EP Vantage 2018 Preview

Amy Brown, Edwin Elmhirst and Jon Gardner – December 2017

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Foreword

The biopharma sector is approaching 2018 in a position of strength. As a hypothesis, this statement is hard to reject. Novel medicines are reaching the market more quickly than ever before; in the past few years large and small drug developers have successfully launched transformative products in a number of therapy areas; investor support for private and public companies is strong; and global demographics signal rising demand for healthcare.

But for those looking ahead, what should alternative hypotheses test? That 2018 holds even more promise? Or that the pace of progress is unsustainable?

There are arguments to be made for both statements.

On the regulatory front, it looks unlikely that the US FDA will swing towards a more conservative stance; the past few years have seen concerted efforts to speed approvals of the most urgently needed new medicines and, more recently, low-cost generics. There are perhaps more uncertainties in Europe, which is grappling with the relocation of the European Medicines Agency post-Brexit. But even here the regulator has made attempts to become more transparent and proactive.

Over the past few years, these regulators have ushered in ground-breaking medicines that promise to shift the outlook for patients suffering from a wide variety of chronic and acute conditions – and reward their developers richly. Many of these scientific leaps forward – like CAR-T or RNA therapies – are expected quickly to become commercial success stories. But how these new launches actually fare in markets that are increasingly sensitive to cost will be closely watched in 2018.

The progress of promising pipeline projects will, as always, have a big influence on how investors feel about the sector. Among the most closely watched are the next generation of immuno-oncology drugs – as a watchword for huge valuations and high expectations, should new combinations and novel targets fail to deliver, confidence in the industry's R&D work more broadly could take a knock.

Next year will certainly see the quest to determine the value of these new technologies and techniques continue – not only for investors but for potential acquirers, many of whom remained on the sidelines in 2017. Predictions of an uptick in M&A in 2018 can already be heard from many quarters, with commentators citing a growing urgency to act for many larger biotech and pharma groups. Small drug makers will not necessarily become easier targets, however; there are few signs that their access to cash will be impeded next year.

The progress of tax reform in the US will be important to those in the business of deal making, and a watchful eye will remain on US policy shifts more generally. However, the Trump administration's inability to pass substantial healthcare reform and an apparent pullback from taking action on drug pricing mean that this is not the live issue it once was. That said, it is also true that unpredictability is a certainty when it comes to the current occupant of the White House.

Still, the issue of drug pricing and affordability will remain at the forefront of many debates next year, particularly in the US. Signs that power is shifting towards payers in more therapy areas would be taken badly by investors.

But, on many measures, 2018 should start strongly for the biopharma sector: closely watched stock indices are not a million miles off 2015's peak, demand for IPOs and secondary fund raisings is strong, and the coffers of venture investors are well stocked. The need for large companies to stock pipelines will never wane, while regulators are sending industry a clear message – deliver the innovation and we will approve it.

However the sector has set itself a high bar over the last few years, with rapid progress in many fields. Expectations are high. Too many disappointments next year would remind heady investors that in this industry, failure is a fact of life.

Report authors | Amy Brown, Edwin Elmhirst, Jon Gardner

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Back to basics – regulation, launches and pipelines

At the start of last year Trump was the sentiment setter. In 2016 the severity of the biotech boom implosion was the big unknown. And, heading into 2015, the million-dollar question was for how much longer the bull run could charge.

As 2018 approaches, an overarching theme is less obvious. US policy shifts, in particular tax reform, and the ongoing drug price debate will be closely followed, although on this topic the power of the US President's Twitter account has diminished.

Macro events will, as always, hold their sway. But it is perhaps the industry's bread and butter – clinical readouts and drug launches – that are emerging as a dominant preoccupation.

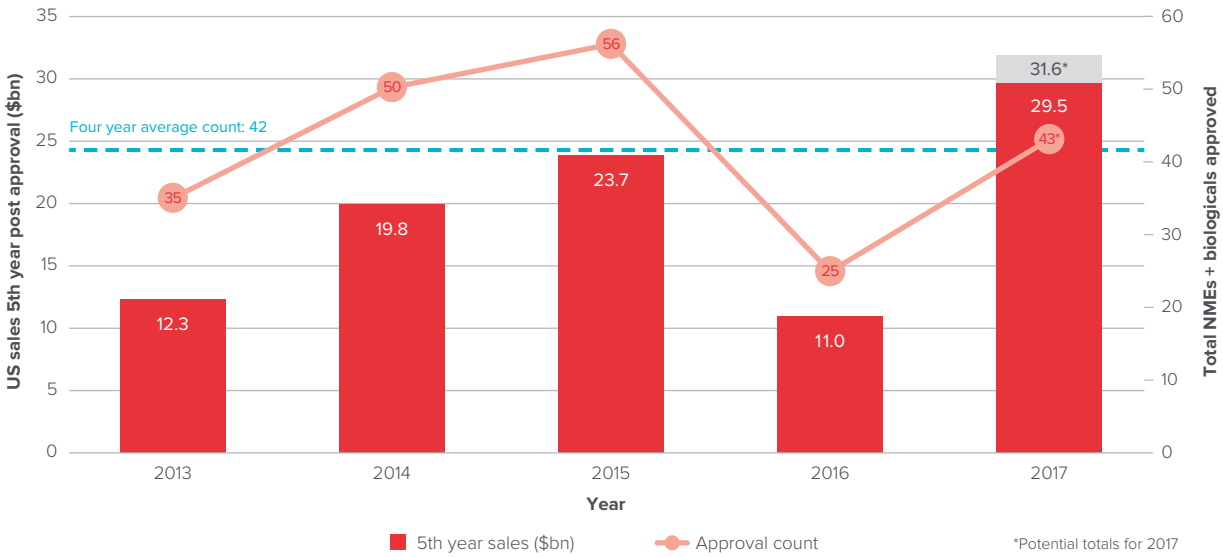
"R&D successes and failures are probably going to be the biggest driver of sentiment next year, all other things being equal," says Ben Yeoh, senior portfolio manager at RBC Global Asset Management. "The immuno-oncology space continues to be a barometer – there will be a lot of attention there."

A look at the output of the US regulator over the past couple of years amply demonstrates that the biopharma sector is in the midst of a very strong run of breakthroughs and launches. A major concern for investors is whether this productivity can continue in 2018.

FDA approval count vs. forecast US sales 5 years after launch

Source: EvaluatePharma® 15 November 2017

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), Imfinzi (Astrazeneca) , Dupixent (Sanofi/Regeneron)



The FDA is on track to green light 43 novel drugs in 2017, which are forecast to be generating a combined $32bn in US sales in five-years' time. A perception of greater leniency from the US regulator is also helping sentiment – stoked by U-turns on the stringent safety requirements for the likes of Eli Lilly's rheumatoid arthritis drug Olumiant and Amicus's Fabry disease treatment migalastat, or the controversial green light for Sarepta's Exondys 51. The agency itself strenuously denies that its hurdles for approval have been lowered, but these cases do little to disabuse industry watchers of the notion of a "friendly FDA".

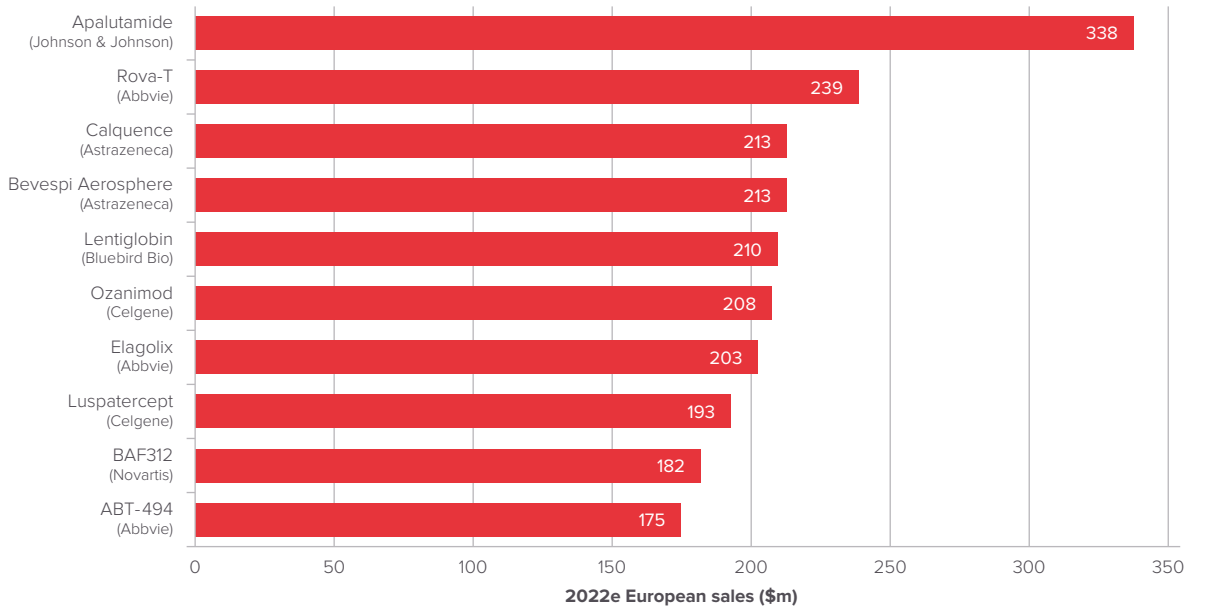
Add to this the fact that the new FDA commissioner, Scott Gottlieb, has been widely embraced by industry and investors alike. His recent efforts to further speed the approval of generic drugs might be giving some branded manufacturers pause for thought, though for the pharmaceutical sector as a whole he has been labelled a good thing.

"I would say the FDA climate is constructive, and we would hope for that to continue," Mr Yeoh says.

The situation in Europe is slightly different, where expected upheaval around the relocation of the region's regulator to Amsterdam could potentially cause delays.

At risk? European sales of late-stage projects

Source: EvaluatePharma® 15 November 2017



With regulators primed to approve innovation, and the sector riding high on several successful years for R&D, 2018 needs to deliver its own swathe of positive pipeline news to show that this momentum can be maintained.

As Mr Yeoh points out, updates from the world of immuno-oncology are the most hotly awaited. Huge leaps forward in cancer care with the anti-PD-(L)1 antibodies and the approval of cutting-edge techniques like CAR-T have raised expectations that the sector can keep delivering at pace.

Wide-ranging research is ongoing, but a handful of clinical trials and projects are being monitored particularly closely. Success with IDO inhibition is perhaps the most immediately pivotal; hopes are high that adding IDO to PD-(L)1 will generate more than just incremental benefit, and add another checkpoint inhibitor to the medical armamentarium, after PD-(L)1 and CTLA4.

And there are numerous other combo studies with novel immune checkpoint targets reading out throughout 2018. While many will continue generating ambiguous or incremental data, some might give investors a more accurate picture of whether a combination strategy is able to add anything above the strong benefits seen with PD-(L)1 blockade.

Keeping an eye on I-O: Checkpoint targets trials to watch out for in 2018

Source: EvaluatePharma® 15 November 2017

Target	Project	Company	Study, indication, combo	Trial ID
Fortunes going up...				
IDO	Epacadostat	Incyte	Echo-301: Melanoma; + Keytruda	NCT02752074
Lag3	Relatlimab (BMS-986016)	Bristol-Myers Squibb	Checkmate-142: Colorectal cancer, + Opdivo	NCT02060188
CD122 (IL-2Rβ)	NKTR-214	Nektar Therapeutics	Pivot02: + Keytruda. Propel: + Opdivo, + Tecentriq	NCT02983045; NCT03138889
...and going down				
Ox40	PF-04518600	Pfizer/Merck KGaA	Javelin Medley: + Bavencio	NCT02554812
CSF-1R	Cabiralizumab	Bristol-Myers Squibb/ Five Prime	+ Opdivo	NCT02526017
CSF-1R	ARRY-382	Array	+ Keytruda	NCT02880371
CSF-1R	Emactuzumab	Roche	+ Tecentriq	NCT02323191
CSF-1R	PD-0360324	Pfizer/Merck KGaA	Javelin Medley: + Bavencio	NCT02554812

Incyte is leading the IDO inhibition field, and is due to release the first rigorous phase III data in this space in the first half of 2018. Echo-301 tests a combination of epacadostat with Merck & Co's Keytruda in first-line melanoma, a tumour type that has already been transformed by the arrival of the anti-PD-1 antibodies.

"That's a huge study because if melanoma fails you can pretty much write off all those other cancers that [epacadostat] is being tested in," says Brad Loncar, a private biotech investor and founder of the Loncar Cancer Immunotherapy ETF.

Incyte has certainly benefited from the immuno-oncology wave – it was valued at more than $30bn in March 2017. And although its share price has fallen by around a third since then, the collapse of such a high-profile asset would send out shockwaves.

Keeping an eye on I-O: Other combo trials to watch out for in 2018

Source: EvaluatePharma® 15 November 2017

Project and target	Company	Study, indication, combo	Trial ID
Tim3			
MBG453	Novartis	+ PDR001 (PD-1)	NCT02608268
TSR-022	Tesaro	Amber: + TSR-042 (PD-1)	NCT02817633
CD40			
RG7876	Roche	+ emactuzumab	NCT02760797
Icos			
JTX-2011	Celgene/Jounce	Iconic: + Opdivo	NCT02904226
ITR			
GWN323	Novartis	+ PDR001 (PD-1)	NCT02740270
CEA			
Cergutuzumab	Roche	+ Tecentriq	NCT02350673
TLR9			
CMP-001	Checkmate Pharmaceuticals	Melanoma, + Keytruda	NCT02680184
IMO-2125	Idera Pharmaceuticals	Melanoma, + Yervoy	NCT02644967
4-1BB (CD137)			
Utomilumab	Pfizer/Merck KGaA	Javelin Medley: + Bavencio	NCT02554812
Urelumab	Bristol-Myers Squibb	Includes B-cell NHL, GBM; + Opdivo	NCT02253992; NCT02658981

Another key I-O target is Lag3, where Bristol's relatlimab has already showed efficacy in Lag3-positive patients who had progressed on anti-PD-(L)1 therapy. And Nektar has already made waves by showing that its CD122 agonist NKTR-214 combined with Opdivo prompted responses in PD-L1-negative subjects, raising hopes that it could turn "cold" tumours "hot".

Still, concern has already been growing that expectations are too high for the speed of progress in this field, and disappointments with Ox40, CSF-1R and Kir bear some of these out. Investors have thus been served several reminders that the questions of what to combine and where are not easily answered.

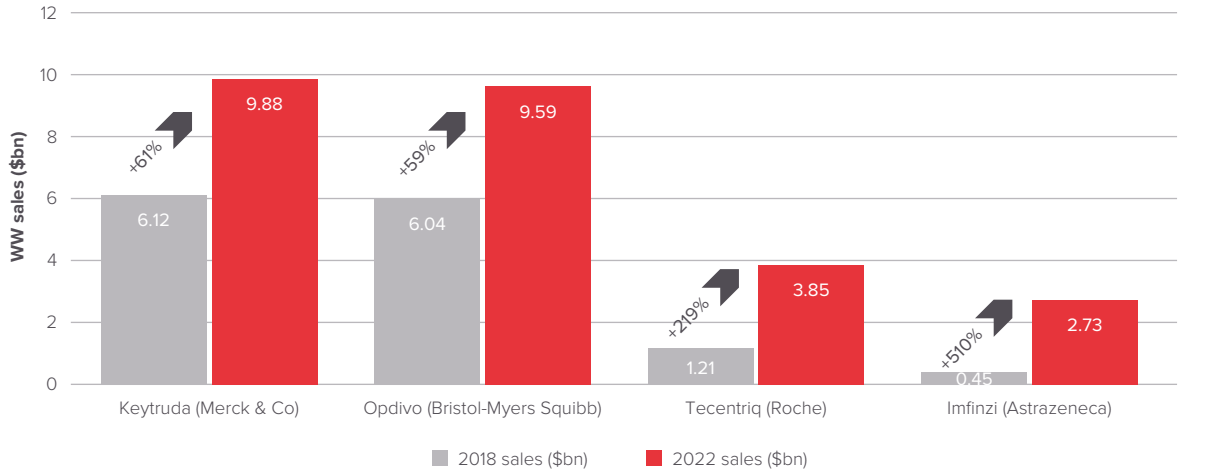
Next year will also contain setbacks – to reassure investors, there must also be progress. It is notable that big pharma groups active in immuno-oncology are also feeling the weight of sky-high expectations.

"People always overestimate near-term change and underestimate the impact of a new technology on long-term change. That has probably happened in immuno-oncology ," Pascal Soriot, chief executive of Astrazeneca, said at a press conference in October.

And Bristol-Myers Squibb executives, at the Jefferies healthcare conference in London in November, went out of their way to remind attendees that their company was about much more than immuno-oncology.

PD-(L)1 MAb sales expectations

Source: EvaluatePharma® 15 November 2017



Of course these big pharma groups have a vested interest in keeping a lid on expectations – several are awaiting hugely important readouts in first-line lung cancer next year, from studies that will also help set the tone around immuno-oncology in 2018.

Bristol's Checkmate-227 is due in the first half, as is the overall survival result from Astrazeneca's Mystic study, which failed to hit on progression-free survival at the first reading. Data from Merck's Keynote-189 have been pushed back to 2019 after the company changed the trial design.

Roche put the cat amongst the pigeons with a surprising hit on progression free survival in the Impower-150 trial in November, which tested the combination of Tecentriq, Avastin and chemotherapy against Avastin and chemo alone. The full data, including overall survival, remain important unknowns and are also due to be released in the first half of next year. However if Tecentriq's advantage over a well-established treatment regimen is confirmed, Roche will find itself in a strong position.

These trials all represent late-stage testing of different combination strategies – they variously look at PD-(L)1 plus CTLA4 or PD-(L)1 plus chemotherapy – so the results will be influential beyond these drugs.

The recent Roche data make for encouraging reading. However failure to push the field forwards elsewhere could prompt growing doubts about some of the promises being made about – and the valuations being ascribed to – other high-profile immuno-oncology projects.

Approvals/early launches – the importance of delivering

Source: EvaluatePharma® 15 November 2017

Product	Company	Key event	2018e WW sales ($m)
Semaglutide	Novo Nordisk	US launch; EU approval (Q1)	368
Olumiant	Eli Lilly	Second FDA review	143
Patisiran	Alnylam	US/EU filing	102
Luxturna	Spark	US approval (28th Jan)	76
Rova-T	Abbvie	Phase II Trinity results (Q2)	73
Ozanimod	Celgene	US/EU filing	46
Epidiolex	GW Pharmaceuticals	US approval (30th Aug)	45
AVXS-101	Avexis	Confirm 2018 filing	33
Inotersen	Ionis	EU approval (Jun-Jul); US approval (6th Nov)	16
Anti-CGRP migraine therapies:			
Aimovig	Amgen/Novartis	US approval (17th May)	128
Galcanezumab	Eli Lilly	US filing	56
Fremanezumab	Teva	US approval (17th Oct)	17
Eptinezumab	Alder	Phase III Promise 2 results (H1)	-

Of course next year will not only be about new cancer treatments – sky-high expectations and eye-watering valuations can be found elsewhere too. Among the smaller players, Spark's progress with what is likely to be the first gene therapy in the US will be closely watched, as will Alnylam's and Ionis's moves towards regulatory review of their ground-breaking RNA-based therapies.

Among the bigger companies, Roche has much riding on its newly approved novel haemophilia treatment, Hemlibra (emicizumab), while the expected arrival of the anti-CGRP therapies for migraine will be a test both of the "friendly FDA" theory, and of whether sellside forecasts for supposedly valuable new drug classes can be relied on.

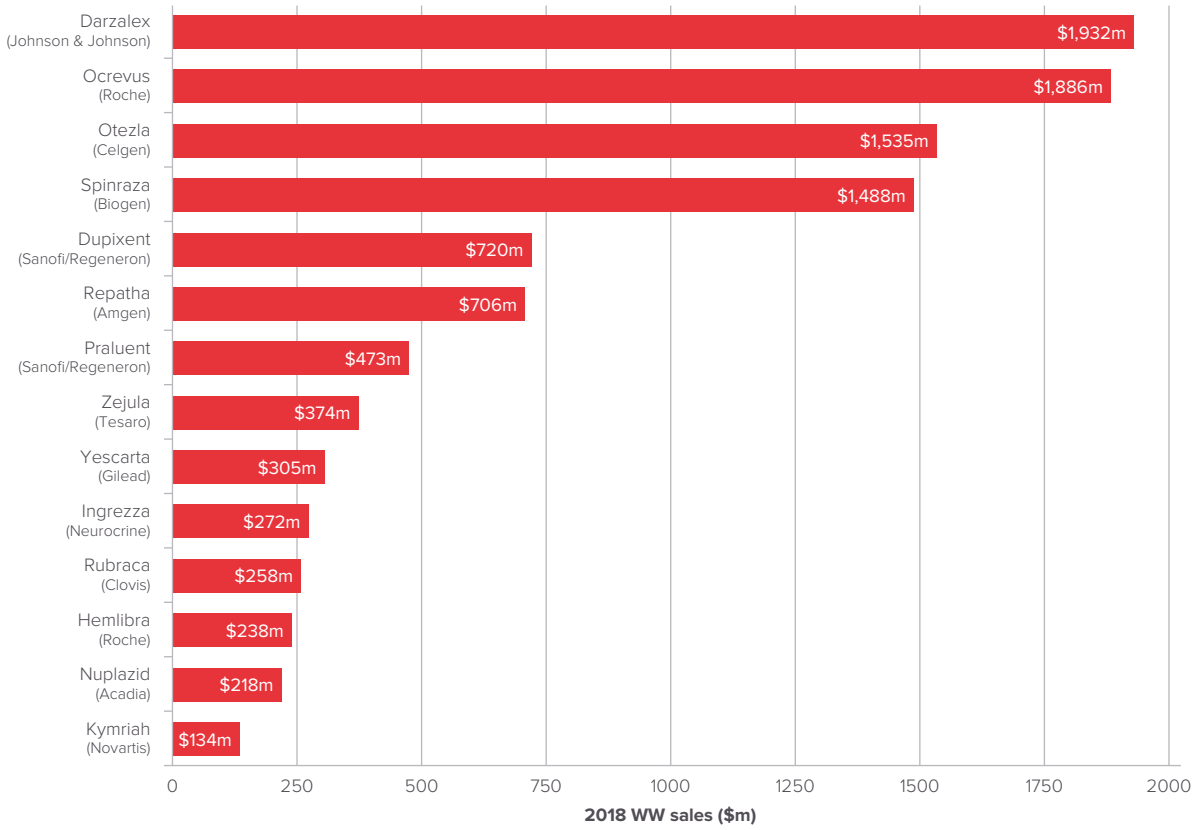
On this theme, the sluggish launches of the cholesterol-lowering anti-PCSK9 agents will continue to be monitored. These products were widely vaunted as future blockbusters but now look like an embarrassing case study in poor foresight, with industry and analysts alike widely failing to predict the reluctance of payers to embrace them.

Also proving a test of payers' patience will be the CAR-T therapies Yescarta and Kymriah. Initial uptake of these cutting-edge therapies will be closely scrutinised to help evaluate the future value of these and rival therapies – and help judge whether Gilead's $12bn acquisition of Kite was worth it. Approvals in broader indications, and in markets beyond the US – Kymriah was recently filed in the EU – will also be hotly awaited.

Also holding the potential to knock some hats off next year would be any ramp-up in the uptake of biosimilars in the US, as a number of substantial biological franchises approach the end of their patented lives.

Recent launches – the importance of meeting expectations

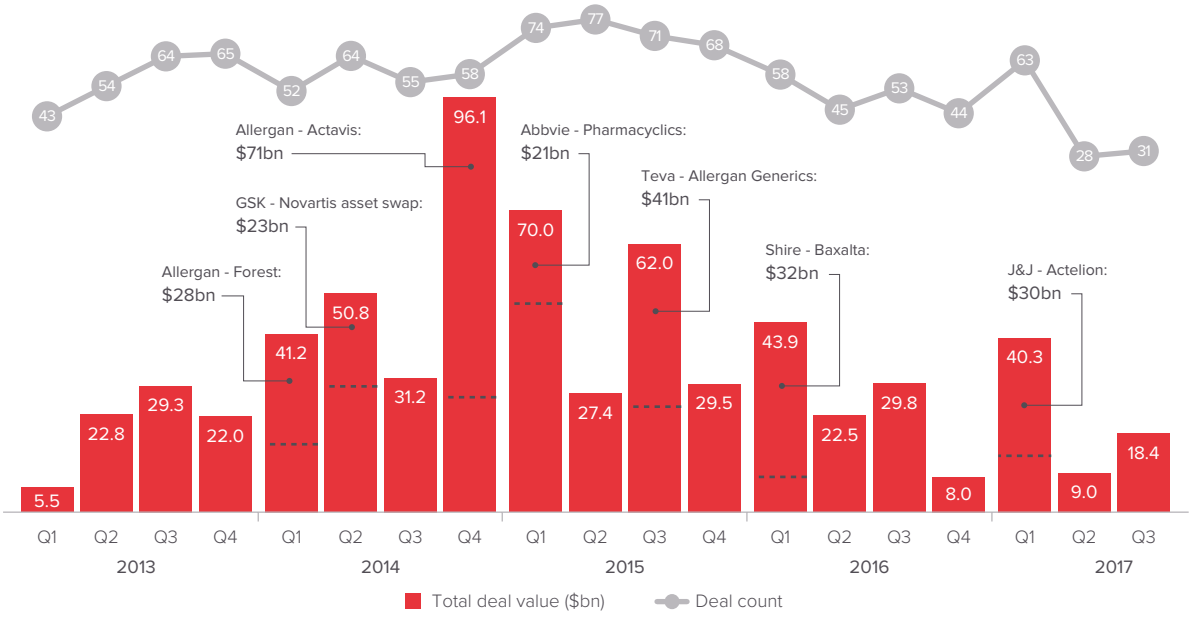
Source: EvaluatePharma® 15 November 2017



Money and markets – deals, financing and valuations

Pharma and biotech M&A transactions announced each quarter

Source: EvaluatePharma® 15 November 2017



Gilead's move on Kite was the type of big-ticket M&A approach that many were hoping to see more of in 2017. With a sector supposedly on pause in 2016, awaiting the outcome of the US election, predictions of an uptick in deal activity prevailed in early 2017 with President Trump secure in the White House.

A look at quarterly deal data suggests that this failed to materialise – the number of biopharma takeovers being struck has continued to fall in 2017.

Many have attributed this in part to lack of clarity on tax reform, which now seems to be moving forward with the House bill agreed upon and the Senate now considering their version. A shift to a territorial system of taxation, dropping the statutory corporate tax rate to 20% and a repatriation holiday are all on the table.

This will be no easy bill to pass, however; the House and Senate proposals still look very different and several Republican Senators have publicly expressed misgivings. An impatient President Trump wants to sign the bill by Christmas, which at this stage looks ambitious. Timelines aside, given the failure on healthcare reform, the GOP is highly motivated to get this bill through.

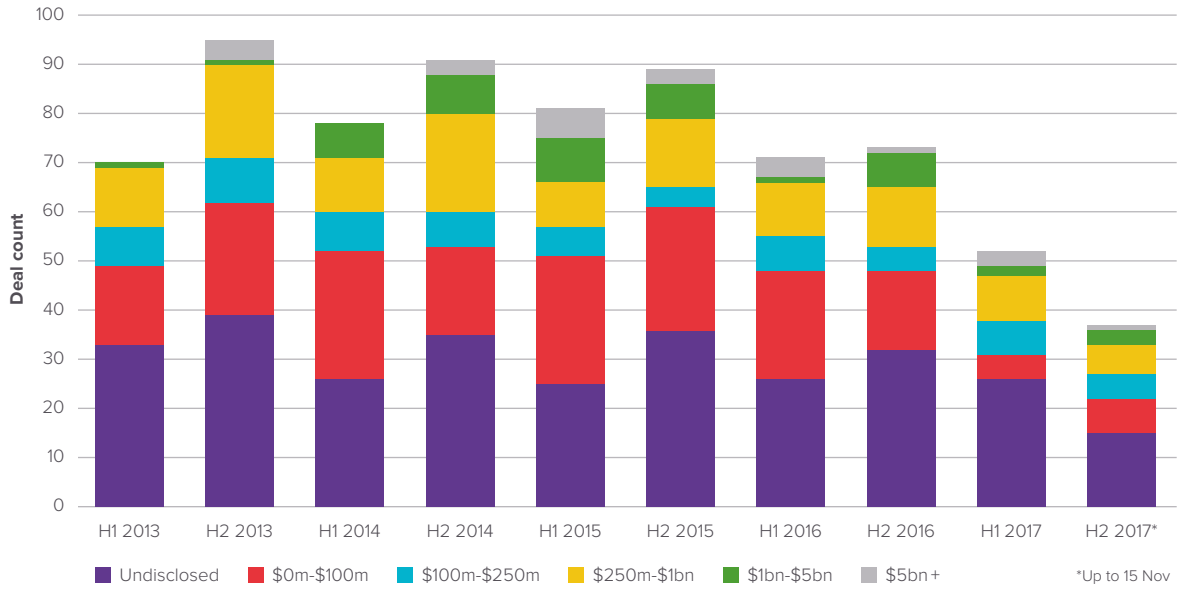
Deal bankers are no doubt slavering over the prospect of $130bn in overseas profits returning to US shores – this is the amount that big pharma and biotech companies are thought to be holding in other territories to avoid America's 35% corporate tax rate. Realistically, though, tax reform would only move the needle for those considering the largest deals.

And the data make it clear that deals in all size brackets have been in decline.

“Tax reform will play in for the Pfizers doing the big deals – for something $15bn or below, tax reform is almost meaningless,” Mr Loncar says.

Deal count by value bracket

Source: EvaluatePharma® 15 November 2017



Building urgency to bolster topline growth in the wake of the deal hiatus could provide another trigger for M&A next year. For those increasingly reliant on older drug franchises in large therapy areas, this need is only becoming greater.

“The industry is going through some very fundamental changes. Companies that rely on legacy products in areas like diabetes or heart diseases are in huge trouble. In these areas, payers have the power. This might mean we see M&A, and that would be the top ingredient for having a good 2018,” Mr Loncar says.

This issue was brought into sharp relief during October’s tumultuous third-quarter earnings season for many large-cap biopharma companies. Missed expectations and mounting concerns for the growth prospects of the likes of Celgene and Biogen, for example, caused a significant selloff.

“Q3 was a horrible quarter for the sector. Companies that didn’t do well traded down, and those that did do well also traded down,” says Salim Syed, senior biotech analyst at Mizuho Securities.

But the drop in share indices that resulted could be a silver lining, he maintains. “Many companies with cash balances have said they are looking to do some sort of M&A. So this gives them the opportunity to go out and buy something at a reasonable price.”

Average deal values of private targets

Source: EvaluatePharma® 15 November 2017

Complaints about unrealistic valuations – from potential buyers at least – have also been cited as a reason for the quiet M&A scene. Whether asset prices are too high remains an ongoing debate – the value of a company or project always depends upon who is buying – though it is clear that in certain areas price tags have soared.

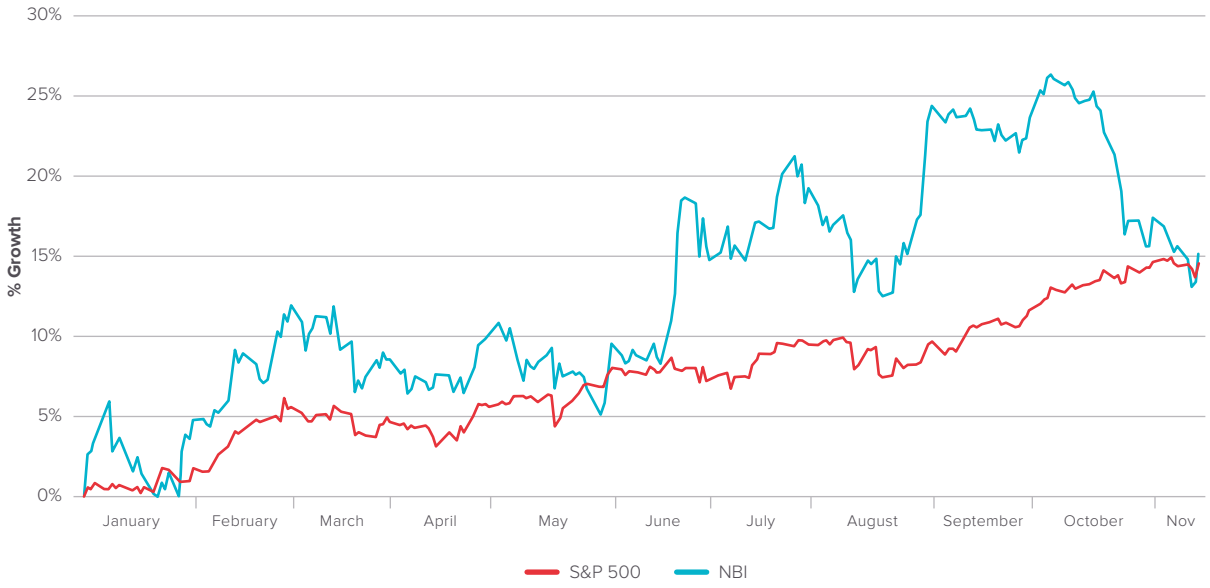
A topline look at average deal values for private takeouts paints a picture of acceleration over the past five years. These averages have been driven higher by deals in red-hot areas like oncology, immunology and rare diseases.

“Early-stage companies in immuno-oncology are overpriced; early-stage companies in the US are generally overpriced,” says Francesco de Rubertis, partner at the European venture capital firm Medicxi.

At the other end of the industry, however, many believe that the picture is different. Mr Syed points out that near-term price-to-earnings valuation ratios suggest that large-cap US biotechs are actually trading pretty cheaply.

“Valuations of large cap biotechs are around 12 times (forward) earnings – historically, trough levels were around 11 times – and US biotech is trading at a discount to big pharma, EU pharma, and the S&P,” he says.

NBI performance 2017



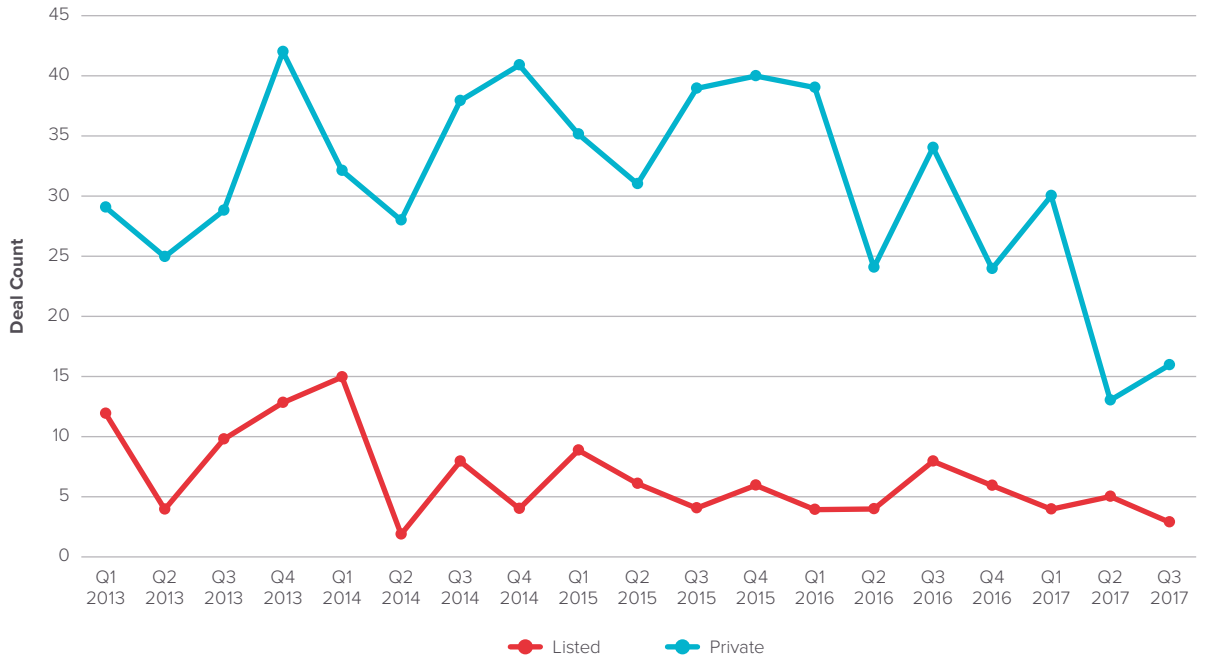
So if valuations of big cap biotechs remain depressed, and progress on tax reform emerges, then perhaps 2018 will see more, larger deals. Pfizer is still most frequently named as an enthusiastic big buyer – favourite targets for the rumour mill currently include Bristol-Myers Squibb and Biogen. And executives from other large players – Merck & Co and Gilead for example – have recently made it clear that they are looking around.

But for those shopping for smaller deals or in competitive R&D fields valuations could remain chunky, particularly if public and private investors continue to hand over cash so readily.

“It’s a seller’s market now, smaller companies have the upper hand when it comes to valuations,” says Mr Loncar. “When a company like Celgene drops as much as it did, that’s a once in 10 years event. There’s a lot of pressure on them right now to fix it, and M&A is the quickest way to show they are doing something.”

M&A deal count by target status

Source: EvaluatePharma® 15 November 2017



Ongoing strength in financial markets will of course depend on macro issues and the absence of global economic or political shocks, all of which remain hard to predict. But, barring these unforeseen events, few see investor support for early-stage biotech dimming significantly next year.

“I think the IPO markets are relatively hot right now. I’ve heard some investment banks on Wall Street talk about companies IPO’ing preclinical data, and I think that’s the first time we’ve seen that since 2015/16,” says Chris Hollowood, chief investment officer of Syncona, a UK-based life science investment firm.

Strong capital markets allow smaller drug developers to contemplate funding later-stage development independently, which inevitably has an impact on deal making. So a busy IPO scene could well have contributed to the decline in the number of private-company take-outs in 2017.

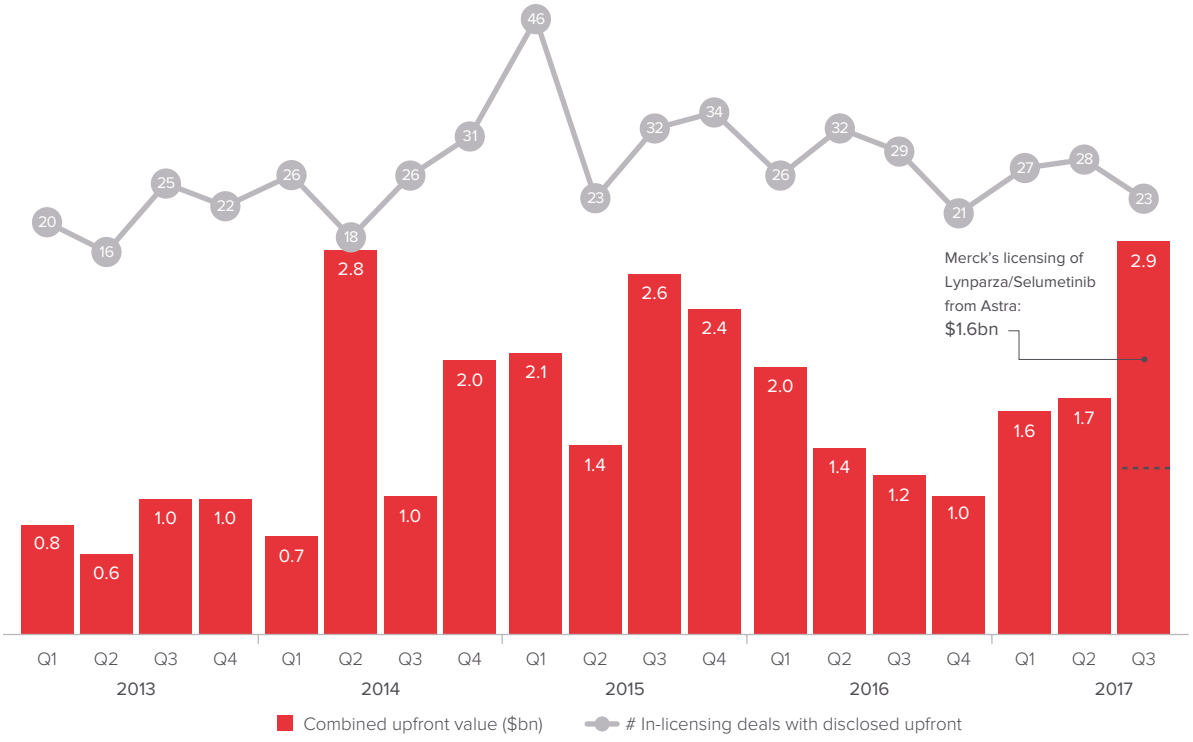
“In today’s market you can clearly arbitrage the ability to go public versus a trade sale. And many times companies will go public – so there is less M&A,” says Sander Slootweg, managing partner at the venture firm Forbion Capital Partners.

In the same way, deal watchers should probably expect another strong year for licensing transactions in 2018, as smaller players seek to retain more of the value of their assets.

The analysis below shows that, while the volume of licensing deals has remained fairly level over the past five years, the amount of money handed over in up-fronts has peaked in the boom years – pointing to more power in the hands of the sellers.

Licensing activity – total upfronts paid and deal volume

Source: EvaluatePharma® 15 November 2017

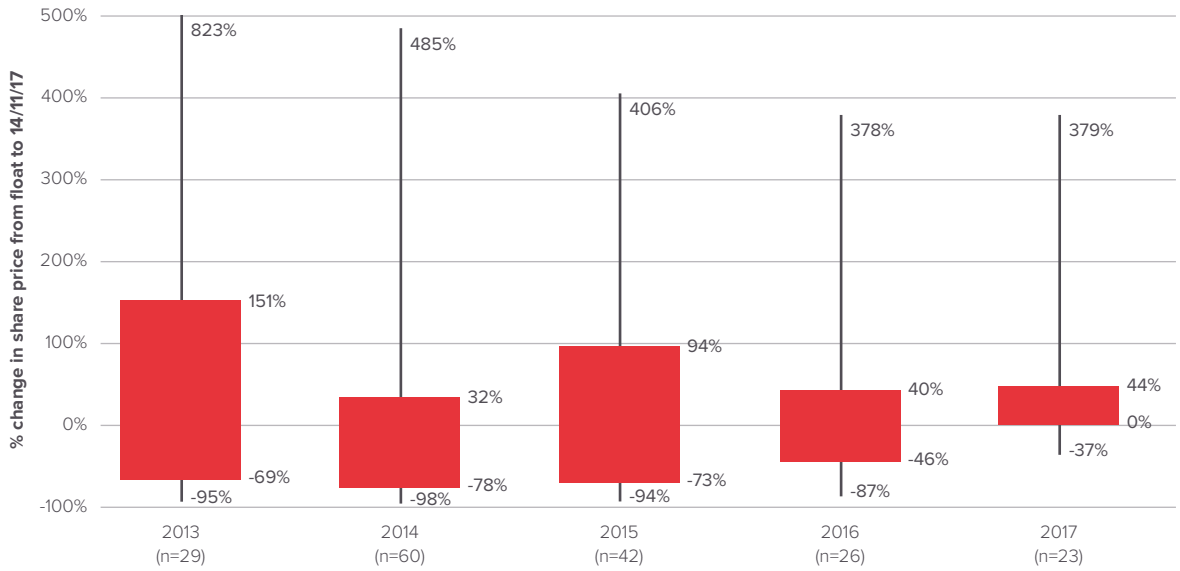


So, unless a highly motivated buyer emerges, it is easy to see how some investor M&A fantasies might not be fulfilled next year. An example of the disappointment that can follow was seen with Loxo Oncology in November, which saw its shares sink in the wake of a huge deal with Bayer over its tumour-agnostic cancer therapies, which included $400m in up-front cash. One reason given for Loxo's slump was that investors had been hoping for a straight takeout.

At the same time, however, these red-hot investment targets need to keep delivering. A market that becomes excessively tolerant of risk is not healthy, and the performance of recent IPOs in particular will be closely watched.

Share price performance of recent Nasdaq-listed drug developers

Source: EvaluatePharma® 15 November 2017



Another signal that 2018 will be a strong year for IPOs is the reappearance of crossover funds in venture funding rounds. These deep-pocketed investors, which largely exited the biotech sector in 2016's lull, help shepherd private companies onto the public markets by supporting large pre-IPO funding rounds.

The ability of venture capital players like Syncona, Forbion and Medicxi to float their investments has been a major boon for the private sector in the past couple of years. Should this trend continue next year, and acquirers start shopping around for assets with more urgency, the venture world could be looking at an even more successful period.

Even in Europe, which has historically trailed the US in its ability to support start-ups, venture firms are feeling optimistic about the coming year. Forbion's Mr Slootweg says that intense competition for deals in the US has pushed up local asset prices, prompting cash-rich venture firms to look to Europe.

"That is a healthy trend as we could do with a bit more capital flowing into Europe. And in later rounds we very much like to get experienced US investors in, to build bridges," he says.

Those bridges could ultimately lead to a Nasdaq listing, where many European companies successfully raised money last year, and will continue to do so in 2018, he predicts.

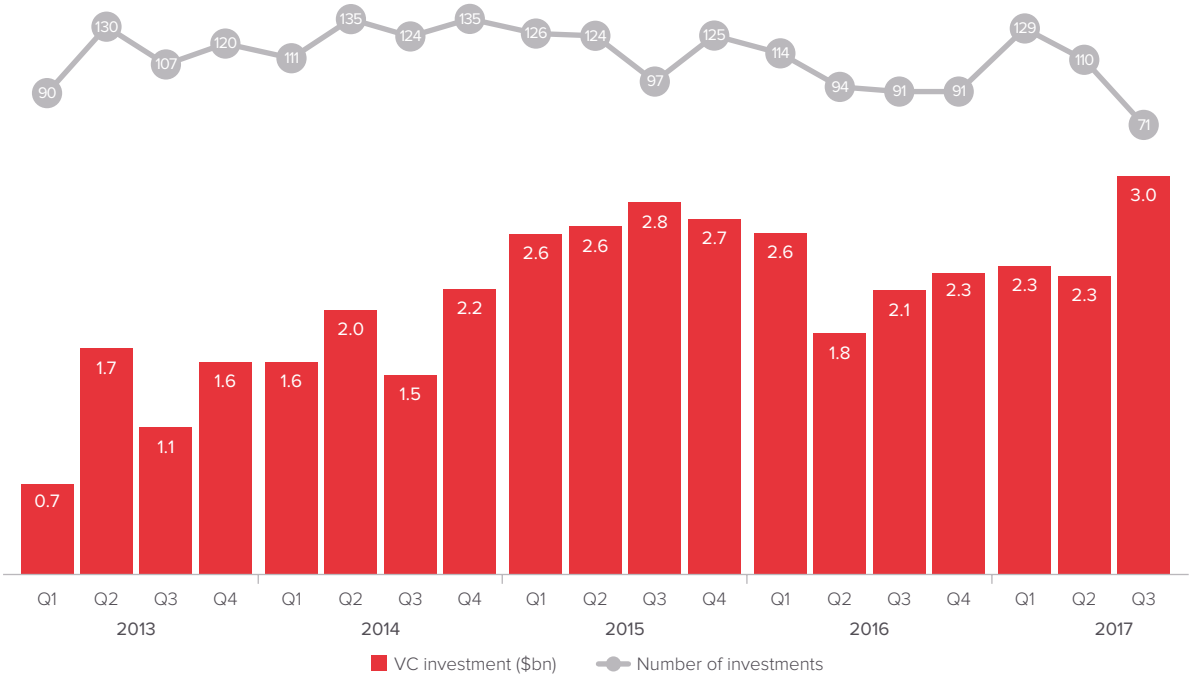
Mr de Rubertis of Medicxi agrees. "Nasdaq is a necessary step for later in the evolution of [a European] company."

Neither sees this as a loss of talent to the US – only the actions of companies that operate on a global marketplace, raising money where knowledgeable investors are more numerous and the pools of capital substantially deeper.

"You need to convince investors that you're building global leading companies, not European leading companies," says Mr Hollowood of Syncona.

Quarterly VC investment

Source: EvaluatePharma® 15 November 2017



Pricing and policy – the US pricing debate

Of course it will not only be financial markets in the US that influence the climate for biopharma companies next year – heightened scrutiny of drug prices in the world's most lucrative medicine market will remain a live issue.

However, it seems likely that the focus of the debate will continue to shift away from any potential actions by central government, towards state level manoeuvring and other sources of market disruption.

Three years of pharma-bashing have yielded almost no US action on drug pricing and even President Trump, the occasional tweet or applause line notwithstanding, appears to have lost interest. His appointment of a former Lilly executive, Alex Azar, as Health and Human Services secretary is surely another positive sign for the sector.

> To a degree the investor base has decided that drug pricing is what it is – it's something we will hear about but it's proven to be something very difficult to change, says Mr Syed of Mizuho.

But state-level action has sparked some worries, especially as California has enacted two laws that could affect pricing strategies – a price transparency law and another that limits the power of pharma to offer discounts as part of patient-assistance programmes. It is too soon to predict how many others might follow the Golden State's lead, but with 2018 an election year for thousands of legislative seats the drug-pricing battleground is shifting to state capitals

Looking ahead to 2018, David Mitchell, founder and president of Patients for Affordable Drugs, says advocates for drug price restrictions could win passage of legislation in between six and 10 states, specifically naming Washington, Oregon, Colorado, Michigan and Wisconsin, where a bipartisan consensus is developing on the issue.

These states are the most fertile ground for these kinds of laws, he says, in part because they have to pay for drugs in their Medicaid programmes and also, in many cases, are legally required to have a balanced budget. “Taking action to lower drug prices is both good policy and good politics,” he says.

None of these actions have been shown to have a real effect on prices so far. But if any gain teeth, or if weighty bills with bipartisan support emerge in 2018, industry and investors will want to pay close attention to what is happening at state level.

Flexing muscles

As the situation stands, drug makers have really only felt falling branded drug prices in huge therapy areas with lots of competition – like diabetes or respiratory medicines. But with the issue moving more into the public consciousness, fears are growing that payers will flex their muscles more widely.

Makers of multiple sclerosis drugs became the villain of the moment in September after members of US Congress demanded information on pricing and distribution channels. It is not inconceivable that the spotlight will fall on other chronic conditions, particularly where cheaper biosimilars are looming, like rheumatoid arthritis.

Signs that the oncology space is coming under pricing pressure would represent a worst-case scenario for the sector. But for now this has not emerged, and has also not been apparent in the rare disease field where huge price tags frequently prompt hysterical headlines.

“When new drugs for rare diseases get approved like Spinraza, you see these terrible stories, but so far I’ve seen no push back on those types of drugs. Spinraza has had a great launch, Neurocrine is off to the races, Sarepta is a poster child. These are the types of things you want to invest in – life-saving or delivering a lot of value,” says Mr Loncar.

Distinguishing between innovation and abuse of market position is not always easy, of course, though tangible fallout from this polarising debate would seem to be limited for now.

Serial disrupter?

Elsewhere in the industry, fears of US government intervention in drug pricing are being replaced by concerns about the entry of a muscular new buyer. The arrival of the online retail giant Amazon in delivery channels is already a dominant talking point, with big pharma, insurers and pharmacy benefit managers all being forced to confront the possibility that “the everything store” could soon be selling prescription drugs.

Amazon’s silence on its plans has stimulated much speculation, with analysts suggesting that it could become anything from an online pharmacy to a full-scale pharmacy benefit manager (PBM). This is more of a worry for the PBMs than pharma at this stage; for drug makers, Amazon would likely be a customer in one form or another, rather than a competitor.

But how this threat shapes up will be a preoccupation next year. Perhaps a more esoteric question for biopharma is what potential Amazon has to improve transparency in the murky world of drug pricing. If the online retailing giant decides to pursue a large role in the supply chain, it will become a customer that could prove to be tougher than today’s PBMs.

Pause or pull back?

In many ways it is easy to see how high expectations have built in certain corners of the biopharma sector.

The checkpoint inhibitors Keytruda and Opdivo arrived in 2014 and in only two years had cumulatively generated revenues of $8bn. In 2017, sales of the five anti-P(L)-1 antibodies now on the market are expected to reach $10bn. Hence the pressure on the immuno-oncology pipeline to keep these revenues growing.

In rare diseases, Alexion and others have shown that blockbuster franchises can be built around tiny patient populations. Novartis and Kite have demonstrated that ground-breaking science can be turned into commercial products, in a relatively short amount of time. And the first bona fide gene therapy is likely to arrive in the US in 2018 in the shape of Spark's Luxturna.

"Science is only getting better in biotech, and these companies are only getting smarter," says Mr Syed at Mizuho. "We're starting to look at how to treat diseases that historically had no standard of care. Look at the number of trials in gene therapy and nucleic acid therapies – this is something that scientists have been working on for the last 50 years. And now it's a reality. People are excited about this stuff."

However, excitement about the long-term gains must be tempered by realism about the short-term challenges. And many of those could become apparent in 2018.

The sell-off in biotech shares in the US in October and early November prompted many to wonder whether investors are only just waking up to these issues.

"I don't think [the sell-off] is a sign of a problem, but maybe a bit of fatigue," says Mr Loncar, pointing out that the IBB and XBI, two closely-followed funds that track Nasdaq-listed biotechnology stocks, are up 20% and 40% so far in 2017. "That's a pretty good year. It's reasonable we are taking a pause."

Should the pause turn into something that looks more like a pullback, then there will be more reason to worry about 2018.

But there is plenty in the pipeline that could go right next year. Regulatory stances are unlikely to shift suddenly, and truly innovative therapies are being reimbursed. Throw in a couple of big deals and an absence of aggressive pricing rhetoric, and the outlook improves even more.

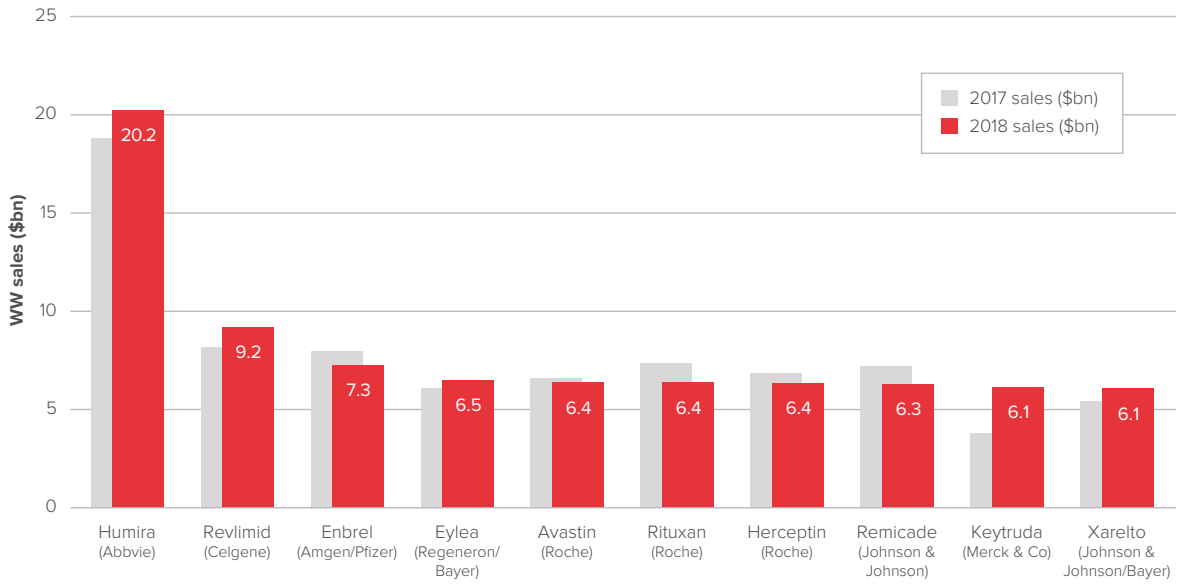
"If you look at the pace of R&D, there has probably never been a better time for a lot of science," says RBC's Mr Yeoh. "We're curing cancers that we've never cured before, we've got new drugs for MS, new treatments for diabetes. Costs aside, we are still making progress on human health."

That progress will continue in 2018, however confident investors are feeling.

Putting 2018 into numbers

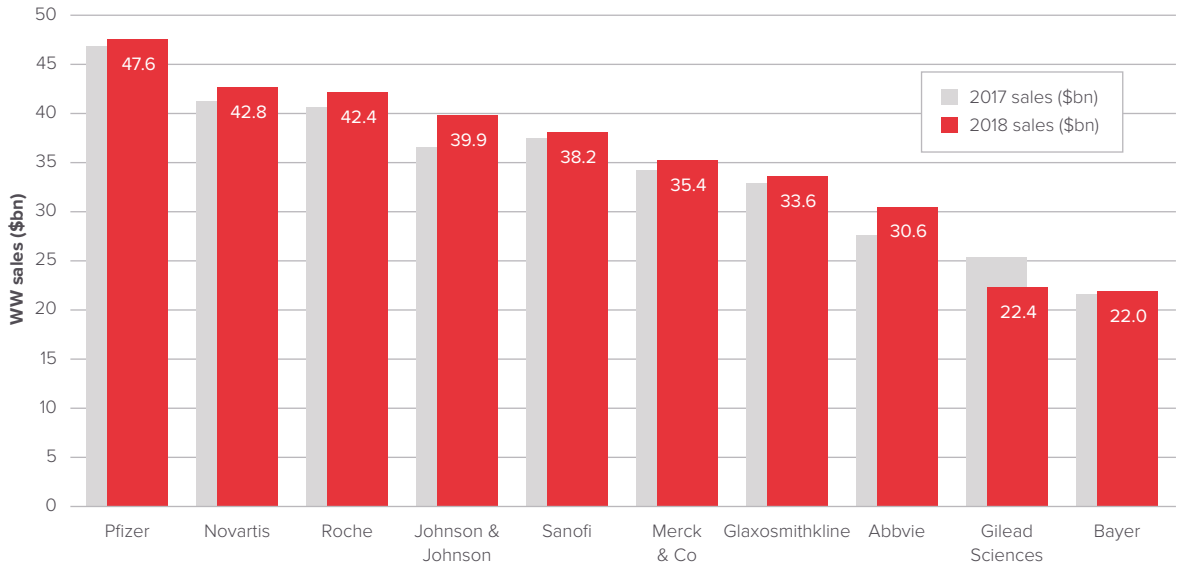
Top 10 drugs by 2018 sales ($bn)

Source: EvaluatePharma® 15 November 2017



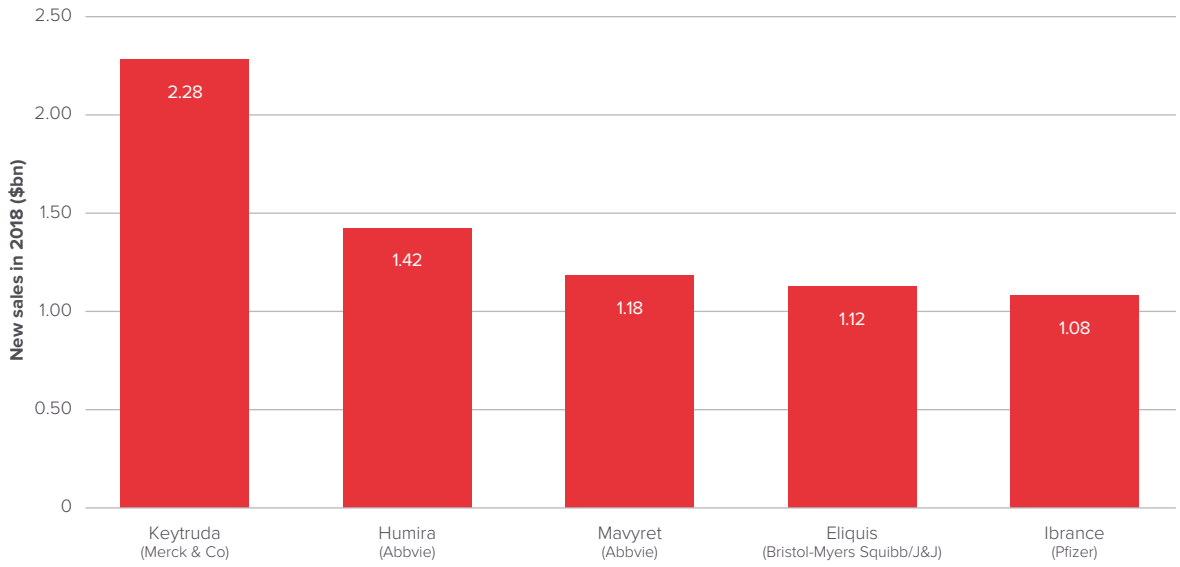
The biggest pharma companies – Rx and OTC sales

Source: EvaluatePharma® 15 November 2017



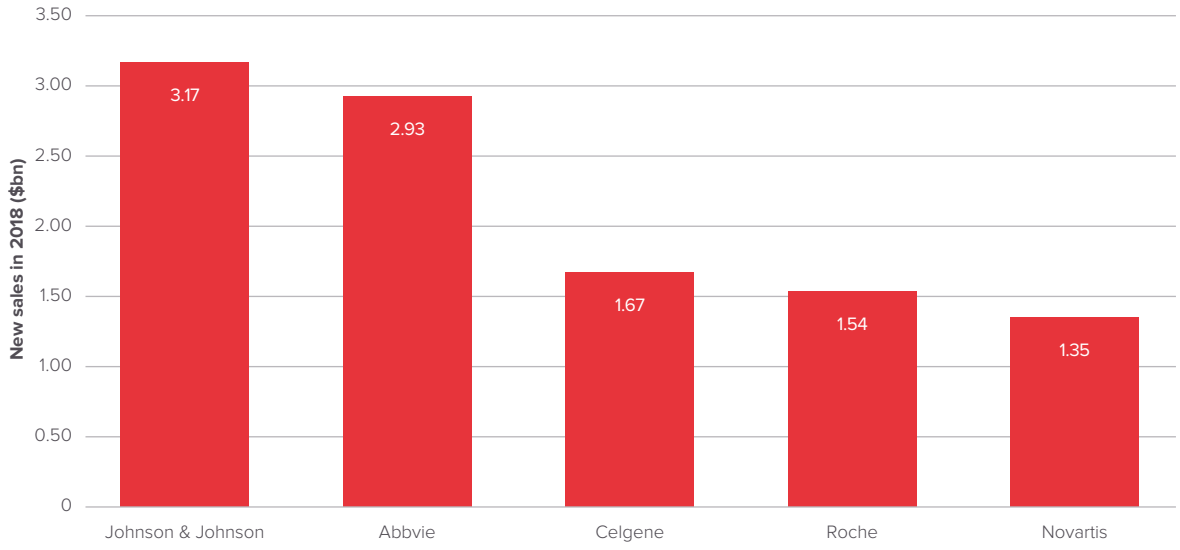
Top 5 drugs in 2018 by forecast year-on-year sales increase ($bn)

Source: EvaluatePharma® 15 November 2017



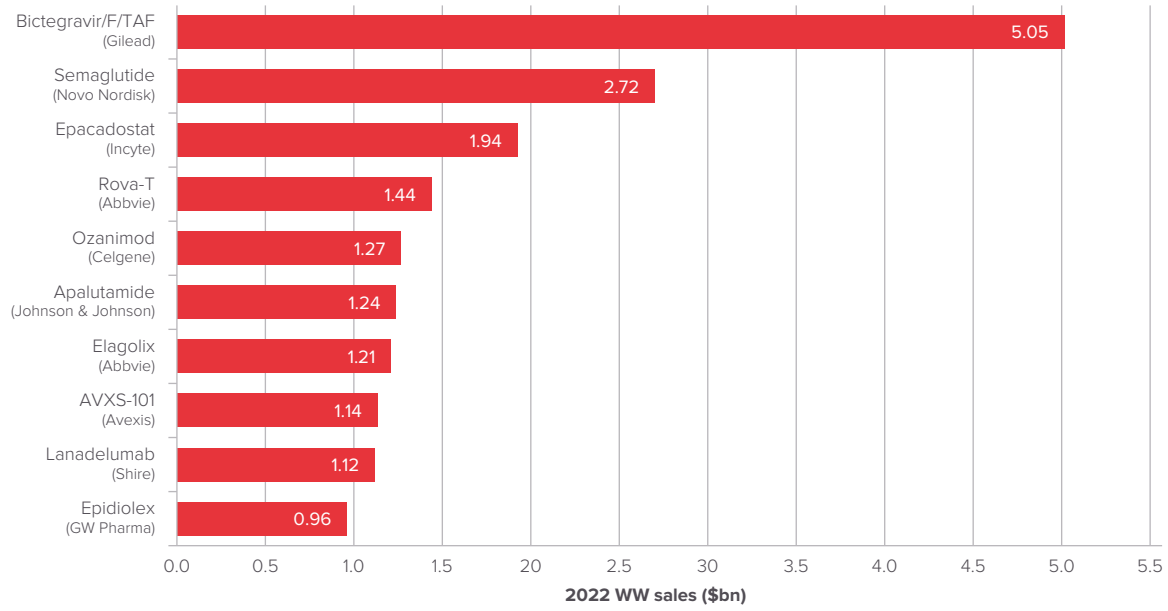
Top 5 companies in 2018 by forecast year-on-year sales increase ($bn)

Source: EvaluatePharma® 15 November 2017



Top 10 potential launches in 2018 by 2022 sales ($bn)

Source: EvaluatePharma® 15 November 2017



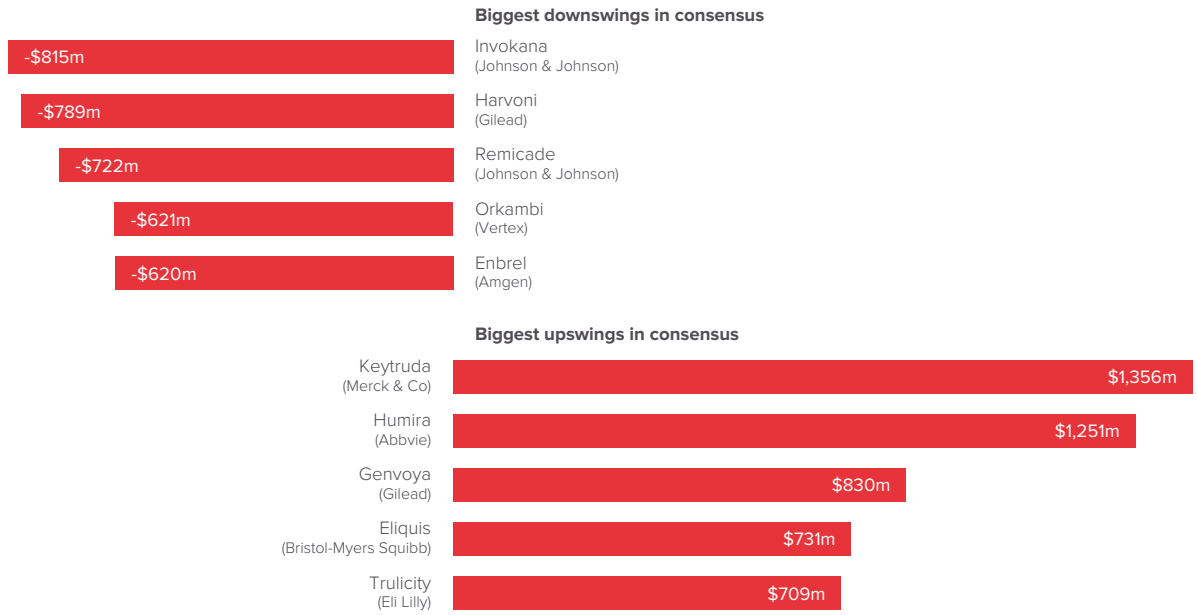
Single product companies approaching launch

Source: EvaluatePharma® 15 November 2017

Company	Product	US approval	2022e sales ($m)
Agile Therapeutics	Twirla	26 December 17	330
Achaogen	Plazomicin	26 October 18	313
Rigel Pharmaceuticals	Tavalisse	17 April 18	287
Tetraphase Pharmaceuticals	Eravacycline IV	Mid-2018 (EU)	237
Æterna Zentaris	Macrilen	29 December 17	56

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

Source: EvaluatePharma® 15 November 2017



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