



Fresh from the biotech pipeline: too much, too fast?

2021 witnessed regulators' continued push to accelerate approvals and adjust to COVID-19, but has the pendulum swung too far in drug makers' favor?

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Looking at 2021's US Food and Drug Administration (FDA) drug approvals, one might not have known there was still a major health crisis underway. More than 50 new drugs were waved through — close to 2018's all-time high and on a par with those in 2020 (Fig. 1 and Table 1), the first pandemic year. On top of its usual workload, the FDA faced political pressure to accelerate already speedy approval timelines for COVID-19 vaccines and therapeutics.

With almost two-thirds of FDA drug funding now provided by industry user fees, speedy reviews are becoming the norm.

But how far can the agency — and other regulators moving to expedite reviews — push non-COVID-19-related approval timelines before there is a serious safety issue or a perceived imbalance between benefit and risk? And, as both pipeline and approvals skew to niche diseases, are current development incentives appropriate to address the chronic diseases that affect most patients?

Another bumper year

Annual FDA drug approvals are double what they were 15 years ago — a sign of scientific progress, sure, but also of an increasingly accommodating regulator whose

relationship with industry is ever more collaborative. Expedited approvals, applied in various guises to new treatment options in areas of unmet need, are the new normal. They accounted for ~70% of all approved new drugs (Table 2).

Oncology again dominated the expedited and regular approvals roster (Fig. 2). The FDA's Oncology Center of Excellence (OCE) — a quasi-autonomous unit overseeing all oncology reviews — “made conscious efforts to send a message to cancer patients that they still matter” despite the pandemic, says Michael McCaughan of Prevision Policy, which analyzes US

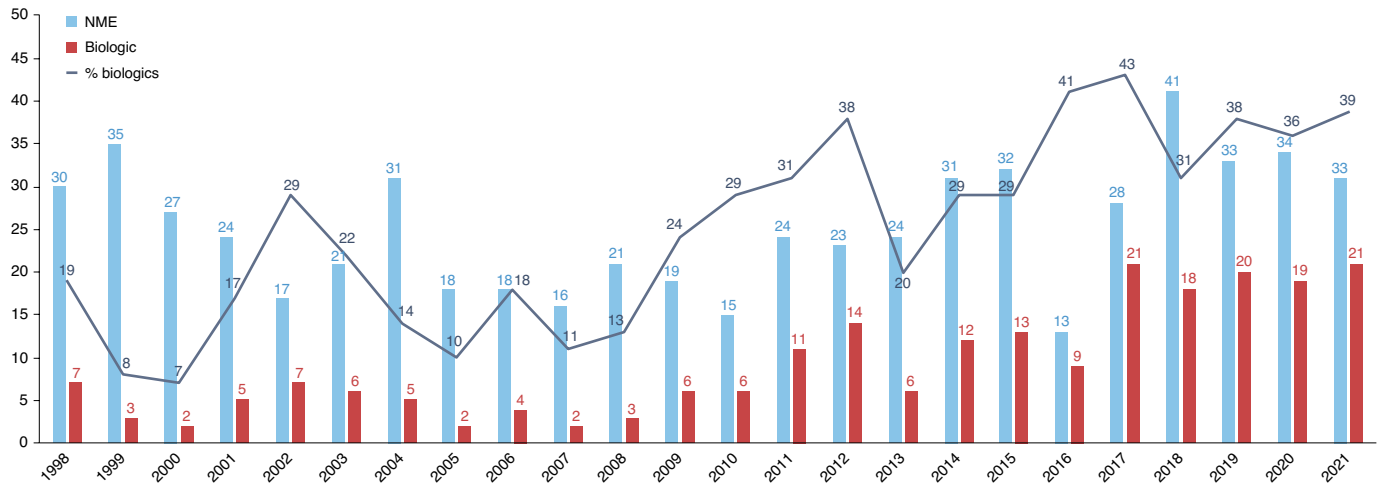


Fig. 1 | Historical FDA approvals. Another strong year for approvals in the United States, pandemic notwithstanding.

biopharma drug regulation, policy and market access. Other regulators shared that message: of the 20 cancer drug approvals, 8 were concurrently submitted and reviewed in other countries through the FDA-coordinated Project Orbis (Fig. 3).

While the pandemic raged on through 2021, Pfizer and BioNTech's mRNA-based COVID-19 vaccine Comirnaty became the first to graduate from Emergency Use Authorization (EUA) to full approval. During the final weeks of the year, as the heavily mutated, vaccine-evading Omicron variant began to spread, EUAs were issued for booster shots of the Pfizer and Moderna vaccines, including in younger age groups. There were also several COVID-19 treatment firsts (Box 1). One of the most notable was on 22 December, when Pfizer's Paxlovid (nirmatrelvir and ritonavir) became the first oral COVID-19 treatment to receive emergency approval for patients with mild to moderate COVID-19 at risk of progression. Paxlovid reduces the risk of hospitalization or death by 89%, and it is easy to take, making it an important tool in combating the virus, especially with over 20% of the US population still unvaccinated. The twice-daily therapy, taken for five days, combines the protease inhibitors nirmatrelvir, which blocks viral replication, and ritonavir, which prolongs the inhibitory effect by slowing nirmatrelvir's breakdown.

The FDA, like other drug regulators, has shown remarkable agility and productivity through the pandemic, adjusting to new work patterns, remote technologies and new levels of international collaboration. But behind the scenes, things were less smooth. The agency has faced staff exhaustion,

management upheaval and criticism over lax standards in its accelerated approval pathway. The FDA also lacked a permanent leader for almost the entire year, which some say led to unpredictable decisions. "When you have a leadership vacuum, staff get more empowered and decisions may be more likely to be taken by particular individuals," says Rob Smith, healthcare analyst at policy research group Capital Alpha.

Exhibit A for unpredictable decisions was the June approval of Biogen's Alzheimer's treatment Aduhelm (aducanumab) despite a negative advisory committee vote. Aduhelm is the first approved drug to tackle part of the underlying pathophysiology associated with Alzheimer's, β -amyloid plaque. But a firestorm raged over the relevance of β -amyloid as a surrogate endpoint, the drug's price tag of \$56,000 per patient per year (reduced by half in December), its generously wide label (narrowed, a month later, from all patients with Alzheimer's to those with mild disease) and the nine years granted to Biogen to provide confirmatory evidence. An investigation is underway by the US Department of Health and Human Services' Office of Inspector General, looking into alleged disputes among FDA staff, allegations of a too-cozy relationship between the FDA's top Alzheimer's regulator Billy Dunn and Biogen, and misuse of accelerated approval. Europe's Committee for Medicinal Products for Human Use (CHMP) voted down the drug in the final days of 2021.

Unusually, the US Centers for Medicare and Medicaid Services (CMS) delayed covering the drug, and in January 2022 proposed paying for it only for patients that participate in qualifying clinical trials. A

final coverage decision, plus the Office of Inspector General ruling, are due later this year — just as FDA Commissioner Robert Califf takes the helm. He'll face a hefty inbox, including how to handle another Alzheimer's monoclonal antibody (mAb) targeting β -amyloid, Eli Lilly's donanemab, which was submitted for accelerated review in October 2021. This drug has also reported marginal efficacy outcomes and failed to meet some clinical endpoints.

Most FDA watchers welcome Califf, a cardiologist and clinical trialist with previous FDA experience (including a brief, uncontroversial term as commissioner in 2016.) Some question his ties to industry — he has recently been senior advisor to Verily Life Sciences — but he is far from the first to face the issue. Califf has already declared plans to streamline clinical trials by cutting bureaucracy and improving data transparency and interoperability.

Such moves would further accelerate development, providing faster access for patients and a boon to industry. Plus, the FDA's goals for 2023–2027, published in 2021, include more expedited reviews in non-oncology indications, as well as staff increases. Made-to-measure drugs for super-rare diseases also got a boost in 2021, as the FDA issued guidance around 'n-of-1' therapies developed for individual patients' specific genetic disease variants. The procedural advice relates to antisense oligonucleotide drugs, the most advanced category of n-of-1 treatments, but is likely to expand beyond.

The COVID-19 emergency added momentum to the FDA's efforts to embrace real-world evidence to support new indications or postapproval requirements.

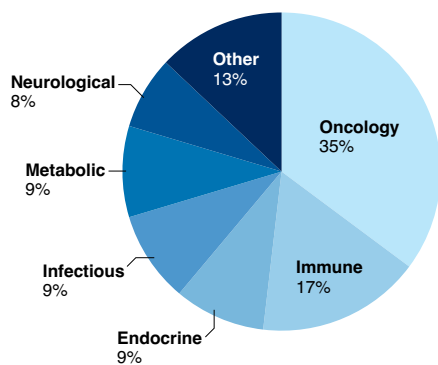
Table 1 | FDA biologics approvals of 2021

Drug name	Generic name	Indication	Molecule
Abecma	Idecabtagene vicleucel	Multiple myeloma	CAR-T cell therapy with anti-BCMA single-chain variable fragment fused to the CD137 (4-1BB) co-stimulatory and CD3 ζ signaling domains
Aduhelm ^a	Aducanumab-avwa	Alzheimer's disease	Fully human IgG1 mAb against a conformational epitope on β -amyloid plaques
Ropeginterferon alfa-2b-njft	Pegylated proline interferon alpha 2b	Polycythemia vera	Pegylated recombinant human interferon- α -2b with addition of a proline at the N terminus
Breyanzi	Lisocabtagene maraleucel	Diffuse large B-cell lymphoma — NHL	Autologous CAR-T cells, expanded in culture, expressing CD19 and a truncated EGFR
Comirnaty	COVID-19 mRNA vaccine	COVID-19 prevention	A 4,284-nucleotide mRNA encoding two proline substitutions to make a prefusion stabilized version of the spike protein
Evkeeza	Evinacumab-dgnb	Dyslipidemia/hypercholesterolemia	Fully human IgG4 mAb against angiopoietin-like 3 with a stabilizing mutation in the hinge
Jemperli ^a	Dostarlimab-gxly	Uterine cancer	Humanized IgG4 mAb against PD-1
Nexviazyme	Avalglucosidase alfa-ngpt	Pompe disease	Recombinant human α -glucosidase conjugated with multiple synthetic bismannose-6-phosphate-tetramannose glycans
Rethymic	Allogeneic thymus tissue	Congenital athymia	Partially T-cell-depleted cultured allogeneic postnatal thymus tissue
Rybrevant ^a	Amivantamab-vmjw	Non-small-cell lung cancer	A full-length human IgG1 bispecific mAb targeting mesenchymal-epithelial transition factor and EGFR
Rylaze	Asparaginase	Acute lymphoblastic leukemia	Recombinant asparaginase produced in <i>Pseudomonas fluorescens</i>
Saphnelo	Anifrolumab-fnia	Systemic lupus erythematosus	Fully human IgG1 mAb targeting interferon- α receptor 1
Skytrofa	Lonapegsomatropin-tcgd	Short stature/growth factor deficiency	Unmodified somatropin (growth hormone) in an inert protective shell, attached with a linker for slow-release (weekly) injections
StrataGraft	Allogeneic keratinocytes	Burn injury	Allogeneic cellularized scaffold containing cultured keratinocytes and dermal fibroblasts in murine collagen
Susvimo	Ranibizumab intravitreal implant	Wet age-related macular degeneration	Antigen-binding segment of IgG1 antibody against VEGF
Tezspire ^a	Tezepelumab-ekko	Asthma	Fully human IgG2a mAb against thymic stromal lymphopoietin
Tivdak ^a	Tisotumab vedotin-tftv	Cervical cancer	Human IgG1 κ mAb targeting tissue factor conjugated to MMAE via a protease-cleavable linker
Vyvgart	Efgartigimod alfa	Myasthenia gravis	Human IgG1 antibody Fc fragment containing several mutations designed to affect Fc fragment interaction with the neonatal Fc receptor
Zynlonta ^a	Loncastuximab tesirine-lpyl	Diffuse large B cell lymphoma	Humanized IgG1 mAb targeting CD19 conjugated to an SG3199 warhead with a pyrrolobenzodiazepine dimer linker
Notable new medical entities			
Amondys 45 ^a	Casimersen	Duchenne muscular dystrophy	22-residue exon-45-skipping phosphorodiamidate antisense oligonucleotide
Empaveli	Pegcetacoplan	Paroxysmal nocturnal hemoglobinuria	Two identical pentadecapeptides covalently bound to the ends of a linear 40-kDa polyethylene glycol molecule.
Leqvio	Inclisiran	Hypercholesterolemia	Triantennary <i>N</i> -acetylgalactosamine-conjugated phosphorothioate, 2'- <i>O</i> -methyl, 2'-fluoro and 2'-deoxynucleic acid-modified siRNA targeting PCSK9 mRNA
Voxzogo ^a	Vosoritide	Achondroplasia	A shortened human C-type natriuretic peptide analog comprising the 37 C-terminal residues plus proline and glycine on the N terminus to confer resistance to neutral endopeptidase
Zegalogue	Dasiglucagon hydrochloride	Hyperinsulinemia/hypoglycemia	29 amino acid peptide with 7 amino acid substitutions relative to native glucagon
Notable biosimilars			
Byooviz	Ranibizumab-nuna	Wet age-related macular degeneration	First ophthalmologic biosimilar Lucentis
Cyltezo	Adalimumab-adbm	Multiple chronic inflammatory diseases	First interchangeable monoclonal antibody, biosimilar for Humira
Semglee	Insulin glargine	Type 1 diabetes	First interchangeable insulin

^aAccelerated approval. ADC, antibody-drug conjugate; IgG, immunoglobulin G; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; NHL, non-Hodgkin's lymphoma; VEGF, vascular endothelial growth factor.

Table 2 | Percentage of drug approvals with expedited review since 2015

2015	60%
2016	73% ^a
2017	61%
2018	73%
2019	60%
2020	68%
2021	76%

^aOnly 22 drugs approved in total**Fig. 2 | 2021 FDA approvals by disease group.** As usual, oncology approvals dominate.

Three sets of draft guidance were published for comment during 2021, covering the use of [electronic health records](#), medical claims data and data from mobile devices and registries; [data standards](#); and [general guidelines](#) around data quality, selection and analysis. The FDA still views real-world evidence as ancillary, supporting rather than replacing conventional interventional trials. But the volume of guidance and further efforts planned in 2023–2027, plus the shift to drugs for rare diseases, where traditional studies are difficult, means it may soon become more important.

A flurry of firsts

2021's approvals were packed with firsts — drugs that hit new targets or provide the first treatment option for a disease subtype or cancer mutation.

One of the most exciting approvals, in drug discovery circles, is Amgen's Lumakras (sotorasib), a small molecule that hits a target previously believed to be undruggable. Lumakras inhibits G12C mutants of the Kirsten rat sarcoma (KRAS) protein, a GTPase that toggles between active, GTP-bound and inactive, GDP-bound conformations and is implicated in many cancers. KRAS G12C is the [most common](#)

[mutation subtype](#) in non-small cell lung cancer (NSCLC). Lumakras works by covalently binding the Cys12 residue near an inducible allosteric switch pocket on KRAS, locking it into an inactive state that stops cell proliferation.

The approval was coordinated, via Project Orbis, with authorities in Australia, Brazil, Canada and the United Kingdom. It illustrates greater international collaboration among regulators, but also, scientifically, the resurgence of covalent molecules and of allostery in accessing drug targets. Many approved drugs (for example, aspirin and penicillin) bind covalently, but the irreversible nature of covalent binding pushed it out of mainstream drug design until the approval of Janssen's Imbruvica (ibrutinib) in 2013 for mantle cell lymphoma, supported by new tools to visualize and understand protein topography in more detail. Imbruvica, a small-molecule inhibitor of Bruton's tyrosine kinase, has since sparked a renaissance of other covalent inhibitor drugs, such as Boehringer Ingelheim's Giltorif (afatinib) and AstraZeneca's Tagrisso (osimertinib) and Calquence (acalabrutinib).

Approvals for genetically defined diseases kept up their strong pace, with two firsts for patients with NSCLC mutated in epidermal growth factor receptor (EGFR) exon 20. Janssen's bispecific mAb Rybrentan (amivantamab-vmjw) and Takeda's oral small-molecule selective kinase inhibitor Exkivity (mobocertinib) both received accelerated approval for people whose disease has progressed after platinum-based chemotherapy; an estimated 2–3% of NSCLCs harbor the mutations.

Rarer diseases, like Duchenne's muscular dystrophy, also continue to be more narrowly sliced. 2021 saw FDA approval of Sarepta's Amondys 45 (casimersen), a phosphorodiamidate morpholino antisense oligonucleotide for the 8% of patients with mutations in the dystrophin gene that are amenable to exon 45 skipping. The company's two other DMD drugs, Exondys 51 (eteplirsen) and Vyondys 53 (golodirsen), cater to the small minorities of patients missing exons 51 and 53, respectively. The treatments prompt translation of a shorter dystrophin protein but were all approved — in an accelerated fashion — under the controversial assumption that increased dystrophin production will lead to clinical benefit. That must be verified in confirmatory trials.

Growing understanding of complement system proteins and effectors is driving programs across other inflammatory and immune-related diseases. ChemoCentryx's Tavneos (avacopan), a small molecule that

selectively inhibits the complement factor 5a (C5a) receptor, was approved in the United States and Japan and received a positive opinion in the European Union as an add-on to standard glucocorticoid therapy in severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, a rare inflammatory disease. Omeros's fully human immunoglobulin G4 (IgG4) mAb narsoplimab is in [phase 3 for immunoglobulin A nephropathy](#) (inflammation of the kidney). It targets mannan-binding lectin-associated serine protease-2 (MASP-2), the effector enzyme of the lectin activation pathway (one of three [complement activation pathways](#)) and has orphan designations in the United States and European Union.

Apellis's peptide drug Empaveli (pegcetacoplan) became in May 2021 the first approved C3 modulator for paroxysmal nocturnal hemoglobinuria, a rare blood disorder in which faulty red blood cells are attacked by the immune system. Empaveli shows greater efficacy in increasing hemoglobin than Alexion's mAbs targeting C5 — Soliris (eculizumab), which was approved in its initial paroxysmal nocturnal hemoglobinuria indication in 2007; and Ultomiris (ravulizumab-cwvz), approved in 2018. That's because C3 is more central to the immune system's complement cascade than the downstream C5 protein: C3 controls both extra- and intravascular hemolysis, whereas C5 is implicated only in intravascular hemolysis.

In November, another peptide drug, BioMarin's Voxzogo (vosoritide), became the first drug approved for achondroplasia, the most common form of dwarfism (also receiving European and UK approvals). People with achondroplasia have an overactive fibroblast growth factor receptor 3 (*FGFR3*) gene, which inhibits bone formation. Voxzogo, an analog of C-type natriuretic peptide, binds to natriuretic peptide receptor B, dampening *FGFR3*'s effects and thereby stimulating bone growth. Voxzogo's accelerated approval demands confirmatory data on final adult height and on clinical issues that can result from achondroplasia, including hearing loss, sleep apnea and skeletal problems.

Achondroplasia affects just 10,000 children in the United States, yet Voxzogo may not be the lone treatment for long — even though some, including advocacy group Little People of America, question whether drugs focused primarily on height are needed at all. Other drugmakers are tackling the aberrant protein cascade in different ways. Ascendis Pharma aims to provide continuous exposure to the bone-simulating C-type natriuretic peptide

Drug	Indication	Breakthrough	Fast Track	Orphan	Rare
Abecma	Multiple myeloma	■		■	■
Aduhelm	Alzheimer's disease		■		
Amondys 45	Duchenne muscular dystrophy		■	■	■
Brexafemme	Fungal infections — non-systemic		■	■	
Breyanzi	Diffuse large B cell lymphoma — NHL	■		■	■
Bylvay	Progressive familial intrahepatic cholestasis		■	■	■
Comirnaty	COVID-19 prevention		■		
Cosela	Bone marrow suppression in small-cell lung cancer	■			■
Cytalux	Solid tumors — imaging		■	■	
Empaveli	Paroxysmal nocturnal hemoglobinuria		■	■	■
Evkeeza	Dyslipidemia/hypercholesterolemia	■		■	
Exkivity	Non-small-cell lung cancer	■	■	■	
Fotivda	Renal cell cancer				■
Jemperli	Uterine (endometrial) cancer	■			■
Korsuva	Pruritus	■			
Leqvio	Dyslipidemia/hypercholesterolemia			■	
Livmarli	Alagille syndrome	■		■	■
Livtency	Cytomegalovirus infection	■	■	■	
Lumakras	Non-small-cell lung cancer	■	■	■	
Lupkynis	Lupus nephritis		■		■
Nexvazyme	Pompe disease	■	■	■	■
Nullibry	Molybdenum cofactor deficiency	■		■	■
Rethymic	Congenital athymia	■		■	■
Ropeginterferon alfa-2b	Polycythemia vera			■	■
Rybrevant	Non-small-cell lung cancer	■			
Ryplazim	Hypoplasminogenemia		■	■	■
Saphnelo	Systemic lupus erythematosus		■		
Scemblix	Chronic myelogenous leukemia	■	■	■	■
Skytrofa	Short stature/growth hormone deficiency			■	
StrataGraft	Burn injury			■	
Tavneos	ANCA-associated			■	
Tembexa	Smallpox		■	■	■
Tezspire	Asthma	■			
Tivdak	Cervical cancer				■
Truseltiq	Biliary tract cancer		■	■	■
Ukoniq	Marginal zone lymphoma — NHL	■		■	■
Voxzogo	Achondroplasia			■	■
Vyvgart	Myasthenia gravis		■	■	■
Welireg	Renal cell cancer	■		■	■
Zegalogue	Hyperinsulinemia/hypoglycemia			■	
Zynlonta	Diffuse large B cell lymphoma — NHL			■	■

NHL, non-Hodgkin's lymphoma; ANCA, anti-neutrophil cytoplasmic autoantibody

Fig. 3 | Drug approvals with expedited reviews in 2021. Expedited approvals accounted for ~70% of all approved new drugs.

with a once-weekly formulation of the protein, TransCon CNP, in phase 2 for achondroplasia. Pfizer's recifercept, also in phase 2, is an FGFR3 decoy: it sequesters FGFR3 ligands to reduce activation of the mutated receptor. BridgeBio Pharma's phase 3 infigratinib is a selective oral tyrosine kinase inhibitor of FGFR1–3, approved in May 2021 as Truseltiq for patients with

advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or rearrangement.

The other pandemic

Other 2021 approval firsts had a wider health impact. Novo Nordisk's Wegovy (semaglutide 2.4 mg) in June 2021 became the first FDA-approved obesity drug to show equivalent efficacy to bariatric

surgery, posting on average 15% weight loss in conjunction with diet and exercise. Semaglutide is not new — the glucagon-like peptide (GLP)-1 analog has been used at lower doses in diabetes since 2017. GLP-1 drugs have been available since 2005. But that's why obesity specialists are so excited: Wegovy works and has a clean safety record, unlike many other anti-obesity drugs.

The virus pandemic has highlighted the additional risks faced by the over 100 million Americans with obesity — explaining, in part, a rush on the drug after launch that led to [supply shortages](#). The inflammation and immune system damage seen in people with obesity are shown to increase the risk of severe COVID-19, hospitalization and death, independently of other factors like age and related conditions. Recent [unpublished](#) research suggests that adipose tissue itself is susceptible to SARS-CoV-2 infiltration and associated inflammation, and may provide a reservoir for viral replication. “The pandemic has finally convinced everyone — payers, employers and the public — that obesity is a disease, associated with health risks,” including heart disease, diabetes, non-alcoholic steatohepatitis and depression, says Louis Aronne, Professor of Metabolic Research at Weill Cornell Medicine's Comprehensive Weight Control Center. “And now we have a drug that works at least twice as well as anything before it.”

CMS doesn't, by law, reimburse anti-obesity drugs, unless they are part of treatment for related conditions such as hypertension or diabetes. But Novo Nordisk says it has achieved 60% coverage across the commercial market and that the drug features on plans offered by the three largest pharmacy benefit managers. Analyst sales forecasts range from \$4 billion to \$9 billion; the drug also has a positive opinion from Europe's CHMP and is under review in Japan.

Novo Nordisk is not alone in seeking to tap into this under-served market. It faces competition from Eli Lilly's tirzepatide, a once-weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist under FDA review for type 2 diabetes and in phase 3 trials for obesity. Combining GLP-1 and GIP peptide agonism appears to be additive, even though some of GIP's standalone effects seem [counter-productive](#) (it appears to increase fat storage, for example.) Tirzepatide is one of industry's most valuable late-stage development candidates, in terms of the net present value of expected future sales. Both drugs are also being tested in heart failure and non-alcoholic steatohepatitis.

Bayer in 2021 provided more options in well-defined corners of two other

Box 1 | COVID-19 firsts

The FDA's Coronavirus Treatment Acceleration Program (CTAP), an emergency program created in 2020 to review and expedite potential COVID-19 therapeutics, was in full swing during 2021. Eli Lilly's bamlanivimab–etesevimab duo of neutralizing IgG1 antibodies got its first EUA in February 2021 for patients with mild to moderate disease at risk of progressing. Distribution of the antibodies — which bind to overlapping epitopes within the receptor binding domain of SARS CoV-2's spike protein — was briefly paused mid-year when Health and Human Services declared the combination ineffective against the Delta and Gamma variants circulating at the time. It has since resumed, and in December 2021 the EUA was re-issued and extended to include certain younger patients.

In May the first COVID-19 'super-antibody', GlaxoSmithKline and Vir Biotechnology's sotrovimab, got its EUA. Unlike first-generation COVID-19 antibodies, sotrovimab — a recombinant human IgG1κ monoclonal antibody — was designed to bind to a highly conserved epitope on the spike protein receptor binding domain, found across all SARS-like coronaviruses – including the

potentially vaccine-evading Omicron.

In November, the UK MHRA approved Merck & Co. and Ridgeback Biotherapeutics' oral antiviral molnupiravir (Lagevrio) for some patients, and the FDA's antimicrobial advisory committee also narrowly voted in favor of the drug, which inhibits viral replication by triggering RNA copying errors. (Molnupiravir is metabolized to the cytidine nucleoside analog *N*⁴-hydroxycytidine.) But France's health authority turned it down, citing lack of efficacy versus Omicron and availability of Roche's casirivimab–imdevimab antibody duo Ronapreve. Full trial data for Lagevrio revealed it to be *less effective than initially thought*, cutting the risk of hospitalization or death by just 30%. The FDA issued an EUA on 23 December, a day after the one for Pfizer's oral Paxlovid, for patients unable to tolerate or access other therapies.

Also in December came the *first EUA for a prophylactic COVID-19 treatment*: AstraZeneca's tixagevimab–cilgavimab duo of neutralizing IgG1 antibodies, Evusheld, for patients who are immunocompromised or who can't tolerate vaccines. It is under review in Europe and the United Kingdom.

widespread chronic diseases: heart failure and kidney disease. Verquvo (vericiguat), co-developed with Merck, is a once-daily, oral, soluble guanylate cyclase stimulator that triggers smooth muscle relaxation via the nitric oxide signaling pathway, addressing the endothelial dysfunction aspect of heart failure. It was approved as an add-on to standard of care for worsening heart failure with sub-45% ejection fraction. A *5,000-patient trial* showed a 10% reduction in the composite risk of death from cardiovascular causes and related hospitalization, although the reduction in cardiovascular-related death alone wasn't significant.

The non-steroidal mineralocorticoid receptor antagonist Kerendia (finerenone) is targeted at the over 35% of adults with type 2 diabetes who also have chronic kidney disease. The drug slows the decline in glomerular filtration rate that can cause kidney and heart failure and was shown to reduce the risks of both.

Both drugs — rare examples, among 2021's approvals, of small molecules for big diseases outside cancer — face challenges from the established sodium–glucose transporter-2 (SGLT-2) inhibitors

used in diabetes. AstraZeneca's Farxiga (dapagliflozin) has also been approved for kidney disease in patients without diabetes, and the class has shown cardioprotective effects in this wider group too, potentially mediated by *several mechanisms*, including lowering blood pressure and inhibiting both cardiac fibrosis and endothelial dysfunction.

In the final days of 2021, the FDA waved through Novartis's cholesterol-lowering Leqvio (inclisiran), a year after a manufacturing-site-related rejection (and EU approval). The double-stranded small interfering RNA drug, which blocks liver translations of proprotein convertase subtilisin-kexin type 9 (PCSK9), was approved, alongside diet and statins, for the 18 million or so Americans with atherosclerotic cardiovascular disease and for those with heterozygous familial hypercholesterolemia. Leqvio is a twice-yearly subcutaneous injection that cuts low-density lipoprotein cholesterol.

Biosimilar and mAb landmarks

Two biosimilars approved in 2021 could also potentially have a large public health impact: Biocon's Semglee (insulin glargine-yfgn), referencing Sanofi's Lantus, and

Boehringer Ingelheim's antibody Cyltezo (adalimumab-adbm), which references the most valuable drug in the world, AbbVie's rheumatoid arthritis treatment Humira. Both were designated as interchangeable — meaning originator drug prescriptions can automatically be filled with the cheaper biosimilar, without prescriber intervention (although some state laws require that prescribers be informed of any switch).

This designation matters. Biosimilar uptake in the United States has been hampered, relative to that in Europe, by aggressive innovator tactics (such as exclusionary contracting) and complex rebate rules that take advantage of the lack of automatic substitution. Interchangeability should remove some of these barriers and help reduce prices — not by the 80–90% seen with small-molecule generics, but by 30–40%, which, given biologics' high prices, is enough to make a dent in drug spending. (Humira made \$16 billion in 2020, nearly 20 years after its launch.) Sanford Bernstein analyst Ronny Gal called Cyltezo's designation “a landmark achievement” for the field. AbbVie's lawyers have staved off Cyltezo, plus a half dozen other FDA-approved Humira biosimilars, until 2023. But in Europe, biosimilar versions of adalimumab had captured *over a third of patients* little more than a year after their 2018 launch.

A third biosimilar, Byooviz (ranibizumab-nuna) from Samsung Bioepis and Biogen, which references Roche's vascular endothelial growth factor (VEGF)-targeting wet age-related macular degeneration drug Lucentis, became the first approved copycat biologic in ophthalmology in the United States and European Union in 2021.

These biosimilar firsts arrived the same year as the *100th originator monoclonal antibody* approval. Three-and-a-half decades after Janssen's muromonab-CD3 (Orthoclone OKT3) to prevent transplanted kidneys being rejected, GlaxoSmithKline's programmed cell death receptor-1 (PD-1) blocker Jemperli (dostarlimab-gxly) was approved for mismatch repair-deficient (dMMR) recurrent or advanced endometrial cancer. Later in the year it was expanded to other advanced solid tumors; about 14% of solid tumor cancers in the United States are believed to harbor dMMR mutations.

Jemperli is the *seventh* PD-1 blocker, joining a busy space still dominated by Merck's Keytruda (pembrolizumab) — which itself received a record eight new FDA-approved indications during 2021. Even OCE chief Richard Pazdur is warning of overcrowding. There are over 2,000 clinical trials of more than 33 different

PD-1 or PD-L1 antibodies, with very little coordination and even fewer comparative studies, he points out in a 15 December [Perspective piece](#) in the *New England Journal of Medicine* entitled “The Wild West of checkpoint inhibitor development.”

Jemperli was hit with COVID-19-related site inspection delays in late 2020, but the drug still benefited from a cluster of fast-lane tickets typical of cancer therapies. It had Breakthrough Designation (preliminary clinical evidence showing substantial improvement on a clinically significant endpoint over available drugs) (Figs. 2 and 3), received Accelerated Approval and, for endometrial cancer, used the Real-Time Oncology Review (RTOR) pilot program, which allows early data submission, potentially shaving three months off average review times.

Expanding antibodies

Antibody drugs like Jemperli accounted for a fifth of all FDA approvals in 2021; biologics as a whole made up just under 40% of those approvals. Innovators continue to eke out their valuable antibody franchises through convenient antibody formulations and delivery mechanisms. Roche’s twice-yearly ocular implant Susvimo (ranibizumab) was approved for wet age-related macular degeneration barely a month after Samsung and Biogen’s Byooviz, which, like its reference drug Lucentis, requires once-monthly administration.

Antibodies’ slow expansion into cardiovascular diseases continued in 2021 with the approval of Regeneron’s Evkeeza (evinacumab-dgnb) for homozygous familial hypercholesterolemia, a rare inherited condition characterized by very high LDL cholesterol. Evkeeza is the first antibody to bind to and block angiopoietin-like 3 (ANGPTL3), which acts in lipid metabolism. It was developed using Regeneron’s VelocImmune engineered mouse platform, also behind one of the two other cardiovascular-focused antibodies, the PCSK9 inhibitor Praluent (alirocumab). (Amgen’s Repatha (evolocumab) is the third). Evkeeza is also in phase 2 for the prevention of acute pancreatitis.

Meanwhile, antibody–drug conjugates (ADCs) have come of age after a shaky history, with several approvals in 2020 and two in 2021. ADC Therapeutics’ Zynlonta (loncastuximab tesirine) in April became the tenth ADC, and the first targeted at the cell surface antigen CD19 with a potent cytotoxic payload of pyrrolobenzodiazepine, for treating diffuse large B cell lymphoma. The cleavable linker is valine–alanine and maleimide.

Seagen and Genmab’s ADC Tivdak (tisotumab vedotin) was [the first tissue](#)

[factor \(TF\)-targeted therapeutic](#); it was approved for recurrent or metastatic cervical cancer. The monoclonal antibody is linked to monomethyl auristatin E, a microtubule inhibitor, and delivers the chemotherapy into cancerous cells via surface TF protein.

CAR-T party

The first chimeric antigen receptor (CAR)-T cell therapy directed at a target other than CD19 arrived in 2021. Bristol Myers Squibb and Bluebird Bio’s Abecma (idecabtagene vicleucel) hits B cell maturation antigen (BCMA), a protein that is expressed by most multiple myeloma cells. After being batted back in 2020 for lack of data, Abecma was approved for relapsed or refractory multiple myeloma after at least four lines of therapy, on the basis of a 127-patient single-arm study. The therapy received conditional approval in the European Union in August.

With the US approval of Bristol Myers Squibb’s CD-19 targeting Breyanzi (lisocabtagene maraleucel) in May for diffuse large B cell lymphoma, there are now five approved CAR-T cell therapies in the United States. (Breyanzi is under review in Europe.) Soon there may be six: [in February 2022](#) the FDA will rule on Janssen and Legend Biotech’s BCMA-targeting ciltacabtagene autoleucel, known as cilta-cel. Early data suggest it could be even more effective than Abecma, with two-thirds of those in a 97-patient study showing no disease progression after 18 months.

CAR-T therapies offer patients with B cell lymphomas and leukemias that have failed alternative therapies a treatment option with potentially long-lasting benefits while avoiding aggressive chemotherapy. They are eligible for multiple expedited categories, while complex, highly personalized manufacturing and administration means they command six-figure price tags. These features explain the [hundreds](#) of pipeline candidates.

For now, CAR-T cell therapies benefit only a few hundred patients. Some developers are seeking to shorten manufacturing time and improve tolerability and convenience in next-generation therapies — including allogeneic (donor-derived) [CAR-T and CAR-NK \(natural killer\) cells](#). Cost is another hurdle facing the expansion of this therapy class. Startup Cellares is one of those working on a scalable manufacturing platform designed to make cell therapies more affordable.

Beefing up CBER for cell therapy

Cell and gene therapies, along with tissue-based products and vaccines, are reviewed by the FDA’s Center for Biologics

Evaluation and Research (CBER). Staff at CBER “were already stressed before COVID-19” with complex cell- and gene-therapy applications, says McCaughan. Pandemic vaccine approvals placed further demands on reviewers. The director and deputy director of the FDA’s Office of Vaccines Research & Review both resigned in the second half of 2021, allegedly due to tensions between the government’s announced timelines for vaccine booster rollout and those that FDA staffers felt were feasible.

Gene- and cell-therapy sponsors reported a drop-off in the quality of communications and advice during the year, and manufacturing site inspections were also delayed for Breyanzi and Jemperli, among several others. “We had to prioritize, and obviously COVID-19 was top of the list,” says Peter Marks, CBER’s head. “Informal sponsor meetings suffered.”

Expanding CBER in preparation for the likely many more cell- and gene-therapy applicants is a prominent goal within the FDA’s Prescription Drug User Fee Act (PDUFA VII) reauthorization [goals and commitments for 2023–2027](#). PDUFA goals, which appear twice a decade, are required for the FDA to receive federal and industry funding. There will be 132 new CBER staff, almost twice as many as the Center for Drug Evaluation and Research will add. Already, “we’re trying to staff up as much as we can,” says Marks. Remote working is widening the applicant pool; so, perhaps, is the prospect of an alternative career for exhausted frontline clinicians who still want to make a difference for patients.

Manufacturing site inspections, of which there is now a huge backlog, will also benefit from a wider and more permanent embrace of digital work patterns. Normally, about a fifth of new drug applications require a pre-approval site inspection. Relying on remote inspections, foreign partners and/or manufacturers’ compliance records cut pre-approval inspections by 55% during the pandemic, according to Office of Pharmaceutical Manufacturing Assessment director Stelios Tsinontides, speaking at an October webinar.

Alongside beefing up staff, the FDA wants to become much more efficient, through modernizing and digitalizing its business and information systems and reducing paperwork.

Too fast?

The FDA’s 2023–2027 goals include further efforts to accelerate approvals. The three-year-old RTOR program, which allows rolling submission of data before full results are available, will expand beyond oncology,

via the Split Real Time Application Review (STAR) pilot. There will be greater discussion of — and, potentially, flexibility around — rare disease endpoints.

Yet the FDA still has some tidying up to do around the accelerated approval pathway, mostly used for oncology. (Aduhelm was an unfortunate exception.) It came under heavy fire in 2021 for failing to chase up required confirmatory trials. Many don't happen, and, even when they do, negative results may not trigger withdrawal — as pointed out in a retrospective study of accelerated cancer drug approvals published in the *British Medical Journal* in August 2021.

The FDA began the cleanup in 2021: OCE head Richard Pazdur's Project Confirm provides a publicly available, searchable database of indications approved under accelerated approval, including drugs that went on to be verified and those that were withdrawn. Through public shaming as much as anything, the effort has led to a record nine 'dangling' indications being withdrawn (voluntarily or otherwise) in 2021. Those include Secura Bio's histone deacetylase inhibitor Farydak (panobinostat) in third-line multiple myeloma, OncoPeptides' Pepaxto (melphalan flufenamide) in fifth-line multiple myeloma, and a third-line gastric cancer indication for Keytruda. "I am a fan of accelerated approvals," Pazdur told senators at a December 2021 hearing. But "we need a

better system to evaluate these products as they're used on the market."

Regulators elsewhere continue to expedite access for drugs that treat rare or under-served conditions. In January 2021, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) launched its Innovative Licensing and Access Pathway (ILAP) in a bid to appeal to developers following the United Kingdom's exit from the European Union. ILAP accepts data on a rolling basis to accelerate access. The first applicant was Merck with Welireg (belzutifan) for cancers associated with von Hippel-Lindau disease, a rare condition characterized by (usually benign) tumor growth on multiple organs. (The drug also received FDA approval in 2021 for the same indication.) Nine others followed in the first quarter of 2021; fees are about \$10,000, depending on joining candidates' stage of development.

Few would argue with faster patient access to effective medicines. The pandemic has shown how rapidly and effectively academia, industry and regulators can mobilize to address public health crises. While a viral respiratory disease continues to ravage lives and economies, some feel it may be time for incentives to develop drugs for less glamorous but more widespread conditions, like obesity or other infectious diseases.

Orphan drug designation and other frameworks successfully reversed challenging dynamics in rare diseases with

small patient numbers. The next frontier is to do something equivalent for major public health risks. Endocrinologists and obesity drug developers would like to see CMS reimburse obesity medications. Passing the US PASTEUR Act to catalyze the development of new antimicrobials through a subscription payment model would be another step in that direction. (The Act was resubmitted in June 2021 but is unlikely to progress in this, or even the next, Congress, according to Capital Alpha's Smith. There is uncertainty about the effects a subscription payment model may have.)

The standout 2021 approval — the first new drug in almost 20 years to address one of society's most pressing chronic neurodegenerative diseases — backfired spectacularly. Aduhelm was one of two non-cancer accelerated approvals, following efforts among the neurology community "to think like those in oncology," says Prevision Policy's McCaughan. CMS's recent proposal to cover only the tiny minority of patients participating in clinical trials shows it playing a more regulator-like role, demanding further evidence. The final coverage decision is due in April, but is unlikely to settle the controversy. □

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