Credit: S.Harris/Springer Nature Limited

2021 FDA approvals

The FDA approved 50 novel drugs in 2021, including the first KRAS inhibitor for cancer and the first anti-amyloid antibody for Alzheimer's disease.

Asher Mullard

The FDA's approval count last year was in line with recent trends, despite the continued impact of COVID-19. The agency's Center for Drug Evaluation and Research (CDER) approved 50 novel therapeutics in 2021, down from 53 in 2020 (FIG. 1; TABLE 1). The 5-year average sits at 51 drugs per year. A decade ago, it was 24 drugs per year.

Further approvals from the FDA's Center for Biologics Evaluation and Research (CBER) include a landmark mRNA vaccine and CAR-T cell products (TABLE 2). Emergency Use Authorizations (EUAs) made the news too, with antibodies and rapidly developed oral antivirals for COVID-19 (TABLE 3). CBER approvals and EUAs are not included in the annual new drug count, however.

Cancer approvals still dominate, accounting for 15 (30%) of the new approvals (FIG. 2). The 5-year average for cancer approvals is 28%. Neurology drugs secured the second most approvals, for the third year running, with 5 (10%) of the new entrants. Infectious diseases and cardiovascular diseases tied for third, with 4 (8%) approvals each.

CDER approvals included the 100th antibody, two antibody–drug conjugates (ADCs), a bispecific antibody, a constrained peptide and two oligonucleotide drugs (FIG. 3).

34 drugs (68%) received priority review, for therapies that the FDA expects to offer 'significant improvements' over the standard of care (FIG. 4). 14 (28%) drugs received breakthrough designations, for therapeutics that could confer 'substantial improvements' over available therapies.

26 (52%) drugs were approved with orphan designations, treating diseases that affect fewer than 200,000 individuals in the USA. 14 (28%) drugs received accelerated approval, with a green light based on improvements on surrogate endpoints that the FDA deems reasonably likely to predict clinical benefit.

The sales potentials of these products continue to drag, however. Analysts expect only eight CDER-approved products to achieve blockbuster status, show average forecasts from Clarivate Analytics's Cortellis database (TABLE 4). Biogen's aducanumab is the only one of these forecasted to break the

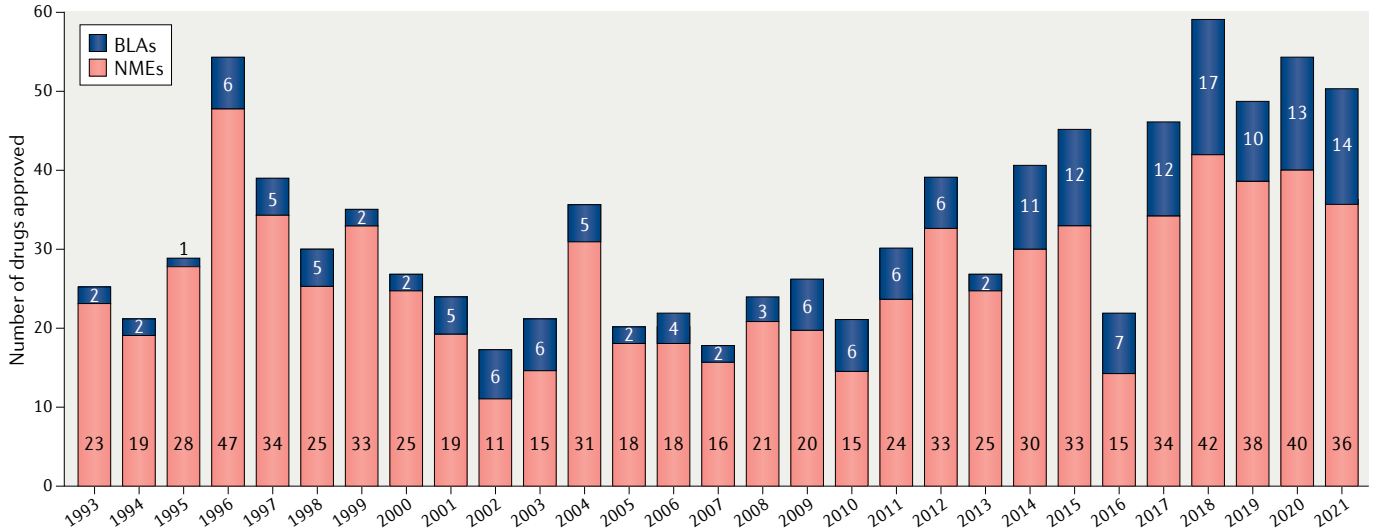

Fig. 1 | **Novel FDA approvals since 1993.** Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See TABLE 1 for new approvals in 2021. Approvals by the Center for Biologics Evaluation and Research (CBER), for products such as vaccines and gene therapies, are not included in this drug count (see TABLE 2). Source: FDA.

Table 1 | **CDER approvals in 2021**

Drug (brand name)	Sponsor	Properties	Indication	Review
Vericiguat (Verquvo)	Merck & Co./Bayer	sGC stimulator	Chronic heart failure	P
Cabotegravir; rilpivirine (Cabenuva Kit)	ViiV	INSTI and an NNRTI	HIV-1 infection	P
Voclosporin (Lupkynis)	Aurinia	Calcineurin inhibitor	Lupus nephritis	P
Tepotinib (Tepmetko)	EMD Serono	MET kinase inhibitor	NSCLC	P, O, A
Umbralisib (Ukoniq)	TG Therapeutics	PI3Kδ and CK1ε inhibitor	MZL, follicular lymphoma	P, O, B, A
Evinacumab (Evkeeza)[a]	Regeneron	ANGPTL3-targeted mAb	HoFH	P, O, B
Trilaciclib (Cosela)	G1 Therapeutics	CDK4 and CDK6 kinase inhibitor	Chemotherapy-induced myelosuppression	P, B
Casimersen (Amondys 45)	Sarepta	Exon 45-skipping ASO	DMD	P, O, A
Fosdenopterin (Nulibry)	BridgeBio	cPMP	MoCD type A	P, O, B
Melphalan flufenamide (Pepaxto)[b]	Oncopeptides	Peptide-conjugated alkylating drug	Multiple myeloma	P, O, A
Dexmethylphenidate; serdexmethylphenidate (Azstarys)	Commave Therapeutics	CNS stimulant	ADHD	S
Tivozanib (Fotivda)	Aveo	VEGFR kinase inhibitor	Renal cell carcinoma	S
Ponesimod (Ponvory)	J&J	S1P receptor modulator	Relapsing multiple sclerosis	S
Dasiglucagon (Zegalogue)	Zealand Pharma	Glucagon receptor agonist	Severe hypoglycaemia	S
Viloxazine (Qelbree)	Supernus	SNRI	ADHD	S
Drospirenone; estetrol (Nextstellis)	Mayne Pharma	Spironolactone and oestrogen analogues	To prevent pregnancy	S
Dostarlimab (Jemperli)[a]	GlaxoSmithKline	PD1-targeted mAb	Endometrial cancer	P, B, A
Loncastuximab tesirine (Zynlonta)[a]	ADC Therapeutics	CD19-targeted ADC	B-cell lymphoma	P, O, A
Pegcetacoplan (Empaveli)	Apellis	Complement protein C3 inhibitor	PNH	P, O
Amivantamab (Rybrevant)[a]	J&J	EGFR×METR bispecific antibody	*EGFR* exon 20-mutated NSCLC	P, B, A
Piflufolastat F-18 (Pylarify)	Progenics	Radiolabelled PSMA imaging agent	Prostate cancer imaging	P
Infigratinib (Truseltiq)	BridgeBio	FGFR2 kinase inhibitor	*FGFR2*-mutated bile duct cancer	P, O, A
Sotorasib (Lumakras)	Amgen	KRAS-G12C inhibitor	$KRAS^{G12C}$-mutated NSCLC	P, O, B, A
Olanzapine; samidorphan (Lybalvi)	Alkermes	Atypical antipsychotic and opioid antagonist	Schizophrenia and bipolar I disorder	S
Ibrexafungerp (Brexafemme)	Scynexis	Triterpenoid antifungal	Vulvovaginal candidiasis	P
Aducanumab (Aduhelm)[a]	Biogen/Eisai	Amyloid-β-targeted mAb	Alzheimer's disease	P, A
Asparaginase erwinia chrysanthemi (Rylaze)[a]	Jazz	Recombinant asparagine-specific enzyme	ALL and LBL, in patients allergic to *E. coli*-derived products	S, O
Finerenone (Kerendia)	Bayer	Non-steroidal MR antagonist	CKD with type 2 diabetes	P
Fexinidazole (Fexinidazole)	Sanofi/DNDi	Nitroimidazole antimicrobial	Sleeping sickness	P, O
Belumosudil (Rezurock)	Kadmon	ROCK2 kinase inhibitor	Chronic GVHD	P, O, B
Odevixibat (Bylvay)	Albireo	IBAT inhibitor	Pruritus in PFIC	P, O
Anifrolumab (Saphnelo)[a]	AstraZeneca	IFNAR-targeted mAb	SLE	S
Avalglucosidase alfa (Nexviazyme)[a]	Sanofi	Recombinant α-glucosidase	Pompe disease	P, O, B
Belzutifan (Welireg)	Merck & Co.	HIF-2α inhibitor	von Hippel–Lindau disease	P, O
Difelikefalin (Korsuva)	Cara Therapeutics	κ-Opioid receptor agonist	Pruritus associated with CKD	P, B
Lonapegsomatropin (Skytrofa)[a]	Ascendis Pharma	PEGylated human growth hormone	Growth failure due to GHD	S, O
Mobocertinib (Exkivity)	Takeda	EGFR kinase inhibitor	*EGFR* exon 20-mutated NSCLC	P, O, B, A
Tisotumab vedotin (Tivdak)[a]	Seagen/Genmab	Tissue-factor-targeted ADC	Cervical cancer	P, A
Atogepant (Qulipta)	AbbVie	CGRP receptor antagonist	Episodic migraine	S
Maralixibat (Livmarli)	Mirum	IBAT inhibitor	Pruritus in Alagille syndrome	P, O, B
Avacopan (Tavneos)	ChemoCentryx	Complement 5a receptor antagonist	ANCA-associated vasculitis	S, O
Asciminib (Scemblix)	Novartis	ABL/BCR–ABL1 kinase inhibitor	Ph^+ CML	P, O, B, A
Ropeginterferon alfa-2b (Besremi)[a]	PharmaEssentia	PEGylated interferon α-2b	Polycythaemia vera	S, O
Vosoritide (Voxzogo)	Biomarin	CNP analogue	Achondroplasia	P, O, A
Maribavir (Livtencity)	Takeda	CMV pUL97 kinase inhibitor	Post-transplant CMV infection	P, O, B
Pafolacianine (Cytalux)	On Target Labs	Fluorescent FR imaging agent	Ovarian cancer imaging	P, O

Table 1 (cont.) | **CDER approvals in 2021**

Drug (brand name)	Sponsor	Properties	Indication	Review
Efgartigimod alfa (Vyvgart)[a]	Argenx	FcRn-binding Fc fragment	Myasthenia gravis	S, O
Tezepelumab (Tezspire)[a]	AstraZeneca/ Amgen	TSLP-targeted mAb	Severe asthma	P
Inclisiran (Leqvio)	Novartis/Alnylam	PCSK9-targeted siRNA	HeFH or ASCVD	S
Tralokinumab (Adbry)[a]	LEO Pharma	IL-13-targeted mAb	Atopic dermatitis	S

[a]Biologic approval. [b]Withdrawn later in the year. A, accelerated; ADC, antibody–drug conjugate; ADHD, attention deficit hyperactivity disorder; ALL, acute lymphoblastic leukaemia; ASCVD, atherosclerotic cardiovascular disease; ASO, antisense oligonucleotide; B, breakthrough; CKD, chronic kidney disease; CMV, cytomegalovirus; CNP, C type natriuretic peptide; cPMP, cyclic pyranopterin monophosphate; DMD, Duchenne muscular dystrophy; FR, folate receptor; GHD, growth hormone deficiency; GVHD, graft-versus-host disease; HeFH, heterozygous familial hypercholesterolaemia; HoFH, homozygous familial hypercholesterolaemia; IBAT, ileal bile acid transporter; INSTI, integrase strand transfer inhibitor; J&J, Johnson & Johnson; LBL, lymphoblastic lymphoma; mAb, monoclonal antibody; MoCD, molybdenum cofactor deficiency; MR, mineralocorticoid receptor; MZL, marginal zone lymphoma; NSCLC, non-small-cell lung cancer; NNRTI, non-nucleoside reverse transcriptase inhibitor; O, orphan; P, priority; PFIC, progressive familial intrahepatic cholestasis; Ph^+ CML, Philadelphia chromosome-positive chronic myeloid leukaemia; PSMA, prostate-specific membrane antigen; PNH, paroxysmal nocturnal haemoglobinuria; S, standard; S1P, sphingosine 1-phosphate; sGC, soluble guanylate cyclase; siRNA, small interfering RNA; SLE, systemic lupus erythematosus; SNRI, selective noradrenaline reuptake inhibitor; TSLP, thymic stromal lymphopoietin. Source: Drugs@FDA.

US$2 billion mark, a speculative bet given the headwinds that this controversial Alzheimer's disease drug faces.

Novel CBER approvals are compensating, with a COVID-19 vaccine breaking records.

Boston Consulting Group's analysis of newly approved agents — including CDER and CBER approvals — found average peak sales of $1.3 billion and a median of $0.5 billion. If the COVID-19 vaccine is excluded, the average falls to $0.8 billion.

Vaccine victories

Vaccines — approved by CBER — were the stars of the 2021 approval show. Pfizer and BioNTech's mRNA vaccine tozinameran (Comirnaty), especially, sets new precedents.

BioNTech started work on this mRNA vaccine for COVID-19 in January 2020, and partnered with Pfizer in March. Phase II/III trials were underway in July, providing safety and efficacy data for an EUA by December 2020. Full approval came through in August 2021, just 1.5 years after the programme started. The average vaccine discovery and development timeline is 10.7 years.

Tozinameran is also breaking commercial records. Analysts forecast sales of over $35 billion in 2021, blowing past $21 billion for the second-place seller, AbbVie's 19-year-old TNF-blocker adalimumab. The previous best launch was for Gilead's antiviral combination of ledipasvir plus sofosbuvir, which earned over $10 billion in its first year on the market for hepatitis C virus infection.

High-income countries have been criticized for buying up too much tozinameran, and Pfizer has come under fire for its pricing and distribution policies.

Moderna's elasomeran (Spikevax) is close behind on both speed and profitability. It too secured an EUA for COVID-19 in December 2020. A full FDA approval is expected by April 2022 (see TABLE 5 for other candidates up for approval in 2022). Analysts forecast elasomeran sales of over $17 billion in 2021.

These successes have driven a surge of investments in mRNA technology — for flu, other infectious diseases and cancer. "We now have the funding to accelerate our cancer pipeline and make it even bolder," said BioNTech CEO Uğur Şahin, whose company is at the forefront of efforts to develop therapeutic mRNA vaccines for cancer.

Pfizer's Prevnar 20, a 20-valent conjugate vaccine for *Streptococcus pneumoniae* serotypes, is slated to hit sales of $4.4 billion by 2027. Prevnar 20 is a next-generation version of Prevnar 13, the world's top-selling vaccine before the arrival of tozinameran.

Analysts also forecast blockbuster status for Merck & Co.'s newly approved 15-valent *S. pneumoniae* vaccine Vaxneuvance.

Cancer capstones

The approval of Amgen's KRAS-G12C inhibitor sotorasib was a major moment for the cancer community.

Researchers identified KRAS as a proto-oncogene over 40 years ago, and

Table 2 | **Selected CBER approvals in 2021**

Biologic	Sponsor	Properties	Indication
Lisocabtagene maraleucel (Breyanzi)	BMS/Juno	CD19-targeted CAR-T cell therapy	DLBCL
Idecabtagene vicleucel (Abecma)	BMS/Celgene	BCMA-targeted CAR-T cell therapy	Multiple myeloma
Prevnar 20	Pfizer	Pneumococcal 20-valent conjugate vaccine	*Streptococcus pneumoniae* prevention
Vaxneuvance	Merck & Co.	Pneumococcal 15-valent conjugate vaccine	*Streptococcus pneumoniae* prevention
TicoVac	Pfizer	Tick-borne encephalitis vaccine	Tick-borne encephalitis prevention
Comirnaty	Pfizer/BioNTech	COVID-19 mRNA vaccine	COVID-19 prevention
Rethymic	Enzyvant	Allogeneic processed thymus tissue	Congenital athymia

BMS, Bristol Myers Squibb; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma. Source: FDA.

Table 3 | **Selected EUAs in 2021**

Therapeutic	Sponsor	Properties	Indication
JNJ-78436735	J&J	Viral vector vaccine	COVID-19 prevention
Bamlanivimab plus etesevimab	Eli Lilly	Spike-targeted mAbs	Mild-to-moderate COVID-19
Sotrovimab	GlaxoSmithKline	Spike-targeted mAb	Mild-to-moderate COVID-19
Tixagevimab plus cilgavimab	AstraZeneca	Spike-targeted mAbs	COVID-19 prophylaxis
Nirmatrelvir plus ritonavir	Pfizer	MPRO inhibitor plus cytochrome p450 inhibitor	Mild-to-moderate COVID-19
Molnupiravir	Merck & Co.	Nucleoside analogue	Mild-to-moderate COVID-19

EUA, Emergency Use Authorization; J&J, Johnson & Johnson; MPRO, main protease of SARS-CoV-2. Source: FDA.

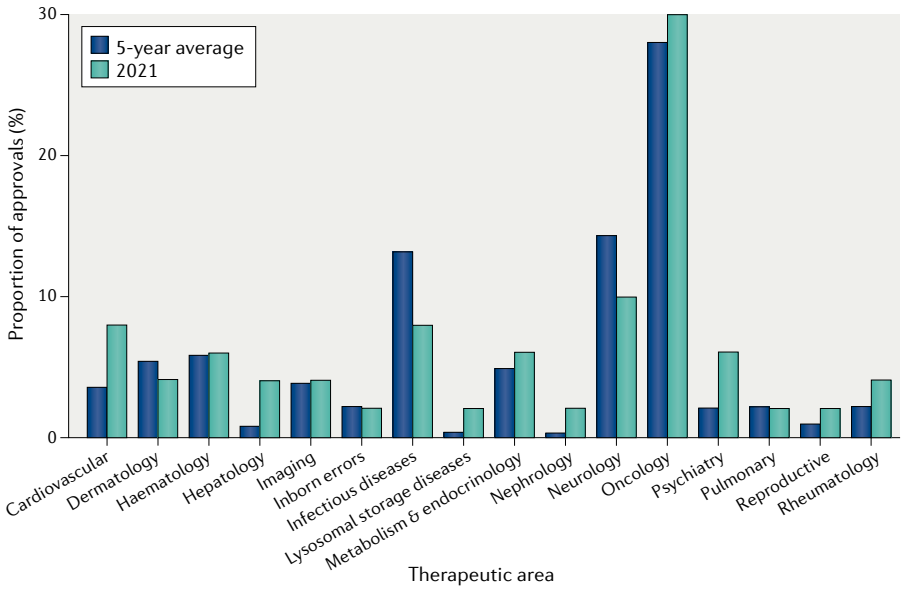

Fig. 2 | **CDER approvals by selected therapeutic areas.** Indications that span multiple disease areas are classified under only one. Source: *Nature Reviews Drug Discovery*, FDA.

have found that it is amongst the most frequently mutated genes in cancers. But the GTP-hydrolysing enzyme has eluded drug developers for just as long, due to the absence of tractable binding pockets. Then in 2013 Kevan Shokat, a chemical biologist at the University of California, San Francisco, discovered an allosteric pocket on the G12C variant of the enzyme, providing a toehold. Industry rushed in.

"I knew that once somebody cracked targeting RAS directly, there would be a lot of interest," said Shokat. "I just didn't know that there would be this much interest."

Amgen's sotorasib is the first of the KRAS crowd to gain approval, for *KRAS*^{G12C}-mutated non-small-cell lung cancer (NSCLC).

But despite approvable activity in this setting, sotorasib has yet to live up to the hopes for this holy grail of cancer targets. Amgen is testing sotorasib in combination with other agents, in various cancers. Analysts forecast sales of US$1.6 billion by 2027.

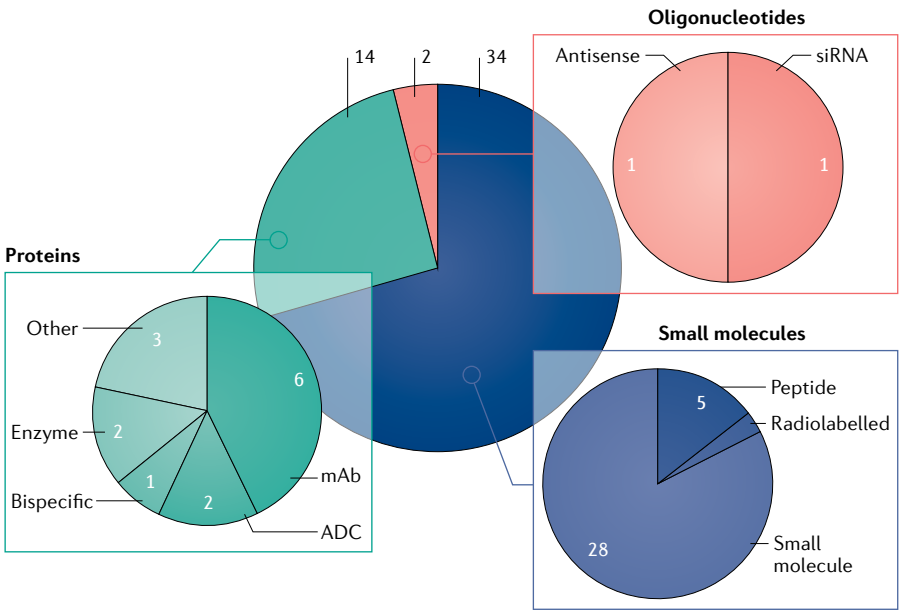

Fig. 3 | **CDER approvals by modality.** Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities (NMEs). Protein-based candidates are approved through biologics license applications (BLAs). ADC, antibody–drug conjugate; mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

Other KRAS-targeted therapeutics are on the way. Mirati expects its KRAS-G12C inhibitor adagrasib to be up for approval in 2022.

Merck & Co.'s belzutifan advances another long-running cancer story. The FDA approved the first-in-class hypoxia-inducible factor-2α (HIF-2α) inhibitor for tumours associated with von Hippel–Lindau (VHL) disease, an inherited disorder associated with well-vascularized tumours. Decades of research into the biology of VHL disease showed that HIF-2α is a key driver of oxygen sensing — paving the way for a novel anti-angiogenic drug and earning a Nobel Prize for Dana-Farber Cancer Institute's William Kaelin and others.

HIF-2α is a transcription factor, another class of targets that medicinal chemists often struggle to drug. Belzutifan, too, was made possible by the 2009 discovery of an allosteric pocket. "There are now new ways to discover chemicals that bind to various nooks and crannies on proteins that aren't necessarily active sites, and a number of people are using these to find allosteric inhibitors," said Kaelin.

Oncologists also gained access to a BCMA-targeted CAR-T cell therapy, with the approval of Bristol Myers Squibb (BMS)'s idecabtagene vicleucel for multiple myeloma. BCMA is expressed on the surface of B cells, and has become a proving ground for antibodies, bispecifics, ADCs and cell therapies. The FDA approved a first BCMA-targeted biologic — GlaxoSmithKline's ADC belantamab mafodotin — in 2020. Idecabtagene vicleucel provides a cell therapy alternative: T cells are harvested from a patient, modified ex vivo to target BCMA, and then re-infused into the patient.

Other BCMA-targeted candidates headed towards the market include Johnson & Johnson (J&J)'s CAR-T therapy ciltacabtagene autoleucel, which is under FDA review.

The FDA has approved 5 other CAR-T therapies, all of which hunt and destroy CD19-expressing cells for blood cancers.

With the FDA's green light for GlaxoSmithKline's PD1-targeted monoclonal antibody (mAb) dostarlimab, the antibody modality hit its 100th approval. The FDA approved a first antibody in 1986, 35 years ago. It now approves around 10 antibody-based products per year.

Dostarlimab is the seventh PD1/PDL1-targeted antibody to market. Sales forecasts for this checkpoint inhibitor reflect its latecomer status. Whereas analysts forecast sales of over $30 billion by 2027 for Merck & Co.'s first-in-class pembrolizumab, they predict just $270 million for dostarlimab in 2025.

The FDA is reviewing four more PD1/PDL1 antibodies for approval in 2022. The FDA's

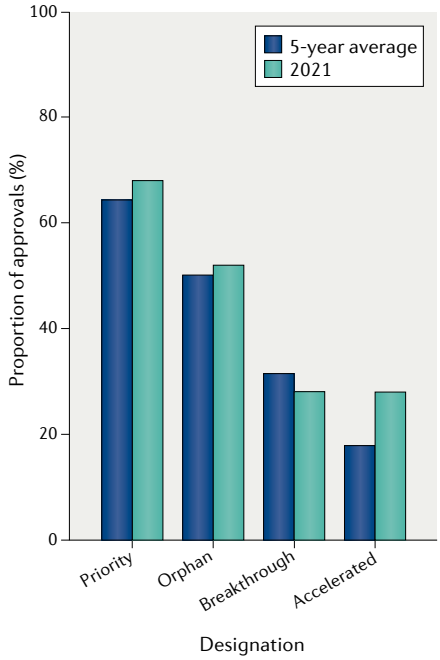

Fig. 4 | **CDER approvals trends.** Source: *Nature Reviews Drug Discovery*, FDA.

Julia Beaver and Richard Pazdur recently wrote that checkpoint inhibitors have become a Wild West of drug development, marked by "a stampede of commercial sponsors, clinical trials, and redundant development plans." They urged drug developers to work better together.

BMS has submitted relatlimab, a first LAG3-targeted checkpoint inhibitor, for FDA review. A decision is due in 2022.

The FDA approved two ADCs in 2021. ADC Therapeutics's loncastuximab tesirine is a CD19-targeted ADC, for B-cell lymphoma. Seagen and Genmab's tisotumab vedotin is a tissue-factor-targeted ADC for cervical cancer. These bring the approved ADC count up to 11. The FDA approved 7 of these in the past 3 years. Emerging clinical data from AstraZeneca's HER2-targeted ADC trastuzumab deruxtecan, approved by the FDA in 2019, shows that new ADCs can deliver considerable benefit over antibody and ADC forerunners.

"The progress here is because we're designing ADCs as whole systems now," said Susan Galbraith, head of Oncology Research & Development at AstraZeneca.

J&J scored an approval for amivantamab, a bispecific antibody targeting EGFR and MET for NSCLCs with EGFR exon 20 mutations, cancers that have been resistant to small-molecule EGFR inhibitors. When amivantamab binds to either receptor's extracellular domain, it blocks ligand binding, promotes receptor–antibody complex endocytosis and degradation, and triggers trogocytosis and antibody-dependent cellular cytotoxicity.

Amivantamab is the third bispecific antibody to market. This antibody format accounts for nearly 20% of the clinical-stage antibody pipeline.

The FDA also approved Takeda's mobocertinib, a small-molecule kinase inhibitor designed to selectively target EGFR with exon 20 mutations for this same indication.

Alzheimer's acrimony

The FDA's approval for Biogen and Eisai's amyloid-β-lowering antibody aducanumab was the year's most controversial decision.

In early 2019, an interim analysis of two phase III trials of aducanumab in Alzheimer's disease failed to find evidence of activity, prompting Biogen to discontinue development. But the company then re-analysed the data, found a hint of an effect and submitted for approval.

In November 2020, an independent FDA advisory panel voted 10 to 0, with 1 abstention, against approval. These experts questioned Biogen's statistical approach and the clinical significance of the claimed effect. The FDA then used the accelerated approval pathway to green-light aducanumab on the basis of its ability to lower amyloid levels — an unproven surrogate endpoint. The FDA gave Biogen until 2030 to confirm that the antibody provides a clinical benefit.

This approval divided the community, and triggered multiple investigations into the FDA's decision-making process.

At the start of the year, analysts were forecasting blockbuster sales of $4.1 billion for Biogen by 2027. But sales have started slowly, and some treatment centres in the USA are refusing to prescribe the antibody. Biogen initially priced aducanumab at $56,000 per year, but has since halved its cost. European regulators rejected the antibody, and Japanese regulators look set to follow suit. The commercial success of this product will depend on whether Medicare, a national insurance programme for people aged 65 and older in the USA, will cover it. In January, it proposed heavy limitations that would only enable coverage for patients enrolled in qualifying clinical trials.

Two more anti-amyloid antibodies could be coming in 2022. Biogen and partner Eisai are finalizing a submission of lecanemab. Eli Lilly is also wrapping up a submission of its donanemab, and hopes to have confirmatory evidence of benefit in 2023.

"Could [the approval of aducanumab] have been done better? I think everyone agrees that this could have unfolded more effectively," Mark Mintun, senior vice-president of neuroscience research and development at Lilly, told *Nature*. "But as the data accumulate, people will get more and more convinced, and the divisions, I think, will disappear."

Other standouts

With the approval of Novartis and Alnylam's inclisiran, a fourth siRNA-based drug has arrived. This modality harnesses RNA interference to reduce the expression of therapeutic targets.

Inclisiran inhibits PCSK9 to lower LDL-cholesterol. The FDA approved two antibodies that target PCSK9 — Regeneron and Sanofi's alirocumab and Amgen's evolocumab — in 2015 for subsets of patients with increased risk of cardiovascular disease, but these products have yet to live up to multi-blockbuster sales expectations. Inclisiran's convenience factor might help it fare better. Whereas the antibodies are dosed every 2–4 weeks, inclisiran can be dosed twice a year.

Alnylam expects that long-acting siRNAs could be transformative across multiple therapeutic areas. "We are at a remarkable period of a renaissance in terms of where this technology could go," said Alnylam's outgoing CEO John Maraganore.

If the FDA approves Alnylam's vutrisiran in 2022, it will be the fifth RNAi approval in as many years.

Regeneron scored another first in the cardiovascular space, with its first-in-class ANGPTL3-targeted mAb evinacumab. Regeneron genetically validated this target in atherosclerotic cardiovascular disease in 2017. It has now secured an approval for homozygous familial hypercholesterolaemia (HoFH), an inherited condition that is characterized by extremely high LDL-cholesterol levels. Another phase III trial is ongoing for the prevention of acute pancreatitis.

Table 4 | **Selected blockbuster contenders in 2021**

Drug (sponsor)	Sales (US$ billions)[a]
Comirnaty (Pfizer)	35[b]
Prevnar 20 (Pfizer)	4.4
Aducanumab (Biogen)	4.1
Finerenone (Bayer)	1.9
Sotorasib (Amgen)	1.6
Inclisiran (Novartis)	1.4[c]
Tezepelumab (AstraZeneca/ Amgen)	1.4
Avacopan (ChemoCentryx)	1.4
Idecabtagene vicleucel (BMS)	1.3
Atogepant (AbbVie)	1.3
Vaxneuvance (Merck & Co.)	1.2
Lisocabtagene maraleucel (BMS)	1.1
Lonapegsomatropin (Ascendis)	1.1

[a]2027 average sales forecast, from Clarivate Analytics's Cortellis, unless otherwise indicated. [b]2021 sales forecast. [c]2025 sales forecast. BMS, Bristol Myers Squibb. Source: Cortellis database.

Table 5 | **Selected approvals to watch for in 2022**

Drug	Sponsor	Properties	Indication	Expected PDUFA
Faricimab[b]	Roche	Angiopoietin-2×VEGF-A bispecific	nAMD and DME	Jan
Sutimlimab[a]	Sanofi	C1s-targeted mAb	AIHA	Feb
Tebentafusp[a]	Immunocore	gp100-targeted TCR fused to CD3-binding Fab	Uveal melanoma	Feb
Lenacapavir[a]	Gilead	Viral capsid inhibitor	HIV	Feb
Ciltacabtagene autoleucel[a]	J&J	BCMA-targeted CAR-T cell therapy	Multiple myeloma	Feb
Relatlimab plus nivolumab	BMS	LAG3-targeted mAb plus PD1-targeted mAb	Melanoma	March
Vutrisiran[b]	Alnylam	Transthyretin-targeted siRNA	hATTR	April
Elasomeran[b]	Moderna	mRNA vaccine	COVID-19 prevention	April
Mavacamten[a,b]	BMS	Myosin inhibitor	Cardiomyopathy	April
Betibeglogene autotemcel[a]	bluebird bio	Lentiviral beta-globin gene therapy	β-thalassemia	May
Tirzepatide[b]	Eli Lilly	GIP/GLP1 co-agonist peptide	Type 2 diabetes	May
Lutetium 177Lu-PSMA-617[a]	Novartis/Endocyte	PSMA-targeted radiopharmaceutical	Prostate cancer	First half 2022
BMS-986165	BMS	TYK2 inhibitor	Psoriasis	Sept
NVX-CoV2373	Novavax	Protein subunit vaccine	COVID-19 prevention	EUA in 2022
Donanemab[a,b]	Eli Lilly	Amyloid-β-targeted mAb	Alzheimer's disease	Filing by Q1
Lecanemab[a,b]	Biogen/Eisai	Amyloid-β-targeted mAb	Alzheimer's disease	Filing by Q2
Adagrasib[a,b]	Mirati	KRAS-G12C inhibitor	NSCLC	Filing planned
Nirmatrelvir plus ritonavir	Pfizer	MPRO inhibitor plus cytochrome P450 inhibitor	COVID-19 infection	Filing planned

[a]Breakthrough therapy designated. [b]Forecasted blockbuster sales by 2027, according to Cortellis database. AIHA, autoimmune haemolytic anaemia; BMS, Bristol Myers Squibb; CAR, chimeric antigen receptor; DME, diabetic macular oedema; EUA, Emergency Use Authorization; Fab, antigen-binding fragment; hATTR, hereditary transthyretin amyloidosis; J&J, Johnson & Johnson; mAb, monoclonal antibody; MPRO, main protease; nAMD, neovascular age-related macular degeneration; NSCLC, non-small-cell lung cancer; PDUFA, Prescription Drug User Fee Act; PSMA, prostate-specific membrane antigen; siRNA, small interfering RNA; TCR, T-cell receptor. Sources: BioMedTracker and Cortellis database.

AstraZeneca and Amgen's tezepelumab is a first-in-class TSLP-targeted mAb for severe asthma. TSLP is an IL-7-like cytokine that modulates multiple inflammatory cascades, and that can trigger allergic, eosinophilic and other forms of inflammation associated with the lung disease. Tezepelumab is the only biologic approved for severe asthma without any phenotype or biomarker limitations on its label. Analysts expect sales of $1.4 billion by 2027.

AstraZeneca's anifrolumab is the first new drug approved for systemic lupus erythematosus (SLE) in a decade. Many SLE patients have elevated levels of type I interferons, and mutations in interferon signalling have been linked with disease susceptibility. Anifrolumab blocks the activity of these cytokines by binding to the type I interferon receptor.

Apellis Pharmaceuticals' pegcetacoplan is the first complement protein C3 inhibitor to secure approval, showcasing continued interest in complement-modulating drugs. The FDA approved the constrained cyclic peptide for paroxysmal nocturnal haemoglobinuria, a rare and potentially fatal blood disorder.

ChemoCentryx's avacopan, approved by the FDA in 2021 for ANCA-associated vasculitis, is the first complement 5a receptor antagonist to gain approval.

Table 6 | **Selected rejected drugs of 2021**

Drug	Sponsor	Properties	Indication
Tralokinumab[a]	LEO Pharma	IL-13-targeted mAb	Atopic dermatitis
Arimoclomol	Orphazyme	Chaperone activation	Niemann–Pick disease
Teplizumab	Provention Bio	CD3-targeted mAb	Type 1 diabetes
Retifanlimab	Incyte/MacroGenics	PD1-targeted mAb	Anal cancer
Roxadustat	AstraZeneca/FibroGen	HIF-PH inhibitor	Anaemia due to chronic renal failure
Oportuzumab monatox	Sesen Bio	EpCAM-targeted immunotoxin	Bladder cancer
Narsoplimab	Omeros	MASP2-targeted mAb	TA-TMA
Tanezumab	Pfizer/Eli Lilly	NGF-targeted mAb	Osteoarthritis pain
Plinabulin	BeyondSpring	Tubulin-binding antineoplastic	Neutropenia/leukopenia

[a]Approved later in the year. EpCAM, epithelial cell adhesion molecule; HIF-PH, hypoxia-inducible factor-prolyl hydroxylase; IL, interleukin; mAb, monoclonal antibody; MASP2, mannose-binding lectin-associated serine protease 2; NGF, nerve growth factor; TA-TMA, transplant-associated thrombotic microangiopathy. Source: BioMedTracker.

"We're going to see a lot of activity [in complement-modulating agents], especially if drug developers can succeed beyond the rare indications," said John Lambris, an immunologist at the University of Pennsylvania.

Whereas COVID-19 vaccines, antibodies and antivirals have shown how fast drug developers can move under pressure, Takeda's maribavir provides a counterpoint. Phase I data from this antiviral were first presented in 1996. The antiviral survived deprioritization and out-licensing, a failed phase III trial, and two company acquisitions before its approval for cytomegalovirus (CMV) infections this year.

If at first you don't succeed

The FDA rejected several applications last year as well (TABLE 6). Some of these could be re-submitted for FDA review shortly. Provention Bio, for example, is working towards re-submitting its CD3-targeted mAb teplizumab for the delay of type 1 diabetes in at-risk individuals. Teplizumab made its clinical trial debut in 1997 for transplant rejection, and leads a pack of T-cell modulating therapies for autoimmune diseases.

Other rejected therapeutics have hit the end of the line. Pfizer and Eli Lilly discontinued development of their NGF-targeted mAb tanezumab this year, after the FDA issued a complete response letter for use in osteoarthritis pain. The FDA placed the once-promising anti-NGF class on clinical hold in 2010, after phase III data showed that these painkillers could cause joint destruction.