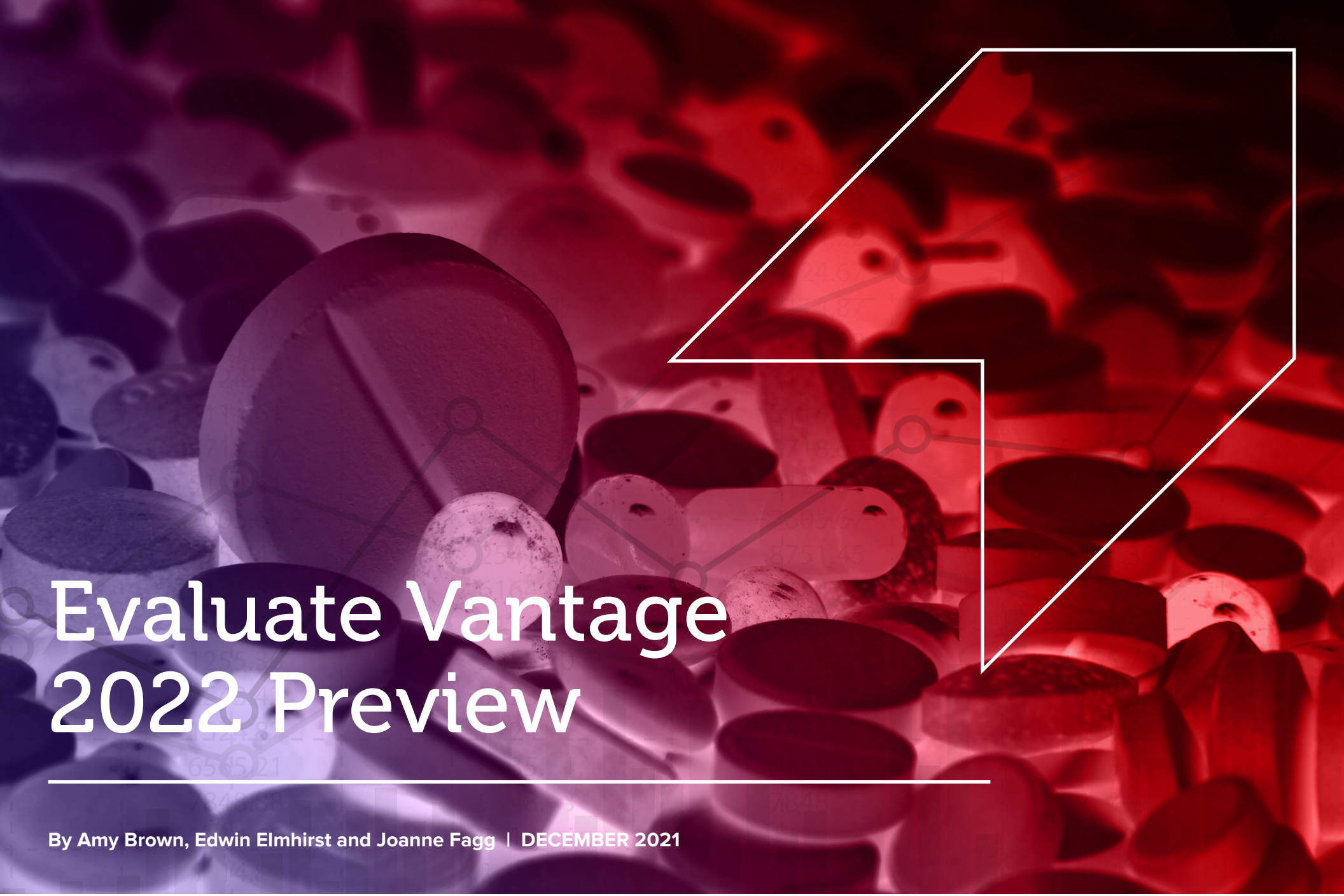


Evaluate Vantage 2022 Preview

By Amy Brown, Edwin Elmhirst and Joanne Fagg | DECEMBER 2021

Evaluate Vantage

Evaluate

Contents

Foreword

Biopharma's attempts to bring the pandemic to an end have dominated headlines in all sections of the media for almost two years. Huge progress has been made towards achieving that goal, but Covid-19 will still be a front-page story in 2022, keeping the sector firmly in the spotlight.

That spotlight will bring some benefits, largely in the shape of broad support – and a lot of money – from investors. But it also means heightened scrutiny, particularly for those that are making billions from successful pandemic vaccines and treatments. As biopharma makes more advances in the Covid-19 battle next year, those profits could increasingly attract unwanted attention.

What companies intend to spend these windfalls on will be another big preoccupation in 2022. Several big names are flush with cash, thanks to Covid-19 and other reasons, and many biopharma watchers are expecting an uptick in M&A next year. Depressed valuations in the wake of a difficult few months on the stock market are another likely trigger for these transactions.

The US biotech sector is ending 2021 in a bear market, the pandemic bubble having burst as investors sought Covid-19 recovery stories in other sectors. Also unhelpful was the flood of very early-stage developers that managed to IPO when the markets were full of enthusiasm for biopharma; lack of progress from these recent flotations could act as a drag on any recovery next year.

Private developers are likely to find it harder to list in the US in 2022, at least in the opening months of the year. This means venture firms will have to look elsewhere for exits, and it is unsurprising that these investors are also predicting more deal making on the way. That said, the venture world is far from facing hardship, with most funds incredibly well stocked.

What looks unlikely to change in 2022 is the regulatory climate in the US, with the FDA showing few signs of shifting its industry-friendly stance. Meanwhile, the Biden administration's ability to push through changes to the US healthcare system also seems limited, with few observers overly concerned about damaging political waves next year.

Not that the issue of overt pricing power is off the table for biopharma. These pressures look more likely to come from within the sector, however. The first real competition is threatening to emerge in oncology's highly lucrative checkpoint inhibitor space, with several Chinese developers, partnered with global majors, poised to launch low-cost anti-PD-(L)1 antibodies. This is only the first of many high-cost therapy areas in the sights of those hoping to grab market share by cutting prices, and this issue will become more prominent in 2022.

Other therapy areas in focus next year include Alzheimer's disease, with several projects hoping to join Aduhelm on the market. Respiratory syncytial virus might also see its first success after years of failure – late-stage trials are due to read out for several developers chasing that opportunity. And cancer will continue to be very closely followed, with late-stage data from the anti-Tigit antibodies of particular interest, as well as bispecifics and antibody-drug conjugates.

After years of plenty the drug development sector is, for the most part, in a good place. Smaller companies are well funded, many larger developers are riding high on Covid-19 successes and the venture capital industry is poised to deploy significant capital. The highs of the pandemic era could never be maintained, and many consider the current retrenchment part of the cycle.

This report attempts to pinpoint the trends that could drive a resurgence and highlight any weak spots that might hamper a recovery. For the first time this Preview comes in two sections: data-driven analyses using Evaluate Pharma, and an interview section, drawing on insights from investors and biopharma participants from across the sector.

Written November/December 2021. All data correct as of November 8, 2021.

INNOVATION AND REGULATION

Growing biopharma's top line: drugs

Vaccines against Covid-19 will continue to make billions next year for Pfizer, Biontech and Moderna, with these firms' jabs expected to bring in at least $50bn in combined revenue. That figure is based on company guidance given in October 2021 and should probably be considered the floor for estimates, with future orders from governments around the world pretty much guaranteed.

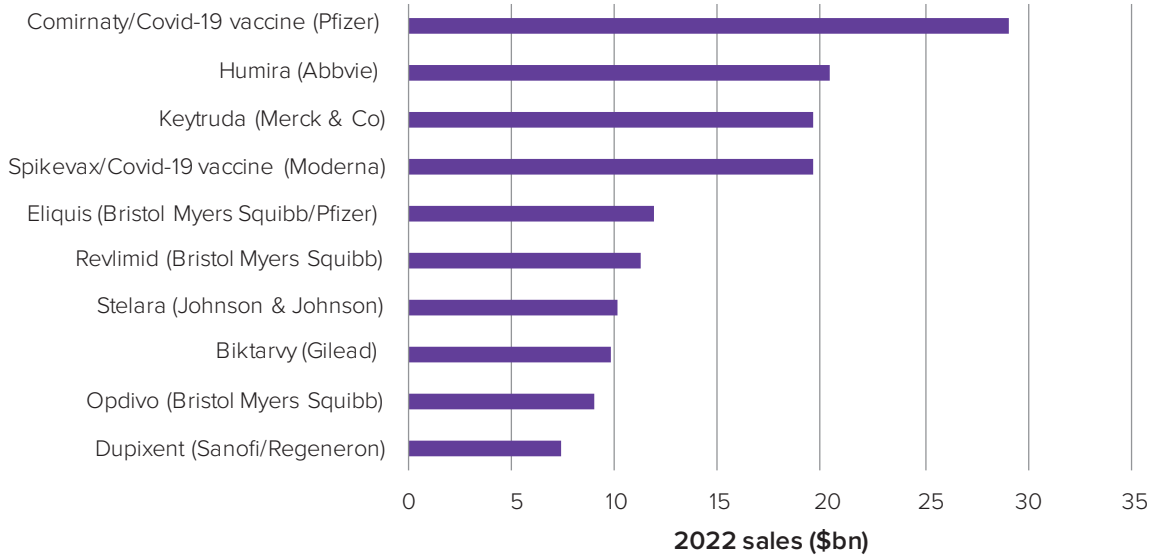
Moderna took a while to get manufacturing ramped up, so 2022 sales of its vaccine are expected to surpass those booked in 2021. For now, 2022 sales of the Pfizer/Biontech shot are forecast to drop on 2021 – which is why Comirnaty does not feature in the biggest new sales generators – though that outlook is far from set in stone.

Outside of pandemic-related products, Humira is forecast to cling on its crown as the biggest selling drug. However, 2022 will be the last year of largesse for Abbvie's anti-rheumatic, with biosimilars due to arrive in the US in 2023.

This will hand pole position to Keytruda. That the Merck & Co cancer antibody is still adding billions of new sales each year is testament to that company's success in broadening the drug's label. Opdivo, Dupixent and Eliquis also feature in both charts, underlining the strength of these huge mega-blockbuster brands.

Abbvie's two new growth drivers make the second analysis, pointing to progress being made in replacing Humira. However, the outlook for the group's Jak inhibitor Rinvoq is increasingly uncertain thanks to safety concerns that could cap the potential of the whole class; how stringently the FDA deals with pending approvals for this and other Jak inhibitors will be a big focus in 2022.

Top selling drugs in 2022



Biggest new sales generators: products

Growing biopharma's top line: companies

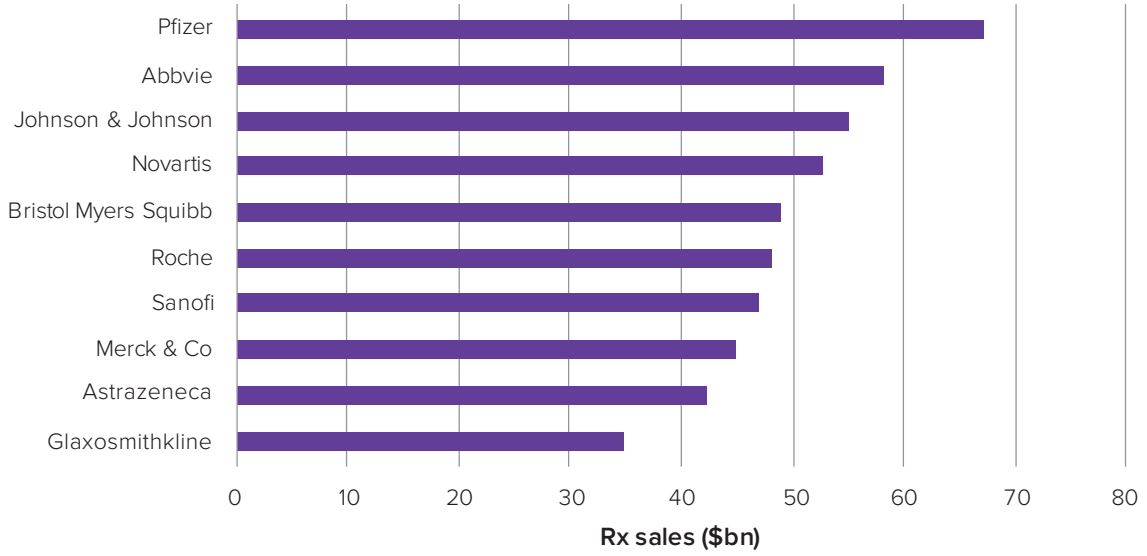
The huge success of Pfizer and Biontech's Comirnaty, sales of which are booked by the former, will make the pharma giant the world's biggest drug maker by prescription sales in 2022 by a comfortable margin. The Covid-19 vaccine is expected to sell at least $29bn next year, a contribution that counts for almost half of the company's projected prescription sales.

Astrazeneca stands out in the biggest new sales generators. Largely this is down to a full year's contribution from the 2020 Alexion acquisition, though the UK company's cancer franchise is also expanding swiftly, with Tagrisso and Lynparza the big growers.

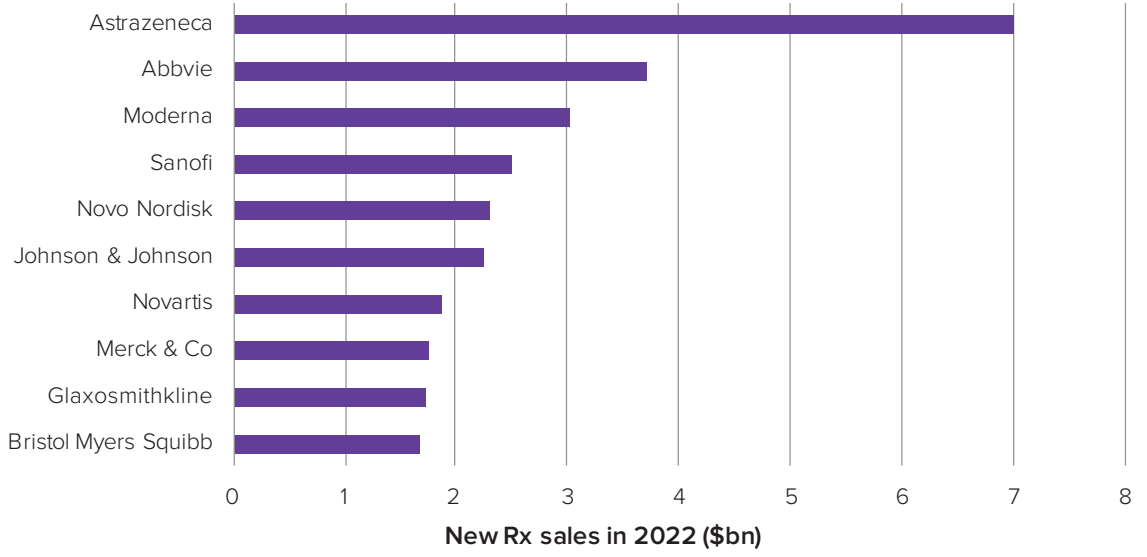
Moderna's Covid-19 vaccine Spikevax is the only reason the biotech features in this analysis, which is typically the realm of big pharma. And despite deep concerns about its growth prospects Glaxosmithkline makes it into both top 10 charts, although much depends on a rebound in demand for its shingles vaccine, Shingrix; prescriptions were seriously curbed by the pandemic.

Notable by its absence here is Eli Lilly, which features heavily in analyses to come in this report, as owner of two of the sector's most valuable pipeline projects. Its cancer drug Alimta loses patent protection next year, which will hit the company's top line, but with tirzepatide and donanemab waiting in the wings Lilly is expected to deliver strong growth in subsequent years.

Biggest companies in 2022, by Rx sales



Biggest new sales generators



Waiting in the wings

Several potential blockbusters are lining up to reach the market in 2022, with Alzheimer's disease poised to provide plenty of regulatory news. Lilly and Roche are striving to join Biogen on the market with their respective projects, although whether this happens next year depends on the FDA's continuing support for accelerated approvals, and on Roche's willingness to file biomarker data.

A third amyloid-beta agent, Eisai's lecanemab, sits just outside the top 10 detailed in the first table; the Biogen-partnered MAb is also in the running for a speedy nod next year.

With two big pipeline hopes up for approvals next year, Bristol Myers Squibb is under pressure to convince investors that it can navigate its fast-approaching Revlimid patent cliff.

Meanwhile, small companies like Mirati and Reata are particularly exposed to delays. Setbacks can never be ruled out for any project, but those owned by small developers should probably be considered high risk.

This is particularly true for assets further back in development, in the second table, many of which are still attracting substantial valuations despite having yet to generate confirmatory pivotal data.

Several readouts are due from Roche's leading anti-Tigit MAb, making 2022 a crucial year for this novel immuno-oncology mechanism. The I-O space could also see the arrival of several follow-on anti-PD-(L)1 MAbs in the US, with the FDA due to decide on Lilly/Innovent's Tyvyt in March and Novartis/Beigene's tislelizumab in July.

Sales forecasts for these two products are not particularly high, but their arrival could herald the start of price competition in this highly lucrative cancer space. The threat of low-cost competition in previously high-cost therapy areas like cancer and immunology is a theme that is likely to develop over 2022.

Biggest potential launches of 2022

Project	Description	Companies involved	Status	2026e sales
Donanemab	Anti-amyloid-beta MAb for Alzheimer's disease	Lilly	Rolling US submission for accelerated approval started Oct 2021	$6.0bn
Tirzepatide	GLP-1/GIP dual agonist for type 2 diabetes, obesity	Lilly	US diabetes approval possible mid-2022 (filed with FDA Oct 2021, Lilly to use PRV)	$4.9bn
Gantenerumab	Anti-amyloid-beta MAb for Alzheimer's disease	Roche	2022 launch assumes Roche files for US accelerated approval	$2.5bn
Deucravacitinib (BMS-986165)	Tyk2 inhibitor for psoriasis, other autoimmune conditions	Bristol Myers Squibb	PDUFA Sep 10 2022; EU approval expected Q4 2022	$2.4bn
Bardoxolone	Nrf2 activator for rare, chronic kidney diseases	Reata	PDUFA Feb 25, 2022	$2.2bn
Tezepelumab	Anti-TSLP MAb for severe asthma	Amgen/ Astrazeneca	PDUFA Q1 2022; EU approval expected H1 2022	$2.0bn
Vutrisiran	RNAi therapy for ATTR amyloidosis	Alnylam	PDUFA Apr 14, 2022; EU approval expected Q4'22	$1.8bn
Mavacamten	Cardiac myosin inhibitor for cardiomyopathy	Bristol Myers Squibb	PDUFA Apr 28, 2022 (extended by 3 mths); EU approval expected H2 2022	$1.7bn
Cilta-cel	Anti-BCMA Car-T for multiple myeloma	Johnson & Johnson	PDUFA Feb 28, 2022 (extended by 3 mths); EU approval expected Q1 2022	$1.7bn
Adagrasib	Kras G12C inhibitor for lung cancer	Mirati Therapeutics	Accelerated approval application expected before YE 2021	$1.7bn

Note: only includes projects not on the market in any region.

Ones to watch: biopharma's most valuable R&D projects

Project	Description	Company	NPV
Lirentelimab (AK002)	Siglec-8 MAb for rare chronic inflammatory conditions of the gut; phase 2/3 data due by YE 2021	Allakos	$6.2bn
Datopotamab deruxtecan (DS-1062)	Trop2-targeted ADC for lung and breast cancers in various phase 2/3 trials	Daiichi Sankyo	$6.1bn
Tiragolumab	Anti-Tigit MAb in phase 3 trials for lung & other cancers	Roche	$5.7bn
CTX001	Gene editing therapy in pivotal trials for sickle cell and beta-thalassaemia	Vertex & Crispr	$5.0bn
Tolebrutinib (SAR442168)	BTK inhibitor in several phase 3 trials for MS	Sanofi	$4.7bn
Iptacopan (LNP023)	Complement factor B inhibitor for complement-driven diseases; in various phase 2 and 3 trials	Novartis	$4.2bn
Mirikizumab	Anti-IL-23 MAb in phase 3 for ulcerative colitis and Crohn's	Lilly	$4.1bn
KSI-301	Intravitreal VEGF-A inhibitor for wet AMD	Kodiak Sciences	$3.9bn
KarXT	M1/M4-muscarinic agonist for schizophrenia in phase 3	Karuna Therapeutics	$3.8bn
Acoramidis (AG10)	TTR stabiliser for transthyretin amyloid cardiomyopathy in phase 3	Bridgebio Pharma	$3.5bn

The cost of research

Another way of identifying the projects likely to be in focus next year is to look at biopharma's most costly development programmes. These tables are derived from Evaluate Omnium's R&D cost module, which provides an estimate of the cost of running a clinical trial.

Disease areas that require vast and lengthy cardiovascular outcome trials to prove a drug's safety will always come out on top in this sort of analysis. Hence the appearance of Lilly's tirzepatide and Novartis's pelacarsen; whether any interim readout will happen for the latter project remains a topic of interest for the Swiss pharma giant's investors.

Roche has run a bigger programme than other amyloid-beta MAb developers with gantenerumab, so in terms of sunk costs has more to lose than rivals should the regulatory winds change in Alzheimer's disease.

Islatravir is Merck's big bet in the long-acting HIV antiviral space, though safety concerns emerged in late 2021, casting doubt on the project's potential. Elsewhere, success in RSV is hugely important for Glaxosmithkline, which is struggling to revive investor support. Pivotal RSV data are due early next year from the company and rivals including Pfizer, making the respiratory disease an area to watch in 2022.

In terms of extending the reach of already marketed drugs, developers continue to invest heavily in PD-(L)1 MAbs. The sums still being spent here demonstrate how seriously the risk of low-cost competition should be taken.

High-cost clinical programmes – R&D projects

Project	Company	Description	Estimated clinical spend in 2022	Estimated total cost of clinical programme*
Tirzepatide	Lilly	GLP-1/GIP dual agonist for type 2 diabetes & obesity	$555m	$2.8bn
Gantenerumab	Roche	Anti-beta amyloid MAb for Alzheimer's disease	$376m	$2.4bn
Islatravir	Merck & Co	HIV antiviral	$352m	$1.4bn
Pelacarsen	Novartis/Ionis	ApoA antisense for high cholesterol and cardiovascular disease	$334m	$1.5bn
GSK3888550A	Glaxosmithkline	Adult RSV vaccine	$288m	$926m

High-cost clinical programmes – marketed drugs

Product	Company	Description	Estimated clinical spend in 2022	Estimated total cost of clinical programme*
Keytruda	Merck & Co	Anti-PD-1 antibody; various cancers	$2.0bn	$15.3bn
Opdivo	Bristol Myers Squibb	Anti-PD-1 antibody; various cancers	$1.7bn	$10.9bn
Tecentriq	Roche	Anti-PD-L1 antibody; various cancers	$836m	$8.5bn
Imfinzi	Astrazeneca	Anti-PD-L1 antibody; various cancers	$809m	$6.6bn
Leqvio	Novartis	Anti-PCSK9 antisense for high cholesterol and cardiovascular disease	$523m	$2.5bn

*Note: The products featured here were selected from among the costliest programmes and are not intended to be a top five. *Estimated costs based on trials registered on clinicaltrials.gov.*

Source: Evaluate Omnium's R&D cost model

The regulatory environment

The US is the world's largest and most profitable market for biopharma, so the moves and moods of that country's drugs regulator are closely monitored. The FDA is widely considered to be in an industry-friendly phase, and there are few reasons to believe that this will shift dramatically next year.

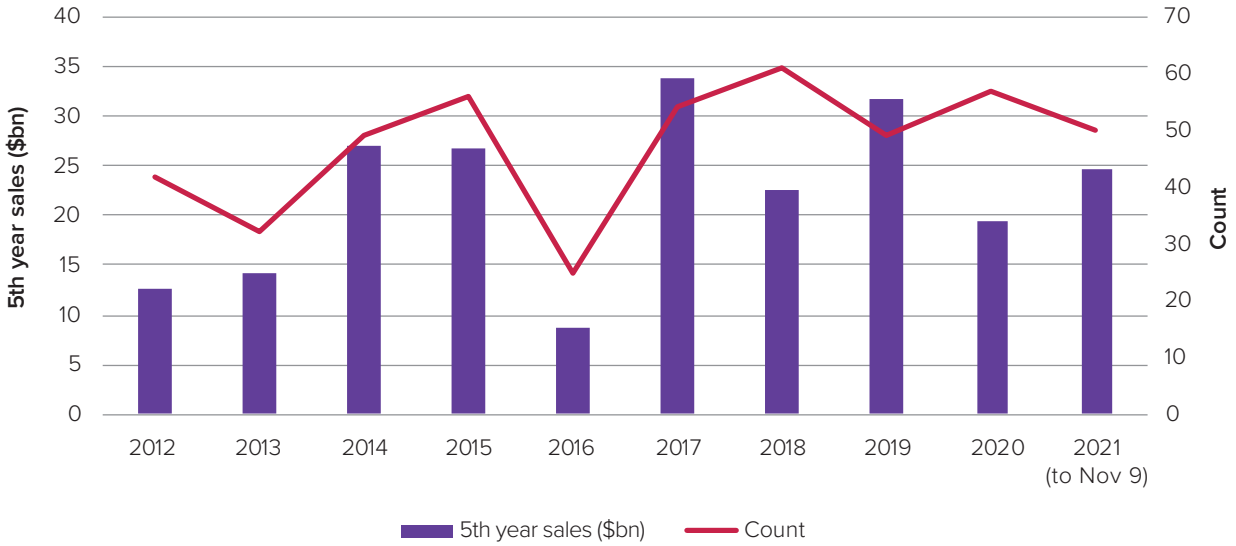
The agency continues to show willing when it comes to quickly ushering in medical breakthroughs, particularly in cancer. The controversial green light for Biogen's Alzheimer's therapy Aduhelm was considered another sign of leniency.

That image will be reinforced should further accelerated approvals follow in 2022 for similarly acting amyloid-beta antibodies.

Still, knockbacks for projects like Fibrogen's roxadustat, a novel anaemia pill that raised concerns about cardiotoxicity, show that the FDA has not completely swung the gates open. This is particularly true in areas where options already exist, even if these are imperfect. The agency has also delayed several applications in 2021 because Covid-19 prevented travel and therefore site inspections.

2021 is certainly tracking in line with recent years in terms of novel drug approvals, this analysis shows. The pandemic did not have as big an impact on regulatory work as many had feared, and this worry is likely to dissipate further next year.

FDA novel drug approvals and fifth-year sales



Note: Count includes CDER and CBER drug approvals, and excludes CBER's reviews of reagents and assays etc. Sales are actual where available, and forecast.

MONEY, MARKETS AND M&A

Stock market performance

Share price performances of large and small cap drug developers diverged over the course of 2021, a trend that looks likely to persist in the opening months of next year. While several bigger groups are being rewarded for Covid-19 and other clinical successes, earlier-stage and higher-risk biotechs are, for now, out of favour.

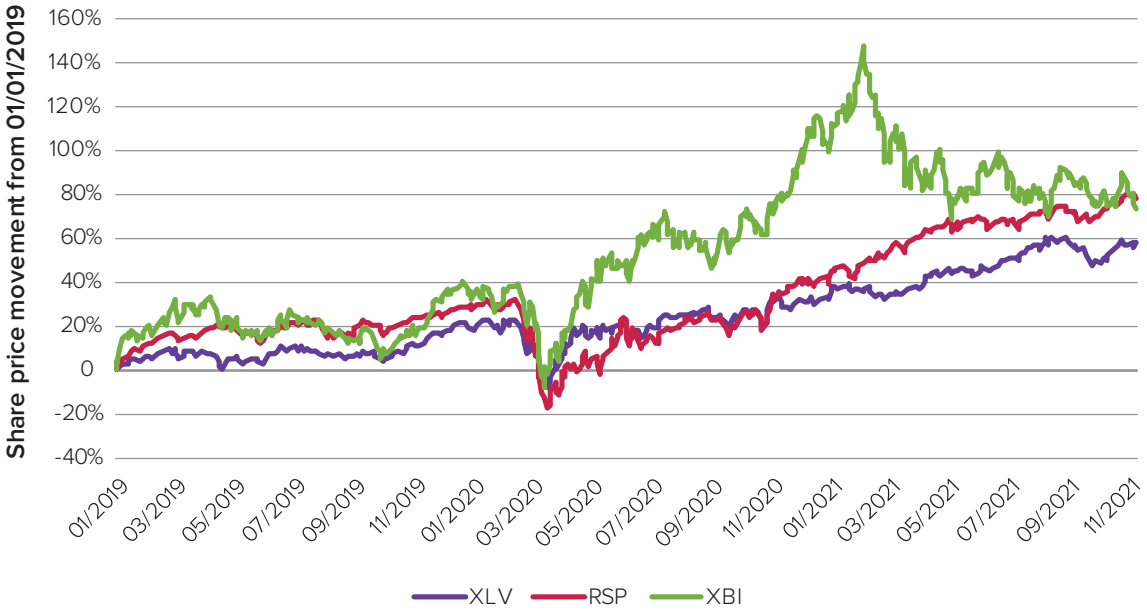
This much is evident from the relative performance of three closely-watched funds, the XBI, XLV and RSP. The first two respectively track small cap biotechs and larger healthcare groups; the RSP tracks the cross-sector S&P 500.

The pandemic outbreak and swift recovery staged by healthcare stocks is clear in this chart, with the smaller groups in the XBI being propelled into bubble territory. That bubble burst in February and, as far as investors are concerned, small cap biotech is now in a bear market, with many anticipating further declines.

Investors blame a number of factors for these market conditions. Most believe that the IPO window opened too wide, allowing too many early-stage developers to float. Others point to a quiet M&A year. The spectre of rising inflation around the globe is also troubling the markets.

Still, it could also be argued that the small cap sector is returning to more sustainable, and less frothy, levels. The declines this year are from heady heights, and many hope that a retreat in valuations will persuade buyers back to the table.

What goes up must come down



Note: This chart shows three equal weighted exchange traded funds tracking US listed companies. XBI includes biotech stocks from across the market cap spectrum. XLV includes healthcare equipment and medtech as well as pharmaceutical companies. RSP includes all stocks in the S&P 500.

Tracking demand for IPOs

A healthy IPO market is important for the biopharma financing ecosystem, but a deterioration is widely expected next year. Hints that investors are becoming less receptive to these new issues can be gleaned from the first chart here, which tracks the success of companies and their bankers at achieving a desired valuation.

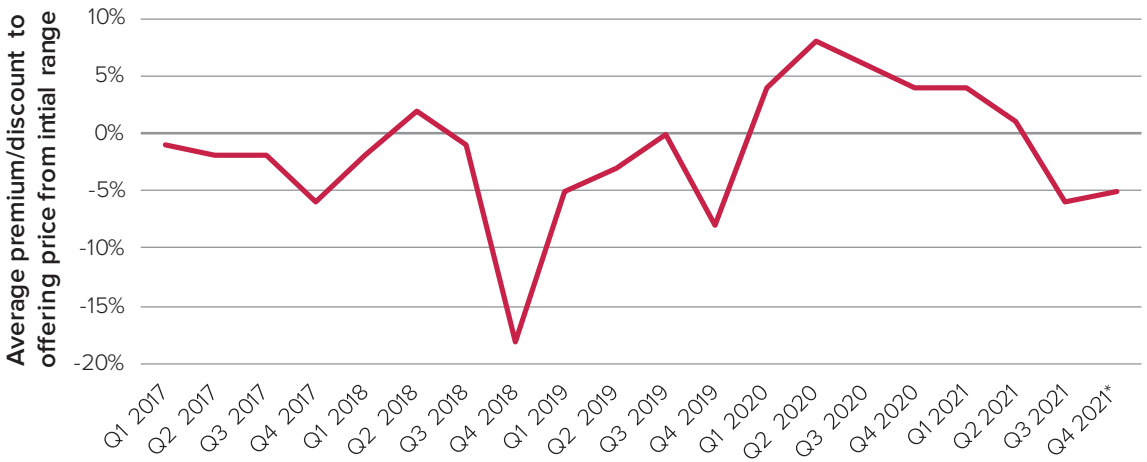
The graph shows the premium or discount achieved at IPO versus the float price initially proposed in registration documents; this is calculated as an average across all Nasdaq flotations each quarter. So-called "haircuts" returned in 2021 after being virtually eliminated by huge demand for new issues in 2020. If pessimistic projections are to be believed this chart will head further south again in 2022.

This is not to say that IPO activity is dimming dramatically, at time of writing at least. The fourth quarter of 2021 commenced with a healthy flow of flotations, and early-stage and preclinical developers continue to raise big pots of cash.

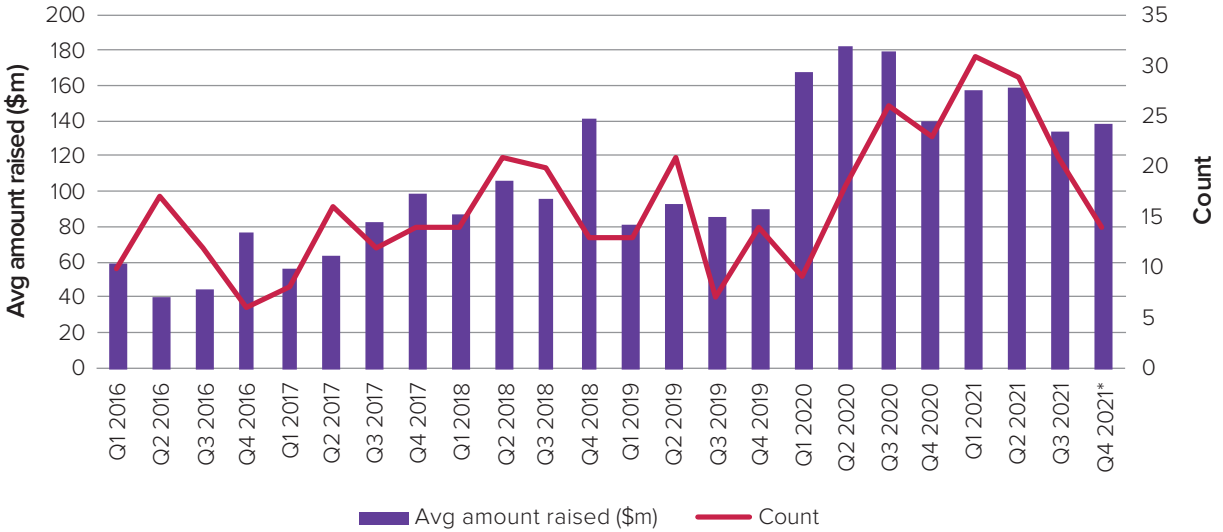
How long investor demand can hold up is the big unknown here. That will depend on wider stock market conditions, and how the sector's newly listed companies perform in the coming months.

Note that the data in this section and those that follow refer only to pure play drug developers. Services companies or those involved in medtech or digital health, for example, have been excluded.

Tracking investor appetite for new issues



Biotech IPOs: will the window stay open in 2022?



**Q4 data run up to November 8, 2021.*

IPOs: historical performance

As can be expected for a group of recently listed developers, 2021's biotech IPOs are trading in a tight range compared with previous years' cohorts. But with both the median and mean return, as of November 9, hovering around zero, demand for this year's new issues can only be described as weak.

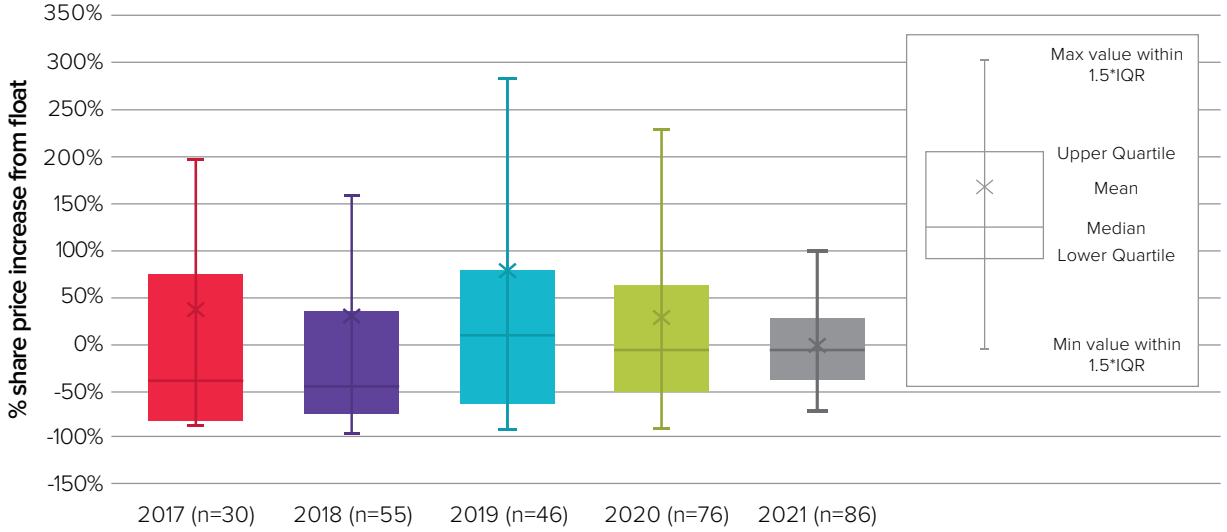
Almost two thirds of 2021's 86 IPOs were trading below their issue price at time of writing. This will have a lot to do with the ongoing bear market for biotech stocks, but it is hardly encouraging for those still hoping to go public.

Some investors believe that the IPO window opened too wide, allowing too many early-stage, and in some cases low-quality, developers to float. It is easy to appreciate how this could end up damaging the sector's reputation.

Bankers must hope that they have delivered enough winners to the market to keep investors happy. There are certainly success stories to be found among recent new arrivals.

Pandemic gainers Moderna and Biontech stand out, though it is notable that one of the best performers, Kodiak Sciences, is not a Covid-19 play. The company features in this report as owner of one of biopharma's most valuable R&D projects, the macular degeneration asset KSI-301.

The outliers: Top performing IPOs each year



Note: Share prices analysed from date of float to November 11. 2021 contains IPOs up to November 8.

The outliers: Top performing IPOs each year

Year	Company	Company description/focus	SP increase from float
2021	Verve Therapeutics	Gene editing medicines for cardiovascular diseases.	163%
	Vera Therapeutics	Immunologic and inflammatory diseases.	129%
	Briacell Therapeutics	Immunotherapies for breast cancer.	125%
2020	Beam Therapeutics	Base editing medicines for genetic diseases.	475%
	Annovis Bio	Neurodegenerative diseases.	438%
	I-Mab Biopharma	Immunotherapies for cancer and autoimmune disorders.	310%
2019	BionTech	mRNA and cell therapies for cancer and other diseases.	1,409%
	Karuna Therapeutics	Psychiatric and neurological conditions.	846%
	Springworks Therapeutics	Oncology and rare diseases.	317%
2018	Kodiak Sciences	Retinal diseases.	1,078%
	Moderna	mRNA therapies for infectious diseases and cancer.	930%
	Arvinas	Protein degradation therapies for cancer, neurological conditions.	475%
2017	Biohaven	Neurological and neuropsychiatric diseases.	616%
	Zai Lab	Oncology and autoimmune diseases (China focus).	382%
	Krystal Biotech	Gene therapies.	375%

Less than Spac-tacular

Many investors have already cooled on Spacs – special purpose acquisition companies – and it should become clear next year whether they have any serious role to play in biotech financing.

Also called blank cheque companies, these listed cash shells offer private groups an alternative route to a stock market listing, effected via an acquisition. The performance of those that have already closed a deal will be monitored next year to help determine whether Spacs are able to deliver high-quality companies to the market.

Their track record so far is not particularly impressive. Of the 18 drug developers that have floated via Spac since the start of 2020, only four have seen share price rises since their respective deals closed, and only one, Cerevel, is a real success story. In fairness, many may need more time to prove themselves, and of course traditional IPOs have also been disappointing.

New SEC regulations could also diminish Spacs' prospects next year. The US financial regulator is expected to tighten rules around financial guidance, conflicts of interest and transparency of disclosures, among others. This could potentially blunt some of the advantages Spacs have over traditional IPOs, with obvious implications.

Best and worst performing biopharma companies listed via Spac since 2020

Merger target	Spac (sponsor)	Date deal announced	Total raised (IPO proceeds + Pipe) ($m)	Market cap at close Nov 24, 2021 ($m)	Share price change to close Nov 24, 2021	Time to close (mths)
Cerevel	Arya Sciences Acquisition Corp II (Perceptive Advisors)	July 2020	440	4,810	236%	3
Vincerx	Lifesci Acquisition (Lifesci Capital)	September 2020	62	247	18%	2.8
Immatics	Arya Sciences Acquisition Corp (Perceptive Advisors)	March 2020	250	720	17%	3.5
Tango Therapeutics*	BCTG Acquisition (Boxer Capital of Tavistock Group)	April 2021	353	911	4%	3.9
Celularity	GX Acquisition (GX Sponsor)	January 2021	138	814	-35%	6.2
4D pharma	Longevity Acquisition (Whale Management Corporation)	October 2020	40	153	-38%	5
NRX Pharmaceuticals	Big Rock Partners Acquisition (Big Rock Partners)	December 2020	Unclear	265	-55%	5.3
Reviva	Tenzing Acquisition (Tenzing)	July 2020	64	54	-62%	4,.8
Gemini Therapeutics*	FS Development Corp (Foresite Capital)	October 2020	216	134	-69%	3.8
Deals yet to close						
Pardes Biosciences*	FS Development Corp II (Foresite Capital)	June 2021	276	n/a	n/a	4.9 to date
EQRX	CM Life Sciences III (Casdin Capital and Corvex Management)	August 2021	1,800	n/a	n/a	3.6 to date

*Note: Assumes $10 pre-announcement share price. *Warrantless structure.*

Source: Spacinsider.com & company statements.

Venture financing and exits

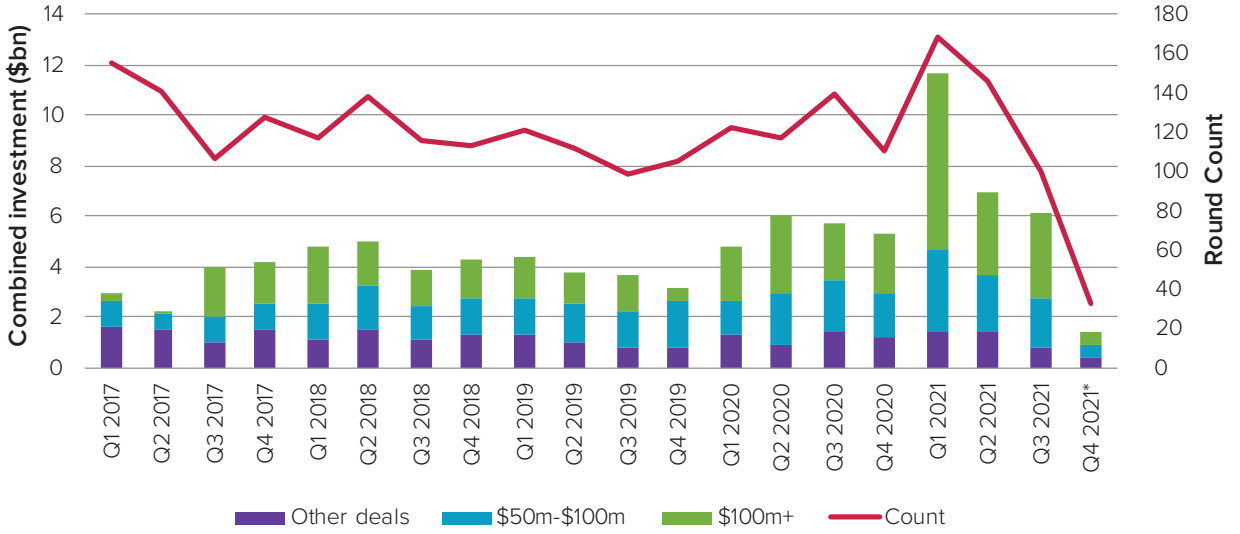
The IPO market might be displaying signs of slowing, but venture capital is showing nothing of the sort. 2021 is on track to break records and, with these private investors continuing to raise substantial new funds, there will be no shortage of cash to deploy next year.

There will be some impact should fewer biotech flotations happen, because this will mean fewer crossover rounds. These large, pre-IPO investments have helped swell the topline numbers in terms of sums raised in recent years. But in many areas private valuations are higher than in the public sphere, so big financings are likely still to be a feature of the venture landscape in 2022.

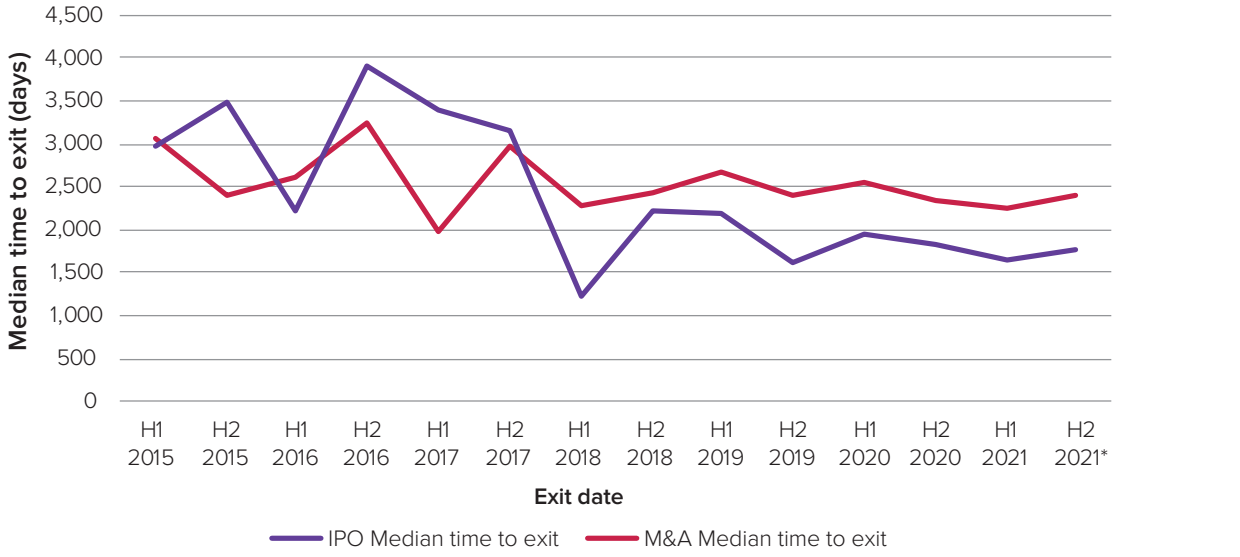
All this largesse means that concerns about overinvestment and inflated valuations persist in the venture capital world, particularly in the US and in certain competitive spaces like cancer and immunology. Large developers remain enthusiastic buyers in these areas, however, and while the cash keeps flowing private biotechs and their backers look set to remain in a strong position next year.

Further bolstering the venture industry is quickening investment cycles, as seen in the median time it takes to either float or sell a start-up. This is readily apparent for IPOs, albeit reflecting the recent IPO boom, on which venture investors have been quick to capitalise.

The good times roll for venture financing



Heading for the exit



*Note: Venture-backed companies only. Time measured from company formation to takeout or IPO. *Q4/H2 data run up to November 8, 2021.*

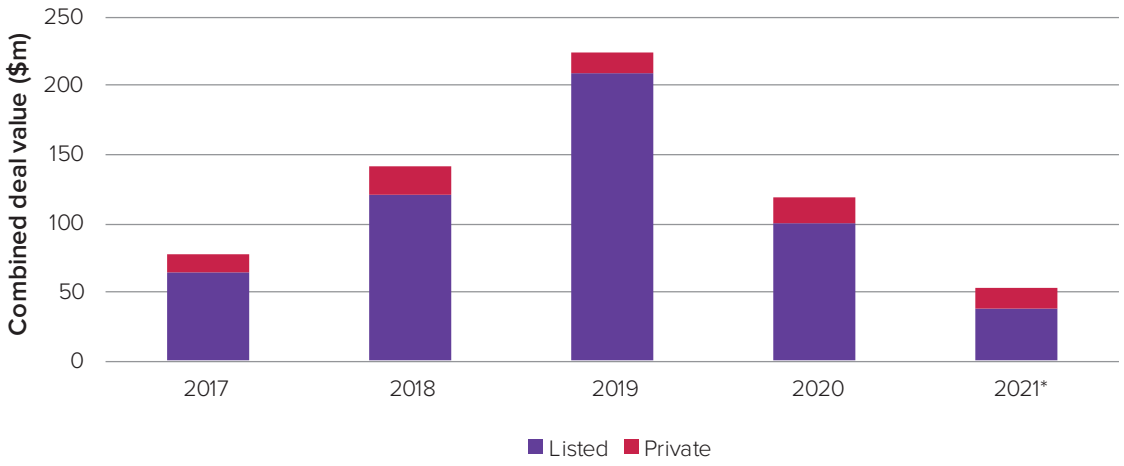
Biopharma buyouts: primed for a rebound?

Hopes are high that more developers will consider selling up next year, their hands forced by retreating valuations and deteriorating equity markets. The strong financing climate has meant that young start-ups have been able to push on alone, an independent streak that has contributed to a very quiet period for M&A.

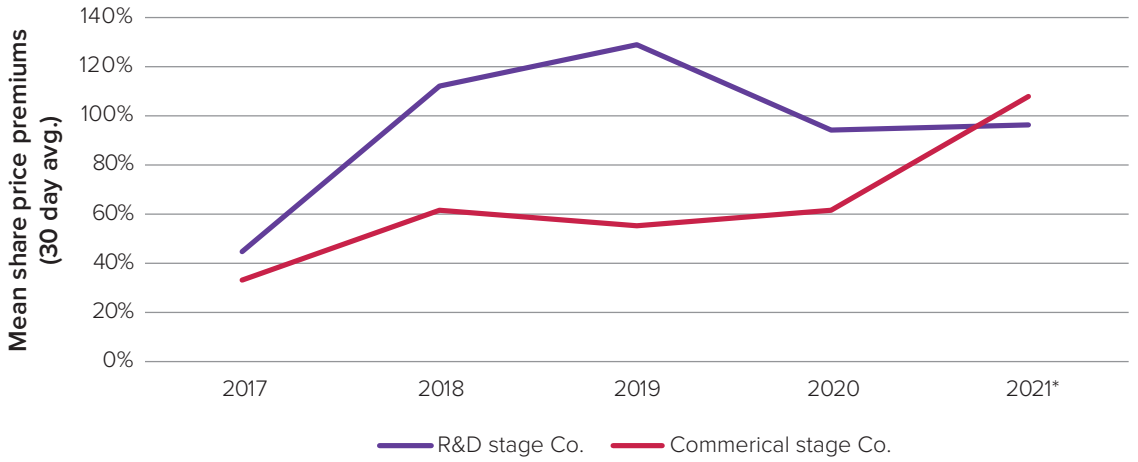
Sky-high valuations have also been putting off buyers, again a situation that has started to solve itself, in the public sphere at least. But this means that, when takeouts have happened, buyers have had to swallow rich premiums.

Premiums for R&D-stage companies do seem to have moderated since the 2019 peak, although these are still hovering at around 100%. And the apparent jump in the premiums being paid for commercial-stage entities must be caveated by the very small numbers involved here: only three such buyouts have happened so far in 2021, dramatically down on other years in this analysis, which each registered between 11 and 15 such deals.

Biopharma buyouts, by total value



Mean takeout premiums



**2021 data collected up to November 8, 2021.*

No signs of a slow down on the licensing scene

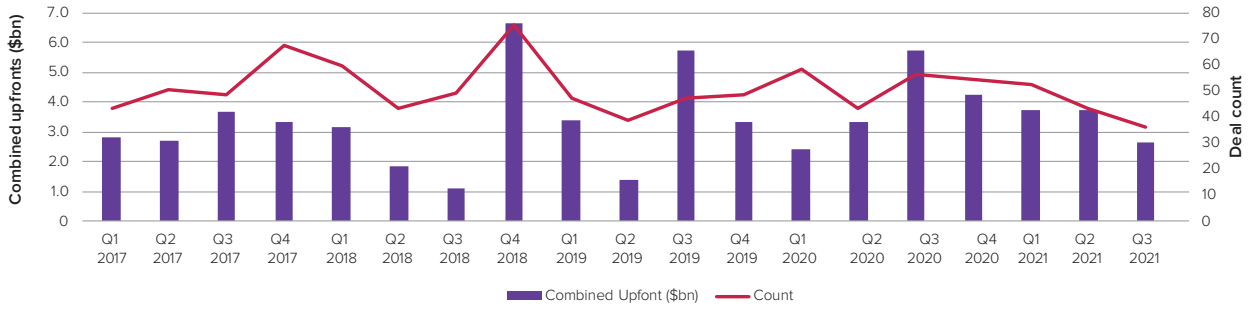
Lofty valuations might be curtailing company buyouts but developers are still busily accessing external innovation via licensing. A notable increase in the average up front paid over the past five years shows that this area of dealmaking has not avoided price inflation, though buyers are at least hedging some risk.

Note this analysis concerns only deals in which the upfront payment was disclosed. This figure is announced in around a quarter of licensing transactions, so the real volume of activity is much higher than this chart suggests. Future milestones are far from guaranteed, however, so focusing on total deal values, or so-called "bio-dollars", will not accurately reflect the actual amount of money changing hands each year.

On this basis, the average upfront paid was $59m in 2017, according to Evaluate Pharma, a sum that climbed to $76m in 2019 and has remained at that level, including over the first three quarters of 2021. It is clear that biopharma sector will exit 2021 a seller's market. With smaller developers still cash rich after years of plenty this seems likely to remain the case in 2022.

A look at the largest up fronts paid in recent years shows that the highly competitive cancer space has been largely responsible for driving prices higher.

Licensing deals



Big spenders: cancer dominates the biggest deals

Licensor/licensee (year of deal)	Details	Upfront cash	Total deal value
Gilead/Galapagos (2019)	10 year R&D collaboration, incl. ph3 IPF asset and ph2b osteoarthritis projects, and options over pipeline.	$4.0bn	$6.9bn
Merck & Co/ Astrazeneca (2017)	Development and commercialisation deal over two cancer drugs, the marketed Parp inhibitor Lynparza and ph2 project selumetinib.	$1.6bn	$8.5bn
Astrazeneca/Daiichi Sankyo (2019)	Global development and commercialisation deal for cancer drug Enhertu.	$1.4bn	$6.9bn
Bristol Myers Squibb/ Nektar (2018)	Global development and commercialisation deal for cancer project bempegaldesleukin (NKTR-214).	$1.0bn	$3.6bn
Astrazeneca/Daiichi Sankyo (2020)	Global development and commercialisation deal for cancer project datopotamab deruxtecan (DS-1062).	$1.0bn	$6.0bn

CLINICAL CATALYSTS IN 2022

Big cap events

2022 clinical catalysts: the big developers			
Project	**Company**	**Upcoming catalyst**	**Trial ID**
Donanemab	Eli Lilly	Anti-amyloid-beta MAb; topline data from ph3 Trailblazer-Alz 4, H2H vs Aduhelm in Alzheimer's disease due H2 2022	NCT05108922
Enhertu	Astrazeneca	Anti-HER2 ADC; ph3 Destiny-Breast04 in metastatic breast cancer with low Her2 expression due H1 2022	NCT03734029
Gantenerumab	Roche	Anti-amyloid-beta MAb; ph3 Graduate 1 and 2 in early Alzheimer's disease due H2 2022	NCT03443973; NCT03444870
Trodelvy	Gilead	Anti-Trop2 ADC; ph3 Tropics-02 in 3L ER+/Her2- breast cancer post endocrine therapy due Q1 2022	NCT03901339
Kisqali	Novartis	CDK4/6 inhibitor; ph3 Natalee in adjuvant HR+ breast cancer due late 2022	NCT03701334
Tiragolumab	Roche	Anti-Tigit Mab; ph3 Skyscraper-01 in 1L NSCLC PD-L1+, Skyscraper-02 in 1L extensive-stage small cell lung cancer, and Skyscraper-08 in 1L oesophageal cancer, all + Tecentriq, due in 2022	NCT04294810; NCT04256421; NCT04540211
GSK3844766A	Glaxosmithkline	RSV vaccine; ph3 Aresvi 004 in adults ≥60 due H1 2022	NCT04732871
Amcenestrant	Sanofi	Oral Serd, ph2 Ameera-3 in 2L ER+/Her2- breast cancer due Q4 2021/Q1 2022	NCT04059484
Giredestrant	Roche	Oral Serd; ph2 Acelera in 2/3L pre/peri/ postmenopausal ER+/Her2- breast cance due mid-2022	NCT04576455
RSVpreF (PF-06928316)	Pfizer	RSV vaccine; ph3 Renoir in adults ≥60 due Q1, ph3 maternal protection trial interim analysis due mid-2022	NCT05035212; NCT04424316
Insulin icodec	Novo Nordisk	Once weekly insulin; ph3 Onwards 1, 2, 3, 4, 5 in T2DM, Onwards 6 in T1DM, due H1 2022	NCT04460885; NCT04770532; NCT04795531; NCT04880850; NCT04760626; NCT04848480
Camizestrant (AZD9833)	Astrazeneca	Oral Serd; ph2 Serena-2 in 2L postmenopausal ER+/Her2- breast cancer due H2 2022	NCT04214288
Efanesoctocog alfa (BIVV001)	Sanofi (partnered with Sobi)	Ultra long-lasting FVIII; ph3 Xtend-1 in haemophilia A due Q1 2022	NCT04161495
RSVPreF3 (GSK3888550A)	Glaxosmithkline	RSV vaccine; ph3 Grace maternal protection trial due H2 2022	NCT04605159
Ad26.RSV.preF	Johnson & Johnson	RSV vaccine; ph3 Evergreen in adults ≥60 due H2 2022	NCT04908683
JNJ-3989 (ARO-HBV)	J&J (from Arrowhead)	Hepatitis B RNAi therapeutic; data from various combination trials due over 2022	NCT05005507; NCT04667104

Source: Evaluate Pharma, company statements and clinicaltrials.gov.

Other events

2022 clinical catalysts: outside of the big developers			
Project	**Company**	**Upcoming catalyst**	**Trial ID**
High-dose Eylea (longer-acting)	Regeneron	8mg dose of the intravitreal VEGF-A inhibitor; ph3 Pulsar in wet AMD, ph2/3 Photon in DME due H1 2022	NCT04423718; NCT04429503
Zuranolone (Sage-217)	Sage Therapeutics/ Biogen	Gaba A modulator; Coral in major depressive disorder due early 2022, Skylark in postpartum depression due mid-2022	NCT04476030; NCT04442503
Lecanemab (BAN2401)	Biogen/Eisai	Anti-amyloid-beta MAb; ph3 Clarity AD in early Alzheimer's disease due Q3 2022	NCT03887455
AK002 (lirentelimab)	Allakos	Anti-siglec-8 Mab; ph2/3 Kryptos & Enigma2 in rare chronic inflammatory conditions of the gut due YE 2021/Q1 2022	NCT04322708; NCT04322604
Valoctocogene roxaparvovec (valrox)	Biomarin	Haemophilia A gene therapy; two-year results from all participants in pivotal Gener8-1 study due early 2022	NCT03370913
CTX001	Cripsr/Vertex	CRISPR/Cas9 gene-edited therapy; filings expected YE 2022, updates in beta-thalassemia and sickle cell disease due throughout the year	NCT03745287; NCT03655678
KSI-301	Kodiak	Intravitreal VEGF-A inhibitor; ph2/3 Dazzle in AMD due early 2022	NCT04049266
Bempegaldesleukin	Nektar (partnered with Bristol Myers)	IL-2 receptor agonist; ph3 in 1L advanced melanoma + Opdivo due early 2022	NCT03635983
Transcon PTH	Ascendis	Parathyroid hormone regulator; ph3 Pathway in adults with hypoparathyroidism due Q1 2022	NCT04701203
Resmetirom	Madrigal	β-selective THR agonist; top-line liver biopsy data from ph3 Maestro-Nash trial due Q3 2022	NCT03900429
Domvanalimab + zimberelimab +/- etrumadenant	Arcus/Gilead	Anti-Tigit MAb/anti-PD-1 MAb/A2A/A2b receptor agonist; Arc-7 combination trial in 1L, PD-L1 ≥ 50% mNSCLC due mid-202 2	NCT04262856
TAK-999	Arrowhead/ Takeda	AAT RNAi therapeutic; biopsy data from pivotal ph2 Sequoia trial due mid-2022	NCT03945292
Rozanolixizumab	UCB	Anti-FcRn MAb inhibitor; generalised myasthenia gravis (gMG) and immune thrombocytopenia (ITP) trials to read out H1 2022	NCT03971422; NCT04124965; NCT04224688; NCT04200456
AMG-890 (olpasiran)	Amgen/ Arrowhead	ApoA RNAi therapeutic; top-line data from ph2 trial due mid-2022	NCT04270760
KarXT	Karuna	M1/M4 muscarinic agonist + muscarinic receptor antagonist; ph3 schizophrenia trials, Emergent-2 and Emergent-3, to report H2 2022	NCT04659161; NCT04738123
PRA023	Prometheus Biosciences	Anti-TL1A MAb; ph2 data in ulcerative colitis and Crohn's disease due Q4 2022	NCT05013905; NCT04996797

Source: Evaluate Pharma, company statements and clinicaltrials.gov.

Covid-19 projects

Covid-19 projects to watch in 2022				
Company	**Project**	**Mechanism**	**Trial details**	**Trial ID**
Anti-virals/treatments				
Pfizer	Paxlovid (PF-07321332 + ritonavir)	Oral antiviral	Ph3 low-risk trial, Epic-SR, and ph3 prevention trial, Epic-PEP, due to report Q1/Q2 2022	NCT04960202; NCT05047601
Merck & Co/ Ridgeback	Molnupiravir	Oral antiviral	Ph3 post-exposure prophylaxis trial, Move-Ahead, due to report H1 2022	NCT04939428
Molecular Partners/ Novartis	Ensovibep	Darpin (antibody mimetic)	Ph2/3 outpatient trial, Empathy, due to report 2022	NCT04828161
Roche/Atea	AT-527	Oral antiviral	Ph3 outpatient trial Morningsky, due to report H2 2022	NCT04889040
Adagio Therapeutics	ADG20	Neutralising MAb	Ph2/3 prevention trial, Evade, and ph2/3 outpatient treatment trial, Stamp, due to report Q2 2022	NCT04859517; NCT04805671
Synairgen	SNG001	Inhaled interferon beta 1a regulator	Ph3 Sprinter trial in hospitalised patients due to report early 2022	NCT04732949
Redhill Biopharma	RHB-107 (upamostat)	Oral serine protease inhibitor	Ph2/3 outpatient trial due to report 2022	NCT04723537
Veru	Sabizabulin	Oral tubulin polymerisation inhibitor	Ph3 in high-risk hospitalised patients due to report H1 2022	NCT04842747
Kiniksa Pharmaceuticals	Mavrilimumab	Anti-GM-CSF receptor alpha MAb	Ph2/3 in Covid-19-related ARDS due to report Q1 2022	NCT04447469
Foresee Pharmaceuticals	FP-025	Oral MMP 12 inhibitor	Ph2/3 in Covid-19-related ARDS due to yield initial data in Q4 2021	NCT04750278
Vaccines				
Sanofi/ Glaxosmithkline	Unnamed vaccine	Monovalent and bivalent recombinant protein vaccines	Placebo-controlled ph3 trial due to report by YE 2021	NCT04904549
Inovio/VGX Pharmaceuticals	INO-4800/ VGX-3100	DNA vaccine	Ph3 Innovate trial due to yield interim efficacy data H1 2022	NCT04642638
Arcturus	ARCT-154	mRNA vaccine	Pivotal development ongoing in Vietnam with partner Vinbiotech, with filing expected by YE 2021; ph2 US booster study results due Q1 2022	NCT05012943; NCT05037097
Vaxart	VXA-CoV2-1	Oral vaccine	Ph2 results due Q1 2022	NCT05067933

Note: Excludes basket trials.

Source: Evaluate Pharma, company statements and clinicaltrials.gov.

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