Vantage 2019 Preview

Amy Brown, Jonathan Gardner and Edwin Elmhirst – December 2018

Vantage

Evaluate

Foreword

Investors are nervous. After months of plenty, biotech has come off the boil.

Biopharma is heading into 2019 on very shaky footing and investors take little comfort from the fact the turmoil has largely been triggered by fears from beyond the sector. It is hard to predict how much further markets might fall, though most agree that a more volatile year is approaching.

The situation is not completely dire, however. For example, few are predicting that 2019 will see a substantial retrenchment in venture funding, though firms are expected to start investing more prudently. And, while the public markets are showing a diminishing appetite for new issues, the IPO window is far from shut. Substantial sums are still being raised by some.

So, while those looking for funds might have to work a bit harder next year, financing options are not expected to completely dry up. This report attempts to identify swing factors that could improve or damage sentiment, and shift that perception over the year.

Excitement about new technologies that are delivering real breakthroughs remains palpable, but several are in launch phase or approaching commercialisation. The harsh realities of the market are already being felt by some, and further struggles could provide investors with another reason to retreat.

Hopes for the immuno-oncology space were significantly reined in after the spectacular failure of Incyte's epacadostat in March, and while expectations are low for substantial progress, a surprise win from another IO combo would lift spirits.

Huge optimism prevails around cell therapy and related techniques, however, and it is in this realm that valuations remain testing. The extent to which companies with unproven technologies can maintain their billion-dollar-plus valuations next year will signal the depths of any downturn; these include Allogene, which is working on allogeneic CAR-T therapies, or those pursuing gene editing like Crispr Therapeutics.

The fact that many of these cash-hungry firms are valued more highly than those with products on the market suggests that the sector is some way from the bottom. A serious setback in one of these rock-star segments, which also includes gene therapy and rare diseases, would be very destabilising.

On the plus side, the US FDA looks like it will remain one of biopharma's best friends. The influential regulator's willingness to speed novel therapies to market on controversially slim evidence has emboldened companies and investors to take ever-greater risks. Perhaps herein lies another red flag. Should the agency alter its stance, the sector would have a real reason for an existential crisis.

The implications of a shift in power in the US are also something to watch for next year. Rhetoric around drug prices in the US could well ramp up again as re-invigorated Democrats attempt to make their mark on healthcare policy. What they can realistically achieve remains to be seen.

Overall, biopharma is not expected to generate a year of record-breaking numbers in 2019. But neither is a serious retrenchment widely expected, at this stage at least. However, with valuations in many areas still looking divorced from progress being made on the ground, there is a good chance that things will have to get worse before they can get better again.

Report authors | Amy Brown, Jonathan Gardner and Edwin Elmhirst

Written: November 2018. All data correct as of November 15, 2018.

Money, Markets and M&A

Anyone hoping that 2018 would be declared another golden year for biotech was painfully disabused in October, when markets started to tumble.

The Nasdaq biotechnology index has been sinking since late summer. Unless a recovery happens in the final weeks of 2018 this closely-watched index will end down on the year, heightening fears that this current retrenchment has some way to go.

The trigger for this change in sentiment was not biotech-specific. Fingers have been pointed at the prospect of rising US interest rates and President Trump's trade wars. High-risk sectors like biotech never fare well in volatile times, and it looks like jittery financial markets have finally called time on the latest biotech bull run.

"We're nine years into a bull market, the longest bull market on record, and the markets needed an excuse to correct," says Vikram Khanna, co-founder of Ikarian Capital, a biotech-focused hedge fund "Everybody is up in arms when the market is going down but no one bats an eye when it's going up, and it has been going up indiscriminately for a long time, including in biotech."

Feeling the pain – the sell-off begins

15 November 2018

Mr Khanna believes that a more rational market should develop next year, albeit one marked by volatility. Many biotechs resorted to spinning data as positive in 2018, he says; in 2019 companies will have to demonstrate solid and unequivocal data to get rewarded with stock price appreciation

It is being widely predicted that conditions for earlier-stage drug companies will get tougher next year. Exactly how tough is the burning question.

“There’s a lot of money around still and optimism for certain areas, so from my point of view there are reasons to remain optimistic,” said Wilson Cheung, a private biotech investor. “Biotech will continue to be a highly volatile sector, so with the caveat that investors, generally speaking, begin to fret less over broad issues like rate hikes, tariffs, etc. biotech should do fine.”

Not everyone is as hopeful, however, particularly as the world’s larger drug makers are also facing headwinds. Big cap biotechs are battling persistent worries about their ability to replace ageing blockbusters, while the pressure to lower drug prices in the US is showing no signs of abating.

This latter issue is making it particularly hard to persuade more risk-averse generalist investors to put money into biotech stocks, something that to a lesser extent is true also of big pharma. Few expect this to change next year.

“The pharma industry is facing uncharacteristic headwinds that … haven’t existed historically. You’re seeing pricing pressure and access issues that are gaining in intensity,” David Lohman, founder and portfolio manager at Diag Capital Management, told the Jefferies Healthcare conference in November.

“You used to be able to have confidence in two to four-year projections, but now you don’t know what’s going to happen in six to eight months. It’s a really different environment.”

All of which makes for predictions of a rocky ride for biopharma next year, in the first half of the year at the very least. How the broader markets fare in the closing weeks of the year will be crucial to set the tone for 2019, as will the sector’s performance after the Ash medical meeting and going into the JP Morgan healthcare conference.

The former showcases the hottest prospects in haematology, a highly valued oncology subsector. Whilst the conference produced some well-received readouts nothing emerged to really set the sector on fire. Even the $5bn takeout of Tesaro by Glaxosmithkline, announced at the same time, only managed to lift spirits for a day.

Meanwhile, in San Francisco the healthcare sector’s highest-profile banking event of the year is associated with deal making. But if eye-catching news fails to materialise from the typically packed-out sessions, or if it’s too easy to walk down the corridors at the breaks, then the year could start on a very downbeat tone, says Andy Smith, a research analyst for Edison Investment Research.

“The best-case scenario for next year is that we are flat. But it looks like we could be heading for a couple of years in the wilderness,” he says. “Hats off to companies that have raised money in the last year or so because it feels like it’s going to get much more difficult for a while.”

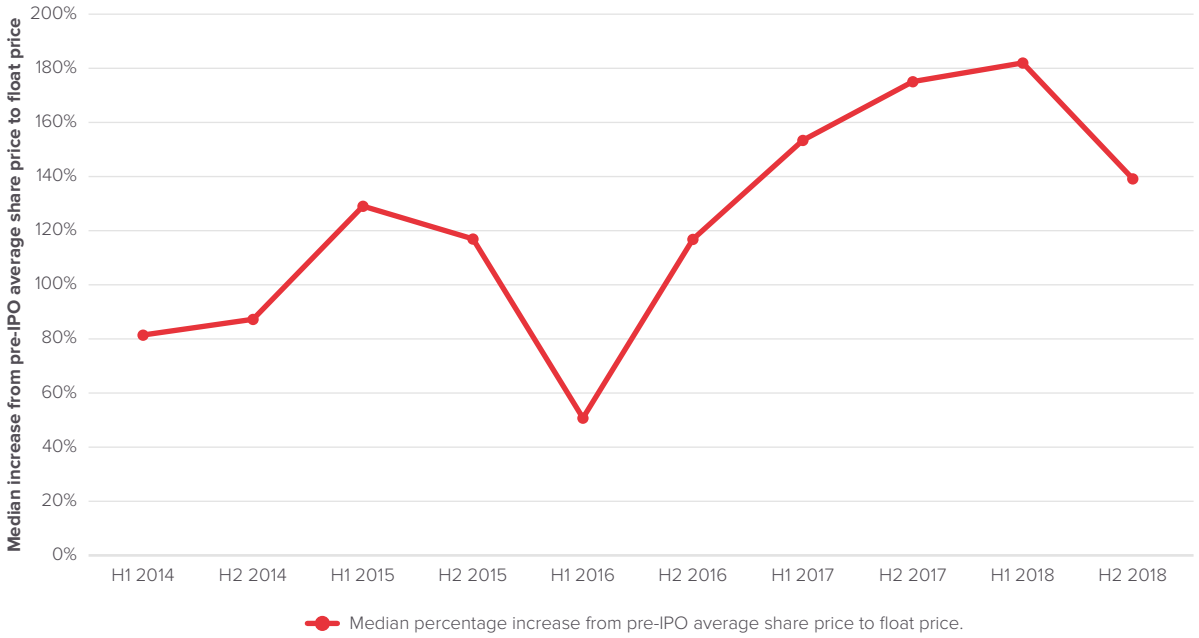
The last couple of months saw a handful of drug developers halt flotation plans, showing that life has already changed for those hoping to tap the capital markets. The median uplift, or “bump” in valuation that investors receive when companies move from private to public hands has been in decline since the middle of 2018, EvaluatePharma data show.

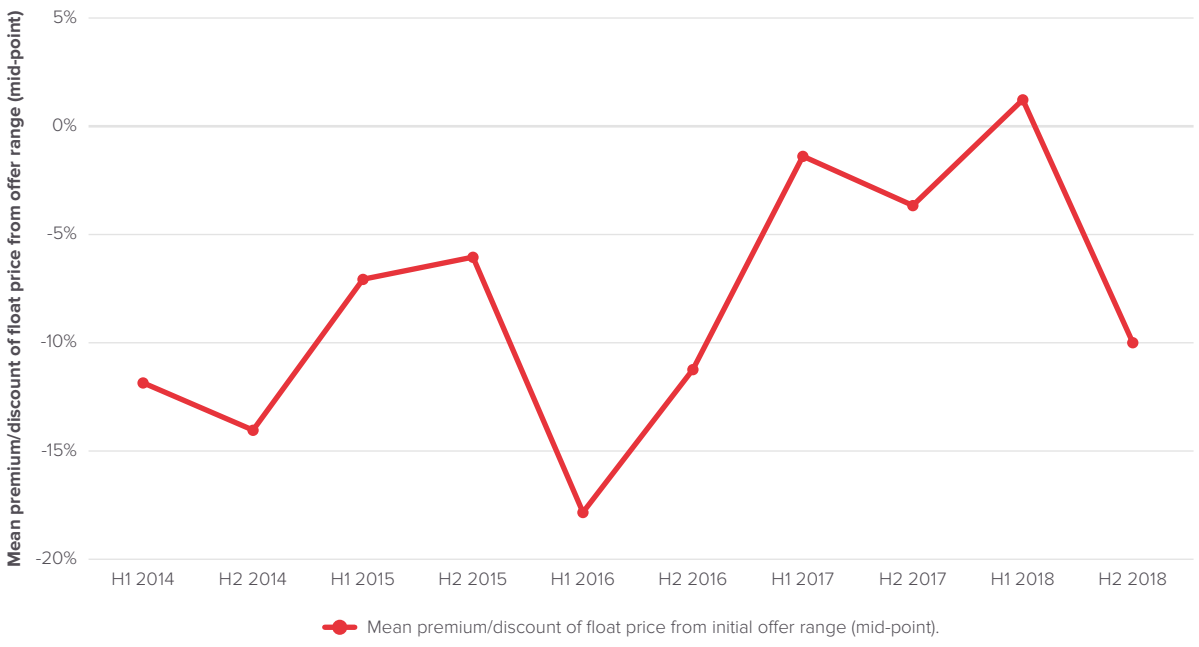
The chart below shows how valuation bumps, reflecting the new public value of a stock versus the average price at which private investors had bought it, have been tempered since hitting a peak in early 2018. This analysis only looks at listings in the US, and was calculated using the average pre-IPO share price, a figure provided in most S-1 documents, and the final flotation price.

Backing up this finding is the second analysis, looking at the “haircuts” required to get IPOs away, which shows how final float prices differ from the initially proposed range. Discounts were virtually unheard of earlier this year, and this graph supports the notion that it is becoming harder to part investors with their money.

Bumps and haircuts – tracking investor appetite for IPOs

Source: EvaluatePharma® 15 November 2018





The data for the second half of 2018 are not complete yet, but it seems like bankers are unable to secure the uplifts they enjoyed earlier this year. Of course this must be kept in perspective, and this graph paints a far from disastrous image – a 140% median bump is better than the 100% that was being achieved two years ago.

Still, there is a good chance that this picture will deteriorate further next year.

“If you are a high-quality company looking to raise capital you can probably still squeak by. But a market downturn like this creates an extra layer of hesitancy, and for poorer-quality companies it will be harder,” says Salim Syed, head of biotechnology equity research at Mizuho.

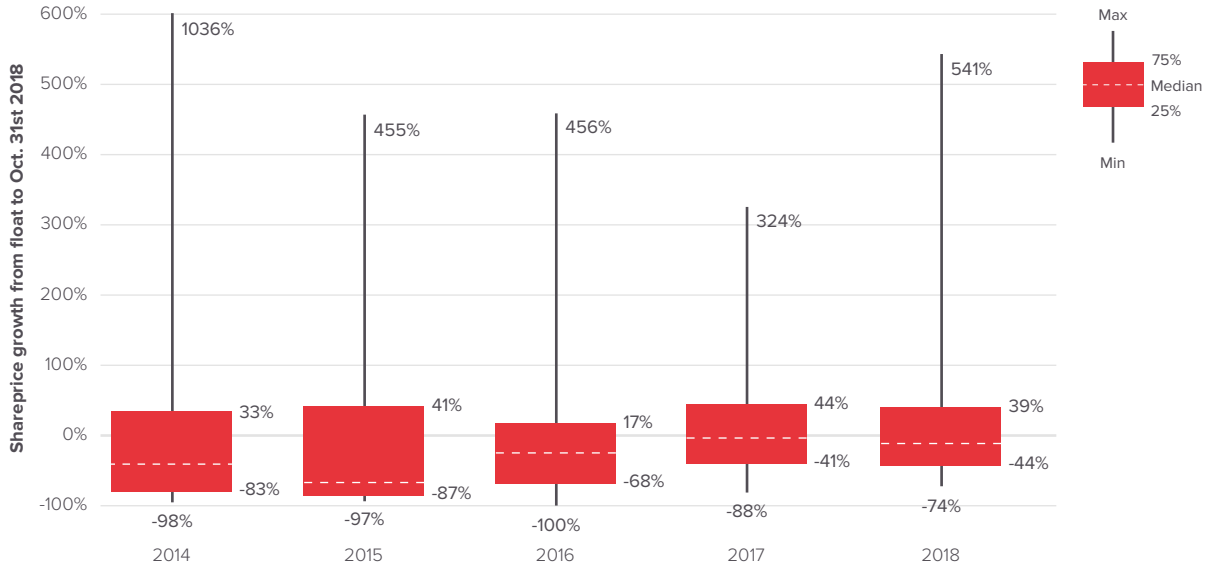
Broader market trends will play a big role in shaping the biotech IPO market next year, but so will the performance of more recent entrants. And, encouragingly, the graph below shows that 2018’s flotations are performing largely in-line with other years.

But the IPO window was so wide open in early 2018 that very early-stage companies, even some that had yet to move into the clinic, were able to float. Given that rates of failure are much higher at earlier stages of drug development, investors could yet find themselves disappointed.

“I have not been a fan of the IPO market this year; the quality has been particularly low. Companies have been going way too early, and that worries me a bit,” says Brad Loncar, a private biotech investor and founder of the Loncar Cancer Immunotherapy ETF. “I personally don’t think you should be on the market unless you have some sort of proof of concept.”

Performance of US biopharma IPOs

Source: EvaluatePharma® 15 November 2018



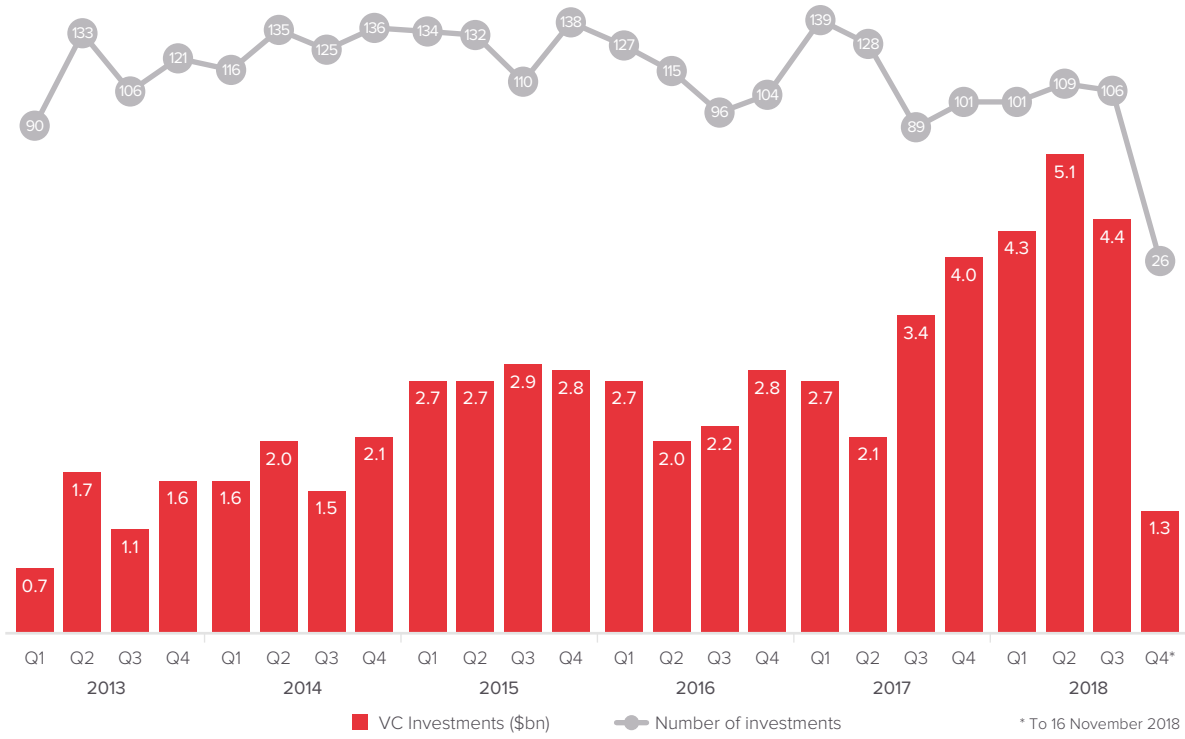
Pricey new issues from the class of 2018 that have yet to prove themselves include Allogene and Rubius, both of which will be watched closely next year. But the biggest test of the market’s appetite for high-risk propositions is surely Moderna. With little in the way of firm evidence to support the company’s mRNA platform, its performance in the coming years could have a big influence on how investors view new prospects emerging from the biotech sector.

If any further evidence is needed that bankers are growing cautious about the future, the decision to float Moderna with 10 banks underwriting the offering is surely it. It is not inconceivable that the company was advised to go for it while it could.

A 20% share price drop on Moderna's first day of trading – erasing $1.5bn of market capitalisation – is surely a sign that investors are already less willing to bet on longer-term promises.

Global quarterly biopharma venture investments

Source: EvaluatePharma® 15 November 2018



Much of the latest IPO boom was fuelled by venture capital firms, themselves flush with cash, pushing their portfolio companies on to the public markets while they had the chance.

The biotech bubble of 2015 was a hugely successful period for these private investors. Returns were boosted by a big uptick in takeouts at ever-higher valuations, while the IPO window opened for the first time in several years. As a result, firms in both the US and Europe were able to amass substantial new funds, which they have spent the past 18 months re-investing.

However, venture firms are also anticipating something of a slowdown next year.

"I wouldn't be surprised to see fewer IPOs next year, and the market might adjust somewhat, but I think it will continue to be a strong market. You don't need record numbers for it to be a strong market," says Thilo Schroeder, partner at Nextech Invest, a venture firm that focuses on oncology.

Records were certainly set by the venture world in 2018. The third quarter alone saw $5.1bn invested in start-up drug developers, according to EvaluatePharma, as firms increasingly chose to support their portfolio companies with ever larger pots of money.

This phenomenon of “shareholder recruitment” – the formation of broad syndicates capable of amassing huge amounts of money for individual start-ups – is showing no sign of going out of fashion in 2019.

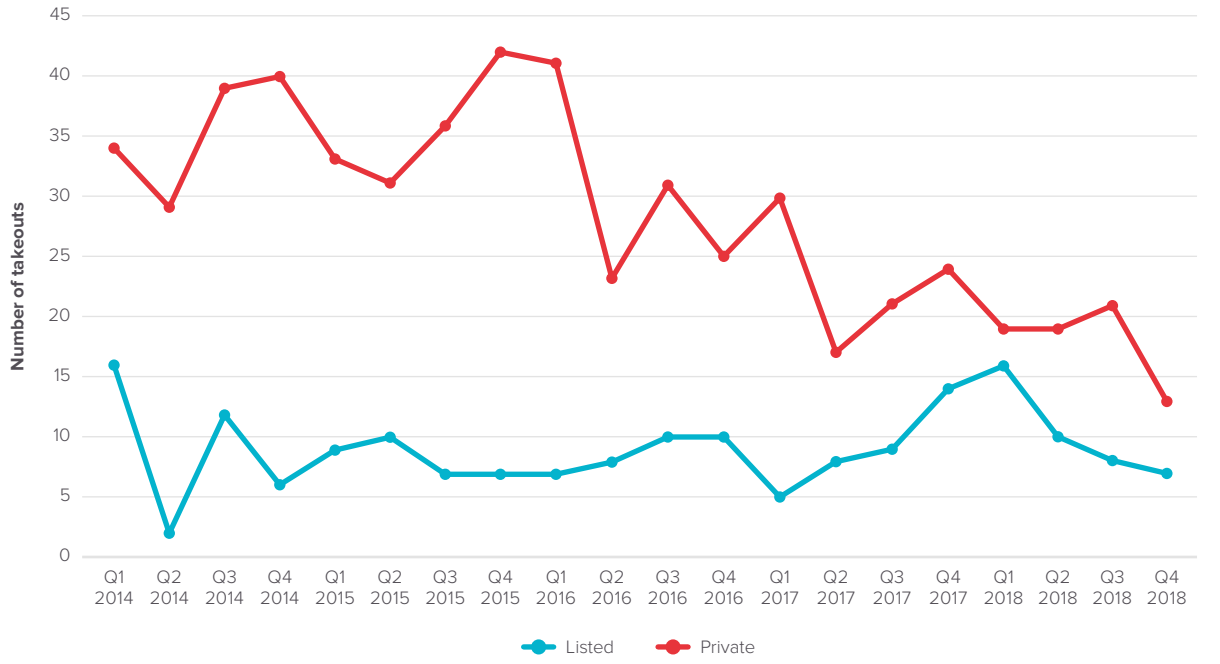
This trend is occurring partly because investors believe that it is important to give platform companies the means to make several shots on goal, Mr Schroeder says. And a bottleneck in talent means that strong balance sheets are needed to attract experienced management teams, another issue that will persist next year.

“There won’t be another batch of chief medical officers with 20 years of experience appearing overnight,” he adds.

However, financings dropped in the third quarter, and a peek at the fourth-quarter numbers hints at another decline. Fears of a protracted market retrenchment will be prompting a more prudent approach, but perhaps these funds are also feeling the lull in M&A over the past 18 months or so, and raising the bar to investment decisions.

Public vs private biopharma takeouts

Source: EvaluatePharma® 15 November 2018



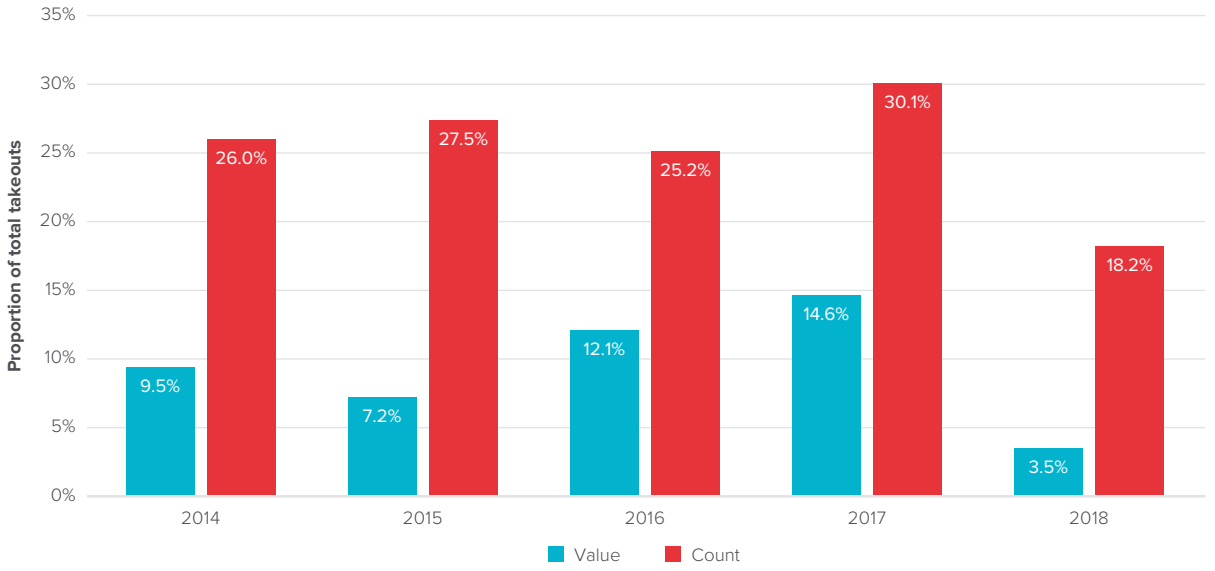
Buyouts remain the most desirable exit route for venture investors, and the graph above shows how takeouts of private companies have plunged since the 2015 bubble.

Equity investors have vocally lamented the lack of takeover activity over the past couple of years, but the analysis above shows that, in terms of the volume of deals being struck, buyouts of public companies have actually remained pretty static.

It is the private buy-outs that have plunged, volume-wise, and a closer look at takeouts of VC-backed companies shows why these firms should be worried heading into 2019. After accounting for at least a quarter of all deals for the past four years, interest in these portfolio companies seems to have waned.

Private VC-backed takeouts as a proportion of total M&A

Source: EvaluatePharma® 15 November 2018



A further dig into the data shows how the number and value of VC-backed deals has fallen this year. After persuading their own investors to part with significant amounts of money over the past couple of years, these are not the sorts of exit trends that venture firms will want to continue going into 2019.

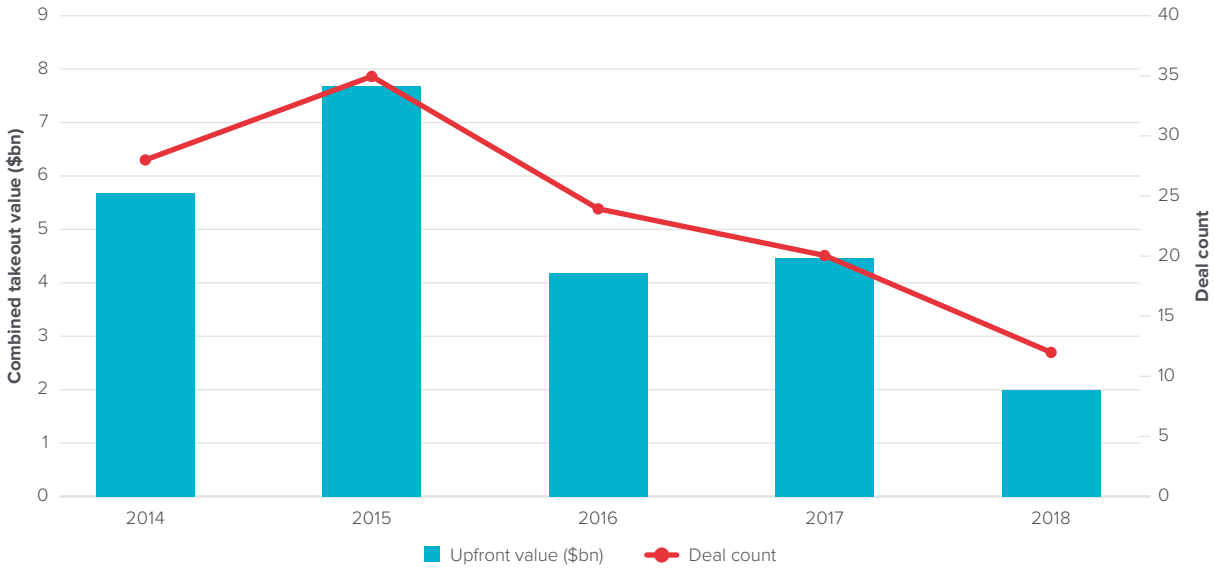
Perhaps biotech's prowess at attracting funds – from public and private sources – has made the sector a victim of its own success. Huge amounts of money have been pumped into red-hot areas like immuno-oncology and cell therapy, to the extent that over-investment has erased scarcity value, some believe.

"When people say there's a lot of innovation going on, the reality is that there are a lot of companies pushing the same frontiers and there's a lot of competition in niche indications. Most initiatives disappoint – look at the IO combos. And when something does work you need to have real scarcity value for someone to make a big punt on it," says Ikarian's Mr Khanna.

The BCMA space is a prime example. The multiple myeloma-relevant antigen is being investigated by at least eight closely-followed CAR-T projects, while others including Glaxosmithkline have antibody-drug conjugate approaches. Bluebird is a key player which has long been considered a takeout target; over-investment in this space could arguably be blamed for deterring interested parties.

Tracking the venture-backed buyouts

Source: EvaluatePharma® 15 November 2018



Another reason cited for the quiet M&A scene is the very poor track record of recent takeovers. Many business development teams have been burned, and acquisitive management teams seem to have been persuaded that no deal is better than a poor deal.

Mr Khanna believes that Intermune, Medarex and Pharmasset were the only truly profitable acquisitions of recent times, while other investors readily point to poor choices.

“Biomarin went for Prosensa, and that blew up. Alexion bought Synageva, which set the company years back. Gilead and Kite remains to be determined. Sales are OK but nowhere near exceptional and overall expectations [for CAR-T] have been dialled down,” says Mr Cheung.

Resetting valuations could be the trigger for M&A next year, particularly as companies that have been forced to launch products alone start to live – or die – by revenue targets. Slow starts for novel technologies like CAR-T and Spark’s gene therapy have followed disappointing launches from companies like the Parp inhibitor players Clovis and Tesaro, all of which have been punished by the stock market.

“There haven’t been a lot of good drug launches lately, other than the PD-1s. For the first time in a long time there are some companies with assets that are actually approved that are priced at rock bottom prices,” says Mr Loncar.

With many large cap companies looking for new growth drivers, valuations could well start to look tempting – Glaxo’s move on Tesaro in December is a case in point. For more deals like this to happen potential sellers – and their investors – will need to forget the highs they were enjoying not that long ago.

Perhaps sentiment will also need to sour further, to force more management teams to seriously consider their options. But those running low on cash will be punished much more quickly in a market downturn. If predictions of further retrenchments come true, by the end of 2019 much of the power will have ebbed back towards buyers.

Regulation, innovation and politics

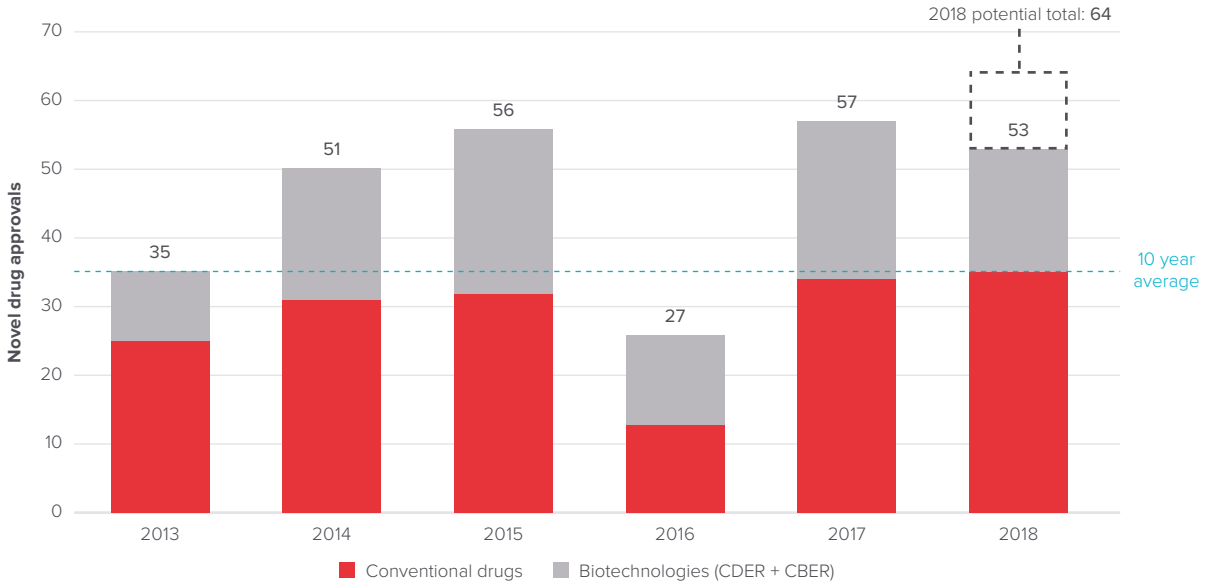
As biopharma heads into a down year the hunt is on for events that might lift investors' spirits – or deepen the gloom.

One thing that looks almost certain is a clement regulatory climate, in the US at least. Four out of the last five years have seen a much higher than average rate of positive outcomes from the FDA, versus the 10-year average. And the agency is on track to greenlight a record number of drugs in 2018.

According to the regulator's own statistics applications have also risen, but not at the same rate; although not much data have been seen for 2018 yet. This uptick presumably largely reflects the FDA's internal efforts to get new drugs to market more quickly and efficiently. Many believe that the jump in numbers is also a result of lower efficacy hurdles.

Annual FDA novel drug approvals

Source: fda.gov; EvaluatePharma® 15 November 2018



There are few signs of this friendly stance shifting next year. A high-profile safety scare could force regulators to start taking a harder look at applications, but these events are almost impossible to predict.

A longer-term question is what this trend means for the quality of the medicines reaching the market.

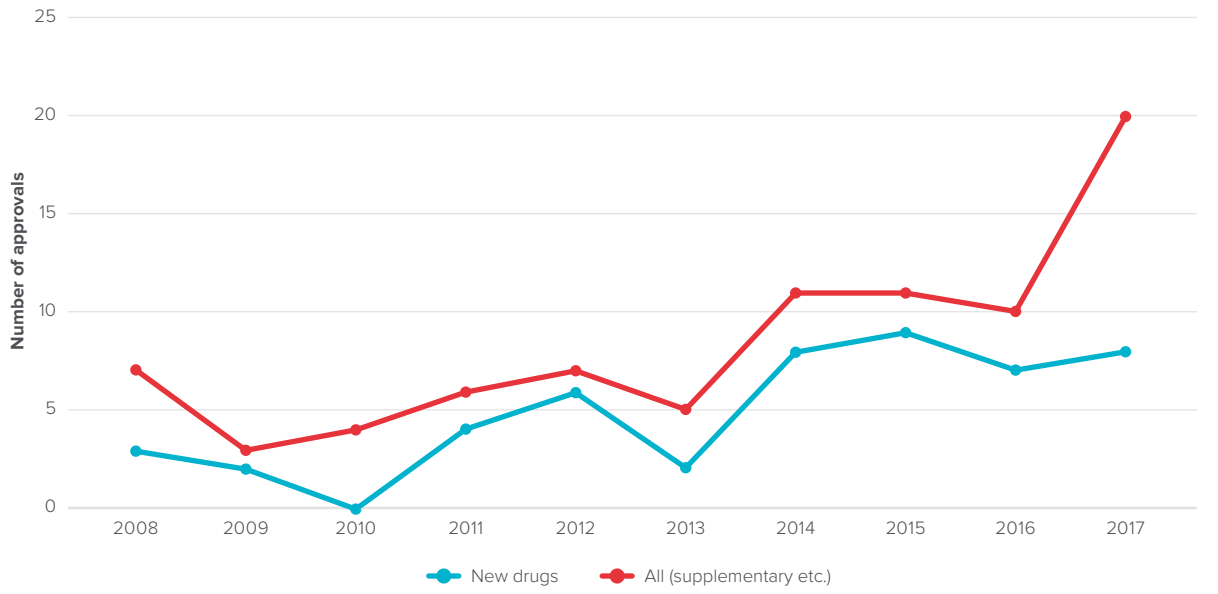
"A lot of this bull market has been driven by a super-permissive FDA. This has emboldened risk-taking by both biotech companies and investors," one investor, who preferred not to be named, told Vantage.

Perhaps growing payer pushback is another sign that the approval bar has been lowered. The FDA would argue that its primary function is to ensure that new medicines are safe, but some counter that this priority is being marginalised in the push to get new drugs to patients at an ever-faster pace.

It is undeniable that industry has unashamedly been using expedited pathways to get faster access to revenue streams, and the chart below shows how FDA approvals based on surrogate endpoints have been growing.

Accelerated approvals based on surrogate endpoints

Source: EvaluatePharma® 15 November 2018



A big jump in the numbers can be seen from 2012, when the breakthrough designation was created. The FDA has not released full statistics for 2018 yet, and intriguingly it looks like this tally will fall substantially this year. After a huge surge in 2017 this is possibly a phasing issue. It might also be no coincidence that 2018 has broadly been considered a disappointing year for oncology, a therapy area that has been a big source of accelerated approval applications in recent years.

Overall, the regulatory landscape looks to be a bright spot for biopharma next year. But if this surge in accelerated applications is a symptom of an industry that has been encouraged to push forward too quickly – in some cases to the detriment of both patients in terms of effectiveness and safety and investors in terms of weak commercial prospects – an era of regulatory permissiveness could hurt the sector over the longer term.

Smoke signals

The checkpoint inhibitor space, to which huge expectations are attached, should be watched closely next year for clues as to whether this lenient regulatory stance is shifting. In the past few months several anti-PD-(L)1 agents have failed to generate supportive evidence that could have converted accelerated approvals into full marketing licences.

Advanced urothelial carcinoma is a prime example, for which five checkpoint inhibitors have been tentatively approved. Several large trials in 2018 failed to establish a clear benefit, yet the FDA went only so far as issuing a safety alert. Follow-up gastric cancer studies have similarly disappointed, as have trials in small-cell lung cancer, yet checkpoint inhibitors remain on the market in these settings.

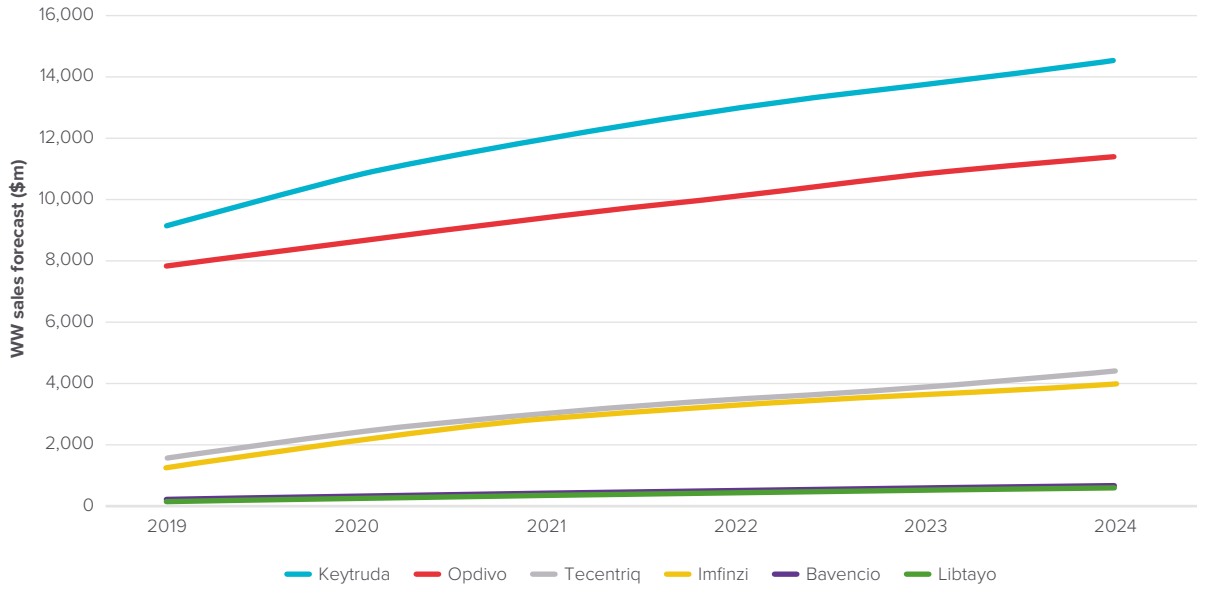
Should the FDA start revoking approvals, industry and investors would get a jolt. Over in Europe regulators have started to bare their teeth, which suggests that patience is wearing thin. The EMA demanded further evidence from both Bristol-Myers Squibb and Astrazeneca on their respective agents, Opdivo and Imfinzi, in lung cancer, to help determine the precise benefit that was being bestowed. The agency also refused to approve Bristol's Opdivo/Yervoy combination in renal cell carcinoma because the respective benefits of the two agents could not be deduced, something that the FDA was apparently happy to overlook.

Efforts to get high-need medicines to market faster have brought real benefits in many disease areas. But it is patients who bear the toxicities and false hope of inconsequential new medicines. It is not hard to unearth complaints that the US regulator has become too lax, while criticism for not chasing up confirmatory studies to support these fast-tracked approvals is growing louder.

Perhaps it will take less than expected for this sector tailwind to weaken.

Chasing checkpoints – sales forecasts for the PD-(L)1 class

Source: EvaluatePharma® 15 November 2018



Another insightful regulatory decision will come in May, when the FDA is due to rule on Bristol's bid to enter the first-line lung cancer space. The company is seeking approval for Opdivo plus Yervoy in patients with high tumour mutation burden. The relevance of this biomarker is far from certain, and this is a decision that could well test the agency's generosity.

A clue as to the outcome can be found in the FDA's verdict on Roche's triple combo of Tecentriq, Avastin and chemotherapy, which gained broad label approval in early December.

Still, neither of these agents is likely to make much of a dent in Merck & Co's hold on this lucrative market segment. The chart above shows just how successful the company has been with Keytruda here and elsewhere – Merck and its rivals' efforts to expand into new patient populations next year will be closely watched.

Important trial readouts from this class next year include Keynote-426, testing Keytruda plus chemo in first-line renal cell carcinoma, which could come in the first few months. There are also two first-line lung readouts from Bristol-Myers: the second part of Checkmate-227 is due in the first half and Checkmate-9LA later in the year.

Long-term guidance due from Bristol-Myers in January will also be influential in setting expectations here. Some expect Opdivo's sales growth to stall later next year, and that revenues could actually decline in 2020. Any admission along these lines from the company could cause further shifts in the outlook for this class.

With six agents now on the market the PD-(L)1 space is looking crowded. The potential for price competition to appear in the coming years is also hard to ignore.

Checkmate?

The huge success of the first wave of checkpoint inhibitors was largely responsible for driving expectations sky high for follow-on IO targets. However, a string of dismal data readouts in 2018 showed that improving on existing agents would be far from easy.

“This has been a very disappointing year for oncology. A lot of money has been invested in the combination approach but the epacadostat failure really deflated the entire category, and both Asco and Esmo [conferences] were very uninspiring,” Mr Loncar says. “There’s a lot of compelling research going on, though, so I’m confident it’s just a down year.”

Still, it is tough to find IO combinations to which high hopes are still being attached. Approaches including Sting agonism, Tim-3, Tigit and Lag-3 are now firmly on the “await more data” pile, though the cytokine space has retained more believers.

Even here, what looks to be waning efficacy for Nektar and Bristol’s IL-2 asset NKTR-214 has dented confidence. Interest could be reignited if Lilly’s IL-10 asset pegilodecakin generates strong mid-stage data. Two lung cancer trials are due to report in the second half: Cypress 1 is investigating what pegilodecakin can add to Keytruda in first-line non-small cell lung cancer patients with high PD-L1 expression (> 50%), while Cypress 2 is being carried out in a second-line setting in PD-(L)1-naive patients with a low PD-L1 expression (1-49%).

Oncolytic viruses are another IO combination partner to watch next year, in the wake of a string of deals over the technology. Results are due in December from a large phase III trial of Amgen’s Imlygic in combination with Keytruda in melanoma patients, and could help gauge what these projects are capable of.

Imlygic’s local delivery limits the potential of this particular readout, but data should start to emerge in 2019 on projects testing intravenously administered products. This includes a study of Oncolytics’ pelareorep – formerly known as Reolysin – in combination with Tecentriq, due mid-year. And Merck & Co could soon show how Cavatak, which it gained via its acquisition of Viralytics, fares systemically; three phase II trials are slated to generate data next year, in various tumour types.

Elsewhere in oncology, haematology promises to keep delivering next year. At Ash, for example, updates from companies including Immunogen, ADC Therapeutics and Regeneron showed that it is worth watching antibody-drug conjugates and bispecifics for progress in leukaemias and lymphomas next year.

“The data that’s been coming out of blood cancers has been amazing. I’ve seen a lot of encouraging things there. And I think next year is going to be a very exciting year for cell therapies,” Mr Loncar says.

Ash again underscored the potential here, with updates from several BCMA targeting CAR-T projects showing advances; the multiple myeloma-relevant antigen is seen as the next big thing after CD19.

Still, it will take a lot to reinvigorate hopes for the commercial prospects of CAR-T, which have been dialled back significantly this year in the wake of slower than expected uptake of Gilead’s Yescarta and Novartis’s Kymriah. Quarterly sales figures will continue to be scrutinised in 2019.

Somewhat surprisingly, these mediocre launches did not prevent hype building around experimental-stage cell therapies in 2018 – companies like Allogene and Autolus managed to float at substantial valuations, for example, considering that their work remains very early.

This means that their progress will also be watched closely in 2019. Allogeneic approaches in particular will be monitored, from companies including Fate Therapeutics and Atara. The latter has a phase III trial due to report in the first half of the year from its project tab-cel, which represents the first pivotal data to be generated by an off-the-shelf T-cell immunotherapy, Mr Cheung points out.

Many will want to see advances made in the autologous space as well. Data from Celgene in particular will be followed, as investors are very keen to see that the $9bn the group spent on Juno was not wasted. Much still has to be proved, in particular the company's claims that its CAR-T products could be differentiated on safety.

The biotech's lead CAR-T project, JCAR017 (liso-cel), is slated to yield registrational data from the Transcend-NHL study next year, setting up a mid-2020 US approval. That is already much later than Juno had bullishly been signalling, back in 2018.

At the Ash meeting Celgene seemed to signal a shift in emphasis towards work in CLL, which is admittedly a much less crowded space for CAR-T projects. However JCAR017 is considered to be one of Celgene's most important future sales growth drivers, so any further delay in getting this asset to market will add further pressure on the beleaguered big biotech.

The small-molecule space also promises to attract attention next year. The recent approval of Loxo Oncology and Bayer's larotrectinib, now trademarked Vitrakvi, represents what could be the first in a new wave of highly selective therapies addressing a broad range of genetic mutations. Investors and competitors will also be watching to see how payers respond to the eye-watering price tag that Bayer has set.

"Undruggable targets are no longer undruggable," says Nextech's Mr Schroeder. "Targets that we know are relevant, KRAS, PI3K, p53, and other well-known oncogenes,they will be addressed soon, in the next five years. The technologies are available now – we have some very different chemical strategies coming into the clinic – and the validation couldn't be stronger."

From cell therapies to IO and small-molecule research, one thing is certain: next year the oncology space will remain one of the hottest in biopharma.

What to watch in 2019 – biopharma's most valuable R&D projects

Source: EvaluatePharma® 15 November 2018

Product	Company	Details	Consensus NPV ($bn)
VX-659 + Tezacaftor + Ivacaftor	Vertex	Cystic fibrosis triplet – phase III data due by YE'18.	14.4
JCAR017	Celgene	Anti-CD19 CAR-T therapy – phase III/II data due 2019 in lymphoma and leukaemia.	8.5
Semaglutide Oral	Novo Nordisk	Oral GLP-1 agonist for type 2 diabetes – filling expected in 2019.	7.6
Aducanumab	Biogen	Anti-beta-amyloid MAb for Alzheimer's – pivotal data due late 2019/early 2020.	7.4
ARGX-113	Argenx	Anti-FcRn Mab for autoimmune conditions – further phase II data and phase III start due in 2019.	6.5
NKTR-214	Nektar Therapeutics	CD122 agonist (IL-2) – further data from Pivot-02 due in 2019.	6.2
Elafibranor	Genfit	PPAR alpha & delta agonist – phase III Nash data due YE'19.	5.5
GSK2857916	GlaxoSmithKline	Anti-BCMA ADC for multiple myeloma – phase II data and phase III start due in 2019.	5.4
Ozanimod	Celgene	S1P modulator – filing in MS due Q1'19.	4.4
DS-8201	Daiichi Sankyo	Anti-HER2/ErbB-2 ADC – phase III breast cancer data due 2020.	4.3
Valoctocogene Roxaparvovec	BioMarin	Haemophila A gene therapy – potential accelerated filing on phase I/II data in H2'19.	4.3
SGT-001	Solid Biosciences	DMD gene therapy – phase I/II interim data due H1'19.	4.3
Voxelotor	Global Blood Therapeutics	Sickle cell therapy – potential accelerated approval in 2019.	3.6
PF-05280586	Pfizer	Rituxan biosimilar – US approval due Q3'19.	3.6
bb2121	Celgene/Bluebird	Anti-BCMA CAR T therapy – phase III data and filing due 2019.	5.4
Filgotinib	Gilead Sciences/Galapagos	JAK 1 inhibitor for RA – phase III data and filing due 2019.	6.6
Pamrevlumab	FibroGen	Anti-CTGF Mab – phase III trials in IPF and pancreatic cancer due to start in 2019.	3.2
Luspatercept	Celgene	MDS/Thalassaemia treatment – filling due 2019.	3.1
MGL-3196	Madrigal Pharmaceuticals	TRb agonist for Nash – phase III trial to start 2019.	3.1
ARGX-110	Argenx	Anti-CD70 Mab for lymphoma/leukaemia – further phase II data due in 2019.	3.0

The above table highlights what the sellside believes to be the sector's most valuable R&D projects, all of which will be tracked closely for progress next year.

One space that is sure to generate news is Nash; believers reckon that the space represents a mega-blockbuster opportunity for industry.

"Nash is an area where sceptics remain, but if we get good data that's a new therapeutic area and a new disease for investors to focus on," says Mizuho's Mr Syed.

Phase III results from four assets could emerge next year, though most pivotal for sentiment are Gilead's selonsertib and Intercept's Ocaliva. Interim data from the former's Stellar-3 and Stellar-4 trials, and the latter's Regenerate study, are all due in the first half. Both companies hope to seek accelerated approval based on fibrosis endpoints.

Cenicriviroc from Allergan and elafibranor from Genfit might also yield pivotal data, although later in 2019. With the likes of Madrigal and Viking looking to head into phase III, this is a space that will continue to grip investors in 2019.

Another potentially very valuable but elusive therapy area is Alzheimer's disease, and next year will undoubtedly contain updates. One of the biggest readouts on the horizon might well slip into 2020, however: Biogen's phase III trial of aducanumab might just sneak into 2019, while it is also possible that another interim look is taken before the final data cut.

Data from Roche's Alzheimer's asset crenezumab are due in early 2020, meaning that the end of next year could see investors taking positions ahead of the readout, according to Mr Syed.

"Alzheimer's is still a very hot topic. The data from Biogen is such a large catalyst, you almost have to play it as an investor," he says.

Finally, hepatitis B could also develop into a therapy area attracting even bigger numbers by the end of 2019 as several companies seek a functional cure. Research remains mid-stage but, should data from closely watched assets from the likes of Assembly Biosciences, Spring Bank or Arrowhead impress, the field will move closer to pivotal testing and set the sector up for some much-needed late-stage excitement.

Launch phase

The CAR-T therapies were not the only novel technologies to disappoint on arrival last year. Gene therapy's flagship launch, Spark's Luxturna, has been slower than hoped, while the early signs for Alnylam's RNAi amyloidosis therapy, Onpattro, have not been encouraging.

Two more gene therapies are slated to hit the market next year: Lentiglobin from Bluebird and AVXS-101 from Novartis. So investors will soon learn whether the earlier launches were outliers or a sign that more conservative assumptions need to be applied to such novel technologies.

Crossing the line – notable projects facing regulatory scrutiny in 2019

Source: EvaluatePharma® 15 November 2018

Product	Company	Indication	Consensus NPV ($bn)	Approval
ALXN1210	Alexion Pharmaceuticals	Paroxysmal nocturnal haemoglobinuria	10.9	PDUFA February 2019
Upadacitinib	AbbVie	Rheumatoid arthritis	8.4	Filing due 2018
AVXS-101	Novartis	Spinal muscular atrophy	7.0	Filed in US and EU October 2018, Japan filing due by end of 2018
Brolucizumab	Novartis	Wet AMD	6.1	Filing due December 2018
LentiGlobin	bluebird bio	Thalassaemia	6.1	Filed in Europe October 2018
Risankizumab	AbbVie	Plaque psoriasis	5.2	PDUFA April 2019
Mayzent (siponimod)	Novartis	Multiple sclerosis	4.6	PDUFA expect March 2019, EMA approval late 2019
Selinexor	Karyopharm Therapeutics	Penta-refractory multiple myeloma	3.0	PDUFA April 2019
AR101	Aimmune Therapeutics	Peanut allergy	2.7	US filing due December, EU due mid-2019

Another important class of new-to-market therapies that will be monitored next year are biosimilars, specifically in the US. Take-up in this potentially very lucrative market has been far from rapid here, though few have tested the waters yet.

Neulasta is probably the fight to watch in 2019: Mylan is already rolling out its version, Fulphila, and Coherus aims to launch Udenyca in the first weeks of next year. The power that branded manufacturers retain in the US, in terms of their ability to negotiate with payers and effectively block biosimilars from formularies, has been blamed for the lack of uptake so far in the US.

But political will to lower drug prices in the US is growing. It is hard to imagine the environment for these lower-cost biologicals getting any worse, and if lawmakers manage to make any progress in their attempts to drive through structural changes in the US healthcare system the struggling biosimilars industry could be one of the first beneficiaries.

US political gridlock?

America's mid-term elections in November saw the country returned once more to a divided government. The big question for biopharma is what this means for efforts to lower the nation's drug prices.

Democrats now control the House of Representatives and will be empowered to pass legislation that would seek to bring down drug costs by mandating direct negotiation on pricing between drugmakers and the US government. But, with congressional power split, the chances of any such bills being sent to President Donald Trump are practically zero.

Compromising with Mr Trump might be the only route to achieving the drug pricing restraints that Democrats want. But handing the President a victory on this issue before the 2020 elections will be very unpalatable.

Whether any successful deal can be struck between the White House and House Democrats will depend on Mr Trump's willingness to compromise and Democratic leaders' calculations about whether, if they reject any deal, they could continue to campaign on this issue.

Cowen analyst Rick Weissenstein believes that the divided government is positive for biopharma on drug pricing issues because it will be very hard to get anything done.

Still, if voters expect lawmakers to deliver restraints on drug prices, House leaders might need to try to make a deal on legislation agreeable to their Senate counterparts and Mr Trump, especially as healthcare has been so vital to winning Democratic votes. The question is whether the mercurial president will want to take part when other issues, like immigration and the economy, appear to be more important to his voter base.

Meanwhile, the outcome of several of the initiatives from Mr Trump's drug pricing blueprint remain up in the air. The firmest proposals are a requirement for pharma manufacturers to disclose the list price of expensive drugs in their advertisements, to link Medicare's reimbursement for physician-administered drugs to international prices, and to allow Medicare Part D plans to more aggressively manage utilisation in three protected classes that include oncology and mental health treatments.

All three are in the early stages of the legal rulemaking process, and almost certainly will be subject to intense industry lobbying, so it is not at all clear that any will become the law of the land, either as is or in a watered-down form.

On the other hand, big pharma seems interested in providing lawmakers ammunition for forging ahead here. The return of drug price rises after a voluntary hold for 2018 – led as usual by Pfizer – will be another variable that will be thrown into the year's policy calculations.

The new normal?

Few would contest that biopharma is heading into 2019 on a decidedly downbeat footing. But despite the ongoing stock market volatility and risk of a rise in drug price rhetoric in the US, many are maintaining an optimistic stance.

“Macro concerns keep us on our toes. In this environment we have to adjust. Science is progressing at an exponential rate, and there are a lot of positives to be found,” says Nextech’s Mr Schroeder.

Mr Loncar agrees. “Biotech goes through peaks and valleys, and we’ve been in a pretty rough valley for the last six months or so. But the thing about our sector is that one piece of good news can turn it all around,” he says.

As things stand in the closing weeks of 2018, that news would have to be very good. Broader markets are showing no sign of stabilising as investors continue to fret about macro issues, and the high-risk biopharma sector will have to work hard to rise in a wider pessimistic climate.

If dented valuations tempt buyers back into the market, the sector could get a boost; the takeout of Tesaro suggests that this might be already happening. However, there also are reasons why business development teams might chose to sit on their hands for a while longer.

The biotech bubble of 2015’s persuaded investors and companies alike that eye-watering price tags could be justified. And the aftermath of a string of overvalued and in many cases disastrous takeovers is now being felt.

“BD executives are wary of being wrong. We have seen some bad decisions that resulted in people losing their jobs. So the safest option is to wait it out, and they’ve been proven right,” says Ikarian’s Mr Khanna. “Barring Sarepta and Neurocrine, all small-to-mid biotechs transitioning into the commercial realm have ubiquitously struggled to meet expectations.”

More eye-catching M&A deals will be needed to convince investors that activity is on the rise. And there is certainly no lack of cash-rich, motivated buyers around.

“Big biotechs are all looking for the next blockbuster, so we might see some buying smaller companies with products on the market, as they start to look cheaper. But that difficult second album is always much more challenging than they expect,” says Edison’s Mr Smith.

A reinvigorated big cap biotech space is also desperately needed to bring non-specialist investors back into the sector. But many worry that these pipeline-poor companies have lost their way.

“It’s very difficult to move an industry up when the large cap leaders are so weak,” says Mr Cheung. “They seem to be in the mindset that they favour buybacks, but I’d like to see them being a bit more aggressive [on M&A].”

Still, if one considers that the fundamental driver of valuations is previous acquisitions, any wave of opportunistic acquisitions could also have a downside. Mr Khanna argues that it could prove damaging to the sector in the long term if successful moves are made now on formerly hot takeout targets that have dropped substantially from highs.

Tesaro, for instance, was 85% off its peak when Glaxo came to the table; even so the market thinks it overpaid.

“If 2x peak sales is what big pharma thinks is fair value in the absolute crimson blue sky scenario, then where does that leave the current crop of [small-to-mid cap companies], most of which are valued well above that, even with the recent correction,” Mr Khanna says.

Unjustifiable valuations might have been putting buyers off last year, but if they start to drop too low, it will be investors who turn away from the sector. Neither extreme situation creates a healthy life science ecosystem.

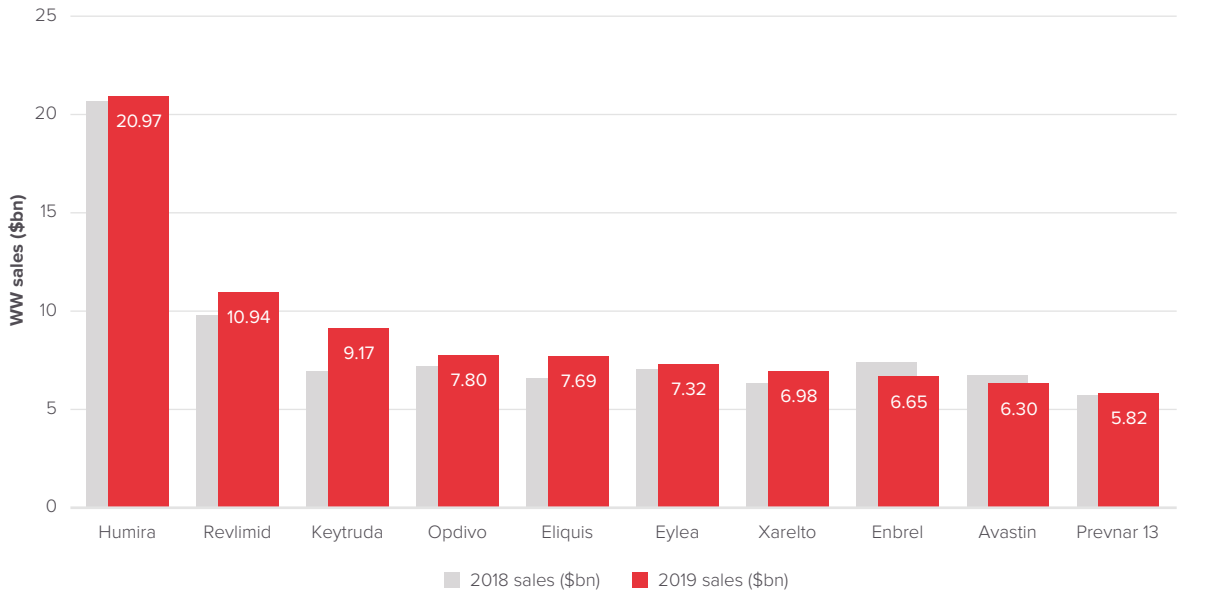
At the end of the day, biopharma thrives or dies by the advances being made. “People need to see innovation – particularly generalist [investors] who look so much at issues like drug pricing,” Mizuho’s Mr Syed says.

It seems highly unlikely that rising stock market tides will buoy the life science sector next year. Innovation needs to be delivered. Over to you, biopharma.

Putting 2019 into numbers

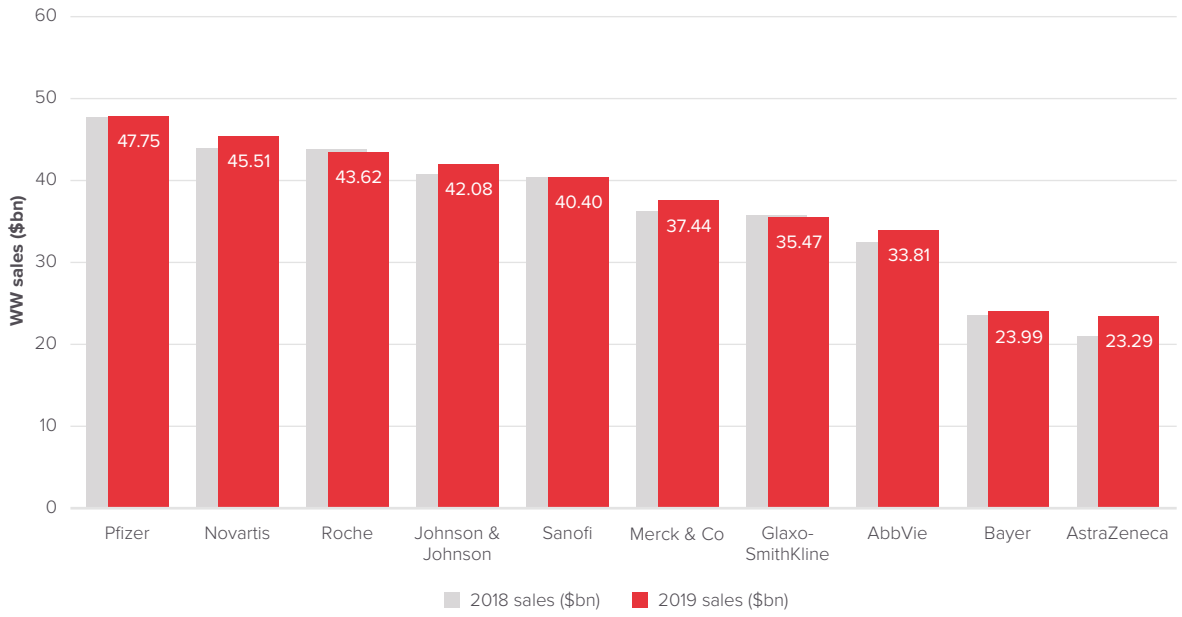
Top 10 drugs by 2019 sales ($bn)

Source: EvaluatePharma® 15 November 2018



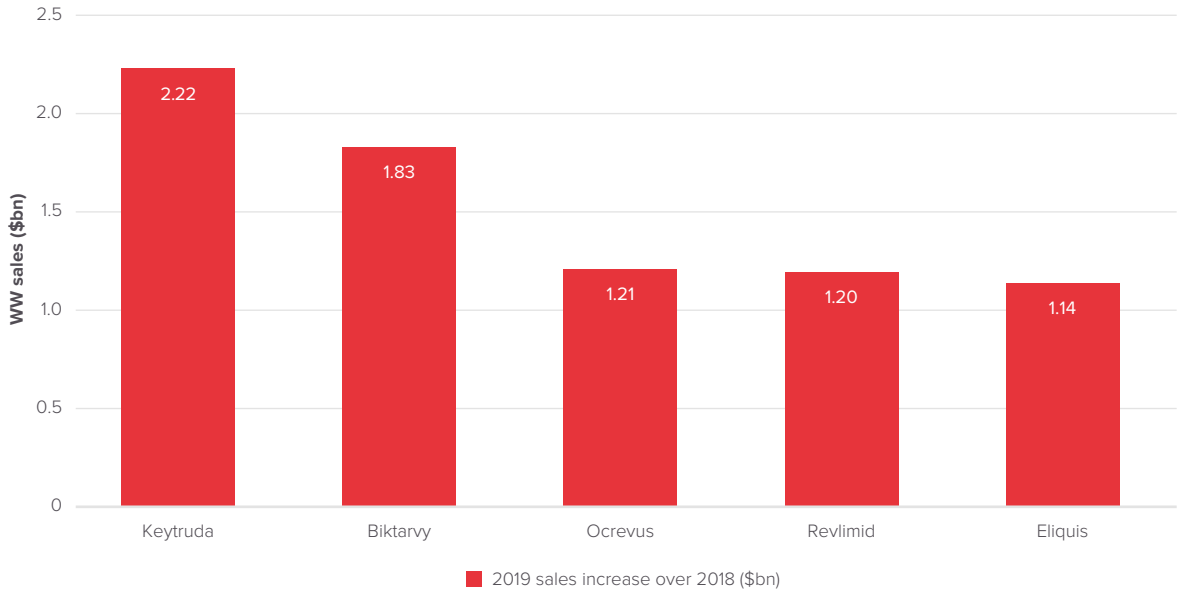
The biggest pharma companies – Rx and OTC sales

Source: EvaluatePharma® 15 November 2018



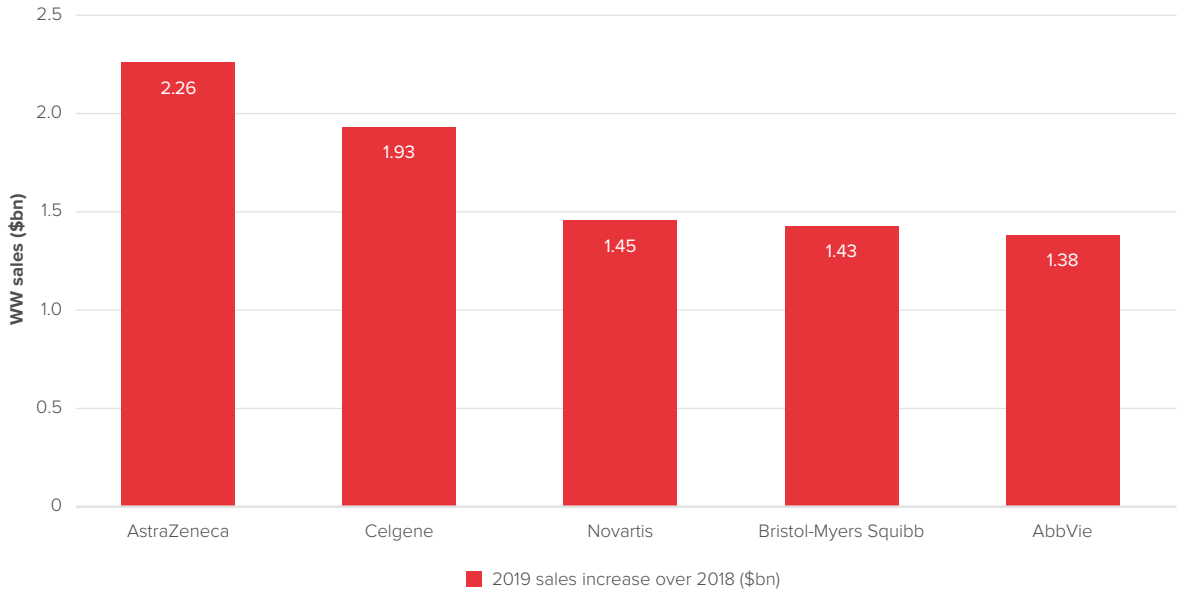
Top drugs in 2019 by forecast year-on-year sales increase ($bn)

Source: EvaluatePharma® 15 November 2018



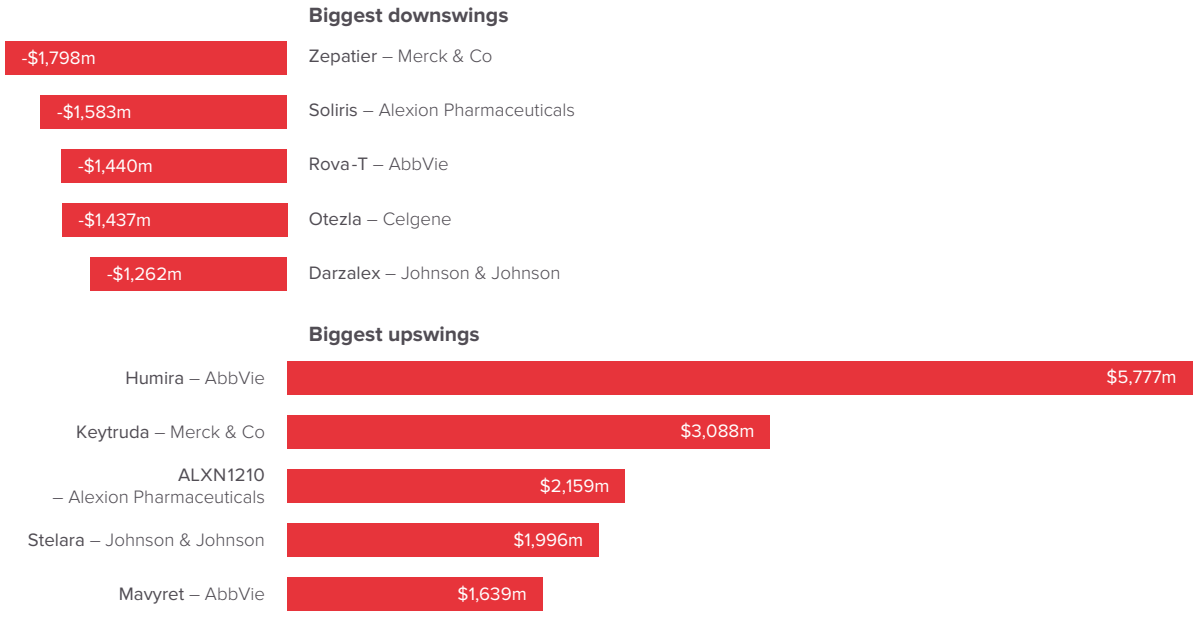
Top companies by new sales

Source: EvaluatePharma® 15 November 2018



Biggest changes to 2018 US sales forecast, over the last 12 months

Source: EvaluatePharma® 15 November 2018



Evaluate

Additional complimentary copies
of this report can be downloaded at:
www.evaluate.com/PharmaBiotech2019Preview

Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

EvaluatePharma offers a global view of the pharmaceutical market's past, present and future performance with consensus forecasts to 2024, company financials, pipelines and deals.

@EvaluatePharma

EvaluatePharma Vision provides the first single view of the risk and reward of the R&D landscape with consensus forecasts, R&D costs at drug and trial level, success rates, predictive timelines and trial outcomes.

EvaluateMedTech tracks, benchmarks, and forecasts global performance for the medical device and diagnostic industry with consensus forecasts to 2024, company financials and more.

@EvaluateMedTech

Evaluate Custom Solutions improves your strategic decision-making with customised solutions and deep insights that draw on our industry expertise and trusted commercial intelligence.

Vantage provides award-winning, thought-provoking news and insights into current and future developments in the industry, and is the only pharmaceutical news service underpinned by Evaluate's commercial intelligence.

@Vantageanalysis

Daily analysis of key industry developments, underpinned by Evaluate's commercial intelligence.

We don't just tell you what's happened – we tell you what it means for you.

Sign up

Vantage
Kickstarting ideas

www.evaluate.com

Evaluate Headquarters
Evaluate Ltd.
11-29 Fashion Street
London E1 6PX
United Kingdom
T +44 (0)20 7377 0800

Evaluate Americas
EvaluatePharma USA Inc.
60 State Street, Suite 1910
Boston, MA 02109
USA
T +1 617 573 9450

Evaluate Asia Pacific
Evaluate Japan KK
Akasaka Garden City 4F
4-15-1 Akasaka, Minato-ku
Tokyo 107-0052, Japan
T +81 (0)80 1164 4754

DEC 2018