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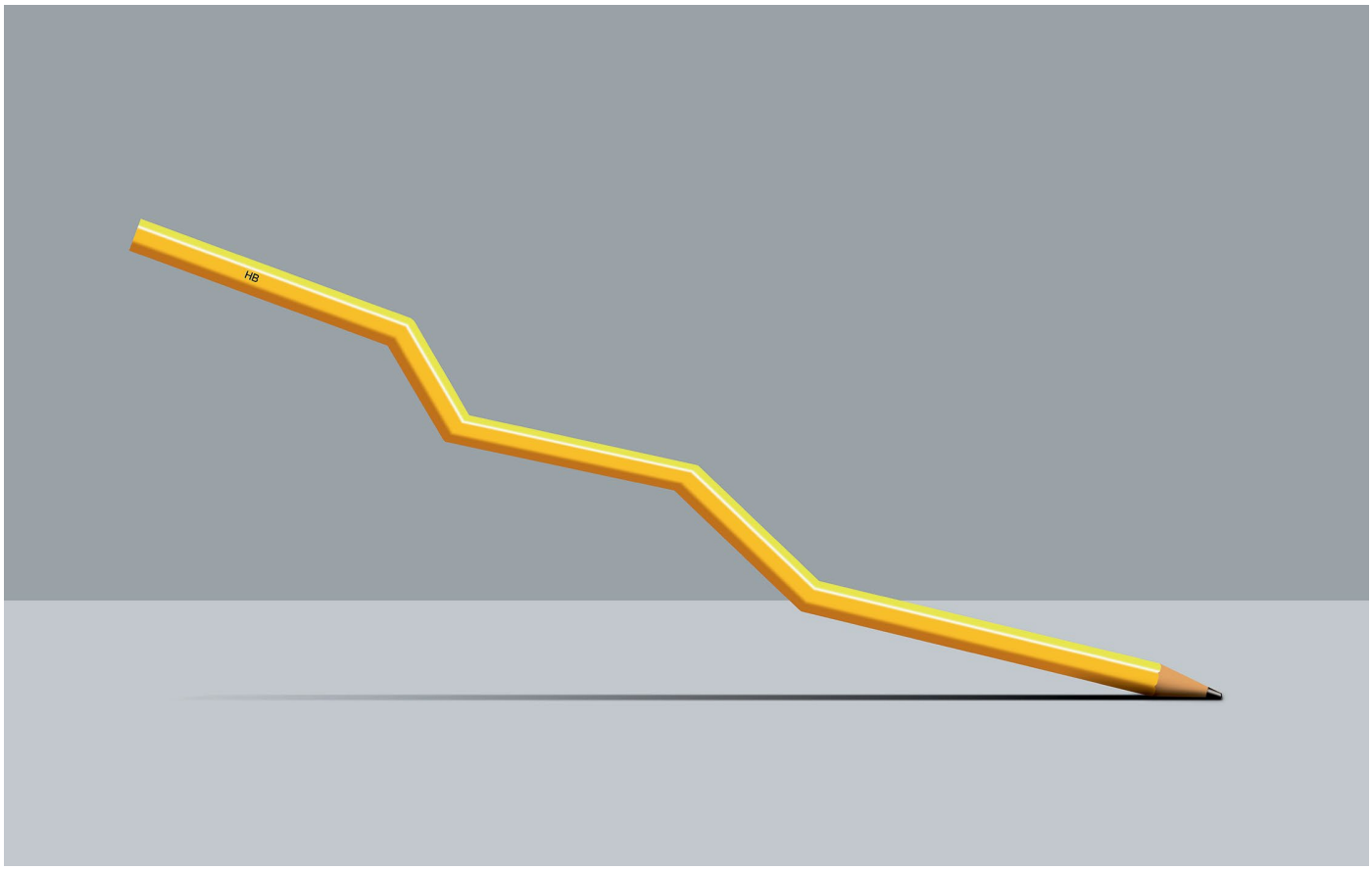

PHARMA BACKS OFF BIOTECH ACQUISITIONS

Rising costs and an uncertain global economy have left many potential buyers sitting on their hands — or partnering instead. **By Melanie Senior**

With public markets in freefall, biotech companies running short of cash hoped that pharma might pick up the slack. "The biggest factor that could turn the sector around is mergers and acquisitions," said one biotech CEO at the start of 2022.

It hasn't happened. At its current pace, 2022 is set to be the slowest year for mergers and acquisitions (M&A) since 2018. By the end of August, the combined value of 2022's acquisitions barely scraped half those seen in 2021 — itself muted relative to 2020 and 2019 (Fig. 1). Total deal value through August 2022 was $41.5 billion, compared with almost $97 billion in 2021 and over $140 billion in 2020, according to BioCentury BCIQ. Deal numbers, if extrapolated out to full year, have fallen less sharply, however, indicating smaller deal sizes (Fig. 1). Pfizer's $11.6 billion acquisition of Biohaven Pharmaceuticals in May is the high point so far in 2022, marking a flurry of mid-year deals each worth over $1 billion (Table 1).

On paper, record big pharma cash reserves, a steep, fast-approaching patent cliff and low public biotech valuations should equal frenzied buying. Mega-blockbusters set to lose exclusivity over next six year represent the biggest threat to sales in decades. Three drugs alone — AbbVie's Humira (adalimumab), Merck's Keytruda (pembrolizumab) and Bristol Myers Squibb (BMS)'s Opdivo (nivolumab) — represent over $45 billion in annual sales. Several big pharma CEOs talked bullishly about deal making during quarterly earnings announcements in early 2022.

But in practice, rising costs, an uncertain macroeconomic climate and a less predictable US Food and Drug Administration (FDA) have given potential buyers pause. "There's no sense of urgency on big pharma's side," says

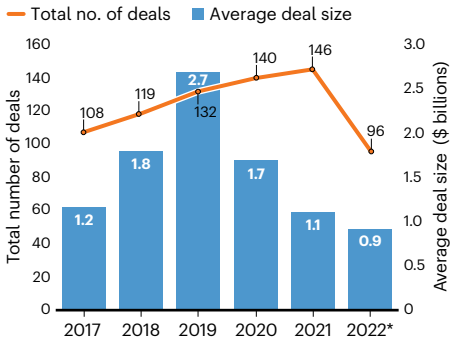

Fig. 1 | Mergers and acquisitions over a five-year period. Average deal size has been falling. *Through August. (Source: BioCentury BCIQ).

one public market investor. Most of those that are shopping are buying marketed or close-to-market assets that immediately fill revenue gaps. Anything earlier isn't worth the risk or additional R&D cost. Big pharma's patent cliff "won't be solved by buying a phase 2 company," sums up Gil Bar-Nahum, managing director at Jefferies' global healthcare investment banking group in London.

The upshot for pre-revenue biotechs: knuckle down, generate strong data and opt for partnerships instead. The risk-off mood "means pharma has flipped [from M&A] into licensing," says Joe Anderson, a London-based partner at venture capital firm Sofinnova.

Risk and cash burn? No thanks

Half of the top ten biggest deals so far in 2022 involve marketed products that provide their buyers with immediate risk-free revenue. Pfizer, flush with COVID-19 cash, wanted Biohaven's migraine drug Nurtec ODT (rimegepant), a small-molecule calcitonin gene-related peptide (CGRP) receptor antagonist approved for both prevention and treatment in an increasingly competitive marketplace. It also liked Biohaven's strong phase 3 cohort, including a back-up intranasal 'gepant' plus three further programs for rare disease indications. Pfizer's August 2022 purchase of Global Blood Therapeutics came with the approved sickle cell disease treatment Oxbryta (voxelotor), though the jewel asset is in phase 2/3. GBT601, a next-generation sickle hemoglobin polymerization inhibitor, could provide something close to a cure for the inherited blood disorder, characterized by misshapen and dysfunctional red blood cells. Another phase 3 candidate, inclacumab, targets P-selectin protein and may reduce frequency of painful vaso-occlusive crises associated with sickle cell disease, along with resulting hospital admissions.

Table 1 | M&A deals worth over $1 billion (up to August, 2022)

Buyer–Seller	Deal value ($ billion)	Therapy area (latest stage)
Pfizer–Biohaven	11.6	Migraine (marketed), obsessive–compulsive disorder, epilepsy, rare diseases
Pfizer–Global Blood Therapeutics	5.4	Sickle cell disease complications (marketed), blood disorders
Bristol Myers Squibb–Turning Point	4.1	Cancer (phase 3)
Amgen–ChemoCentryx	3.7	Rare autoimmunity (approved)
GlaxoSmithKline–Affinivax	2.7	Viral infection, cancer (phase 2)
GSK–Sierra Oncology	1.9	Myelofibrosis (submitted)
SD Biosensor/SJL Partners–Meridian Bioscience	1.5	Diagnostics
Novo Nordisk–Forma Therapeutics	1.1	Sickle cell disease, rare blood disorders (phase 2/3)

Source: BioCentury BCIQ

BOX 1

Gene and cell therapy stumbles

Recent setbacks serve as a reminder that new technologies take time to get off the ground.

UniQure's phase 1b/2 Huntington's disease gene therapy candidate triggered unexpected severe side effects in two patients this summer; Modi'in, Israel-based VBL Therapeutics' phase 3 ovarian cancer adenovirus candidate failed to meet its survival endpoints; and two children with spinal muscular atrophy reportedly died after treatment with Novartis's gene therapy Zolgensma (onasemnogene abeparvovec). The FDA in May asked again for more data on BioMarin's hemophilia A adeno-associated virus candidate valoctocogene roxaparvovec, two years after an initial rejection and request for further studies. BioMarin re-submitted the drug in September 2022.

The US agency did approve bluebird bio's lentivirus-based Zynteglo (betibeglogene autotemcel) for β-thalassemia in August 2022 and, a month later, Skysona (elivaldogene autotemcel) for cerebral adrenoleukodystrophy, but both had previously been put on clinical holds, forcing the company to cut cost and restructure. Priced at $2.8 million and $3 million, respectively, Zynteglo and Skysona face reimbursement challenges and are unlikely to transform the company's fortunes overnight.

Cell therapy approaches have also faltered. Red blood cell therapy company Rubius Therapeutics in September axed its two lead clinical programs and slashed three quarters of its staff, after clinical and manufacturing setbacks. The FDA in July 2022 put a hold on Beam Therapeutics' IND application for an anti-CD7 multiplex-edited allogeneic chimeric antigen receptor T cell (CAR-T) cell therapy for relapsed or refractory T cell acute lymphoblastic leukemia. Developing T cell cancer therapies beyond their early promising results has proven more arduous than expected. "It has taken longer than people hoped, and been more difficult, to get to the next generation of CAR-T cell therapies," says EQT Life Sciences' O'Keeffe, citing the five years since Novartis's Kymriah (tisagenlecleucel) and Gilead's Yescarta (axicabtagene ciloleucel) were approved.

M&A deals for gene and cell therapy companies have also slowed. Through September 2022 there were just eight, under half the number seen in the previous year. Among 2022's deals are Vertex Pharmaceuticals' acquisition of stem cell company ViaCyte, with its type 1 diabetes program, and Galapagos' purchase of CellPoint, whose lead CAR-T cell therapy is in phase 1/2 trials. In early October, as *Nature Biotechnology* went to press, AstraZeneca snapped up ailing gene therapy venture LogicBio Therapeutics for $68 million, or just over $2 a share — a fraction of what it would have had to pay for the adeno-associated virus-based gene therapy company anytime during the previous three years.

BOX 2

US drug pricing rules add to uncertainties stifling M&A

From 2026, the US government will negotiate prices for some drugs. Precisely which ones remains to be seen, but the new rules could make some treatments far less commercially attractive, giving potential buyers another reason to pause. The Inflation Reduction Act, signed into law in August 2022, sees federally funded Medicare (which covers people over 65) negotiate the price of ten top-selling outpatient drugs in 2026, rising to 20 three years later. Other cost-control measures include rebates on any Medicare drugs whose prices rise faster than inflation, caps on maximum negotiated prices and, for manufacturers who refuse to negotiate, punishing excise taxes on prior year sales.

Industry lobby group PhRMA warns that the law will kill innovation. Yet not all drugs will be subject to negotiations: those with available generics or biosimilars, those on the market for less than 7 years (for small molecules) or 11 years (for biologics), or those that cost Medicare less than $200 million in 2021 will be excluded. So the bill won't substantially eat into market exclusivity periods (5–7 years for small molecules and 12 for biologics). Expensive injectables and other hospital-administered products won't be subjected to negotiation until 2028. Orphans approved for only one rare disease and those that cost Medicare less than $200 million annually are also excluded. So are drugs that account for more than 80% of a single company's revenues — a common scenario for rare-disease-focused biotechs.

This rejiggering of the commercial arithmetic for some mainstream and orphan treatments could contribute to slower M&A. Another unintended consequence of the law may be higher drug launch prices — including for orphans — as disgruntled manufacturers seek to squeeze as much as they can out of new products before potential negotiations kick in and as they seek to avoid fines for above-inflation annual price rises along the way.

Rare diseases are also the focus of Amgen's $3.7 billion August purchase of ChemoCentryx. Tavneos (avacopan) is an oral selective complement 5a receptor inhibitor approved in October 2021 as an adjunctive treatment for patients with severe forms of a rare autoimmune condition called active anti-neutrophil cytoplasmic autoantibody-associated vasculitis.

Despite big pharma holding an estimated $350 billion combined cash (and up to half a trillion available to spend), according to SVB Securities, some appear hesitant to take on earlier-stage programs whose funding requirements will eat into their profits during acutely uncertain times with double-digit inflation, fragile supply chains, and expensive talent. Many would rather "pay $5 billion for something certain than take a bet at $500 million," says Jefferies' Bar-Nahum.

That may be true unless you're Roche, which in early September paid $250 million up front for US-based Good Therapeutics and its PD-1-regulated interleukin (IL)-2 receptor agonist platform. Designed to avoid systemic immune activation seen with unfettered IL-2 receptor agonists like Proleukin (aldesleukin), the technology complements Roche's in-house phase 1 program combining an anti-PD-1 antibody with an IL-2 variant. Good Therapeutics' program is still preclinical.

Most of the $26 billion that Pfizer has spent on acquisitions over the last 12 months went to revenue-generating companies, but the figure (which is still less than its expected 2022 COVID-19 vaccine revenues) also included phase 1/2 cancer company Trillium Therapeutics ($2.2 billion) and ReViral ($525 million), which has a phase 2 respiratory syncytial virus vaccine candidate.

What to buy?

So risk, although out of fashion, isn't entirely off the table if it comes with strong signs of efficacy and good strategic fit. BMS in June paid $4.1 billion for Turning Point Therapeutics, which expects to file lung cancer drug repotrectinib later this year for potential approval in 2023. Repotrectinib adds a competitive precision oncology asset to BMS's existing franchise: the tyrosine kinase inhibitor targets ROS1 and NTRK mutations, complementing BMS's non-small-cell lung cancer stable including Opdivo (nivolumab), Yervoy (ipilimumab) and Opdualag (nivolumab and relatlimab). A longer response duration may give repotrectinib an edge over Roche's Rozlytrek (entrectinib), approved in 2019 for cancers harboring the same mutations.

GlaxoSmithKline's (GSK) vaccine-franchise-boosting $2.1 billion acquisition of Affinivax comes with a pneumococcal vaccine candidate that is still in phase 2, but that has breakthrough designation and includes more pneumococcal serotypes than approved vaccines. The British-based pharma also spent $1.9 billion on Sierra Oncology as it rebuilds an oncology franchise discarded almost a decade ago. Sierra's lead myelofibrosis candidate momelotinib – since submitted to FDA for myelofibrosis with anemia – inhibits activin A receptor, type I (ACVR1), Janus kinase (JAK) 1 and JAK2. It would complement GSK's Blenrep (belantamab mafodotin) for relapsed or refractory multiple myeloma.

For a few big pharmas, determining what to buy could be another source of delay. Once-hot areas like gene and cell therapy have stumbled clinically and commercially (Box 1), while new US drug pricing rules may change the arithmetic on some mainstream treatments (Box 2). Pharma management may be asking, "Do we want to be in the same franchises as before, or make a big, bold new bet – and if so, where?", suggests one investment banker.

Regulatory uncertainty may be another headwind. New FDA drug approvals are the slowest they have been for three years, and the number of complete response letters – rejections – is up. "There's criticism about what FDA is thinking, and how it's thinking," says Nooman Haque, managing director, life sciences and healthcare at Silicon Valley Bank for EMEA. Observers point to a recent turnaround on Amylyx Pharmaceuticals' amyotrophic lateral sclerosis drug Relyvrio (sodium phenylbutyrate and taurursodiol), approved by the FDA months after an advisory committee voted to reject the drug, yet later reversed its decision, plus the controversial approval of Biogen's Aduhelm (aducanumab) in 2021, as evidence of less predictable regulator.

Against this backdrop, robust data – or an approval stamp – matter more than ever. "Whatever the modality, if a product is approved, everyone will look at it," says Bar-Nahum.

Partnerships preferred

If they like it, they will partner. "Often big pharma seems to prefer to invest in just the asset, rather than take on an entire company,"

Table 2 | Top licensing agreements of 2022

Companies	Headline	Up-front cash ($ millions)
Enable Injections (research partner) Sanofi (research partner) Blackstone Life Sciences (investor)	Sanofi and Blackstone will collaborate to advance an innovative treatment for multiple myeloma	330
Gilead Sciences (licensor) Dragonfly Therapeutics (licensee)	Gilead and Dragonfly announce strategic research collaboration to develop natural killer cell engagers in oncology and inflammation	300
Pfizer (research partner) Beam Therapeutics (research partner)	Pfizer and Beam enter exclusive multi-target research collaboration to advance in vivo base editing for rare diseases	300
Orion (licensor) Merck & Co. (licensee)	Merck and Orion announce global collaboration for the development and commercialization of ODM-208, an investigational steroid synthesis inhibitor for the treatment of metastatic castration-resistant prostate cancer	290
Cullinan Oncology (licensor) Taiho Pharmaceutical (licensee)	Cullinan and Taiho announce strategic collaboration to jointly develop and commercialize CLN-081 (TAS6417), as well as Taiho's acquisition of Cullinan Pearl	275
Chimerix (seller) Emergent BioSolutions (buyer)	Emergent to acquire from Chimerix exclusive worldwide rights to Tembexa (brincidofovir), an FDA-approved smallpox oral antiviral for all ages	238
Orna Therapeutics (licensor) Merck & Co. (licensee)	Merck partners with Orna to develop and commercialize vaccines and therapeutics using Orna's oRNA-LNP technology	150
Sanofi (licensee) IGM Biosciences (licensor)	Sanofi and IGM announce collaboration agreement for oncology, immunology and inflammation targets	150
Roche (licensee) Repare Therapeutics (licensor)	Repare announces a worldwide license and collaboration agreement with Roche for camonsertib (RP-3500)	125
Menarini (licensee) NewAmsterdam Pharma (licensor)	NewAmsterdam Pharma and Menarini sign licensing deal to commercialize obicetrapib in Europe	122
Roche (licensee) Poseida Therapeutics (licensor)	Poseida grants Roche exclusive rights to develop and commercialize allogeneic CAR-T cell therapies for hematologic malignancies	110
Bristol Myers Squibb (licensee) Century Therapeutics (licensor)	Century and BMS enter into a strategic collaboration to develop induced pluripotent stem cell-derived allogeneic cell therapies.	100
Exscientia (research partner) Sanofi (research partner)	Exscientia and Sanofi establish strategic research collaboration to develop artificial intelligence-driven pipeline of precision-engineered medicines	100
F2G (licensor) Shionogi (licensee)	Shionogi and F2G enter strategic collaboration to develop and commercialize antifungal agent olorofim in Europe and Asia	100
Kiniksa Pharmaceuticals (licensor) Genentech (licensee)	Kiniksa grants Genentech worldwide rights to develop and commercialize vixarelimab	100

with associated staff and R&D costs, says Stephanie Léouzon, partner and head of Europe at Torreya. Biopharma and diagnostics partnership deals around preclinical assets are trending higher than in previous years, while the number of clinical-stage partnerships is down about 30% (Fig. 2a). More than 30 pre-approval licensing deals so far this year have involved up-front payments greater than $50 million, though the proportion of those that are preclinical (41%) is higher than it has been in any of the last five years (Fig. 2b).

One of the largest partnerships so far this year saw Merck pay $290 million up front to license Orion's phase 2 prostate cancer drug targeting CYP11A1 and take it through costly pivotal trials — just as the Espoo, Finland-based biotech was moving into cash-preservation mode. The small molecule blocks steroid hormones and their precursors, dampening supply to the hormone-dependent cancer. Gilead forked out $300 million up front for Dragonfly Therapeutics' IND (investigational new drug)-stage natural killer cell (NK) engager DF7001 and options on other NK programs to potentiate cancer immunotherapy (Table 2).

Pharma risk appetite is much healthier when it comes to partnerships. Roche's August tie-up with Poseida Therapeutics, worth $110 million up front with equal near-term milestones, makes a bet on allogeneic CAR-T cell therapies against targets in B cell lymphomas, multiple myeloma and other blood cancers — the most advanced of which is in phase 1. In October, Pfizer ponied up $300 million up front to collaborate on base editing solutions for rare diseases with Beam Therapeutics. "It's not that pharma won't take on risk, but they are looking for things that are novel and fit a real need," says Torreya's Léouzon.

Pharma's flip to partnering is good news for biotechs seeking to hang on to R&D programs for longer. It can also help with fundraising. After Shionogi of Osaka, Japan in May paid $100 million up front for European and Asian rights to Manchester, UK-based F2G's phase 3 antifungal olorofim, which treats invasive aspergillosis, the private biotech was able to secure a $70 million round, led by new investors Forbion and Sofinnova, for US late-stage development and commercialization of the product.

The record-breaking sums raised by life sciences venture capital in 2020 and 2021 — totaling almost $60 billion, according to Torreya and CapitalIQ — plus growing interest in biotech from large private equity groups, have prompted a flurry of growth and cross-over funds to support late-stage biotechs. These options, alongside royalties and debt financing, provide biotech with alternatives to initial public offerings or sales to pharma as those traditional routes get tougher. "These much deeper capital pools allow biotechs to take their products further," says Anderson.

Fundraise on good data

Good data still open the funding taps — even for public biotechs.

Alnylam raised almost $1 billion just weeks after presenting positive data for Onpattro (patisiran) in transthyretin-mediated amyloidosis (ATTR) with cardiomyopathy. (The drug is already approved for the hereditary form of the rare heart condition.) Alnylam

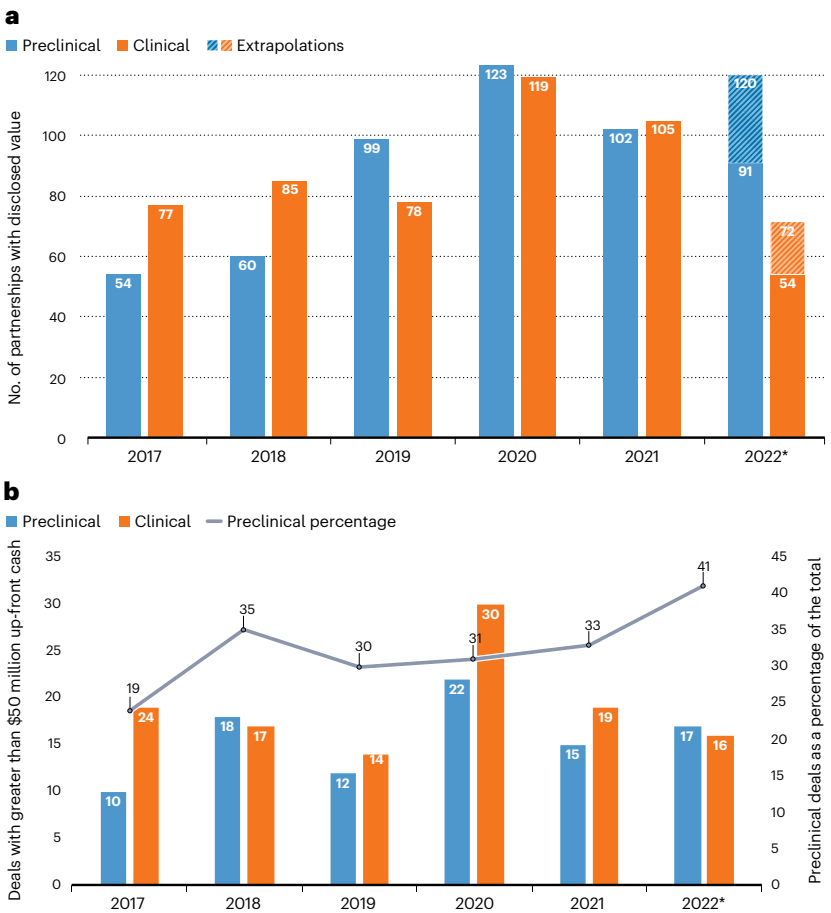

Fig. 2 | Partnerships between pharma and biotech over five years. a, Preclinical deals outpace clinical-stage deals. **b**, Deals with greater than $50 million up-front cash. Percentages are calculated of 'all deals', which include clinical, registrational and postapproval (the last two not shown). (Source: BioCentury BCIQ).

BOX 3

Merck tried to buy Seagen

Merck was reportedly on the hook for as much as $40 billion in its attempts earlier this summer to buy Seagen. It could have been the year's largest deal — and Merck's biggest for a decade. The Seattle-based antibody-drug conjugate player has four marketed cancer drugs and a dozen in the pipeline, ideal to help fill Keytruda's shoes after 2028. But talks stalled in August, due, allegedly, to disagreements over valuation.

Adjusting to lower valuations brought on by the public market reset has been difficult for biotech investors and management teams. Those with at least 18 months of cash can afford to resist what they perceive as lowball acquisition offers, if they are on the table. Others struggling to access funding — at any valuation — aren't likely to be the ones that pharmas want anyway.

offered $900 million of convertible senior notes (short-term debt that converts into equity). UK-based, Nasdaq-listed Verona Pharma in mid-August raised $150 million in a public share offering after announcing positive topline results from the first of two phase 3 studies of its chronic obstructive pulmonary disease drug ensifentrine. The inhaled dual phosphodiesterase (PDE) 3 and PDE4 inhibitor met its primary and some secondary endpoints, showing improved lung function and reduced exacerbations.

Canada's Xenon Pharmaceuticals, based in Burnaby, British Columbia, raised $287 million in a public offering after positive phase 2b open-label expansion study data from its daily epilepsy pill XEN1101, a selective Kv7.2 and Kv7.3 potassium channel opener.

Biotechs that aren't quite at data readout should focus their efforts and funds on getting there – and avoid overpromising in the meantime. Even if big pharma isn't buying avidly now, "they'll look back in two years' time at what you say now and see if it was realistic," says Bar-Nahum.

Biotechs with insufficient cash to get to the next milestone have few choices. Record numbers of biotechs are exploring 'strategic options', according to Torreya, noting in an August 2022 report that "countless boards are effectively volunteering to pull out of the marketplace."

Yet while Torreya and other banking or advisory firms predict a more active M&A spree this autumn as a result, venture capital investors are preparing for the market gloom to last. They're putting three or four years' worth of cash into their portfolio companies, rather than one or two, to ensure they reach the next data point, says Sofinnova's Anderson.

A single, high-profile deal or data read-out may help trigger action. Merck reportedly tried to buy Seagen earlier this year in a deal claimed to be worth up to $40 billion. Talks apparently stalled, but if a deal had been signed, Seagen investors' cash windfall could have been recycled back into the sector, driving up valuations and building confidence, suggests Bar-Nahum (Box 3). Top-line data for Biogen and Eisai's Alzheimer's candidate lecanemab in late September lifted both companies' share prices, along with those of close competitors Roche (with gantenerumab) and Eli Lilly (with donanemab). It also boosted valuations at other, earlier-stage companies working in the field, but hasn't (yet) unleashed a dealmaking frenzy.

Buyers can afford to soft-pedal. Big pharma needs to do more to fill pipelines and revenue gaps. But for now, many are thinking, "Let these companies finance themselves, and we'll pay more for them later," says Geraldine O'Keeffe, partner at EQT Life Sciences in Amsterdam.

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