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FRESH FROM THE BIOTECH PIPELINE: RECORD-BREAKING FDA APPROVALS

New drug approvals reached an all-time high in 2023, with five gene therapies, the first CRISPR–Cas9-edited therapy and a disease-modifying Alzheimer's drug. **By Melanie Senior**

The US Food and Drug Administration (FDA) approved a record-breaking 71 new medicines in 2023. There were one or two controversial decisions and a slight drop in first-in-class approvals. But overall, the numbers may help assuage concerns of a more restrictive regulator following 2022's sub-40 approval tally and signal a back-to-business FDA following the official end of the US COVID-19 public health emergency in May.

Small-molecule New Drug Application (NDA) approvals outnumbered Biologics License Application approvals in 2023, but only just: 48% of new approvals were biologics, a share beaten just once, in 2022. This reflects the continued march of new biologic modalities and a strong year for the staffed-up Center for Biologics Evaluation and Research (CBER), the FDA division covering vaccines, cell and gene therapies and blood products (Fig. 1).

Among 2023's new approvals are the first CRISPR–Cas9-edited cell therapy — Vertex

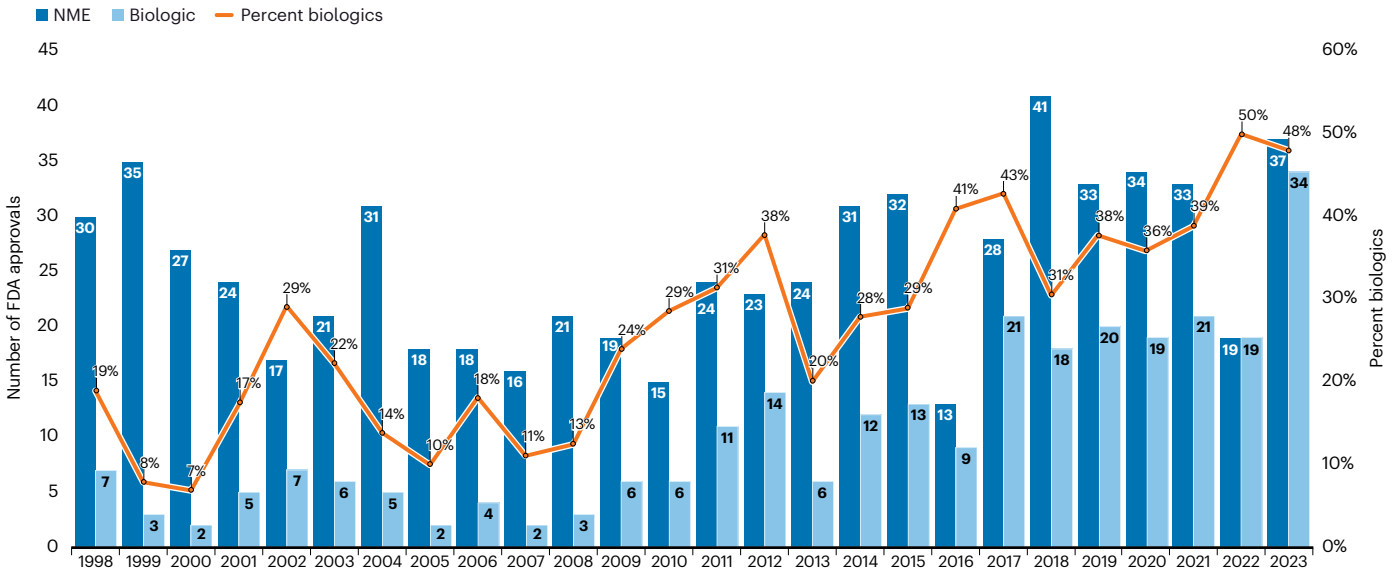

Fig. 1 | FDA new drug approvals (CDER and CBER). The US regulator approved record numbers of new drugs in 2023.

Pharmaceuticals and CRISPR Therapeutics' Casgevy (exagamglogene autotemcel), one of two new treatments for sickle cell disease — four more gene therapies, and the first disease-modifying Alzheimer's drug to gain full approval, Eisai and Biogen's amyloid-fighting antibody Leqembi (lecanemab). Respiratory syncytial virus (RSV) was hit with two new vaccines and one preventative therapy. In all, there were over a dozen new antibody-based drugs, including a quartet of cancer-fighting bispecific T cell engagers.

CBER's multimodal haul also contained Takeda's enzyme replacement therapy (ERT) Adzynma (purified ADAMTS13) for congenital thrombotic thrombocytopenic purpura — one of three new ERTs — and Seres Therapeutics' Vowst, microbiome-enhancing fecal spores delivered via oral capsules to prevent recurrent *Clostridiodes difficile* infection (Table 1).

The FDA's Center for Drug Evaluation and Research (CDER) also approved drugs across several modalities. As well as the small molecules and antibody-based therapies, 2023 saw four new oligonucleotide-based drugs, including one RNA aptamer, one small interfering RNA (siRNA) and two antisense molecules (Table 2). This wide-ranging category is likely to continue to expand: Evaluate Pharma forecasts that RNA- and DNA-based drugs will be worth over $60 billion by 2028. An approval filing is expected in 2024 for Sanofi's phase 3 hemophilia A and B candidate fitusiran, an siRNA targeting antithrombin licensed from Alnylam, after delays due to dosing alterations.

New options for big diseases, though orphans dominate

More than half 2023's approvals were orphan drugs for rare diseases — a proportion that has become typical in recent years given the incentives to develop these niche drugs. Eli Lilly's oral Janus kinase (JAK) inhibitor Jaypirca (pirtobrutinib) received two green lights, in mantle cell carcinoma and chronic lymphocytic leukemia; Novartis's Fabhalta (iptacopan) became the first oral drug for paroxysmal nocturnal hemoglobinuria and Regeneron's Veopoz (pozelimab) pioneered treatment for the rare immune disorder CHAPLE disease (complement hyperactivation, angiopathic thrombosis and protein-losing enteropathy). UCB Pharma delivered two new drugs for the rare neuromuscular condition myasthenia gravis: targeted complement 5 inhibitor Zylbrysq (zilucoplan) and antibody Rystiggo (rozanolixizumab) targeting the neonatal Fc receptor.

There were also new options for more widespread conditions, reflecting a reinvigorated industry interest in larger markets — including the tricky central nervous system space. Leqembi's January Accelerated Approval was translated six months later into full approval for patients with mild Alzheimer's disease; Eli Lilly's donanemab, turned down for Accelerated Approval in January 2023, was refiled for traditional approval during the second quarter. (Leqembi is given every two weeks to those with confirmed amyloid-β pathology; donanemab is a monthly injection.) Sage Therapeutics' γ-aminobutyric acid (GABA)-A receptor modulator Zurzuvae (zuranolone) fell short of a hoped-for nod in major depressive disorder but became the first oral drug for post-partum depression. Fabre-Kramer Pharmaceuticals' oral partial serotonin receptor 5HT1a agonist Exxua (gepirone ER) finally made it in major depressive disorder after three failed attempts over the previous two decades. Its hoped-for differentiating factor versus well-established selective serotonin uptake inhibitors like Prozac is lower rates of sexual dysfunction. Patients with migraine seeking a fast-acting calcitonin gene-related peptide receptor (CGPR) antagonist can now turn to Pfizer's new nasal spray Zavzpret (zavegepant).

2023 also welcomed the first vaccines against RSV, a widespread pathogen that can cause serious illness in very young or immunocompromised people. GSK's Arexvy and Pfizer's Abrysvo were both approved in May for those over 60. In August, Abrysvo won an additional approval as the first maternal vaccine, administered to pregnant women in weeks 32–36 to protect their infants from the virus after birth.

Further protection against RSV came in the form of Sanofi and AstraZeneca's antibody Beyfortus (nirsevimab), which targets the fusion protein (F) on the RSV virion's surface. Given as a single seasonal shot to infants at high risk, Beyfortus is more convenient than predecessor Synagis (palivizumab) from Sobi, which requires monthly dosing. That advantage, and particularly high RSV-linked hospitalization rates in 2022–2023, likely

Table 1 | Biologic approvals in 2023

Sponsor	Therapy; modality	Indication
Biologics approvals by CDER		
Biogen, Eisai	Leqembi (lecanemab); anti-amyloid-β antibody	Alzheimer's disease
Chiesi	Lamzede (velmanase alfa); ERT	α-mannosidosis (manifestations outside the central nervous system)
Incyte, MacroGenics	Zynyz (retifanlimab); anti-PD1 antibody	Advanced or metastatic Merkel cell carcinoma
Chiesi, Protalix Biotherapeutics	Elfabrio (pegunigalsidase alfa); PEGylated ERT	Fabry disease
AbbVie, Genmab	Epkinly (epcoritamab); bispecific CD3 × CD20 T cell engager antibody	Relapsed or refractory diffuse large B cell lymphoma
Roche	Columvi (glofitamab); bispecific CD3 × CD20 T cell engager antibody	Diffuse large B cell lymphoma
UCB Pharma	Rystiggo (rozanolixizumab); neonatal Fc receptor-targeting antibody	Myasthenia gravis
Pfizer, Opco	Ngenla (somatrogon); once-weekly glycosylated human growth hormone analog	Growth deficiency
AstraZeneca, Sanofi	Beyfortus (nirsevimab); antibody	Prevention of respiratory syncytial virus lower respiratory tract infection
Janssen	Talvey (talquetamab); bispecific GPRC5D × CD3 T cell engager antibody	Relapsed or refractory multiple myeloma
Pfizer	Elrexfio (elranatamab); BCMA × CD3 bispecific antibody	Relapsed or refractory multiple myeloma
Regeneron	Veopoz (pozelimab); C5 complement-inhibiting IgG4 antibody with proline substitution	CD55-deficient protein-losing enteropathy (CHAPLE disease)
Amicus	Pombiliti (cipaglucosidase alfa); ERT	Late-onset Pompe disease
UCB Pharma	Bimzelx (bimekizumab); dual-specificity inhibitor of IL-17A and IL-17F	Moderate to severe plaque psoriasis
Eli Lilly	Omvoh (mirikizumab); IL-23 p19-inhibiting antibody	Ulcerative colitis
Coherus BioSciences	Loqtorzi (toripalimab); anti-PD1 antibody	Recurrent or metastatic nasopharyngeal carcinoma
Evive Biotech, Aurobindo	Ryzneuta (efbemalenograstim alfa); long-acting granulocyte colony-stimulating factor fusion protein	Chemotherapy-associated neutropenia
Biologics approvals by CBER[a]		
Takeda	Adzynma (human rADAMTS13 (recombinant a disintegrin-like and metalloproteinase with thrombospondin motifs 13)); ERT	Congenital thrombotic thrombocytopenic purpura
Octapharma	Balfaxar (prothrombin complex concentrate); coagulation factor	Acquired coagulation factor deficiency induced by vitamin K antagonist therapy (such as warfarin)
BioMarin Pharmaceuticals	Roctavian (valoctocogene roxaparvovec); adeno-associated virus-based gene therapy	Severe hemophilia A
CellTrans	Lantidra (donislecel); pancreatic islet cellular suspension	Type 1 diabetes with elevated HbA1c
Sarepta Therapeutics	Elevidys (delandistrogene moxeparvovec); adeno-associated virus-based gene therapy	Duchenne's muscular dystrophy with confirmed *DMD* gene mutation
Krystal Biotech	Vyjuvek (beremagene geperpavec); herpes simplex virus-based gene therapy	Wounds in dystrophic epidermolysis bullosa
Seres Therapeutics	Vowst (fecal microbiota spores, live)	*Clostridioides difficile* infection
Gamida Cell	Omisirge (omidubicel); hematopoietic cell therapy	Reduction of infection and neutrophil recovery time in patients with blood cancer undergoing umbilical cord blood transplantation
Bioverativ Therapeutics	Altuviiio (Fc-VWF-XTEN); recombinant antihemophilic factor fusion protein	Hemophilia A (prophylaxis, treatment of bleeding)
Bluebird bio	Lyfgenia (lovotibeglogene autotemcel); lentiviral β-globin gene therapy	Sickle cell disease
Vertex Pharmaceuticals	Casgevy (exagamglogene autotemcel); CRISPR–Cas9-edited gene therapy	Sickle cell disease
GC Biopharma	Alyglo (intravenous human immune globulin)	Primary humoral immunodeficiency

Table 1 (continued) | Biologic approvals in 2023

Sponsor	Therapy; modality	Indication
Pfizer	Abrysvo; vaccine	Respiratory syncytial virus disease prevention in adults over 60 and women 32–36 weeks pregnant
GSK	Arexvy; vaccine	Respiratory syncytial virus disease prevention in adults over 60
Emergent Product Development	Cyfendus (anthrax vaccine adsorbed, adjuvanted)	Postexposure prophylaxis for *Bacillus anthracis*
Valneva	Ixchiq (chikungunya vaccine, live)	Chikungunya virus disease prevention
Pfizer	Penbraya (meningococcal groups A, B, C, W, Y vaccine)	Prevention of disease caused by *Neisseria meningitidis*

[a]Excludes human plasma products and screens Source: FDA.

Table 2 | Oligonucleotide-based drug approvals in 2023

Sponsor	Therapy; modality	Indication
AstraZeneca, Ionis Pharmaceuticals	Wainua (eplontersen); antisense oligonucleotide that inhibits transthyretin production	ATTR polyneuropathy
Novo Nordisk	Rivfloza (nedosiran); siRNA targeting lactate dehydrogenase	Primary hyperoxaluria type 1
Astellas (via Iveric Bio purchase)	Izervay (avacincaptad pegol); PEG-bound RNA aptamer that inhibits complement protein C5	Geographic atrophy secondary to age-related macular degeneration
Biogen, Ionis Pharmaceuticals	Qalsody (tofersen); antisense oligonucleotide targeting superoxide dismutase 1 (SOD1)	Amyotrophic lateral sclerosis with *SOD1* mutation

PEG, polyethylene glycol; siRNA, small interfering RNA. Source: FDA

contributed to Beyfortus's ongoing supply shortages this winter season, prompting prioritization guidance from the Centers for Disease Control and Prevention. Sanofi and manufacturing partner AstraZeneca have launched a preordering program for the 2024–2025 RSV season.

Supplies of weight-loss-inducing glucagon-like peptide-1 receptor agonists also failed to meet burgeoning demand in 2023, notwithstanding the widely anticipated November approval in obesity of Eli Lilly's diabetes medicine Zepbound (tirzepatide). Zepbound is expected to outpace even Novo Nordisk's first-to-market Wegovy (semaglutide) in a red-hot market now valued at over$100 billion.

Sickle cell disease is classified as a rare disease in the United States, but it is the most common genetic disorder in the country, affecting 1 in 500 African Americans, or about 100,000 people. The arrival of two new gene therapies — approved on the same day in December — is therefore noteworthy, both for eligible patients and for payers. Casgevy uses CRISPR–Cas9 to edit patients' own blood stem cells to raise levels of fetal hemoglobin, thereby reducing red blood cell sickling and the resulting vaso-occlusive crises. Bluebird bio's Lyfgenia (lovotibeglogene autotemcel) also genetically modifies blood stem cells, in this case adding a functional β-globin gene to produce HbA^{T87Q}, which is similar to adult hemoglobin.

Both are complex, one-time treatments costing millions of dollars: Lyfgenia was launched at a list price (before discounts or deals) of $3.1 million and Casgevy at $2.2 million. The FDA estimates that only about a fifth of patients with sickle cell disease will be eligible, but the still-huge budgetary impact on anxious payers is prompting innovative contracts. Bluebird has already signed two outcomes-based deals offering discounts if patients are hospitalized within three years of treatment as a result of vaso-occlusive events. Both drugs were fast-tracked through several FDA expedited pathways; only Lyfgenia carries a black box warning for hematological malignancies.

In mid-January, FDA also approved Casgevy for transfusion-dependent β-thalassemia. The UK and Saudi Arabia have already approved Casgevy across both indications, and the European Medicines Agency has given a positive recommendation.

Cancer tops 2023 approvals, no thanks to ADCs

Oncology's dominance remained in 2023, with 15 novel therapies accounting for over 20% of approvals. Four new T cell-engaging bispecific antibodies doubled the ranks of these two-armed proteins, which draw together healthy T cells and cancer-linked antigens. Pfizer's Elrexfio (elranatanab) binds T cells' CD3 protein and B cell maturation antigen (BCMA) on myeloma cells; Janssen's Talvay (talquetamab) draws together CD3 and novel target GPRC5D. Both received Accelerated Approval for late-line use in refractory multiple myeloma. A pair of CD3 × CD20 bispecifics, Roche's Columvi (glofitamab) and AbbVie's Epkinly (epcoritamab), were conditionally approved for large B-cell lymphoma.

The oncology armamentarium also got another pair of PD-1 blocking antibodies, Incyte's Zynyz (retifanlimab) for the aggressive skin cancer Merkel cell carcinoma and Coherus BioSciences and Shanghai Junshi BioSciences' Loqtorzi (toripalimab) for recurrent or metastatic nasopharyngeal carcinoma. Daiichi Sankyo's Vanflyta (quizartinib), an oral type 2 FLT3 inhibitor, arrived for the roughly one-third of newly diagnosed patients with acute myeloid leukemia who have changes in the *FLT3* gene (known as internal tandem duplication).

One red-hot modality that does not feature in the FDA's 2023 roster is antibody–drug conjugates. These targeted agents, which load cancer-directed antibodies with cytotoxic payloads, drove almost $100 billion worth of mergers, acquisitions and licensing deals in 2023, according to Evaluate. Pfizer's $43 billion acquisition of Seagen was at the heart of the ADC party, which continues this year with deals such as Johnson & Johnson's $2 billion acquisition of Ambrx Pharma (see "Cancer-targeting antibody–drug conjugates drive dealmaking frenzy").

Yet 2023 saw fewer, rather than more, approved ADCs, following AstraZeneca's withdrawal of CD22-directed Lumoxiti (moxetumomab pasudotox) in hairy cell leukemia owing to the availability of alternative, less complex treatments (like BRAF

inhibitor Zelboraf (vemurafenib)). Still, with a dozen ADC hopefuls in phase 3 trials and almost 40 in phase 2, according to Citeline's Biomedtracker, more will follow. Daiichi Sankyo and Merck & Co.'s HER3-targeting patritumab deruxtecan for EGFR-mutated, previously treated non-small-cell lung cancer has a June 2024 FDA action deadline; Daiichi Sankyo and AstraZeneca's phase 3 TROP2-directed ADC datopotamab deruxtecan is hotly anticipated in hormone receptor-positive, HER2-low or negative breast cancer.

Best of the rest: infectious, inflammatory and neurological diseases

Infectious diseases product approvals came closest to cancer in numbers, with 11 new therapies or vaccines approved in 2023 (Fig. 2). These include Pfizer's Paxlovid (nirmatrelvir ritonavir), the first oral COVID-19 pill, and its meningococcal disease vaccine Penbraya; Tarsus Pharmaceuticals' Xdemvy (lotilaner), an anti-parasitic for *Demodex* blepharitis (inflammation of the eyelids due to tiny mites); and the RSV trio.

The half dozen hematology approvals included the two sickle cell therapies and a pair of potentially transformative hemophilia A drugs. Sanofi and Sobi's fusion protein Altuviiio (efanesoctocog alfa) is a long-acting recombinant factor VIII that can be dosed once weekly while BioMarin Pharmaceuticals' Roctavian (valoctocogene roxaparvovec), delivering a working copy of the factor VIII gene, may offer some patients a one-time solution. (It was initially rejected in 2020.)

High approval counts across inflammatory diseases (six) and neurology (eight) may have helped fuel strong dealmaking interest in these fields in 2023, including Merck & Co.'s $10.8-billion acquisition of inflammation-focused Prometheus Biosciences and AbbVie's $8.7 billion deal for neurosciences firm Cerevel Therapeutics.

Neurology's eight new approvals, including Leqembi, put the therapy area in third place, behind oncology and infectious diseases. This once deprioritized field may generate further news in 2024. Karuna Therapeutics' xanomeline trospium, a M1/M4 muscarinic receptor agonist (and peripheral antagonist) awaiting approval for schizophrenia, has a September action date, enticing Bristol Myers Squibb to pay $13.6 billion for the company in December. (Cerevel's selective M4 receptor agonist emraclidine is in phase 2 trials for schizophrenia.) Eli Lilly expects a decision early this year for Alzheimer's candidate donanemab, and Lykos

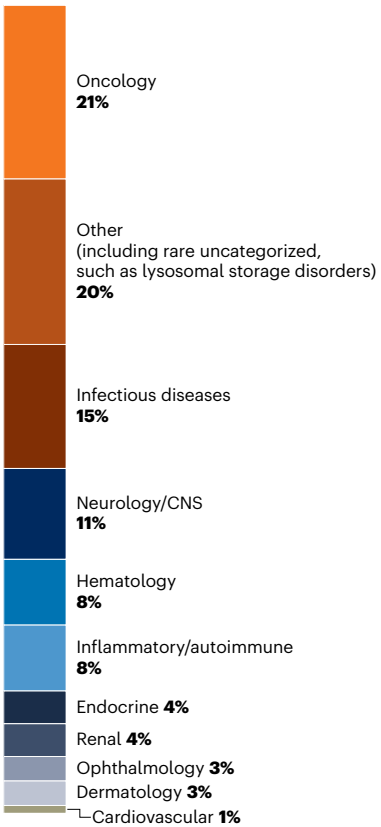

Fig. 2 | FDA approvals by therapy area. CNS, central nervous system.

Therapeutics (previously known as MAPS Public Benefit Corporation) in December submitted to the FDA its psychedelic midomafetamine for post-traumatic stress disorder.

Midomafetamine, an N-substituted amphetamine analog, is the active ingredient in the street drug 'ecstasy'; growing interest in the therapeutic potential of psychedelic drugs prompted draft FDA guidance in mid-2023 to support sponsors' clinical investigations (Box 1).

The inflammatory diseases treatment haul included two new ulcerative colitis medicines. Lilly's Omvoh (mirikizumab), after an initial rejection due to manufacturing concerns, became the first drug to antagonize the p19 subunit of interleukin (IL)-23. Pfizer's oral once-daily sphingosine-1 phosphate (S1P) receptor modulator Velsipity (etrasimod) was approved for ulcerative colitis in October, months after its Litfulo (ritlectinib) arrived for severe cases of the autoimmune disease alopecia areata, characterized by patchy hair loss. Litfulo is an oral inhibitor of Janus kinase 3 (JAK3) and tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase and will compete with Lilly's Olumiant (baricitinib), which in 2022 became the first drug approved for adults with the condition. Litfulo is approved for adolescents over 12 and is in development for ulcerative colitis, Crohn's disease and vitiligo.

UCB Pharma's Bimzelx (bimekizumab) was approved for moderate to severe plaque psoriasis. It is the first antibody to selectively hit two inflammatory cytokines, IL-17A and IL-17F. (Since it binds both cytokines at one site, rather than at two different sites, it is not referred to as a bispecific antibody.) Bimzelx has been approved in the European Union since 2021; US approval was held up by pandemic-related inspection delays and a safety signal. EU authorities in June added psoriatic arthritis and active axial spondyloarthritis to the drug's label. The Brussels-headquartered group expects peak sales of $4.3 billion.

Uncertainties remain

FDA's 2023 approvals were not without controversy, and some stats paint a less bright picture. For instance, CDER's share of first-in-class approvals, at 36%, is slightly below the ten-year average. The "almost 90%" of FDA's decisions that happened on or before the Prescription Drug User Fee Act approval deadline leaves seven that didn't – notable given the agency's typically squeaky-clean timeliness record. (The drug firms that pay the FDA's user fees want predictability on timelines.) Most of the setbacks were due to COVID-19-related constraints on accessing Chinese manufacturing sites, though a delay to the Priority Review of Iovance Biotherapeutics' lifileucel, a tumor-infiltrating lymphocyte cell therapy for advanced melanoma, was apparently due to resource constraints at the FDA.

A couple of contestable decisions stood out in 2023. Alnylam's siRNA drug Onpattro (patisiran) failed to win an anticipated label expansion into transthyretin amyloidosis (ATTR) with cardiomyopathy, despite a favorable advisory committee vote. Yet Sarepta's gene therapy for Duchenne's muscular dystrophy, Elevidys (delandistrogene moxeparvovec), was approved despite briefing documents recommending otherwise. The approval, three weeks after the priority review deadline, came after CBER director Peter Marks overruled the review team; Marks has been vocal in his willingness to support these novel approaches addressing rare, undertreated conditions.

Safety still comes first, though: FDA's November review of chimeric antigen receptor (CAR)-T cell therapies translated, in

BOX 1

Digital guidance grows but AI a challenge

The FDA in 2023 issued draft guidance on the use of decentralized trials and finalized its guidance on the use of digital health technologies for remote trial data collection — bids to embrace and embed positive examples of greater study resilience uncovered during the pandemic. There was also final guidance on the use of real-world evidence from new or existing registries in support of drug applications. Cell- and gene-therapy products got two draft guidances covering manufacturing changes and potency assurance, and there was guidance on remote monitoring of all drugs' manufacturing and holding facilities.

Digital's unstoppable spread across healthcare prompted the establishment of the FDA's Digital Health Advisory Committee in October. The committee will consider and advise on how FDA may regulate tools incorporating artificial intelligence, machine learning and augmented reality, as well as digital therapeutics, monitoring systems and wearables. AI offers huge potential to overhaul care delivery and will be a focal point for 2024: in January, the FDA approved BrainSee, AI-powered software that uses MRI scans and cognitive test scores to predict the likelihood of patients with mild cognitive impairment progressing to Alzheimer's-associated dementia.

Yet the FDA can't regulate AI on its own, warned commissioner Robert Califf at the Consumer Electronics Show in Las Vegas in January. He also highlighted the need to recruit and train AI-literate staff at FDA — a challenging proposition for a government agency given sky-high private sector salaries.

January 2024, into a class-wide boxed warning requirement on the risk of secondary blood cancers. (Gilead Sciences' Tecartus (brexucabtagene autoleucel) was, unlike the other CAR-Ts, spared specific reference in amended safety labeling.) CAR-T cell therapies had a difficult year: there were no new approvals, and a patient death led to a clinical hold on Arcellx's phase 2 BCMA-targeted CAR-T cell therapy in refractory multiple myeloma.

Overall, though, the 30 partial or full clinical trial holds imposed by the FDA in 2023 were below the 40-plus holds seen during each of 2022 and 2021. GSK and Mersana's STING-agonist-targeting ADC XMT 2056 in gastric cancer and solid tumors was among those held, due to a severe adverse event.

FDA issued 51 complete response letters – rejections – in 2023, more than in each of the previous three years, according to Biomedtracker. Yet these represented a lower share of the year's successful approvals.

There were fewer Accelerated Approvals: just 11 drugs benefited from the conditional pathway (of which 8 were in oncology), taking 2022 and 2023's counts below the ten-year average, according to Evaluate. The drop-off likely follows increased scrutiny of sponsors' commitment to confirmatory trials and the requirement to prove such studies are underway when an Accelerated Approval is granted. Eli Lilly's Accelerated Approval application for donanemab was rebuffed in January – perhaps predictably given the backlash following the FDA's June 2021 Accelerated Approval of Biogen's Aduhelm (aducanumab), against advisory committee recommendations. (The drug's European application was withdrawn.)

Still, the FDA continued to make avid use of other expedited review pathways. Priority Review and Fast Track programs accounted for 56% and 45%, respectively, of CDER approvals. In 2022, the equivalent shares were 57% and 32%. Overall, almost two-thirds (65%) of 2023's new drugs were accelerated in some way. This year, CBER is piloting another new rapid-access program for up to six candidates in rare pediatric and neurological diseases: the Support for Clinical Trials Advancing Rare Treatment (START) will test more rapid FDA–sponsor communication, hoping to inform more efficient development of rare-disease drugs.

Questions linger over FDA's use of advisory committees, which provide expert advice on complex issues related to drug approvals and add transparency to decision-making. Their use has been falling for the past few years, according to a 2023 study published in JAMA Health, though by law they are mandatory for all new molecular entities unless the agency specifically waives their use. The first half of 2023, however, saw 19 advisory committee meetings, more than in the previous few years, according to Michael McCaughan, founding member at Prevision Policy, which analyzes regulatory and policy trends. "It looked as if things were back to normal," he says. CDER chief Patrizia Cavazzoni also said, during an April webinar, that she wanted more advisory committees. But in the second half of 2023, advisory committee meetings dried up again: there were just six. FDA Commissioner Robert Califf said in early 2024 that changes to the process are underway, but what those changes entail remains unclear.

FDA cannot address access bottleneck

FDA's long list of new drug approvals does little to address the downstream challenge of ensuring innovations get to those who need them. As commissioner Califf noted at the UCSF-Stanford Center of Excellence in Regulatory Science (CERSI) summit in San Francisco in January 2024, US life expectancy is falling, despite $4 billion in health care spending.

Opioid overdoses play a part in that sobering reality – something the FDA has spent years trying to combat. Across healthcare, FDA approval is necessary but not sufficient for treatment access. Payers – including government payer the Centers for Medicare and Medicaid Services – determine how easily most new medicines reach patients. They are concerned by the growing share of high-priced gene and cell therapies, including for less rare conditions like sickle cell disease; by soaring demand for obesity drugs; and by biosimilars' painfully slow US uptake.

The FDA approved five new biosimilars in 2023, noting in its 2023 approvals report how this category can help reduce patient and system costs. There were three biosimilar firsts in 2023 – drugs without previous copies: Sandoz's Tyruko is a copy of Biogen's multiple sclerosis drug Tysabri (natalizumab); Biogen's Tofidence, a biosimilar of Roche's rheumatoid arthritis treatment Actemra (tocilizumab); and Amgen's Wezlara which references Janssen's autoimmune disease drug Stelara (ustekinumab). The FDA approved Wezlara as an interchangeable biosimilar, which means that pharmacists can exchange the product without prescriber authority. Two older biosimilars, to Humira (adalimumab) and Lucentis (ranibizumab), were also granted interchangeable status during 2023.

CDER waved through over 80 small-molecule 'first' generics, including copies of advanced kidney cancer drug Votrient (pazopanib), rheumatoid arthritis drug Xeljanz (tofacitinib), breast cancer treatment

Ibrance (palbociclib) and over a dozen copies of Takeda's attention deficit hyperactivity disorder drug Vyvanse (lixdesamphetamine). Cavazzoni wants to remove barriers facing development of complex generics (inhalers, injectables and patches) and to streamline biosimilar development, she noted in the April Alliance for a Stronger FDA webinar.

One outlier on 2023's approvals list is TheracosBio's sodium–glucose co-transporter-2 (SGLT-2) inhibitor Brenzavvy (bexagliflozin), which, although reviewed as an NDA rather than the abbreviated NDA used for generics, quickly joined Mark Cuban's Cost Plus Drugs' low-cost offerings months after approval. Cost Plus provides patients direct access to (mostly generic) drugs at wholesale cost plus a fixed 15% markup and is one of several efforts to upend the complex US drug distribution chain and its many middlemen.

In a similar vein, Eli Lilly launched a new consumer-facing website, LillyDirect, offering patients direct access to its popular obesity treatment Zepbound, which some payers do not cover.

Both moves signal shifts in the relationships between pharma, payers, providers and patients that are likely to continue in 2024 and beyond.

What to expect in 2024?

2024's anticipated approvals include Madrigal Pharmaceuticals' thyroid hormone receptor-β selective agonist resmetirom for nonalcoholic steatohepatitis with liver fibrosis. Amgen's tarlatamab could become the first delta-like ligand 3 (DLL3)-targeting bispecific T cell engager for small-cell lung cancer while Jazz Pharmaceuticals' dual HER2 blocker zanidatamab may arrive for HER2-amplified biliary tract cancer. Merck's activin signaling inhibitor sotatercept, a fusion protein, could offer a new mechanism of action in pulmonary arterial hypertension, and the year may also welcome two new paroxysmal nocturnal hemoglobinuria treatments, Roche and Chugai Pharmaceutical's crovalimab and Amgen and Daiichi Sankyo's biosimilar eculizumab.

Pfizer may bring another gene therapy for hemophilia B with fidanacogene elaparvovec, an engineered version of the *FIX* coagulation gene, and Autolus Therapeutics' obecabtagene autoleucel for acute lymphoblastic leukemia could add to CBER's list of CD19 CAR-T cell therapies. There may be further competition to Arexvy and Abrysvo in older populations from Moderna's messenger RNA-based RSV vaccine candidate.

FDA veteran Janet Woodcock retires this year after more than three decades during which she strongly influenced the drug approval process, including expedited review pathways. FDA watchers point to other highly experienced individuals remaining at the agency, though, including senior advisor Robert Temple; director of Oncology Center of Excellence Richard Pazdur; and Peter Marks, who joined in 2012.

Another recent change is Elizabeth Jungman's appointment as Califf's chief of staff. She was previously director in CDER's Office of Regulatory Policy, where she was "invaluable in handling high-profile, politically charged and sensitive policy matters," according to the CDER's Cavazzoni.

Let's not read too much into that for 2024.

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