNAi therapeutics are in phase III trials for other indications. Next-generation delivery approaches stand to offer improved therapeutic indices and opportunities beyond liver diseases.

The agency also approved Ionis Pharmaceuticals' inotersen for the treatment of hereditary TTR-mediated amyloidosis in 2018. Inotersen is a single-stranded oligonucleotide that uses an antisense mechanism to lower TTR expression. It is the fifth antisense drug to gain approval.

In a closely watched race, the agency approved three calcitonin gene-related peptide (CGRP) antagonists for the preventive treatment of migraines. First across the finish line was Amgen and Novartis's erenumab, which binds to the CGRP receptor. Months later, Teva secured approval for fremanezumab and Eli Lilly got the green light for galcanezumab. Both of these antibodies target the CGRP ligand itself. Analysts expect that erenumab and galcanezumab will both reach blockbuster status, with respective sales of $1.6 billion and $1 billion by 2024.

Drug developers were working on small molecules against the CGRP target for decades, before achieving success with their antibody-based approaches.

Erenumab is also the first G protein-coupled receptor (GPCR)-targeted antibody to secure an FDA approval, just beating Kyowa Hakko Kirin's CCR4-targeted lymphoma therapy mogamulizumab to this title. GPCRs are the most commonly exploited therapeutic targets for small-molecule drugs, but they have proved challenging for antibody developers. Scientific and technological advances are opening up these targets to antibody interventions, and around 10 antibodies against other GPCR targets are now in the clinic.

Loxo Oncology and Bayer's larotrectinib scored the first approval for a drug that was developed entirely for a tissue-agnostic cancer indication. Whereas cancer indications are typically defined by the tissue of origin of the cancer, larotrectinib is approved for use in all solid tumours that have neurotrophic receptor tyrosine kinase (NTRK) gene fusions.

The FDA granted a supplementary approval to Merck & Co.'s PD1 blocker pembrolizumab for all tumours with microsatellite instability-high (MSI-H) signatures in 2017, but this immunotherapy was already approved and used at the time on a tissue-dependent basis. Larotrectinib, by contrast, was developed specifically for a tissue-agnostic indication. In January 2019, Eli Lilly bought Loxo for $8 billion for rights to larotrectinib and the rest of the firm's pipeline. Although some oncologists suspect that opportunities for tissue-agnostic drugs may be limited, a number of other tissue-agnostic candidates are in development by Loxo and others.

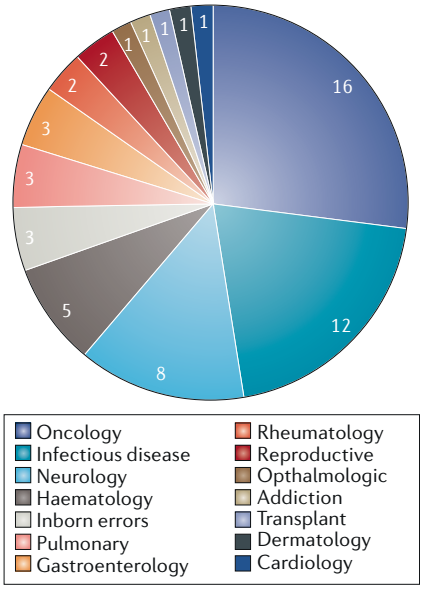

Fig. 3 | **CDER approvals by therapeutic area in 2018.** Source: *Nature Reviews Drug Discovery*.

Other new oncology approvals are by contrast set to face more competition. Regeneron and Sanofi's cemiplimab, approved for cutaneous squamous cell carcinoma, is the sixth PD1–PDL1 blocker to make it to market in the US. Analysts nevertheless still expect the immunotherapy to reach blockbuster status. Pfizer's lorlatinib, for the treatment of ALK-positive non-small-cell lung cancer, is the fifth ALK inhibitor to market. And Pfizer's glasdegib, for acute myeloid leukaemia, is the third hedgehog pathway inhibitor to market.

Notable global health, infectious disease approvals included GlaxoSmithKline's

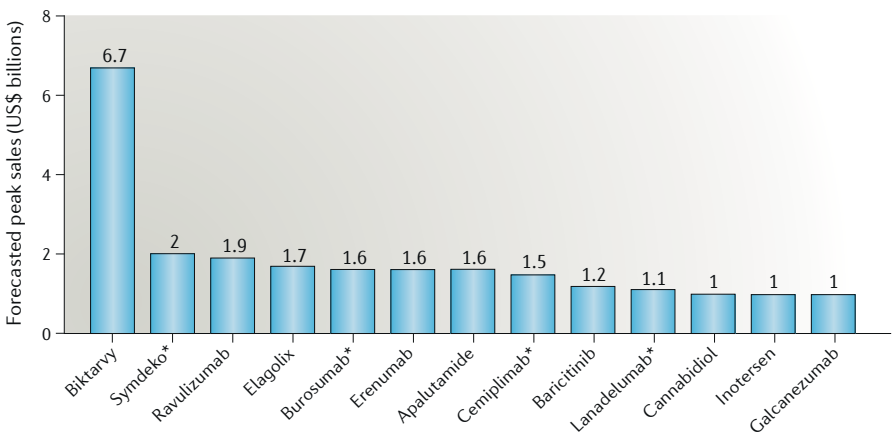

Fig. 4 | **2018's potential blockbuster approvals.** Sales forecasts are average, annual, global consensus estimates for candidates that are expected to reach blockbuster status by 2024, as reported in Clarivate Analytics' Cortellis database on January 8. *Drugs with breakthrough therapy designation.

tafenoquine, for the treatment of *Plasmodium vivax* malaria, and Medicines Development for Global Health's moxidectin, for river blindness. Tafenoquine, first discovered 40 years ago, provides a key new tool to purge *P. vivax* from patients. Moxidectin is the first new drug for river blindness to gain approval in 20 years. Both approvals show how non-profits are using repurposing and re-prioritization strategies to advance drugs at low cost.

Other infectious disease standouts include Roche's polymerase acidic endonuclease inhibitor baloxavir marboxil, the first novel flu drug to reach the market in 20 years, and TaiMed Biologics' ibalizumab, the first monoclonal antibody to be approved for the treatment of HIV-1 infection.

GW Pharmaceuticals' cannabidiol (CBD) is the first marijuana-derived drug to gain approval. CBD has activity that is distinct from the effects of tetrahydrocannabinol (THC), which causes the intoxication and euphoria associated with marijuana. CBD is approved for the treatment of two rare and severe forms of epilepsy, Lennox–Gastaut syndrome and Dravet syndrome. GW Pharmaceuticals and other firms are also developing CBD and THC for the treatment of other indications.

2019 is set to see another robust approval cohort, if not necessarily quite as large as 2018. As of the end of November 2018, sponsors had filed 43 applications for regulatory review. Drugs that are currently under review include Johnson & Johnson's fast-acting antidepressant esketamine, Aimmune's peanut-based peanut allergy treatment AR101, and Novartis's gene therapy for spinal muscular atrophy, onasemnogene abeparvovec (TABLE 4). The FDA has cautioned, however, that a US government shutdown could cause regulatory timelines to slip. It also limits the agency's ability to accept new drug applications.

Table 2 | **Selected CBER approvals in 2018**

Biologic name	Sponsor	Properties	Indication
Coagulation factor Xa (Andexxa)	Portola	Recombinant modified human factor Xa protein	Reversal of anticoagulation in rivaroxaban and apixaban-treated patients
Anti-haemophilic factor (JIVI)	Bayer	Recombinant DNA-derived factor VIII concentrate	Haemophilia A
Paediatric hexavalent combination vaccine (Vaxelis)	Merck & Co./ Sanofi	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, Haemophilus b conjugate and hepatitis B vaccine	Children from 6 weeks through 4 years of age

Source: FDA

Table 3 | **Selected Complete Response Letters and Refuse to File letters in 2018**

Drug name	Sponsor	Properties	Indication	Status
Ozanimod	Celgene	$S1P_1$ and $S1P_5$ receptor modulator	Multiple sclerosis	Resubmission expected
Volanesorsen	Akcea Therapeutics/Ionis Pharmaceuticals	Apolipoprotein CIII antisense	Dyslipidaemia and hypercholesterolaemia	Resubmission expected
Oliceridine	Trevena	Biased opioid agonist	Acute pain	Undisclosed
Stannsoporfin	Mallinckrodt	Haem oxygenase inhibitor	Hyperbilirubinaemia	Undisclosed

Source: BioMedTracker

Table 4 | **Selected potential approvals for new drugs in 2019**

Drug name	Sponsor	Properties	Indication	Expected PDUFA date
Sacituzumab govitecan[a]	Immunomedics	Anti-TROP2 antibody–drug conjugate	Breast cancer	January
Cladribine	Merck KGaA	Purine nucleoside analogue	Multiple sclerosis	January (third review)
Caplacizumab	Sanofi	Anti-vWF nanobody	Thrombotic thrombocytopenic purpura	February
Esketamine[a]	Johnson & Johnson	Fast-acting antidepressant	Major depressive disorder	March
Brexanolone[a]	SAGE Therapeutics	$GABA_A$ receptor modulator	Postpartum depression	March
Siponimod	Novartis	S1P receptor modulator	Multiple sclerosis	March
Risankizumab[b]	AbbVie	IL-23 antibody	Psoriasis	April
Quizartinib[a]	Daiichi Sankyo	FLT3 inhibitor	Acute myelogenous leukaemia	May
Onasemnogene abeparvovec[a,b]	Novartis	Gene therapy	Spinal muscular atrophy	May
AR101[a,b]	Aimmune Therapeutics	Peanut flour	Peanut allergies	August
Erdafitinib[a]	Johnson & Johnson	Pan-FGFR inhibitor	Bladder cancer	September
Upadacitinib[a,b]	AbbVie	JAK1 inhibitor	Rheumatoid arthritis	December
Romosozumab	Amgen	Sclerostin antibody	Osteoporosis and osteopenia	2019 (second review)

Review timelines may be affected by the US government's partial shutdown. PDUFA, Prescription Drug User Fee Act. [a]Breakthrough-designated drug. [b]Forecasted blockbuster sales by 2023, according to Cortellis database. Sources: BioMedTracker, Cortellis database.