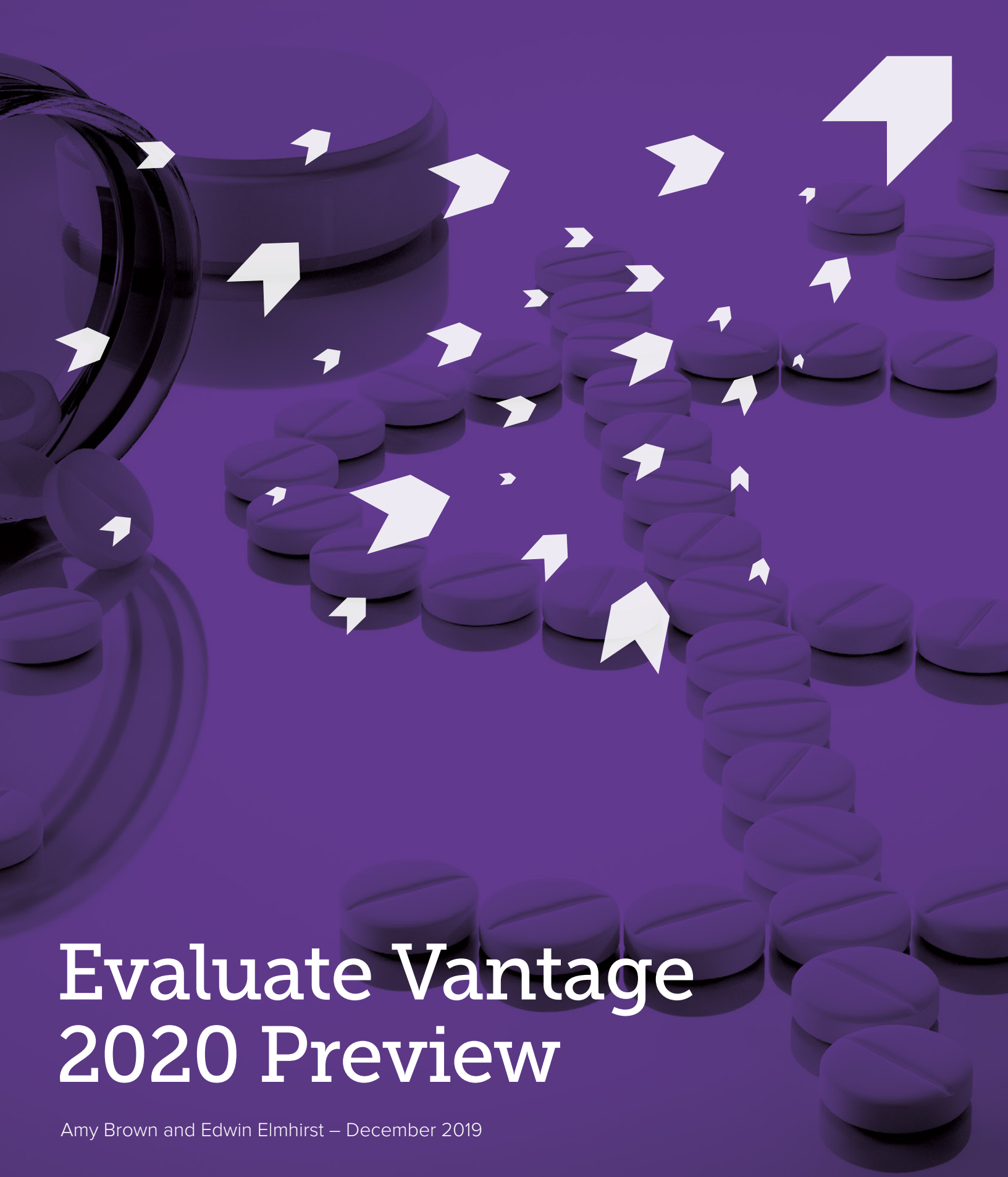


Evaluate Vantage 2020 Preview

Amy Brown and Edwin Elmhirst – December 2019

Evaluate Vantage

Evaluate

Foreword

Biopharma is braced for a rocky ride in 2020.

Rhetoric around drug pricing is only going to increase as the US presidential election gets closer, keeping a sector already unpopular with voters under the spotlight. While political gridlock means that US lawmakers are not expected to agree on any new measures any time soon, it is clear that the cost of medicine will remain a live issue next year.

This is all likely to translate into a volatile time on the stock market. The IPO window is not expected to completely close next year, but equity investors are probably not going to be as receptive as in 2019. Venture investors too could adopt a more prudent stance towards financings, particularly if it starts to look like their own funds will need to last longer.

Using in-depth analyses of recent M&A, IPO and venture financing activity, as well as interviews with market participants, this report attempts to look at where this activity is heading next.

The unpredictability of stock markets and other macro-economic issues mean it is hard to predict how the financial health of the sector might change. Events from outside the sector can quickly shift sentiment towards the high-risk drug development industry.

Something that can be described with more authority is where biopharma's growth will come from next year. Using EvaluatePharma data, this report pinpoints the sector's biggest sales growth drivers next year, and highlights the companies that are capturing that growth. Certain mechanisms of action are projected to add billions of dollars in extra revenues in 2020, while there are surprisingly few brakes on biopharma's top line. No prizes for guessing that cancer drugs feature prominently here.

The report also identifies the most highly valued R&D projects, and the clinical programmes that are consuming huge amounts of money. Along with the biggest new medicines that could reach the market in 2020, these analyses describe some of the sector's most closely tracked programmes.

Readers can also take a glimpse into areas of over and under-investment – vital intelligence for companies with business development decisions to make, and for the investors that back these efforts.

The November market rally means that the biotech sector is heading towards a triumphant finish to 2019. Whether this can be maintained for much longer is now the dominant question on investors' minds.

Report authors | Amy Brown and Edwin Elmhirst

Written December 2019. All data correct as of November 15, 2019.

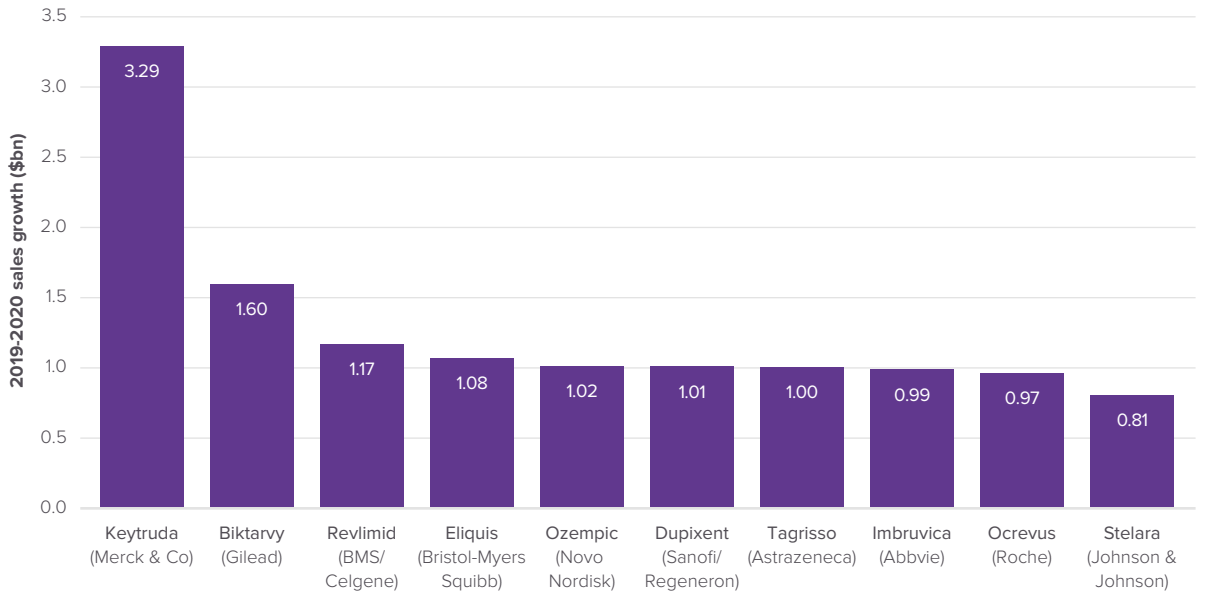
2020 in numbers: where the biopharma sector's growth is coming from

Advances in oncology over the past decade mean that this field has become a major preoccupation for the biopharma space. In terms of both where new sales are coming from and where funds are being directed, cancer drugs and the companies that develop them dominate overviews of the sector.

This is true of both short and long term outlooks. Next year, for example, eight drugs are expected to add $1bn or more in new sales, and four of them are cancer drugs. The ability to charge relatively high prices in oncology helps these products to feature prominently, though it is also true that several of them represent real breakthroughs.

Product growth 2019-2020: the biggest new sales generators

Source: EvaluatePharma® November 2019



That Merck has played its hand to perfection in the anti-PD(L)1 antibody class is abundantly clear from this chart. Should the huge growth forecast for Keytruda next year come to pass, it will yield 2020 sales of $13.9bn; this is a huge sum for an individual product to generate in a year, putting the checkpoint inhibitor on track to become the second-biggest selling drug next year.

Next year's biggest seller does not feature among the biggest growth drivers. Abbvie's Humira, along with the whole anti-TNF space, is flatlining thanks to the arrival of cheaper versions of several projects that utilise this mechanism. Growth or no growth, annual sales of $18.7bn could be considered a nice problem to have.

A fair representation of older products in the chart above shows the longevity of some of these huge franchises. Revlimid is father of the house, having arrived in 2006 and still growing strongly more than a decade later, although this is a product notorious for enjoying steep price rises. These sales will now be booked by Bristol-Myers Squibb, which also sells another big grower, the blood thinner Eliquis.

The chart below looks more broadly at the mechanisms expected to drive the sector's combined top line next year, or act as a brake. These analyses are all based on EvaluatePharma's sellside-derived consensus.

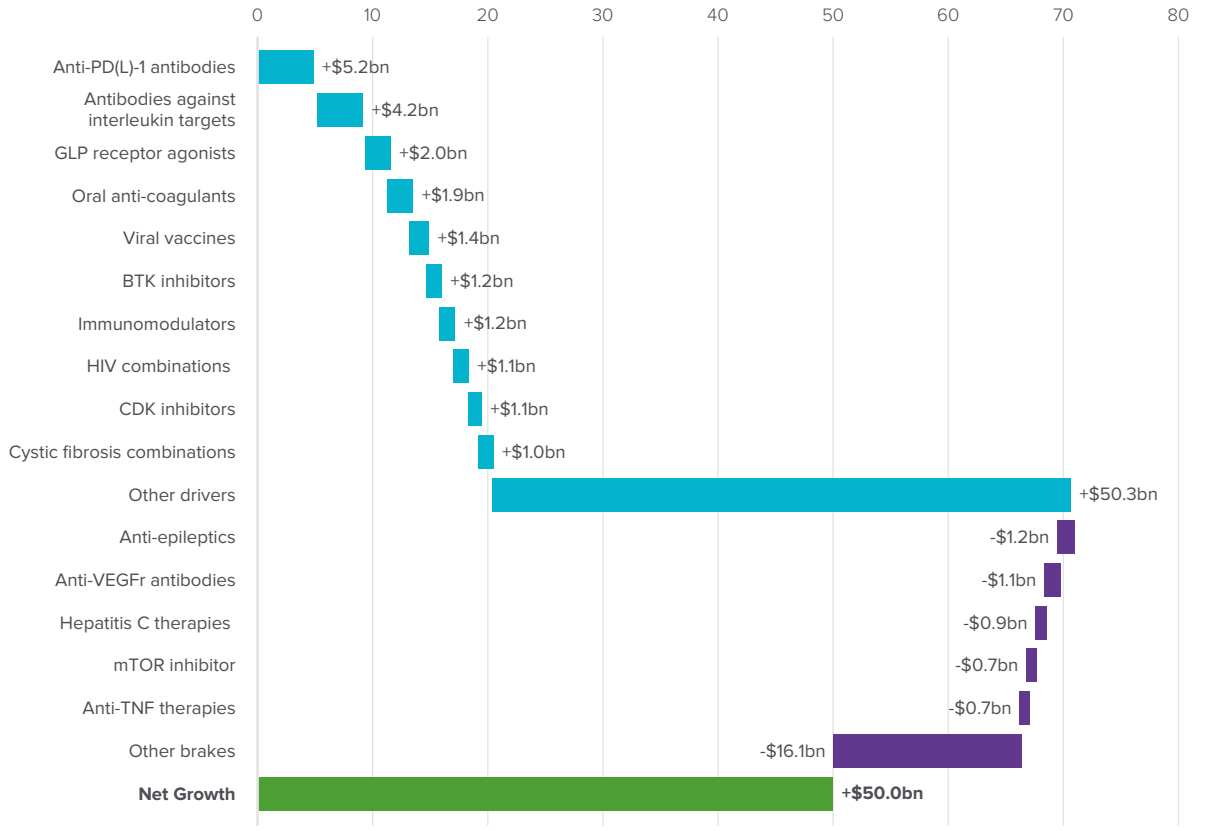
Several of these mechanisms include the leading products above and it can be seen how certain drugs dominate their particular niche. Keytruda, for example, will contribute more than half of the new sales created by antibodies targeting anti-PD(L)1. The immunomodulatory category is represented entirely by Revlimid; the pathways through which the blood cancer treatment exerts its effects are still not fully known.

Antibodies with various interleukin targets have been grouped here, though they target a wide range of autoimmune and inflammatory conditions, such as asthma and psoriasis. Dupixent and Stelara are big beasts here.

Despite significant pricing pressure throughout the diabetes disease area, several of these mechanisms are expected to see major growth next year. GLP receptor agonists in particular are set to expand, driven by Novo Nordisk's Ozempic; the SGLT2 inhibitors fall just outside this chart with an anticipated $1bn in new sales in 2020.

The biggest drivers and brakes to the sector's top line, by therapy area

Source: EvaluatePharma® November 2019



Vaccines are not considered a particularly exciting area of biopharma but they remain a big growth area, albeit largely consolidated into the hands of three companies: Glaxosmithkline, Merck & Co and Sanofi.

Remarkably, a rare disease now stands as a sector growth driver, though cystic fibrosis is dominated by one company, Vertex Pharmaceuticals, which is capturing all the sales growth here. Another rare disease, the childhood wasting condition spinal muscular atrophy, is also just outside this analysis with an anticipated $900m in new sales next year, the majority of which come from Novartis's gene therapy Zolgensma.

It is the huge cost of these products that places them in this analysis. Vertex's new cystic fibrosis triple Trikafta was priced at $310,000 a year, while Zolgensma, a "one-and-done" treatment, comes in at just over $2m, making it the most expensive single payment drug in the world.

It is notable how few brakes exist next year, to the extent that biopharma's total prescription sales are expected to grow by $50bn next year, according to EvaluatePharma. This will not escape the notice of those attempting to keep a lid on drug prices.

The biggest arrivals expected in the US in 2020

Source: EvaluatePharma® November 2019

Product	Setting	Companies involved	Status	2024e WW sales ($m)
Trastuzumab Deruxtecan	Her2 positive breast cancer	Daiichi Sankyo/Astrazeneca	Q2 PDUFA date	2,412
Palforzia	Peanut allergy treatment	Aimmune Therapeutics	January PDUFA date	1,279
Ozanimod	Relapsing-remitting MS	Bristol-Myers Squibb (ex-Celgene)	25 March PDUFA date; EU decision due H1'20	1,598
Inclisiran*	Hyperlipidaemia	Novartis	US submission by YE'19	1,529
Roxadustat	Anaemia caused by kidney disease	Astrazeneca/Fibrogen/Astellas	US submission due Q4'19	1,488
Sacituzumab Govitecan	Metastatic triple-negative breast cancer	Immunomedics	BLA resubmitted December 2019	1,436
Filgotinib	Rheumatoid arthritis	Gilead/Galapagos	Filed in EU, Japan; US filing due by YE'19	1,280
Valoctocogene Roxaparvovec	Haemophilia A gene therapy	BioMarin	Filed in EU, US submission due by YE'19	1,212
Rimegepant	Migraine	Biohaven	30 June PDUFA	897
Risdiplam	Spinal muscular atrophy	Roche	May 24 PDUFA	803

*Consensus based on analysts covering The Medicines Company, not Novartis.

Swift regulatory action by the FDA moved a couple of 2020's biggest launches into 2019. Vertex's latest cystic fibrosis therapy Trikafta was green lit in October – three months after filing and five months before its official PDUFA date. Global Blood Therapeutics' sickle cell treatment, Oxbryta, won approval three months ahead of schedule.

Uptake of both will be closely tracked next year. Sellside analysts reckon sales of Trikafta will reach nearly $4bn by 2024, while Oxbryta could hit $1.6bn, according to EvaluatePharma. Novartis's Adakveo won approval a couple of weeks prior to Oxbryta, also in sickle cell, and this disease will be a big focus for investors next year.

The FDA's quick work in these rare diseases means that Daiichi Sankyo and Astrazeneca's Her2 targeting antibody-drug conjugate (ADC), trastuzumab deruxtecan, looks to be the biggest US approval decision next year, commercially speaking.

The partners are positioning the product as a “better Herceptin”, and the sellside has attached some very big numbers to the project. Data from the Destiny-Breast01 trial demonstrated why Astrazenenca was moved to pay $1.4bn up front for the project. An impressive 61% of heavily pre-treated patients responded to treatment, though safety will have to be closely watched. Lung complications occurred at a rate that could pose a threat to usage in earlier lines of therapy, upon which these loft sales forecasts rely.

Other projects here still have much to prove, despite fast approaching the market. Aimmune is building up to launch its peanut allergy treatment early next year, but a lot of investors are betting against this product’s chances of commercial success. Elsewhere, doubts about the durability of Biomarin’s haemophilia A gene therapy valrox still have to be cleared up.

Novartis’s newly acquired RNAi therapeutic inclisiran could squeeze into 2020, if its regulatory journey runs smoothly. Esperion’s bempedoic acid falls just outside this ranking with projected 2024 sales of $716m, and is another big cardiovascular project to launch next year, with a decision due in February.

Amarin looks set to be selling Vascepa in a much broader setting next year as well. Having witnessed the hugely disappointing arrival of the anti-PCSK9 antibodies these companies have presumably learnt how not to launch a new cardiovascular drug, though fears about their prospects will grow should other suitors not emerge for either Amarin or Esperion.

Outside of cardiology, roxadustat will be one of the most closely tracked filings next year, given that the Astrazeneca-partnered project has never really been able to shake safety concerns.

It is also worth noting that tislelizumab, the anti-PD-1 antibody that Beigene reacquired from Celgene in the wake of the Bristol-Myers bid, is launching in China next year. The product is forecast to become a blockbuster in its domestic territory by 2024, though its prospects elsewhere are likely to be much lower, given that it would be very late to market in this category.

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

Source: EvaluatePharma® November 2019

Product	Description	Company	Phase	NPV ($bn)
Tirzepatide	Dual GIP-GLP1 agonist for type 2 diabetes	Eli Lilly	Phase III	11.72
BMS-986165	Tyk2 inhibitor for psoriasis and other autoimmune conditions	Bristol-Myers Squibb	Phase III	6.74
TransCon Growth Hormone	Long-acting human growth hormone	Ascendis Pharma	Phase III	5.36
Bempegaldesleukin	IL-2 receptor beta agonist, various cancers	Nektar Therapeutics	Phase III	4.80
SAGE-217	Gaba-A modulator for depression	Sage Therapeutics	Phase III	4.78
Tezepelumab	Anti-TLSP MAb for asthma	Amgen	Phase III	4.70
Mirikizumab	Anti-IL23 MAb for psoriasis and other autoimmune conditions	Eli Lilly	Phase III	4.66
mRNA-2752	IL-23, IL-36g & OX40 mRNA therapeutic for various solid tumours	Moderna	Phase I	4.62
Efgartigimod	Anti-neonatal FcRn MAb for IgG-mediated autoimmune diseases	Argenx	Phase III	4.41
RG7828	Anti-CD20 & CD3 bispecific MAb for blood cancers	Roche	Phase II	4.12

Note: Excludes products forecast to launch next year. NPV based on sellside consensus sales. Forecasts for SAGE-217 collated before the failure of the phase III Mountain study.

The next analysis looks at the most highly valued R&D projects, as determined by EvaluatePharma Vision's NPV Analyzer, which is based on the sellside's consensus sales forecasts.

Topping the list with an eye-watering net present value of almost $12bn is Eli Lilly's attempt to bring a new mechanism to the diabetes market. Diabetes is a fiercely competitive space that has been subject to substantial pricing pressure, mainly in older drug categories like insulin. This means that any new mechanisms will have to offer substantial advantages over existing approaches.

A clear cardiovascular benefit is also a bare minimum, and whether tirzepatide can live up to any this remains to be seen. Data from the pivotal Surpass programme are unlikely to start emerging until late in 2020. Tolerability issues, specifically gastrointestinal side effects, means that the project has much to prove.

The fact that Lilly has already started work on a follow-on asset is perhaps telling. A GIP/GLP glucagon tri-agonist should enter phase II next year; diabetes rival Novo Nordisk is also pursuing this mechanism and is due to release phase I data on its project, NN1706, before the end of 2019. This is an early field of research that will be closely watched next year.

Another high value asset is Bristol-Myers' Tyk2 inhibitor, BMS-986165, which should yield data from two large psoriasis studies in the second half of the year. As well as placebo Bristol-Myers is also pitting the project against Otezla – notably, this is the product that was sold to Amgen to win antitrust regulators' blessing for the Celgene takeover.

Bristol-Myers pocketed $13.4bn for Otezla, a move that could prove even more profitable if it can show that it has a more effective psoriasis treatment in BMS-986165. Otezla is considered to be safer but less effective option to biologicals in psoriasis, and Bristol-Myers is presumably confident that '165 will come out on top.

Pfizer and Johnson & Johnson are also working with Tyk2 inhibitors, so this is a mechanism to watch next year.

Ascendis stands out in this list as a rare smaller drug developer with a highly valued asset. Success with its long-acting human growth hormone means that the Danish company now sports a $5bn valuation, which leaves little room for disappointment.

Europe also contributes another big ticket asset in the shape of Argenx's efgartigimod, the sector's leading anti-FcRn project, intended to treat a range of rare autoimmune conditions. After a spate of deal-making in 2019 this space will of great interest next year; having raised almost $500m in November, Argenx seems to have every intention of pushing on alone for now.

Sage-217 is also in the hands of a smaller company, and the failure of the phase III Mountain study in early December, which wiped billions from Sage's market cap, shows how precarious these forecast are. All the sales figures that provide the basis for the valuations listed here are estimates, and all projects are vulnerable to the clinical setbacks that are a fact of life of this sector.

Some of the projects look more likely to implode, however, with Nektar's NKTR-214 a case in point. The sellside is resolutely maintaining some big numbers for this project despite manufacturing problems and questions over efficacy. With definitive data unlikely to emerge until 2021 the real value of NKTR-214 remains hard to know.

Similarly a few brave analysts are already pencilling in substantial numbers for Moderna's mRA-2752, which remarkably is still in phase I. Data due next year should provide a clearer picture here.

Roche's bispecific antibody, RG7828, or mosunetuzumab, was another star of the Ash medical meeting, generating durable responses in an impressive proportion of very poor prognosis non-Hodgkin lymphoma patients, some of whom had relapsed after Car-T therapy. This is exactly the sort of progress that threatens developers of some of the more complex cell therapy approaches.

It is also interesting to note that oncology accounts for only three of the top 10 most highly valued R&D projects. True, cancer projects tend to target smaller niches now, but this could also reflect the fact that the next wave of immuno-oncology assets are taking a lot longer to arrive than expected.

The targeted oncology space has seen huge progress, of course, though backers that have been throwing money at cancer more broadly will want to see evidence next year that this huge investment is paying off.

EvaluatePharma Vision's R&D cost module provides a different way at finding the sector's biggest research projects. This provides an estimate of the cost of clinical programmes using real world data: company disclosed product-level spend and clinical trial patient numbers are combined to create cost per patient benchmarks by technology and therapy type. Utilising a matching algorithm, these benchmarks are applied to all commercially relevant clinical trials to estimate their cost, which can then be aggregated by product.

The table below looks at some of the most costly research projects currently underway.

Most expensive clinical programmes – R&D projects

Source: EvaluatePharma® Vision November 2019

Project	Companies involved	Mechanism of action	Estimated clinical spend in 2020 ($m)	Estimated total cost of clinical programme (historic and forecast, $bn)
CSL112	CSL	HDLR agonist	621	2.69
Fasinumab	Regeneron/Teva/Mitsubishi Tanabe	NGF antibody	464	2.16
Inclisiran	The Medicines Company	PCSK9 inhibitor	446	2.85
Fidanacogene elaparvovec	Pfizer	Factor IX gene therapy	420	1.42
Filgotinib	Galapagos/Gilead Sciences	JAK1 inhibitor	416	3.58
Tirzepatide	Eli Lilly	GIP/GLP-1 receptor agonist	366	0.77
PT027	AstraZeneca	LABA-ICS combination	352	0.77
BMS-986165	Bristol-Myers Squibb	TYK2 inhibitor	320	1.14
Efpeglenatide	Sanofi	GLP-1 receptor agonist	307	0.93
SHP647	Takeda	Integrin receptor antibody	305	1.48

An under-the-radar heart attack therapy in development by the Australian blood product specialist, CSL, stands out. CSL112 is an apoliprotein A-1 infusion that therapy that is being tested for its ability to reduce the incidence of secondary cardiovascular events after an initial heart attack.

A 17,400-patient study, Aegis II, is largely responsible for the bulk of the estimated clinical spend, though results are unlikely to emerge until 2021.

Next year should also see results emerge from Regeneron and Teva's 5,331-patient study of the long-term safety and efficacy of fasinumab in osteoarthritis pain. A huge amount of money has been thrown at the anti-NGF antibodies – the first projects entered the clinic over a decade ago – but safety concerns stalled development.

The need for effective non-opioid painkillers prompted developers to look again, though whether a therapeutic window can be found remains to be proven. The potential for these agents to accelerate joint damage in certain cases means lower doses are now under consideration, which obviously compromises effectiveness.

This analysis throws up a couple of other R&D projects that will be getting a lot of attention next year. Pfizer's haemophilia B gene therapy, licensed from Spark, is unlikely to complete its pivotal study until 2021, though many will be hoping for an interim update next year.

Finally, Takeda will presumably be hoping to complete the divestment of SHP647 next year. The company was required to commit to sell the anti-integrin antibody in return for antitrust clearance of its Shire takeover; the project has a similar mechanism to the Japanese group's blockbuster Crohn's and ulcerative colitis treatment, Entyvio.

A substantial 8,000-patient pivotal programme is ongoing with SHP647 in these same settings, which Takeda is presumably now bankrolling. The company has told investors to expect income from future divestment of up to $10bn in the coming year, and the sale of the former Shire asset presumably makes up a big chunk of that forecast.

This next table looks at drugs already on the market, but that are still consuming vast amount of research dollars.

Most expensive clinical programmes – marketed drugs

Source: EvaluatePharma® Vision November 2019

	Companies involved	Mechanism of action	Estimated clinical spend in 2020 ($m)	Estimated total cost of clinical programme (historic and forecast, $bn)
Keytruda	Merck & Co	PD-1 antibody	1,693	12.25
Opdivo	Bristol-Myers Squibb/Ono	PD-1 antibody	1,141	9.31
Ozempic	Novo Nordisk	GLP-1 receptor agonist	1,010	6.28
Imfinzi	AstraZeneca	PD-L1 antibody	936	6.35
Tecentriq	Roche/Chugai Pharmaceutical	PD-L1 antibody	890	6.94
Rinvoq	AbbVie	JAK1 inhibitor	835	4.21
Yervoy	Bristol-Myers Squibb/Ono	CTLA4 antibody	819	7.62
Olumiant	Eli Lilly	JAK1 & JAK2 inhibitor	774	3.96
Lynparza	Astrazeneca/Merck & Co	Parp inhibitor	382	3.42
Rybelsus	Novo Nordisk	GLP-1 receptor agonist	454	2.87

Oncology stands out once again: The anti-PD-(L)1 players continue to throw huge amounts of money at these drugs, to support approvals in new indications and gain a competitive edge.

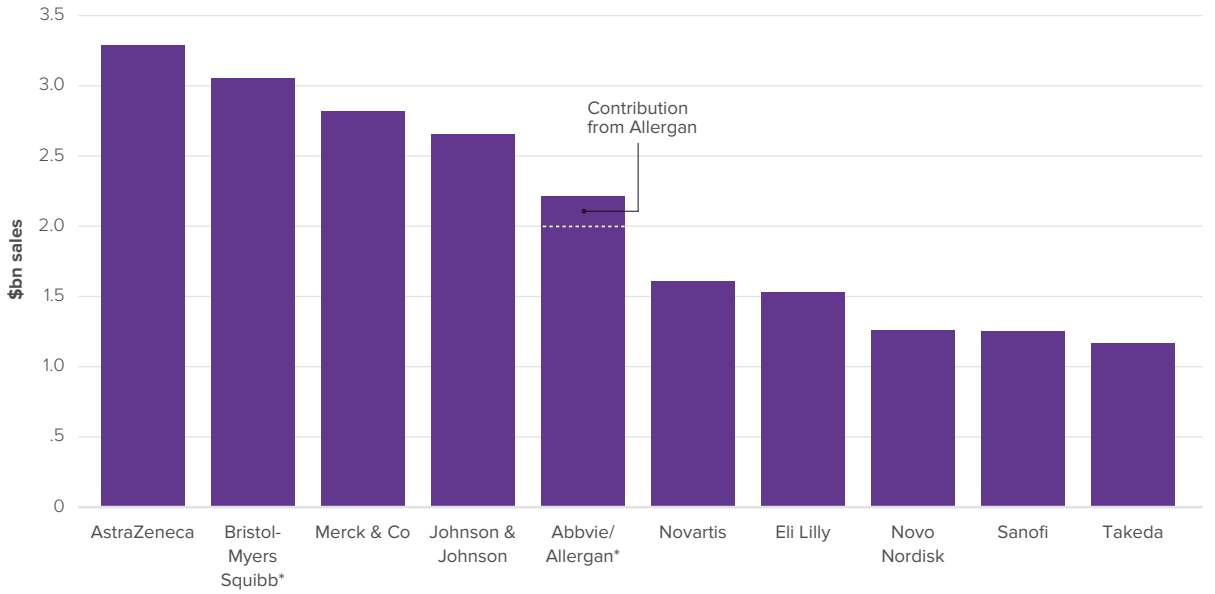
Once again, Keytruda is a league apart, though the billions that Merck is estimated to have spent on the drug are being returned in commercial success. Arguably, its smaller rivals in this space – Astrazeneca and Roche, for example – have yet to justify this level of spend.

Diabetes projects that require huge cardiovascular outcome studies will inevitably be expensive programmes to run, hence Novo Nordisk featuring here. Eli Lilly and Sanofi's work in this disease area features in the look at expensive R&D programmes, above; Lilly has yet to start an outcome study for tirzepatide, a move that will require the company to be supremely confident in this product's potential.

The cost of the Jak inhibitor programmes also stand out: the breadth of autoimmune conditions in which they are being tested, from rheumatoid arthritis to Crohn's disease and ulcerative colitis, means these are expensive drugs to bring to market. Gilead and partner Galapagos are on track to launch the latest asset in this field next year; should filgotinib win approval, it is expected to quickly make a big impact, and its launch will be one of the most closely tracked next year.

Growing the top line: biggest new sales generators in 2020 (Rx & OTC)

Source: EvaluatePharma® November 2019



* Estimate from Evaluate merged company profile

The addition of Shire's top-line helps Takeda join the ranks of the companies with the biggest projected top-line growth next year. Bristol-Myers Squibb also gets a clear boost from the Celgene takeover, though the arrival of Revlimid generics in 2022 means that pressure on the pharma giant to find new sources of growth will not let up for long.

That Abbvie is gaining very little top line uptick from its move on Allergan shows just how financially motivated that deal was.

Standing out is Astrazeneca which has several successful oncology franchises to thank for its pole growth position. Tagrisso in lung cancer and the Parp inhibitor Lynparza have proven themselves highly effective targeted cancer drugs; its anti-PD(L)1 contender, Imfinzi, might be lagging Keytruda and Opdivo but sales of the product are forecast to reach almost $2bn next year – hardly a commercial failure.

While fighting off the Pfizer bid back in 2024 Astra's chief executive, Pascal Soriot, boasted that the company's revenues could reach $45bn in 2023 – the sellside currently estimates $36.3bn for that year. This is unlikely to concern shareholders: Astrazeneca has been one of the best performing big pharma stocks this year with shares trading close to a record, and currently standing around 35% above the price that Pfizer was offering.

The gate keepers

The boom that the biophama sector been enjoying over the past few years has been facilitated in no small part by an increasingly cooperative and flexible regulatory regime at the US FDA. The stances that the FDA adopts play an important role in setting investor sentiment towards the biopharma sector, and not only because the US is the biggest acquirer of medicines globally.

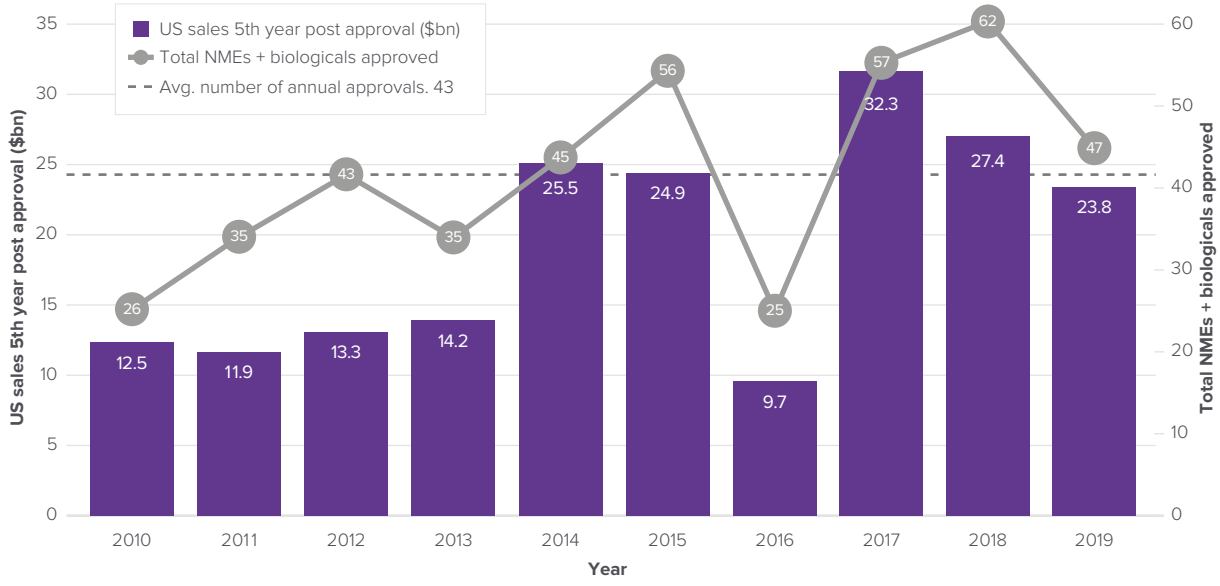
A ten year view of novel drug approvals in the US shows how numbers have climbed recently. The sector's focus on rare diseases or poorly served niches in the oncology world has a lot to do with this focus, which the FDA has rewarded with very fast decisions. There are few signs that the US regulator's industry-friendly stance will substantially shift next year.

In Europe, too, regulators are attempting to get novel treatments to patients faster, though the less transparent European Medicines Agency, and regional differences throughout the continent, make tracking the data from Europe much harder.

Gene therapy is perhaps one area to watch: an Evaluate Vantage analysis has revealed a sharp spike in clinical holds on these projects, from one in 2017 to four last year and eight so far in 2019. This could simply reflect the increased work on this novel approach, but it is clear that the FDA is keeping a watchful eye on progress.

FDA approval count vs. 5th year US sales

Source: EvaluatePharma® 2019 approvals up to 26/11/19



2010 – Prevnar 13 (Pfizer), Victoza (Novo Nordisk), Prolia/Xgeva (Amgen)
2011 – Xarelto (J&J/Bayer), Eylea (Regeneron/Bayer)
2012 – Eliquis (Bristol-Myers Squibb/Pfizer), Stribild (Gilead)
2013 – Sovaldi (Gilead), Tecfidera (Biogen)
2014 – Opdivo (Bristol-Myers Squibb), Harvoni (Gilead)
2015 – Orkambi (Vertex), Ibrance (Pfizer)
2016 – Tecentriq (Roche), Epclusa (Gilead), Venclexta (Abbvie)
2017 – Ocrevus (Roche), Dupixent (Sanofi)
2018 – Biktarvy (Gilead), Epidiolex (GW Pharmaceuticals)
2019 – Trikafta (Vertex), Rinvoq (Abbvie), Skyrizi (Abbvie)

With a month left to go of 2019 at time of writing, the FDA had green-lit 47 novel agents, slightly ahead of the 10 year average. This cohort carries a fifth year sales potential – based on sellside consensus – of $23.8bn, a figure that also looks respectable, over a ten year view.

Of course these straightforward measures of productivity are far from the end of the story. Concerns exist about what some consider the overuse of accelerated approvals and lack of oversight of confirmatory studies, for example, while the development of expensive new products that offer little improvement over existing therapies will continue to be held up as bad news for patients.

But while novel technologies like gene therapy and RNA-based projects continue to reach the market with very little hold-up, the FDA will continue to be seen as one of the sector's tailwinds.

A couple of pivotal decisions due next year will be used as yardsticks of the regulator's generosity. The biggest is probably Biogen's Alzheimer's asset, aducanumab, which the company sensationally grabbed out of the scrapheap in October, and has promised to file for approval early next year.

Presentation of certain cuts of the pivotal data at a medical conference in early December contained hints of effectiveness, but the post-hoc nature of the analyses left many questions unanswered. The advisory committee hearing that will inevitably be convened next year will provide the FDA's first thoughts on all this, and will be a hugely pivotal moment for the biopharma sector.

A green light will be interpreted as Sarepta 2.0, and a further demise in standards of evidenced-based medicine. Roadblocks will be criticised for delaying patients' access to potentially life-changing therapies.

Another big decision is Intercept's Ocaliva application for approval in Nash. The drug is already on the market in a smaller setting, which is why this does not feature in the analyses of new arrivals above. But as potentially the first approval in this poorly-defined and hard-to-diagnose condition, Ocaliva represents something of a watershed moment for a field that has seen huge amounts of money thrown at it.

Big arguments in favour of approving aducanumab and Ocaliva are being made based on unmet need. The third big regulatory decision, of Astrazeneca and Fibrogen's roxadustat, will rest on the anaemia project's ability to prove its advantages over existing standard of care.

The huge and complex clinical programme that supports roxadustat means delays could easily occur. Still, any sort of serious derailment here would probably hit confidence in company disclosure, rather than be taken as a shift in regulatory stance.

Where the money driving the growth is coming from

Talk to pretty much any biopharma investor about what concerns they have for next year, and fallout from the US presidential election gets first mention. Uncertainty around who might next occupy the White House and the changes any new administration might usher in; closer scrutiny of the sector's pricing practises as the campaigning intensifies: this all adds up to volatility on the stock markets.

Reform of how the US pays for its medicines is of course a major aim of the current Trump administration. The need to temper drug prices is something on which Republicans and Democrats broadly agree – mainly because of huge support from voters across the board – and attempts to bring forward legislation are underway.

The sides are miles apart on what reform should actually look like, however. And because very little progress has been made towards consensus in the last three years the threat of substantive change, in the short term at least, has dimmed for many investors.

The polarisation of US politics has a lot to do with this. Even if the Democrats and Republicans manage to agree on a way forward, the parties are seen as incapable of working together, particularly in the run up to the election. The push for impeachment is another destabilising issue.

"I'm less worried about drug pricing on a government, top-down basis than in the last cycle," Jason Kantor, a biotechnology analyst with the investment firm Artisan Partners, says. "There's such gridlock. I would be really surprised if anything meaningful comes at the legislative level for the next while."

Mr Kantor was speaking at the Jefferies Healthcare Conference in London in November.

New legislation is thought most likely to emerge after November 2020. And while investors are for now downplaying the chances of near term material changes to reimbursement and rebate structures, concerns could easily escalate again.

The political will to bring about changes will be on show next year as the election approaches, providing a constant reminder to investors. Candidates for the presidency are well aware that drug pricing is a big issue for US voters, who generally hold the biopharma sector in very low regard.

"Pharma and biotech is definitely in the cross hairs, and the industry's reputation in DC is pretty low right now," says Dan Mahony, a partner at the healthcare-focused investment firm Polar Capital.

Still, he believes that rhetoric could decrease as November 2020 approaches.

"At the moment we are at the maximum point of uncertainty, anything can be thrown at the wall. But soundbite policy aspirations become policy over the next three or four months, and that has to be costed and you get a bit closer to reality," he says.

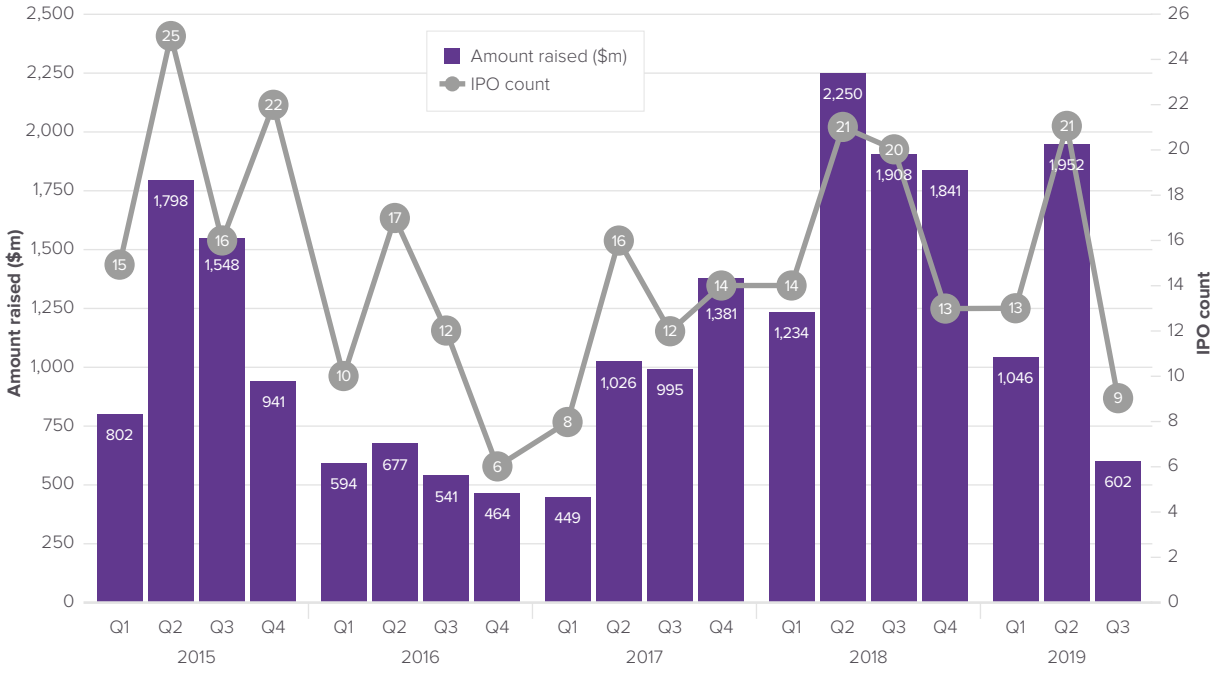
Presumably this depends on none of the more progressive Democrat candidates emerging as frontrunners. The identity of President Trump's Democrat opponent remains a crucial unknown.

While progressive candidates like Elizabeth Warren have threatened to tear up certain healthcare structures in the US, to the huge alarm of investors and industry, the chance of these left-leaning candidates beating Trump at the polls are less clear. The implications of the late-arrival of Michael Bloomberg to the Democrat nominee race also have yet to play out.

Another term for Trump would probably be considered pretty good news for the sector, though political wins and losses for the major parties in Congress will also determine the likelihood of meaningful reform making any progress. Whatever unfolds in the coming months on the US political scene, the biopharma sector is braced for scrutiny.

Biotech IPOs by quarter on Western exchanges

Source: EvaluatePharma® November 2019



Note: Excludes medtech.

The most immediate impact of greater stock market volatility next will be felt in the IPO market. Indeed, investors and companies are already feeling the effects.

Carolyn Ng, managing director at the cancer-focused venture firm Vertex Ventures HC says it is already becoming harder to predict whether private companies will be able to float.

“Most companies that are coming to us for funding right now are highly concerned about whether it’s at all possible to go out to the public markets next year. The majority are trying not to,” she says.

Much depends on broader market conditions next year; as well the US political situation, macro-economic factors like changes in interest rates will dictate the market’s appetite for high-risk biotech stocks. All of this is very unpredictable, of course, and companies are making the most of the window while it remains open.

At the moment the Nasdaq Biotechnology Index is looking like exiting 2019 on a high note: after a difficult summer was followed by an autumn slump for biotech stocks, a remarkable November rally has put it back on a high for the year. Any company still harbouring ambitions for a public life will be very keen to make the most of this resurgence, and it is already looking like the final three months of 2019 will surpass the third quarter in terms of IPOs.

By mid-November, 13 drug developers had floated on Western exchanges in the fourth quarter, raising a total of $1.2bn, according to EvaluatePharma. The chart above counts only companies involved in the development of human therapeutics; it excludes medtech and diagnostics, for example, and therefore provides a look at the most risky end of the biotech spectrum.

This late flurry notwithstanding, investors are still expecting something of a retrenchment next year, particularly of the most high-risk propositions. It would be surprising to see preclinical companies managing to get away next year, for example.

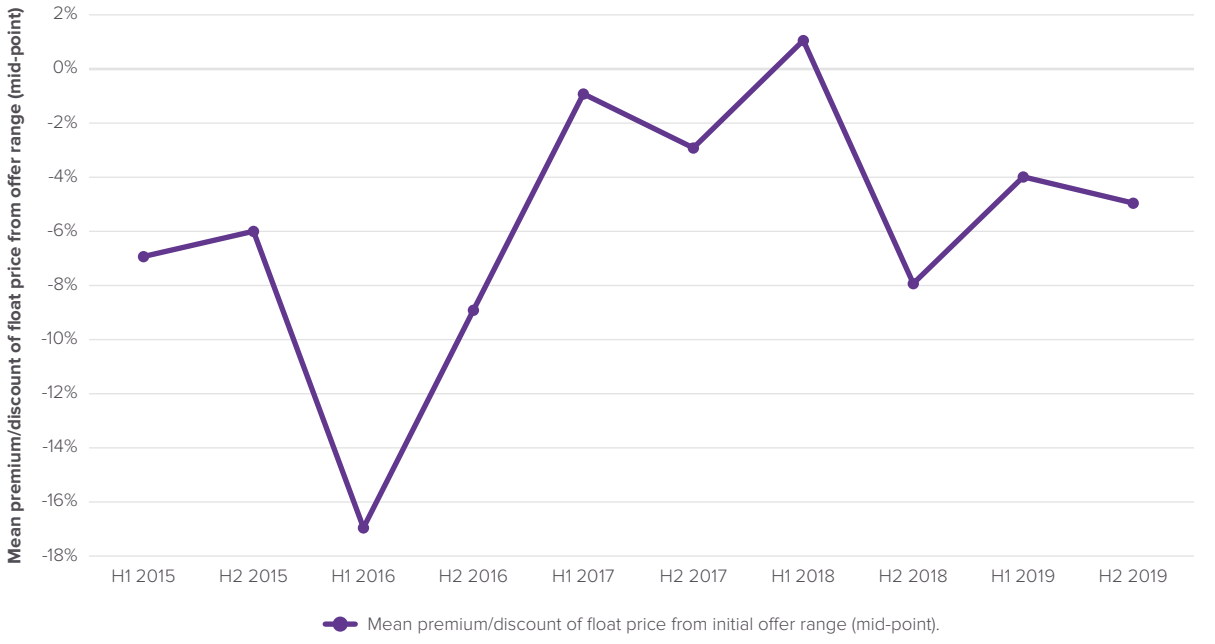
“Bankers are now advising companies to gather more data, or at least have some clinical proof of concept before they consider a public offering,” Ms Ng says.

Søren Møller, managing director of Novo Seeds, an early-stage European venture fund, agrees.

“We don’t think the IPO market will go away, but we may run into some bumps in the road. Timing will be everything,” he says.

Bumps and haircuts – tracking investor appetite for IPOs

Source: EvaluatePharma® November 2019



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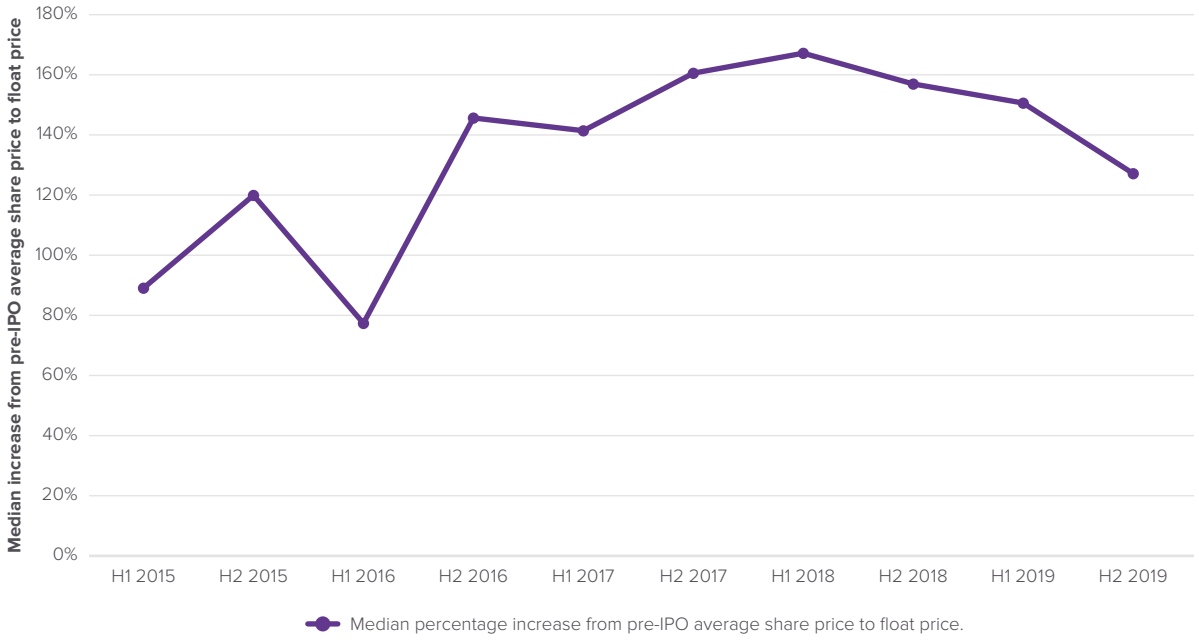
Bumps and haircuts – tracking investor appetite for IPOs (continued)

Source: EvaluatePharma® November 2019



Public investors' appetite for new issues can be gleaned from the charts above. The first shows that this year, compared with earlier periods, companies have had to take bigger discounts to their initially proposed valuations to get new shareholders on board. Given that the markets are expect to get tougher next year, an upwards trend in 2020 would be surprising.

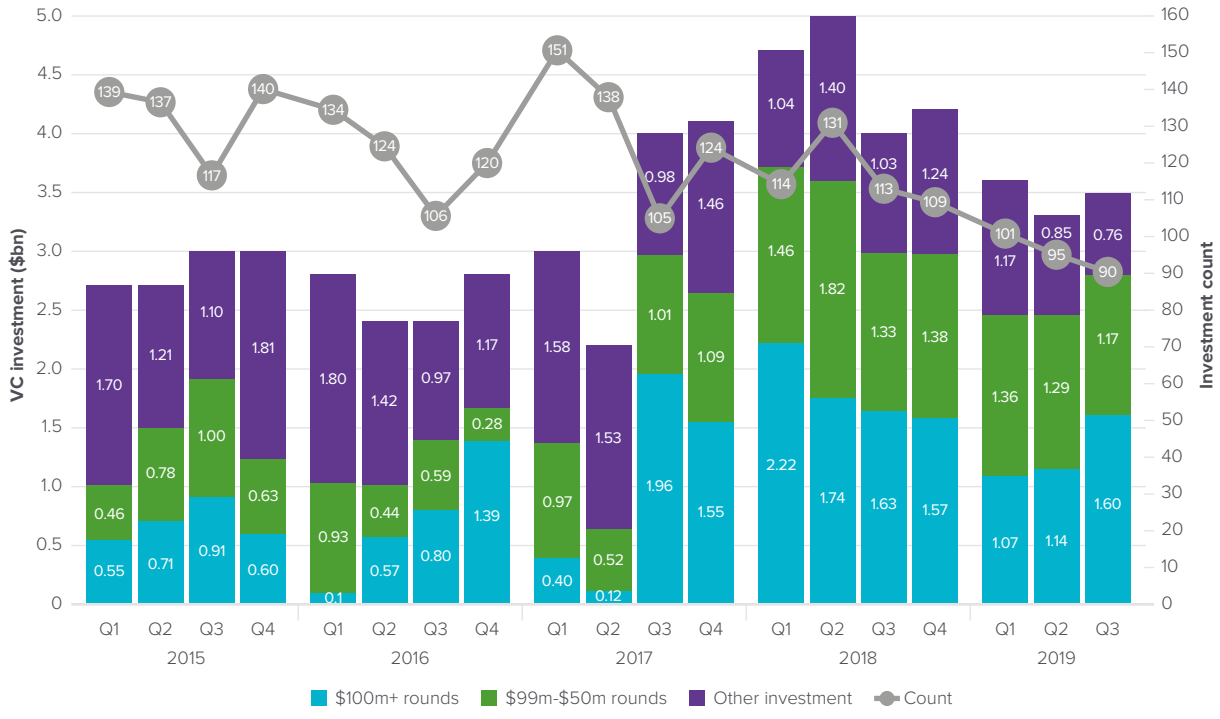
The second chart suggests that private investors have had to temper their returns this year when passing portfolio companies onto the stock market. This analysis was calculated using the average pre-IPO share price, a figure provided in most S-1 documents, and the final flotation price. Again, it would be surprising to see this calculation of rate of return move higher next year.

Both of these analyses include only US listings, which account for the vast majority of biotech IPOs. This ratio is unlikely to change next year.

"We have no companies considering a European listing," says Roel Bulthuis, managing director of Inkef, a European venture firm, adding that poor liquidity remains the big issue for small-cap stocks in these regions. "Insider participation is high, and you have to ask yourself: is that where you want to be, rather than raising another venture round?"

Global quarterly biopharma venture investments

Source: EvaluatePharma® November 2019



Climbing valuations in the private sphere, and the phenomenon of ever-larger funding rounds, means that venture investors need the public markets to be receptive to new issues now more than ever. This is particularly true for those funds backing the very big deals; $100m-plus financings are now far from unusual.

A flotation is certainly not an exit – substantial insider participation is now common, particularly with the big IPOs – but in many cases only the public markets are able to offer a step up on price.

“If your post-money valuation comes to several hundred million dollars, there are few deals where venture investors will make a decent return on that valuation. So the public markets will be the preferred option,” says Novo Seeds’ Mr Møller.

If the markets close next year many companies, and their investors, will be wondering where to go next. And this does not only apply to later-stage drug developers. The substantial series A and B rounds that have become so common result in sizeable valuations, but they do not necessarily result in clinically advanced projects.

There are few investors willing to pick up very early stage start-ups at some of the valuations that are out there, Mr Bulthuis says. As long as cash continues to flow readily into venture firms’ coffers this will not necessarily turn into a problem. But the ability of highly-valued, early-stage companies to re-finance will be monitored closely next year. Whispers of down rounds will be telling.

A look at the venture cash that young drug developers have raised in the past year or so shows that sums invested have moderated somewhat. However this is an industry that remains very well-funded and keen to deploy capital.

Neither does the trend towards mega-rounds show any sign of abating, the previous graph shows. But this raises another concern: that the venture sector's largesse is not always driven by the honourable intentions that are frequently cited to explain growing round sizes. It is said that big pots of money mean strong investor syndicates that are able to sufficiently fund a robust, well-managed company to proof of concept, sometimes with several shots on goal.

But venture firms are also motivated to invest their funds rapidly so they can raise the next one while their own investors, called limited partners or LPs, remain keen. Huge interest from LPs – which can be pension funds, family offices or sovereign wealth funds – in alternative asset classes like venture has fuelled the boom of the past four years.

In much the same way that venture firms advise their portfolio companies to raise money while they can, the groups are themselves making the most of the clement conditions.

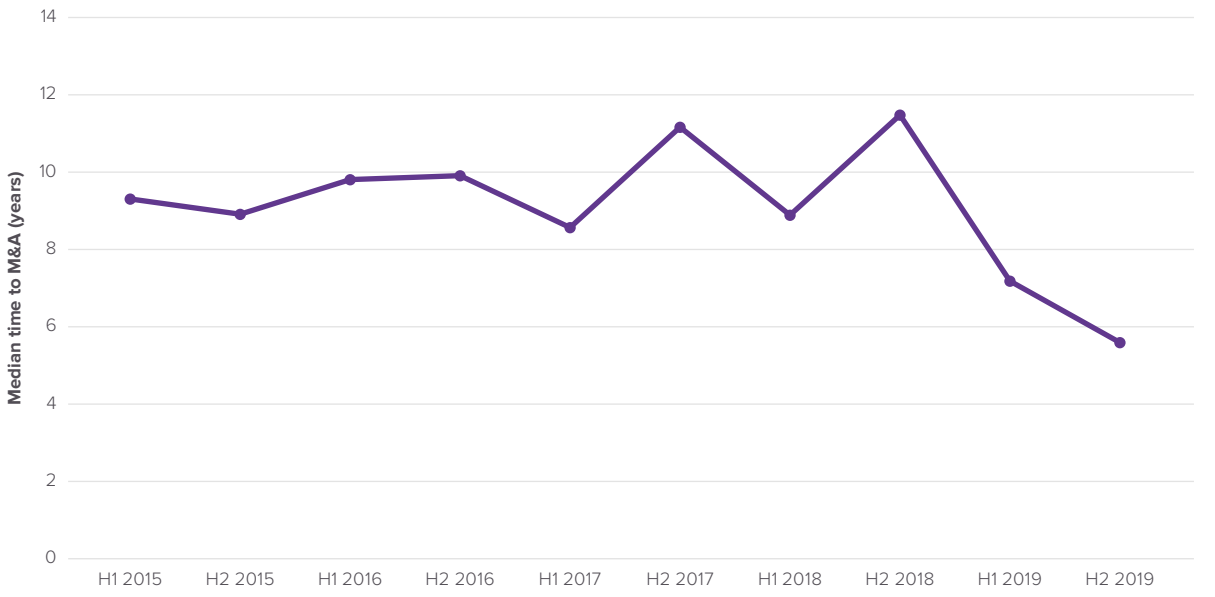
"I like the fact that we are concentrating capital around the best ideas, but when your investment phase is driven by the desire to get ready for the next fundraising, rather than fundamentally your belief that these are the right companies and the right valuation levels, then you have to start being careful," says Inkef's Mr Bulthuis. Inkef has the Dutch pension fund, ADB, as its sole LP.

Carolyn Ng from Vertex Ventures agrees.

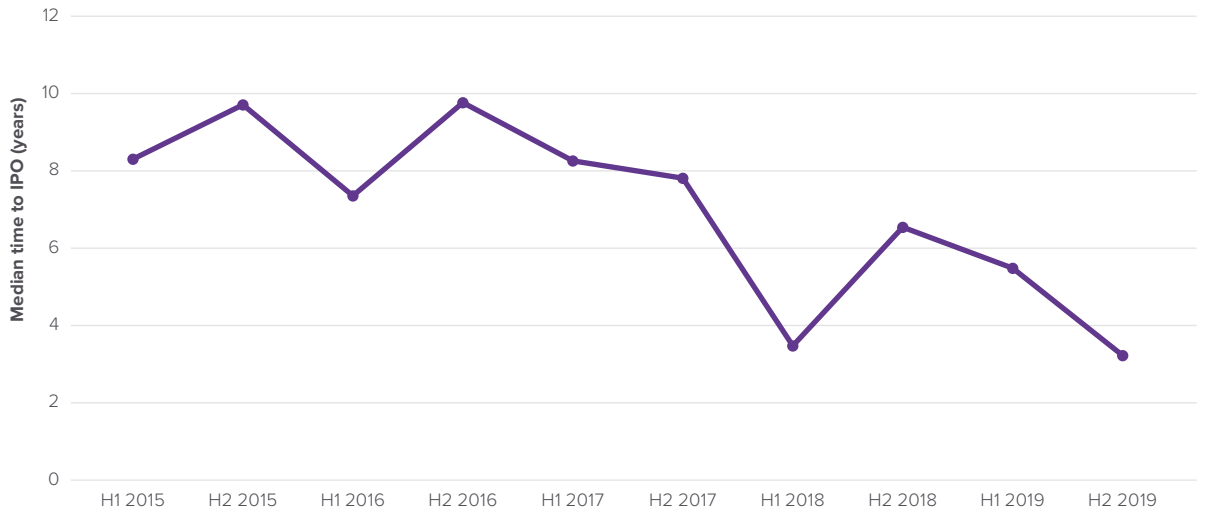
"It's hard to exert investor discipline when there is so much capital to deploy. And historical data suggests that when fund sizes increase, it's harder to maintain or improve the returns generated from smaller funds," she says.

Median time to M&A from established date

Source: EvaluatePharma® November 2019



Median time to IPO from established date



Note: Venture-backed companies only.

As well as monitoring the re-financing of highly valued start-ups next year, venture firms will be watching the exit environment. Considerable success in both floating and selling their portfolio companies over the past few years has helped retain LP's backing, and none will want to see punchy valuations hold back deals.

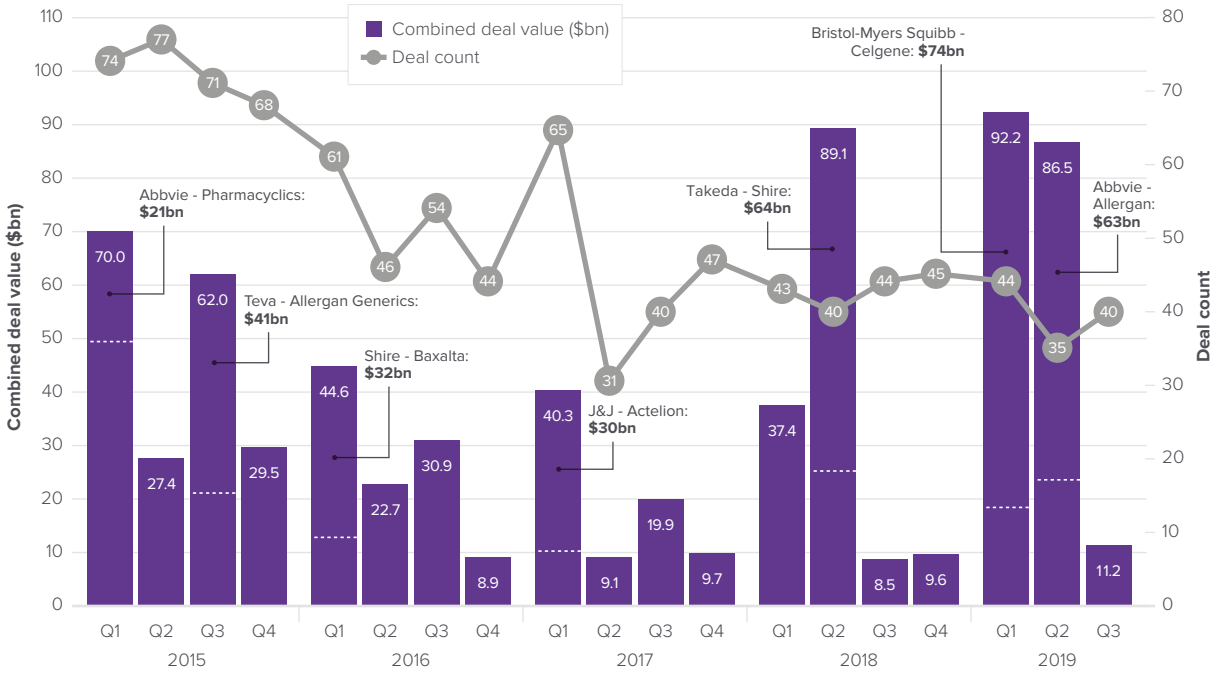
There are few indications that this has been happening in 2019: the charts below show that the industry will be heading into next year buoyed by some favourable statistics.

A clean takeout remains the favoured exit for venture investors, and the first analysis suggests that these sorts of deals have been happening quicker since mid-2018. This was constructed using companies' disclosed established dates rather than first fundraising; the growing trend for operating in "stealth mode" in the early months or years means that the date of first fundraising is not always available.

Time to IPO has also been falling – a function of welcoming public markets – though this is more likely to reverse next year. Overall, funds are likely to read these charts as endorsements of their investment approaches; and with no lack of willing buyers among the sector's larger drug developers, interest from potential acquirers is not expected to wane.

Pharma and biotech M&A transactions announced each quarter

Source: EvaluatePharma® November 2019



The huge takeovers of Celgene and Allergan in 2019 and Shire the year before has produced some record-breaking M&A years for the biopharma sector in terms of the amount of capital deployed. On deal volume the story has been slightly different.

An uptick in M&A is typically predicted at the beginning of any new year, though the graph above suggests that this Christmas wish – on the part of that bankers and advisers at least – has failed to materialise in recent years. The volume of acquisitions happening has stayed stubbornly flat since 2016.

Again, this analysis only concerns the deal making activity of drug developers – it excludes sectors like medtech and diagnostics, for example. It does however encompass all forms of acquisition, such as buyouts of business units or single product purchases.

The availability of capital, both public and private, has kept options open for young companies in recent years, so it is not surprising that the deal volumes have stayed flat. The state of the equity markets next year will help determine whether any power shifts back towards the buyers.

Some believe that the cash-rich bigger beasts of the sector, several of which are under pressure to find new sources of growth, will be forced to act next year. Gilead is frequently named as a group that needs to buy new growth.

Steven Slaughter, managing director of Manulife Investment Management, told the Jefferies Healthcare Conference in November that he sees the potential for hostile bids to happen next year.

“There are enough interesting targets where management teams don’t want to sell, but in the large-cap world balance sheets are becoming so large they just have to deploy some capital,” he said.

Another issue that potential buyers will have to contend with next year is an increasingly watchful US antitrust watchdog. The FTC's demands likely delayed the Celgene takeover and more notoriously has prevented Roche from completing its purchase of Spark Therapeutics. Should this deal collapse, regulatory considerations will have to move up the agenda for companies and investors alike.

Still, the larger takeovers of 2019 that did happen – The Medicines Company for $9.7bn, Array Biopharma for $11.4bn and Loxo Oncology for $8bn – show that when big pharma wants an asset, the price seems almost immaterial.

This also applies to R&D-stage takeouts: Novartis paid $8.7bn for Avexis while Eli Lilly spent $1.6bn on Armo Biosciences, both one-product companies. If the Spark deal closes, Roche is on the hook for $4.8bn.

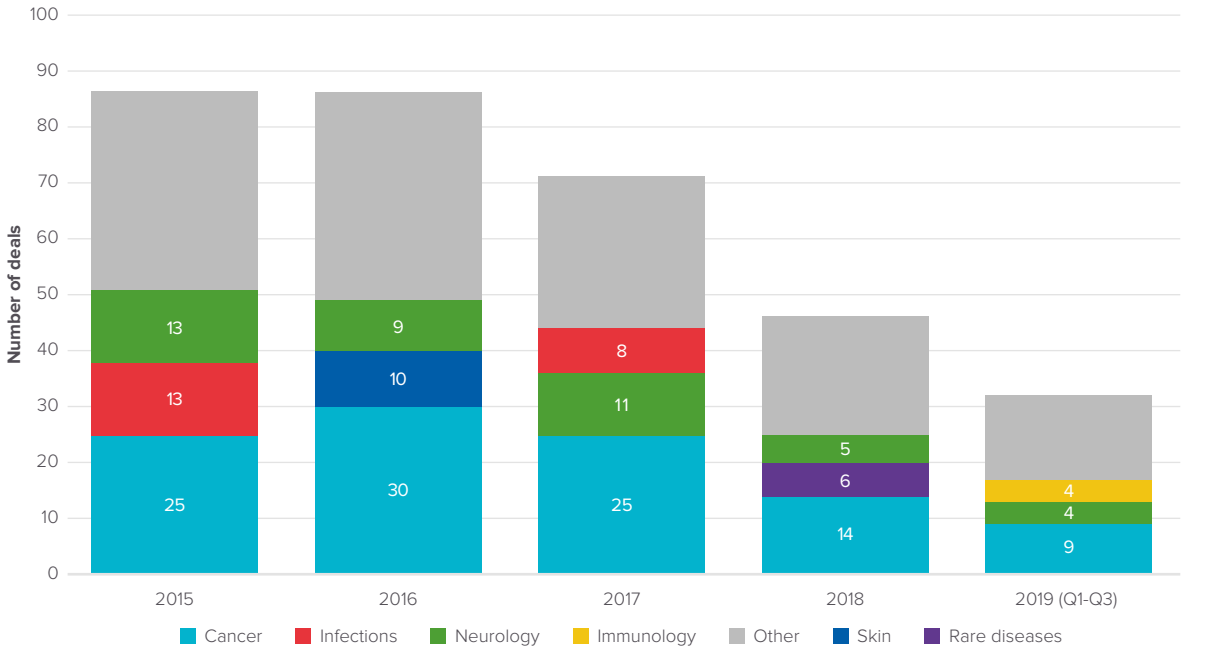
"The first consideration of [big buyers] is to get the product," says Inkef's Mr Bulthuis. "In most therapeutic areas there's enough competition to make that drive the price, rather than the underlying valuation."

Still, it seems highly likely that the use of structured acquisitions will increase next year. Upfront fees and milestone payments in takeouts of earlier-stage companies are increasingly being employed by buyers to mitigate the testing valuations that some of these start-ups have achieved.

"A few years ago pharma started shying away from straight acquisitions [of earlier-stage companies]," says Hakan Goker, director at M Ventures, the venture arm of Merck KGaA. "There is a glass ceiling everywhere and you have to make sure you are below that ceiling if you want to maintain a multiple on your investors' money."

Company takeouts by therapeutic focus of most advanced asset

Source: EvaluatePharma® November 2019



The final issue to consider here is where all this money will be flowing therapeutically. There will be a confluence of venture funds, public investors and pharma buyers around the hottest areas, though the smart money will also be trying to work out where the field's gaze might move next.

The chart above looks at takeouts of research-stage drug developers, grouped by the target's primary focus. The drop-off in these deals in the wake of the 2015-2016 boom is apparent, and while the data for 2019 is not yet complete many will be hoping that deal volume does not dip any further.

This issue aside, the analysis highlights oncology's dominance one again. With the caveat that numbers are small here, a trend away from this field can perhaps be detected. Intense competition, and testing valuations, has been prompting investors to looks elsewhere

"We are starting to see increases in investment into other areas, like immunology, neurodegeneration, women's health," says M Venture's Mr Goker, who adds that valuation is only one reason. "A lot of funds are over exposed to certain therapeutic areas, and that becomes hard to justify to LPs."

Neurology too has remained a consistent interest; should Biogen succeed in getting aducanumab to market, this could well drive further interest into the Alzheimer's space.

However it also seems that some of the most over-invested spaces could disappoint next year. Nash, where much work remains early-stage and tangible progress could fail to emerge, is one example. Immuno-oncology, where the hundreds of combination studies being conducted is making it hard to peel out what will work best, is another, says M Venture's Mr Goker.

The most red flags are being raised over cell therapies, however, a space where some of biopharma's pluckiest valuations can be found. A huge amount of money is still being invested here, driven by differentiations in technology – the use of T cells or NK cells, for example. But most companies are still working with the same targets, and evidence of these various approaches' relative advantages remains a long way off, says Inkef's Mr Bulthuis.

"In this area you will not see meaningful data unless you get into a serious clinical trial. I find it very hard as a VC to justify investing in that." He says the cell therapy space now feels like "a big company's game".

The capital needs of advanced fields like cell and gene therapies do still need to be determined, says Vertex Venture's Ms Ng. "We are excited about those areas, but the question is whether you can exist as a small early-stage company, or do you need a big build-out at the get go?".

This seems to suggest that backers of highly valued cell therapy plays will be required to double down on their investments next year, and beyond.

One area that is widely expected to stay red hot is targeted oncology. "These approaches are not going out of fashion anytime soon," says Ms Ng.

The challenge for companies and investors that want to remain active in these areas is finding niches that have not been over-invested. In oncology, that is becoming ever harder.

Biopharma's phase II and III pipeline, by therapy area and success scoring Source: EvaluatePharma® Vision November 2019

The chart above shows what a few years of huge investment into one therapy area can do. This maps out all the phase II and III novel molecules in development, judged to have a chance of reaching the market next year in a particular indication. This is derived from EvaluatePharma Vision's Product Specific PTRS module, which calculates an individual project's probability of regulatory and technical success. This combines machine learning with traditional analytics, and incorporates over 50 attributes that have been identified as predictive of the success or failure of clinical development.

Cancer projects clearly dominate the sector's mid and late-stage pipeline. This analysis also points to therapy areas in which there is a good chance of several new products reaching the market: as well an oncology, cardiovascular disease has a good number of products in advanced stages.

Of course these top-level looks are interesting only up to a point. The following charts drill down to the broader indication level, to pinpoint areas of over- and underinvestment. These analyses plot the number of novel molecules in development against the number on the market, with the first taking a 30,000 foot view.

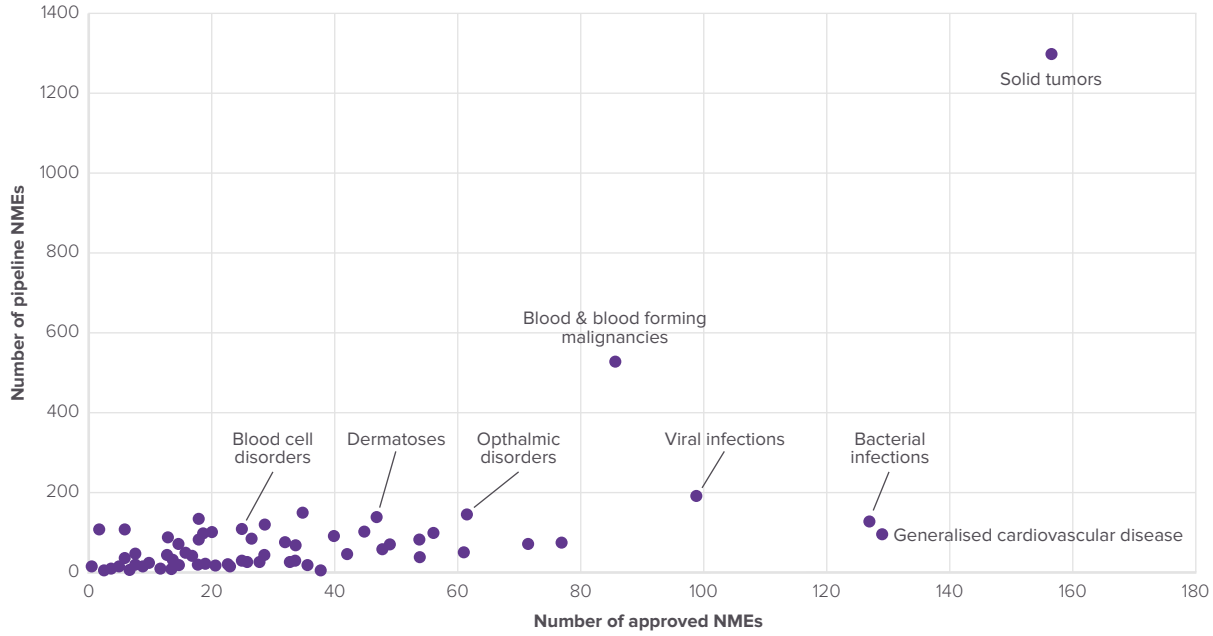
Oncology, specifically solid tumours, is once again in a different league, though the numerous organs that cancer can affect make this a very big therapeutic area. It should be remembered that this chart does not take account of epidemiology.

The attention that blood cancers have received is also apparent, and the ratio between pipeline and marketed assets is actually pretty similar to the solid tumour effort. Not so cardiovascular disease, a setting that is mostly comprised of hypertension drugs and cholesterol or other lipid lowers. The huge number of drugs on the market in this field points to the challenges in this space for new entrants, as developers of the anti-PCSK9 antibodies found.

On the flip side, eye disorders have a big pipeline of novel mechanisms coming through, as do dermatoses, a group which includes psoriasis and eczema. These looks like fields which will only get more competitive.

An overview of indication density

Source: EvaluatePharma® November 2019



The final analysis here zooms into the bottom left hand corner of the above chart, to find the indications where few useful mechanisms have been found. Again, incidence is not factored in here, but this area of the chart does not only feature small disease areas.

Hepatic disorders, for example, include Nash, a potentially huge area. Dementia, which afflicts millions and on which the industry has been working for decades with very little success, is here too. Stroke has seen a few more drugs reach the market but remains poorly served; still, this remains a field for the bravest of developers.

But this analysis also throws up autoimmune disorders, a rare disease space that has seen an explosion of interest in recent years. This is where Alexion has found huge success with Soliris, and therapies for other complement-mediated conditions are chasing that same model.

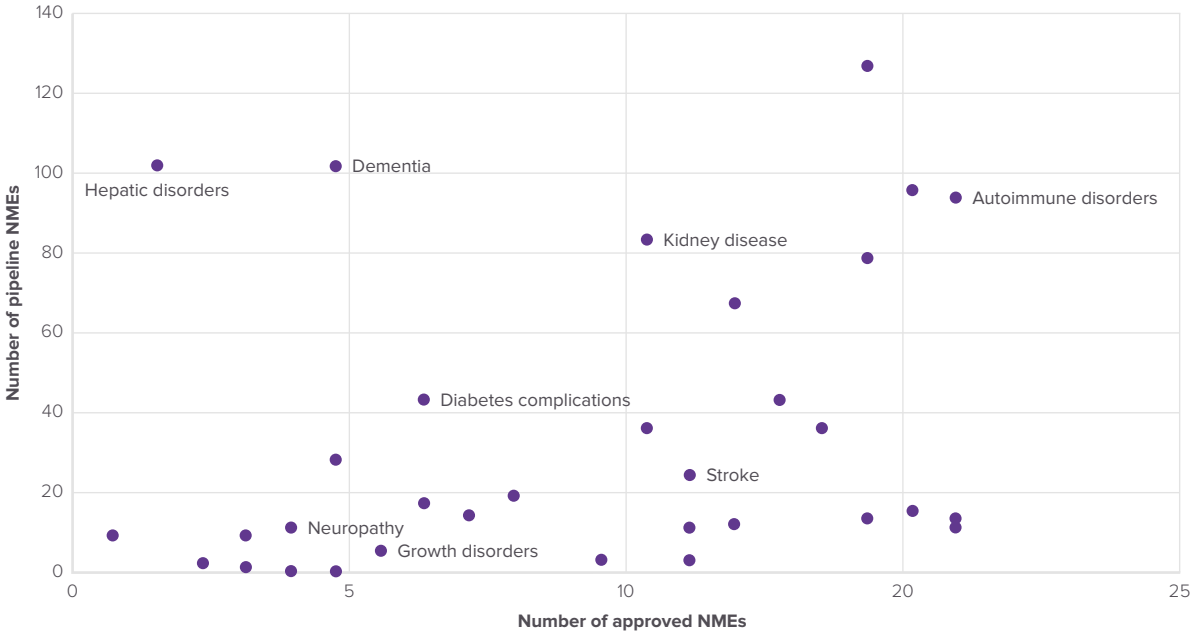
A lot of the smart money is still fishing for opportunities in this area of the chart: disease areas with inadequate standards of care and where big steps forward can be made, preferably delivered by a novel technology or mechanism. That many of these opportunities are rare conditions is all the better, the thinking goes, as this often means augmented regulatory pathways and greater pricing power.

But pushback against the high prices that industry wants to charge for innovation is only growing stronger. This fact must not be forgotten as investors or acquirers seek out and attempt to put a value on the next big thing.

“Most early-stage investors don’t really take into account the pricing of a drug,” says Vertex Ventures’ Ms Ng. “But we need to seriously reconsider the way we are going to price our therapies, under increasing political pressure. We need to consider how this is going to affect the way we invest, and how we think about the valuation of companies.”

Finding the space: low activity indications

Source: EvaluatePharma® November 2019



Onwards and upwards?

Participants in any sector will always be on the lookout for cracks and weak spots, and several have been highlighted in this report. And while certain concerns will persist next year, many see reason for optimism.

“We’re looking at it all very positively, from the early-stage investor angle,” says M Venture’s Mr Goker. “We remain very excited about the science that we see, there are a lot of investors that are very highly active in creating and seeding companies and have enough cash to get them to later stages of development.”

Even in Europe, which has often found itself in the shadow of the US, venture capitalists are optimistic.

“In general, it’s a great market,” says Inkef’s Mr Bulthuis. “For many years companies have been complaining about the difficulties in Europe compared to the US, the dripfeeding of capital, but a lot of that has gone.”

And for now, the public markets are rewarding progress with strong share price appreciation. The market rally that started in early October is showing no sign of fading at time of writing, in early December, and some investors believe it is being driven by a real uptick in optimism.

“There has been good news from all angles lately: clinical, M&A, and political,” says Brad Loncar, a private investor. “A couple of months ago Elizabeth Warren, who would be very punitive to the industry, had strong momentum and now that seems to be fizzling somewhat.”

Others are more sceptical, and believe much of the momentum is being driven by funds that were taken by surprise by the sudden uptick, after a dismal summer. “The indices have run and most funds need to play catch up so are going after everything without much due diligence,” says one biotech investor, who prefers not to be named.

The burning question is whether the rally will continue into next year and whether, unlike 2019, any upturn will be more widely felt.

“Performance has been quite narrow this year, the tide has not lifted all boats,” says Dan Mahony of Polar Capital. “There hasn’t been a lot of risk appetite. I think that’s beginning to change but it’s a fickle thing – some small caps are recovering but I don’t know whether it will persist into next year.”

Larger biotechnology companies have been a big area of disappointment, and the likes of Gilead, Biogen and Amgen are all seen as suffering from similar problems: aging franchises and thin pipelines. A broad sector recovery will be hard while the big beasts of the industry remain out of favour with investors.

Relative growth of NBI and S&P 500

Source: EvaluatePharma® November 2019

Others are predicting a more sudden end to this rally: Julia Skripka-Serry, a private investor and former biotech fund manager, believes a market correction is inevitable. She points to examples like Karuna and Allakos, both of which boast now multi-billion dollar valuations on the back of ostensibly positive but still early-stage data.

“Who doesn’t think that’s insane? Some of these valuations are not sustainable,” she says.

Events in the US could easily provide the trigger. While the chance of near-term, substantive changes to America’s healthcare system seem as far away as ever, the biopharma sector’s pricing practise are under intense scrutiny. That is not going to let up next year, in the US or elsewhere, and in fact will only intensify as drug developers, and investors, increasingly turn their attention towards the sort of therapies that can more easily command a high price.

Partly this search for the next big thing is driven by the price-limiting efforts of payers, who over the past decade have successfully put a lid on prices in areas from diabetes to respiratory drugs.

“Drug pricing in general is flat or very low single digits, so that forces you to look for companies with pipeline and innovation, because those large-base businesses are not going to grow at the same rate as they have been,” Artisan’s Mr Kantor told the Jefferies Healthcare Conference.

Next year will be full of deals to access that innovation. It will also be filled with discussions about how society can afford to pay for the real clinical and technological breakthroughs that are coming to market at an ever-faster pace.

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