



Pharma, Biotech & Medtech 2018 in Review

Amy Brown, Elizabeth Cairns, Edwin Elmhirst – February 2019

Vantage 

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Vantage Pharma, Biotech and Medtech 2018 in review

Looking back over 2018, it is clear that the year was one of contrasts for biopharma companies. The medtech sector was fairly placid in comparison.

For drug developers, areas of disappointment included the failure of acquisition activity to pick up, something many had hoped for at the beginning of the year. In the research sphere, the red hot immuno-oncology space was marked by clinical blow ups and lack of progress from experimental mechanisms. And for commercial-stage companies the downward pressure on drug pricing, and negative political rhetoric on the issue, continued apace.

Macroeconomic issues weighed at the end of the year, causing stock market gains clocked up by the biotech sector over the first nine months to be painfully erased. Big pharma retained its status as something of a safe haven, while medtech companies also escaped much of the damage.

The devices sector also saw a sharp drop in the number of acquisitions closed last year – hardly unexpected after the fireworks of 2017 – which allowed private equity groups to come to the fore as buyers. The quietude of the medtech merger scene had knock-on effects on other aspects of the industry, with a steady fall in venture capital deals – in terms of both the number of rounds and the amount spent – across the year. The rounds that were raised showed funds exhibiting a notable interest in digital health companies, with their relative speed and ease of development and proven attractiveness as acquisition targets.

Conversely, over in drug development the venture industry produced a banner year, investing a staggering \$16.8bn in global start-ups. A slowdown was evident by the end of 2018, but the private financings sector remained in rude health, helped in no small part by enthusiastic demand for new issues.

Biotech IPOs also set new records last year, with equity investors also showing interest in medtech companies. Intriguingly, given the generally dismal fourth quarter on the stock exchanges, it was the final period that saw a new high for device players.

The FDA again showed itself to be biopharma's friend in 2018, green lighting a record number of novel medicines. Meanwhile, the number of high-risk devices approved fell sharply from the 2017 total, corresponding with the agency's repeated vows to increase the stringency of its regulatory processes. An increase in lower-risk devices, cleared for sale via the de novo pathway, went some way towards compensating for this.

This round up of the major data points describing the progress of biopharma and medtech companies last year paints a mixed picture, but there are more signs of health than of weakness. Some of the bars set in 2018 will be tough to beat, but in many areas the foundations are in place for another strong year.

Report authors | Amy Brown, Elizabeth Cairns, Edwin Elmhirst – February 2019

Unless stated, all data are sourced to Evaluate and were compiled in January 2019.



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Pharma and Biotech 2018 in review

The year ends with a whimper for biotech stocks

In September biotech was heading for a safe, albeit unspectacular, 2018. But then the fourth quarter happened.

As broader indices fell it was high-risk stocks like biotech that took a disproportionate hit: the closely-tracked Nasdaq Biotechnology Index lost a fifth of its value over the three-month period, amounting to a very painful end to the year for investors in this sector.

The year-end slump turned a 15% nine-month climb for the NBI into a 9% year-end decline. Big pharma thus resumed its traditional role as provider of a safe haven of sorts.

Indices

Stock index	% change in 2018
NASDAQ Biotechnology (US)	(9%)
S&P Pharmaceuticals (US)	5%
Dow Jones Pharma and Biotech (US)	0%
S&P 500 (US)	(6%)
DJIA (US)	(6%)
Dow Jones STOXX 600 Healthcare (EU)	(3%)
Thomson Reuters Europe Healthcare (EU)	(5%)
Euro STOXX 50 (EU)	(15%)
FTSE-100 (UK)	(13%)
TOPIX Pharmaceutical Index (Japan)	(7%)

Of course, everything is relative. The anaemic 5% full-year increase in the S&P Pharmaceuticals index, for instance, only looks impressive because all the other key biopharma indices ended 2018 either flat or in the red.

And, while investors clearly fled from risk, macroeconomic issues were also behind the FTSE-100 and Euro Stoxx 50's double-digit falls. The Japan index had stood up 17% at the end of September, but this proved to be the peak that launched an 18% crash in the fourth quarter.

If any single company was to blame for this it was Takeda, one of that index's biggest constituents. Takeda's unpopular \$64bn takeover of Shire resulted in the Japanese group being crowned the biggest value destroyer of the big caps outside big pharma, sitting on a 42% year-end share price fall.

The other end of the \$20bn of value that Takeda lost is a gain of just \$6bn for Shire, so clearly the Japanese group is suffering a broader crisis of confidence. Its poor performance was only marginally worse than that of Bayer, which is also being punished heavily for an unpopular acquisition, that of Monsanto.



Celgene stands as a sorry laggard, a fact that goes a long way to explaining why Bristol-Myers Squibb managed to agree to buy the big biotech for \$74bn in January. The price tag is 35% below Celgene's peak valuation, showing how the fourth quarter retrenchment in share prices has at least made some companies affordable.

Other big drugmakers (\$25bn+): Top risers and fallers in 12 months

Source: Evaluate[®] January 2019

Top 3 risers	Share price 12-mth change	Market capitalisation (\$bn)	
		YE 2018	12-mth change
CSL (AUD)	31%	59.6	9.9
Shire (\$)	12%	122.2	5.8
Amgen (\$)	12%	53.3	(1.5)
Top 3 fallers			
Takeda (¥)	(42%)	41.3	(19.8)
Bayer (€)	(42%)	65.1	(42.3)
Celgene (\$)	(39%)	53.3	5.8

The weighty fallers above shielded the poor performances of Celgene peers like Gilead, off 13% for the year, and Novo Nordisk, down 11%. Amgen found itself in the top gainers club only thanks to a \$10bn share buyback; its market cap actually shrank 1% over 2018.

So what about those big pharma safe havens? Once deeply unexciting companies like Lilly and Pfizer now stand as shining beacons among the sector's most rewarding investments. Even Glaxosmithkline ended the year up 13% as its recent corporate rejig showed that the group really did want to be a pharma company.

The share price of Merck & Co, meanwhile, continues to reflect that company's growing domination of lung cancer treatment with immuno-oncology – at the expense of Bristol-Myers Squibb and Roche. The former has now been forced into a megamerger, but the latter's fall is surprising given its huge new growth drivers Ocrevus and Hemlibra.

Johnson & Johnson's 8% fall was due to a disastrous December, in which a Reuters report accused the group's consumer division of concealing the presence of asbestos in baby powder.

With more winners than losers in J&J's cohort the key question going into 2019 – apart from who will be the next Bristol and Celgene – is how much longer drug price increases can be relied on to boost the performance of the biggest pharma players.

Big pharma companies: Top risers and fallers in 12 months

Source: Evaluate[®] January 2019

Top 3 risers	Share price 12-mth change	Market capitalisation (\$bn)	
		YE 2018	12-mth change
Eli Lilly (\$)	37%	122.6	29.7
Merck & Co (\$)	36%	198.7	47.0
Pfizer (\$)	21%	252.3	35.8

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Top 3 fallers	Market capitalisation (\$bn)		
	Share price 12-mth change	YE 2018	12-mth change
Bristol-Myers Squibb (\$)	(15%)	84.8	(14.0)
Johnson & Johnson (\$)	(8%)	346.1	(28.7)
Roche (SFr)	(1%)	210.6	(4.7)

The year-end wild ride on the stock exchanges led to some unexpected companies topping the table when it came to mid- and small-cap biopharma. So it was that Japanese groups, led by Sumitomo Dainippon Pharma, were the top mid-cap gainers in 2018.

Settlement of patent disputes over depression drug Latuda, potentially delaying generic competitors until 2023, drove Sumitomo shares up at the end of November. That positive news allowed the company to top even Eisai, the best performer at nine months. Shares in Eisai were lifted in 2018 by positive-looking, if controversial, data for Alzheimer's project BAN2401.

The only non-Japanese group in the mid-cap risers was Ipsen, which has benefited from its partnership with Exelixis on Cabometyx as well as strong signals that it intends to expand in oncology and the US market.

The big fallers had the usual troubles of clinical failure or strategic misadventures. Leading the fallers was Perrigo, which scored a triple with an unexpected management shift, an unpopular business unit spin-off and a surprise year-end tax bill from Irish authorities.

Alkermes was hit repeatedly by setbacks for depression drug ALKS 5461, the last of which was a negative FDA advisory committee vote in November. Meanwhile, Nektar's shares collapsed as the promise of its IL-2-stimulating project NKTR-214 faded over the year.

Mid cap companies (\$5-25bn): top risers and fallers in 12 months

Source: Evaluate[®] January 2019

Top 5 risers	Market capitalisation (\$bn)		
	Share price 12-mth change	YE 2018	12-mth change
Sumitomo Dainippon Pharma (¥)	109%	12.3	6.3
Eisai (¥)	33%	22.4	5.2
Taisho Pharmaceutical Holdings (¥)	23%	8.8	1.5
Daiichi Sankyo (¥)	20%	22.1	3.3
Ipsen (€)	13%	10.9	1.0
Top 5 fallers			
Perrigo Company (\$)	(56%)	5.3	(7.0)
Aspen Pharmacare (ZAR)	(51%)	4.2	(6.1)
Alkermes (\$)	(46%)	4.6	(4.0)
Nektar Therapeutics (\$)	(45%)	5.7	(3.9)
Bluebird bio (\$)	(44%)	5.4	(3.5)



Among the small caps, Amarin was the clear winner: a surprise smash hit with Vascepa, which showed a cardiovascular benefit in the Reduce-It study, added more than \$3bn to the company's value last year.

Sanbio was lifted by data suggesting its stem cell project SB623 showed benefit in traumatic brain injury patients. This company provides a prime example of why huge gains can be short lived in biotech: the failure of a stroke trial in January erased almost three-quarters of Sanbio's value, meaning the company is likely to end up as one of 2019's biggest fallers.

Last year, that crown was also taken by those suffering clinical and commercial failure.

Synergy fell into bankruptcy after failing to make a living from constipation drug Trulance; Faron's lead asset Traumakine failed to show a benefit in respiratory distress syndrome; and Celldex's glembatumumab vedotin crashed out in triple-negative breast cancer, prompting the group to discontinue all research.

Small cap companies (\$250m-\$5bn): top risers and fallers in 12 months

Source: Evaluate* January 2019

		Market capitalisation (\$m)	
	Share price 12-mth change	YE 2018	12-mth change
Top 5 risers			
Amarin (\$)	239%	4,480	3,394
Arrowhead Pharmaceuticals (\$)	238%	1,145	870
Mirati Therapeutics (\$)	197%	1,379	965
Pacific Biosciences of California (\$)	180%	1,107	762
Sanbio (¥)	151%	3,575	2,276
Top 5 fallers			
Synergy Pharmaceuticals (\$)	(95%)	28	(522)
Melinta Therapeutics (\$)	(95%)	46	(449)
Gtx (\$)	(94%)	19	(259)
Faron Pharmaceuticals (€)	(93%)	20	(274)
Celldex Therapeutics (\$)	(93%)	34	(367)

Related Vantage coverage

Top 5 risers	
Amarin (\$)	Amarin lands the catch of a lifetime
Arrowhead Pharmaceuticals (\$)	Looking for new mechanisms to cure hepatitis B
Mirati Therapeutics (\$)	-
Pacific Biosciences of California (\$)	Illumina bets on Pacific, not nanopores
Sanbio (¥)	Daily Market Movers: Global Majors & Industry (2 Nov 2018)
Top 5 fallers	
Synergy Pharmaceuticals (\$)	Daily Market Movers: Global Majors & Industry (26 Oct 2018)
Melinta Therapeutics (\$)	-
Gtx (\$)	GTX's value leaks away with incontinence failure
Faron Pharmaceuticals (€)	Snippet roundup: Pivotal fluffs from Faron and Fasenna
Celldex Therapeutics (\$)	Celldex puts the negative in triple negative



Company buyout and licensing deal activity disappoint in 2018

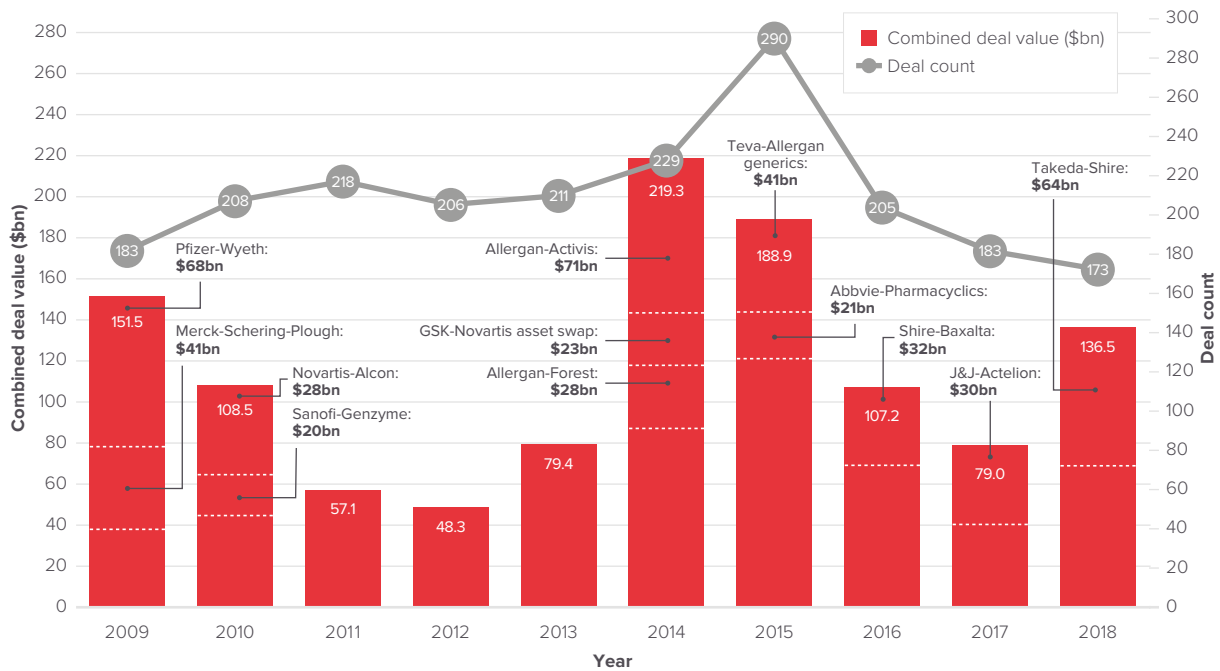
The quick-fire takeouts of Celgene and Loxo Oncology in the opening weeks of 2019 might have caused many to forget just how quiet the biopharma M&A scene was last year. Make no mistake, it was slow: even in the post-financial crash years the sector managed to sign more transactions than in 2018.

A look at historical data from EvaluatePharma illustrates the extent of the dealmaking slowdown in 2018. Big ticket mega-mergers inflate the dollars spent, of course, and Takeda gave biopharma's M&A bill a big boost in 2018, however it is transaction volume that really indicates activity levels.

This analysis looks only at companies developing human therapeutics, buying other developers of these medicines – arguably the highest-risk end of the sector – and excludes subsectors like medtech or genomics.

A decade of biopharma M&A

Source: Evaluate* January 2019



The sector really entered the current slow period in 2016, and given that the 2014/15 bubble had seriously deflated by then, this is not surprising. It is also notable that, more recently, activity seems to have been focused in the early months of the year. The desire to win column inches throughout the high profile JP Morgan Healthcare conference, which takes place every year in January is probably a factor here.



Those who think the deal desert is finally coming into bloom again should probably remember that the last three years all opened impressively, but then went on to wilt.

Last year's takeover of Shire by Takeda actually emerged in the first quarter, but was only formally accepted in May. And as with the Actelion and Baxalta deals of the preceding years, the transaction represented the big news of the year, with dealmaking slowing in the following months.

Talk of a resetting of valuations is spurring hopes that this year's opening bang will not immediately fade to a whimper. The removal of Celgene, one of the sector's most enthusiastic dealmakers, from the market is something of a negative: the biotech struck two of 2018's biggest deals.

There are plenty of other motivated buyers out there. The metric to watch, however, is the number of transactions being announced in the coming months. Only this will indicate whether underlying demand really is picking up, outside of these headline-grabbing buyouts.

Biggest M&A deals announced in 2018

Source: Evaluate* January 2019

Date announced	Acquirer	Target	Value (\$bn)
May	Takeda	Shire	64.2
Jan	Sanofi	Bioverativ	11.6
Jan	Celgene	Juno Therapeutics	9.0
Apr	Novartis	Avexis	8.7
Jan	Celgene	Impact Biomedicines	7.0
Dec	Glaxosmithkline	Tesaro	5.1
Jan	Sanofi	Ablynx	4.8
Apr	Les Laboratoires Servier	Shire's oncology business	2.4
Oct	Novartis	Endocyte	2.1
May	Eli Lilly	Armo BioSciences	1.6

Related Vantage coverage

Takeda	Fifth time's the charm as Takeda seals the deal with Shire
Sanofi	Sanofi bets against haemophilia gene therapy
Celgene	Juno falls to Celgene
Novartis	Avexis buy endorses gene therapy and gives Biogen a headache
Celgene	JP Morgan – Celgene makes an eve-of-meeting Impact
Glaxosmithkline	Glaxosmithkline's Tesaro move: start of a new acquisition wave?
Sanofi	Sanofi's Ablynx buy leaves no doubt about its pipeline troubles
Les Laboratoires Servier	Shire taunts Takeda with oncology sale
Novartis	From zero to hero, Endocyte completes a remarkable transformation
Eli Lilly	Lilly joins the cytokine gold rush with Armo deal

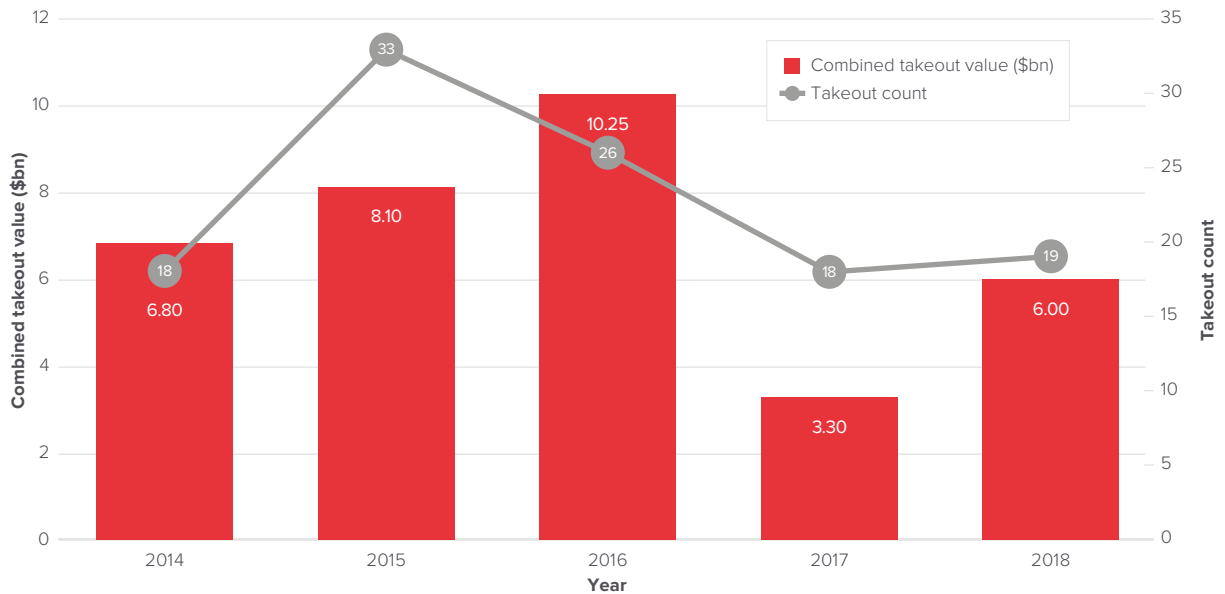


One group of investors that can take comfort from last year's performance is venture firms: buyouts of start-ups backed by venture cash did more than simply hold up last year.

More portfolio companies were bought for more money than in 2017, though activity remains below the 2015-16 peak. Given the broader M&A market trends this is pretty respectable, however, and will go some way to help justify the huge amount of money that is still sloshing around the venture world.

Buyouts of venture-backed drug developers

Source: Evaluate[®] January 2019



An adjunct to the M&A market is licensing deals, a vital source of non-dilutive funding for small drug developers. Worryingly for these companies and their investors, this activity slowed last year, to a five-year low.

Perhaps activity was muted by sky-high asset valuations, as with the company buyout scene.

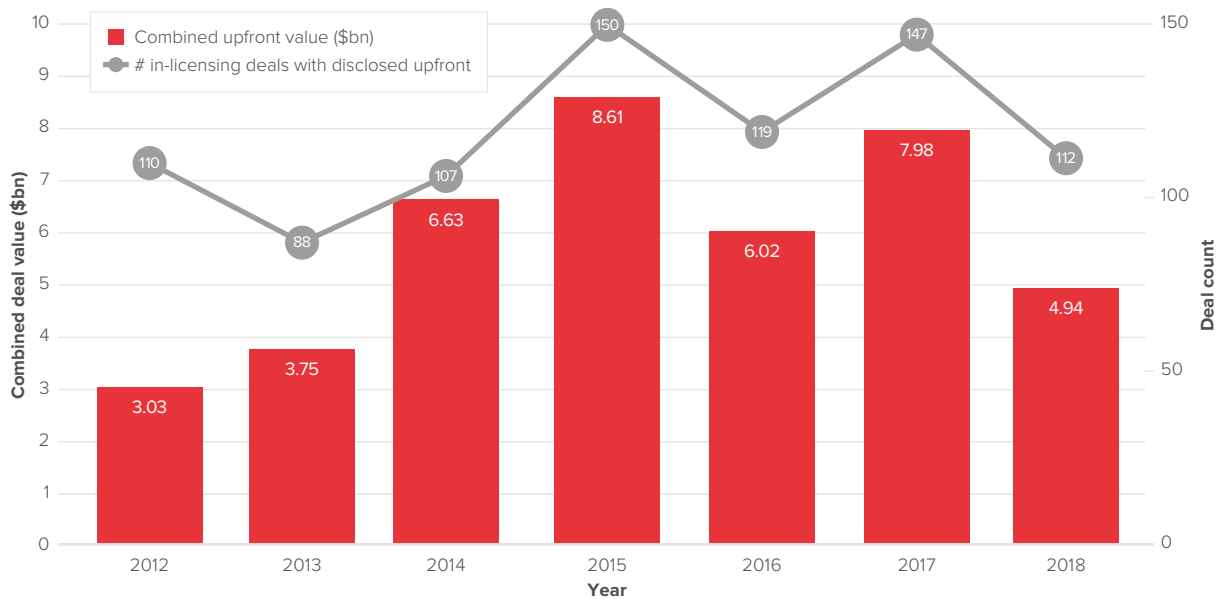
This analysis only includes licensing deals where an up-front value was disclosed, focusing on the most significant transactions that biopharma companies struck. It ignores the “bio-dollar” value that is frequently never realised, and focuses on the initial cash sum that changes hands.

This means that the count of transactions shown here under-represents the true level of licensing activity, though the trends will be largely representative of the entire market.



Biopharma's licensing deals: combined upfront payments and deal count

Source: Evaluate* January 2019



Large deals inevitably skew the numbers, a case in point being the tie-up between AstraZeneca and Merck & Co primarily over the former's Parp inhibitor, Lynparza, in 2017. This cost an initial \$1.6bn, the largest upfront figure since at least 2010; Bristol-Myers Squibb's \$1bn payment to corner Nektar's immuno-oncology hope NKTR-214 last year ranks as the second-largest, tied with the \$1bn that Merck & Co paid Bayer for certain rights to various cardiovascular projects back in 2014.

Deals of this size can quickly inflate the top-line values, and it tends to be oncology products that attract such large sums: three of the five largest up-fronts this decade have been paid for cancer assets. This highly competitive therapy area generated fewer up-front dollars last year than has been seen recently, providing another explanation for the dip.

If the M&A fails to pick up as hoped this year, companies and investors will have to hope that his apparent lull in licensing activity is short lived.



Biopharma's record venture year ends with a slowdown

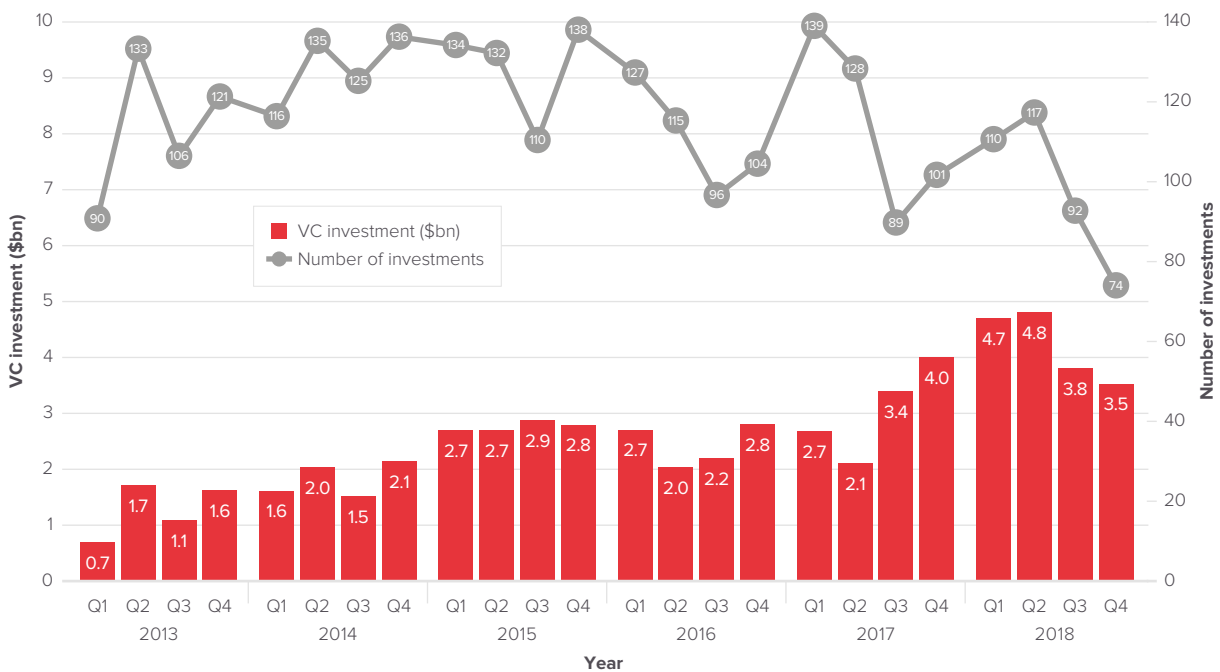
Anyone with even a half an eye on the venture capital industry should be aware that 2018 was a spectacular year. Driven by an explosion in huge funding rounds, private drug developers raised almost \$17bn globally even as the number of financings dropped to the lowest for a decade.

The sum raised smashed 2017's previous record by an impressive 39%; the venture world saw unprecedented investment activity across all sectors last year, and biopharma was no exception. Still, many assume that 2018 will not be repeated – the second quarter of the year looks to have been the peak – meaning the extent of any slowdown remains a big question for 2019.

This analysis of EvaluatePharma data includes only those companies involved in developing human therapeutics – the highest-risk end of biotech venture investing – and excludes subsectors like medtech or genomics.

Global quarterly biopharma venture investments

Source: Evaluate* January 2019



Investments are not expected to fall off a cliff this year. Venture funds are still very well stocked and able to raise new capital and the IPO window is open, for now at least, which bodes well for exits. Meanwhile the previous M&A analysis showed that the start-ups that these funds are creating are proving attractive to buyers.

However a return to levels seen in 2015 and 2016, years that were still pretty respectable historically speaking, is not unimaginable.



The recent funding peak was surely never sustainable and the drop in equity markets in October provided a timely reminder that the global bull run – a long-running period of climbing share prices – would not charge on forever. As such, investors look to have adopted a more prudent stance and figures for the first quarter of 2019 will be watched with interest, to see which way the venture winds are blowing.

Annual venture capital investments

Source: Evaluate* January 2019

Date	Investment (\$bn)	Financing count	Avg per financing (\$m)	No. of rounds ≥\$50m	No. of rounds ≥\$100m
2018	16.8	393	42.7	128	37
2017	12.1	442	29.9	72	16
2016	9.7	442	23.4	48	13
2015	11.0	514	22.5	56	13
2014	7.3	512	15.4	35	4
2013	5.1	457	12.6	12	3

This analysis of EvaluatePharma data shows that 37 drug developers raised more than \$100m apiece last year, more than double the number doing so in 2017. With ever fewer companies sucking up ever larger proportions of investment capital, the quality of the science emerging from these start-ups is another big unknown for 2019.

The answer to this will take much longer to emerge, of course. Meanwhile, the decline in Moderna's share price since it has been in public hands shows that not all investors share some of the stratospheric private sector valuations that have been achieved recently.

Many believe that over-availability of capital can have a detrimental impact on the quality of investments. Perhaps a return to something that looks more like normal in 2019 should be welcomed.

Top venture rounds of 2018

Source: Evaluate* January 2019

Company	Investment (\$m)	Round	Date
Moderna Therapeutics	500	Series Undisclosed	February
Samumed	438	Series A	August
Relay Therapeutics	400	Series C	December
Cerevel Therapeutics	350	Seed Capital	October
Allogene Therapeutics	300	Series A	April
Biontech	270	Series A	January
Cstone Pharmaceuticals	260	Series B	May
Brii Biosciences	260	Seed Capital	May
Celularity	250	Series A	February
Viela Bio	250	Series A	February



A bumper year for biotech flotations

The buoyant biopharma IPO scene set several new records in 2018, a notable achievement given the stock market turmoil of the fourth quarter.

Last year, new arrivals tapped investors for a record \$7.23bn, with the average amount raised tipping over \$100m for the first time, according to EvaluatePharma's tally of new issues. This analysis encompasses all developers of human therapeutics floating on Western stock exchanges.

Biotech IPO market by year

Source: Evaluate* January 2019

Year	No. of IPOs	Amount raised (\$bn)	Avg. amount raised (\$m)	No. raising >\$100m
2018	68	7.2	106	31
2017	50	3.9	77	15
2016	45	2.3	51	3
2015	78	5.1	65	17
2014	97	6.5	67	18
2013	54	3.3	60	7
2012	19	1.0	51	2

An examination of quarterly trends also shows few signs of the turmoil on the markets in the fourth quarter. Many assumed that the October sell-off would puncture the biopharma IPO bubble, but notably two of the year's biggest flotations – Moderna and Allogene – got away in the final months of the year.

True, the fourth quarter did dip compared with the prior quarters, and a handful of companies did shelve flotation plans citing market conditions. It should also be remembered that the Moderna IPO accounted for a third of the \$1.8bn raised in the fourth quarter; had this company not got away, the picture would look somewhat weaker.



Source: Evaluate* January 2019

Biotech initial public offerings by quarter on Western exchanges



The burning question is what awaits those hoping to brave the markets in 2019.

The value of Moderna has dropped considerably since its December IPO, and the mRNA researcher is now valued at a lower level than at its last private financing. This is arguably more a sign of Moderna's bloated valuation rather than of wider market sentiment. Allogene, for example, is on the way to doubling its market cap since floating in October.

In fact, there are few signs that the market cooling has tempered appetite for biotech new issues. A healthy number of young drug developers are gearing up to achieve a stock market listing in the opening months of 2019. The government shutdown delayed some ambitions but the arrival of the likes of Alector and Gossamer Bio, both sporting billion dollar-plus valuations, shows that public investors are still interested in the sector.

Top biotech IPOs on Western exchanges in 2018 (all Nasdaq)

Source: Evaluate* January 2019

Company	Date	Amount raised (\$m)	Share price change to YE18
Moderna Therapeutics	Dec	604	(34%)
Allogene Therapeutics	Oct	373	50%
Rubius Therapeutics	Jul	277	4%
Orchard Therapeutics	Oct	225	12%
Tricida	Jun	222	57%



Still, an analysis of the discount or premium that recent flotations achieved compared to their initially proposed price range does suggest that new hopefuls will have to work harder to get investors on board. Prior to the fourth quarter of 2018, proposed valuations were pretty much accepted, but this all changed in October.

It will be interesting to see how this graph develops as 2019 progresses. Markets have recovered somewhat in the opening weeks, but overall investors are predicting a tougher period ahead, largely due to macroeconomic concerns.

Perhaps the healthy queue of hopefuls indicates that those with public ambitions are rushing to get out the door while they still can. This could prove a wise strategy. The IPO window can bang shut very quickly.

Tracking haircuts: average float price premium/discount to initially offered range (mid-point)

Source: Evaluate[®] January 2019



Note: NASDAQ IPOs only



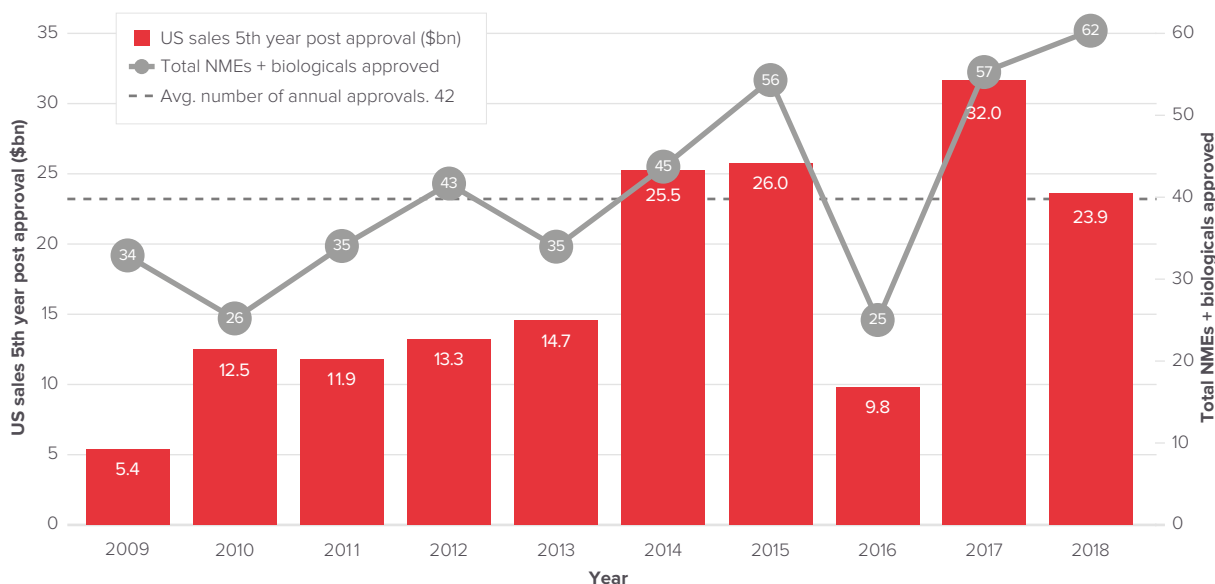
US FDA sets a new record for novel drug approvals

The US FDA approved 62 novel medicines last year, setting a new benchmark of productivity for a biopharma sector propelled by several years of strong investor support.

This new approval record is slightly tarnished when looking at the commercial potential of each year's cohort: 2017 remains the banner year for combined 5th year sales. This is not to say that 2018 was disappointing: last year's new arrivals are forecast to be selling \$24bn by 2023, signalling that biopharma's R&D engines remain in good condition.

FDA approval count vs. 5th year US sales

Source: Evaluate* January 2019



- 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), Eplusa (Gilead), Venclexta (Abbvie)
- 2017** – Ocrevus (Roche), Dupixent (Sanofi)
- 2018** – Biktarvy (Gilead), Epidiolex (GW Pharmaceuticals)

Drawing on EvaluatePharma's consensus of sellside forecasts, fifth-year sales have averaged at \$23.4bn over 2014-17, bang in line with 2018's total.

It will take some going to beat 2017 on sales potential. That year saw the arrival of Roche's multiple sclerosis treatment Ocrevus and Sanofi/Regeneron's autoimmune antibody Dupixent, two mega-blockbusters that gave a big boost to the topline number that year.

This analysis includes all drug approvals issued by both the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.

Looking at individual approvals, 2018 saw the launches of an entire class of new migraine drugs in Aimovig, Emgality and Ajovy; 17 cancer drugs, including six for haematological cancers; and the first RNAi therapeutic in Alnylam's Onpatro.



Top approvals of 2018

Source: Evaluate[®] January 2019

Product	Company	2024 US sales (\$bn)
Gilead Sciences	Biktarvy	5.0
GW Pharmaceuticals	Epidiolex	1.5
Amgen	Aimovig	1.5
Shire	Takhzyro	1.2
Array Biopharma	Mektovi	1.2

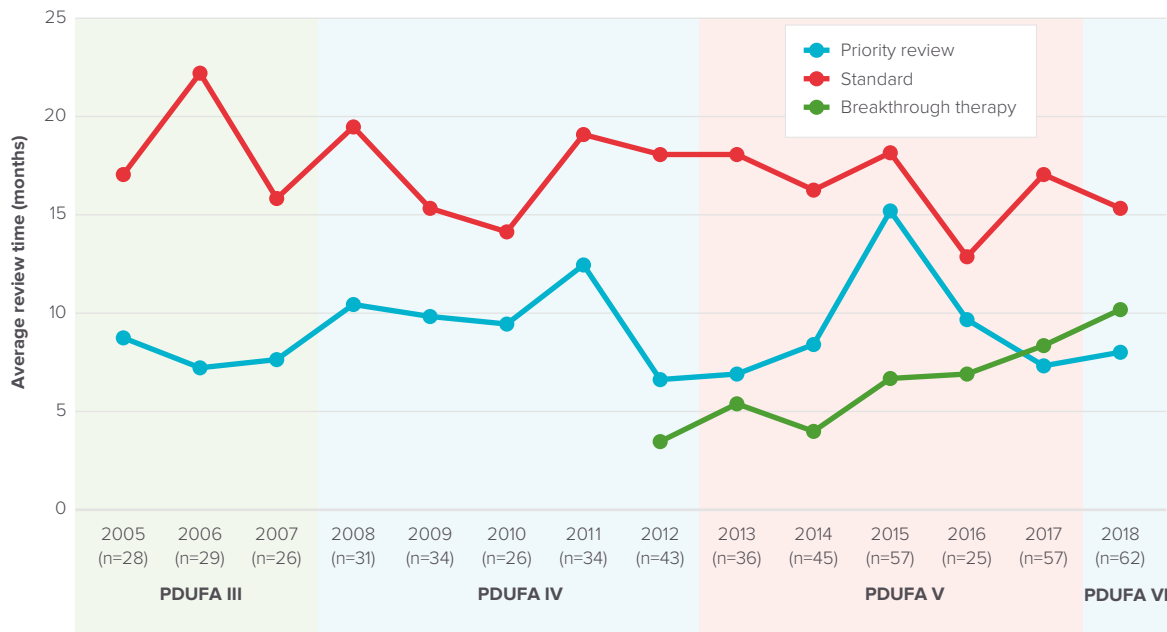
Behind the raw numbers, 2018 saw a slight reduction in average approval times, to 10.6 months. This came because of a faster than average standard review cycle, while priority reviews slowed slightly.

There was one potentially concerning trend: drugs awarded breakthrough therapy designations did not move through especially swiftly, with an average approval time greater than for those with priority review.

The apparent slowdown for the highest-priority drugs could be down to volume: 31 of the 62 approved drugs had priority review and 13 had breakthrough status.

CBER+CDER average approval times

Source: Evaluate[®] January 2019





Still, an FDA in overdrive has also helped the biopharma sector enjoy several years of apparent heightened productivity. And there are few signs that this era of regulatory permissiveness is coming to an end, though the US government's shutdown in January must cast some doubt over whether 2019 will be quite as remarkable.

Several blockbuster hopes are lining up for review this year, and in fact this year's biggest arrival, Alexion's Soliris follow-on, Ultomiris, has already reached the market.

Timelines for other projects have been less sure due to the US government shutdown. And uncertainty could return if there is another extended closure.

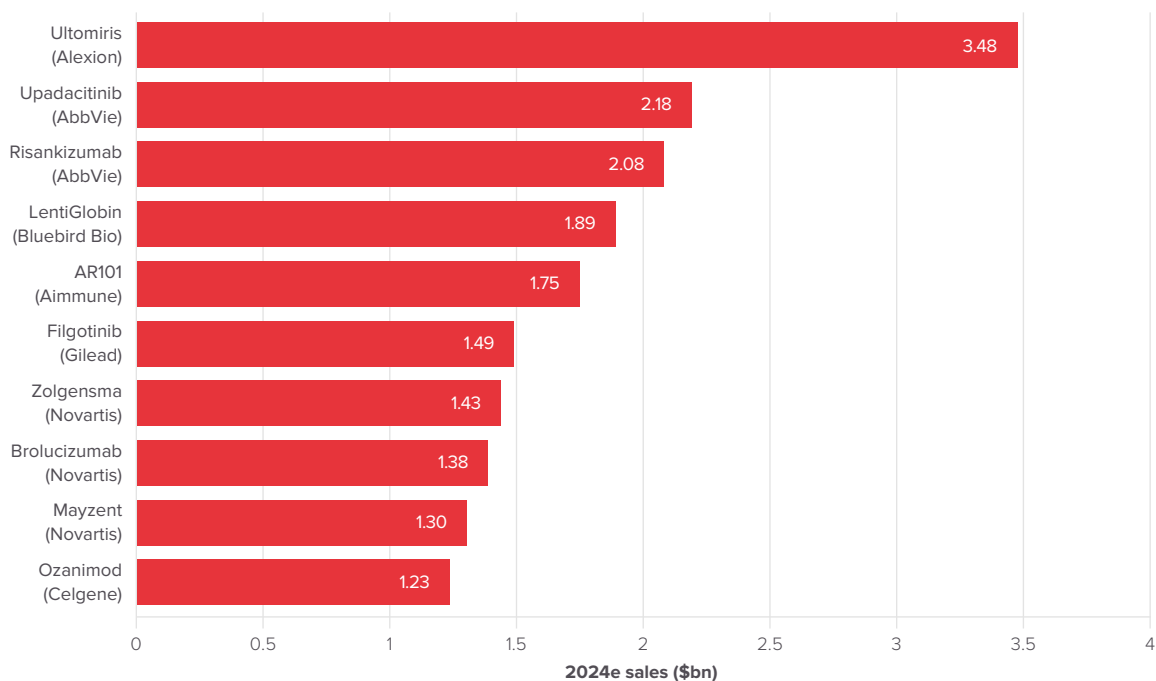
Particularly notable reviews of 2019 include two gene therapies, both of which could transform the treatment of previously intractable diseases. US regulators will deliver their verdict on Novartis's Zolgensma for SMA in May, while the European agency is due to rule on Bluebird's LentiGlobin for beta thalassemia in the second quarter.

Should these gene therapies pass the regulatory hurdle, the next issue will be price. Both are likely to surpass the million dollar mark, and spark furious debate.

Drug affordability promises to remain a very live issue in 2019, and while biopharma has rightfully won plaudits for delivering innovation in areas of huge unmet need, it has been slow to innovate on pricing. If the sector wants to payers to embrace these expensive new technologies and therapies, then that needs to change.

Top 10 potential launches in 2019 by 2024 sales (\$bn)

Source: Evaluate[®] January 2019





Vantage Medtech year in review 2018

The fourth quarter sell-off hurt big medtech less than big pharma

Medtech stocks, traditionally a bit of a refuge when things go wrong on the broader exchanges, did indeed have a better year than biotech or even pharma. But the poor fourth quarter still took a toll.

A look at the indices of US-listed medtech stocks shows a familiar pattern – rising value until late September and then a jagged decline to the end of the year. In Europe the picture is different: the fourth-quarter fall is present, it's just that the first three quarters were not that great to begin with.

The following analyses covers only companies who obtain more than 40% of their revenues from the sale of diagnostic or therapeutic medical technology.

Indices

Stock index	12-mth % change
Thomson Reuters Europe Healthcare (EU)	(6%)
Dow Jones U.S. Medical Equipment Index	15%
S&P Composite 1500 HealthCare Equipment & Supplies	13%

Fortunately for Nasdaq-listed Dexcom, leader of the big-cap risers, the gains it made in its extraordinary third quarter far outweighed its fourth-quarter retrenchment. The blood glucose sensor maker ended the year with a share price increase of 109%, enabling it to leap categories from its previous mid-cap status.

This is mostly down to the launch of its G6 device. In March this became the second continuous glucose monitor to gain US approval without the requirement for regular fingerstick calibration – but the first whose approval specifically permits its interoperability with devices from other developers.

Large cap (\$10bn+) medtech companies: Top risers and fallers in 2018

Source: Evaluate[®] January 2019

Top 3 risers	Share price 12-mth change	Market capitalisation (\$bn)	
		YE 2018	12-mth change
Dexcom (\$)	109%	10.6	5.7
Abiomed (\$)	73%	14.6	6.4
Boston Scientific (\$)	43%	48.9	14.9

Continues over the page...



Market capitalisation (\$bn)			
Top 3 fallers	Share price 12-mth change	YE 2018	12-mth change
Olympus (¥)	(22%)	10.3	(2.9)
Zimmer Biomet (\$)	(14%)	21.2	(3.3)
Align Technology (\$)	(6%)	16.8	(1.1)

Often, the spectacle of a company chasing acquisition after acquisition is an alarming one for shareholders, speaking as it sometimes does of a need to try anything to forestall falling sales. Not so Boston Scientific, investors in which appear to have been delighted by its nine takeovers in the last 12 months.

Not even the takeover of BTG, which at \$2.4bn conferred a higher valuation on the fairly lacklustre target than it had enjoyed for 17 years, was capable of harshing Boston's backers' buzz.

It is a surprise to see Align Technology among the fallers. Across 2017 Align recorded the greatest rise by a big-cap medtech since Vantage started tracking the performance of these companies, more than doubling its valuation. Last year, though, it suffered a more precipitous drop than most, shedding 47% of its value in the final three months. That it was only 6% off from the start of the year is a testament to its excellent second and third quarters.

Overall in 2018 there was more for big-cap medtech to celebrate than bemoan. Only five groups in this cohort lost value, and the average fall, 9%, was less than the average gain among the risers, 25%. Moreover the increases were greater and the decreases less than in the biopharma sector. 2018 was a rocky year for large medtech, but its reputation as a sanctuary – relatively speaking – remains intact.

Other significant risers and fallers in 2018 (ranked on market cap)

Source: Evaluate* January 2019

Market capitalisation (\$bn)			
Top 5 risers	Share price 12-mth change	YE 2018	12-mth change
Haemonetics (\$)	72%	5.2	2.1
Novocure (£)	68%	3.1	1.3
Elekta (SKr)	55%	4.3	1.2
Tandem Diabetes Care (\$)	1,509%	2.2	2.2
Caredx (\$)	243%	1.0	0.8
Top 5 fallers			
Dentsply Sirona (\$)	(43%)	8.3	(6.8)
Sysmex (¥)	(41%)	9.8	(6.6)
Convatec (\$)	(33%)	3.6	(1.7)
Cyberdyne (¥)	(75%)	0.6	(1.8)
Accelerate Diagnostics (\$)	(56%)	0.6	(0.8)



Rises among big-cap medtechs were put spectacularly in the shade by small-cap Tandem Diabetes Care, which achieved a 12-month percentage share price growth of unprecedented and almost incredible proportions, and has set a record that must surely stand for years to come. The price of the insulin pump maker's stock rose by more than 1,500% in 2018.

Among the mid-cap groups increases were more modest. The leader, Haemonetics, recorded an increase of just 75%, a slower rate of growth than the big cap medtechs. Perhaps this mid-range cohort might get more interesting next year – after all, Tandem might well be among them by that time.

A number of factors contributed to Tandem's rise, though it is arguable whether any can be said to explain it. The June approval of the group's t:slim X2 insulin pump in the US was its most significant achievement in terms of its products, and pushed its share price up by 25%.

Tandem also benefited, as did many diabetes device developers, from Johnson & Johnson closing its Animas insulin pump business in October 2017. The appeal of the t:slim X2 allowed Tandem to poach an estimated 3,000 of the 15,000 US Animas patients.

Perhaps the main factor is that the company is springing back from a low point. In November 2016 the approval of Medtronic's MiniMed 670G, a basic artificial pancreas, knocked 60% off Tandem's stock. Even with 2018's 1,500% rise the company has still not regained its ground.

2018 was a quiet year for M&A, and as such generally allowed listed companies to rise or fall based on their underlying performance. Perhaps in the coming year inorganic moves might play more of a role.



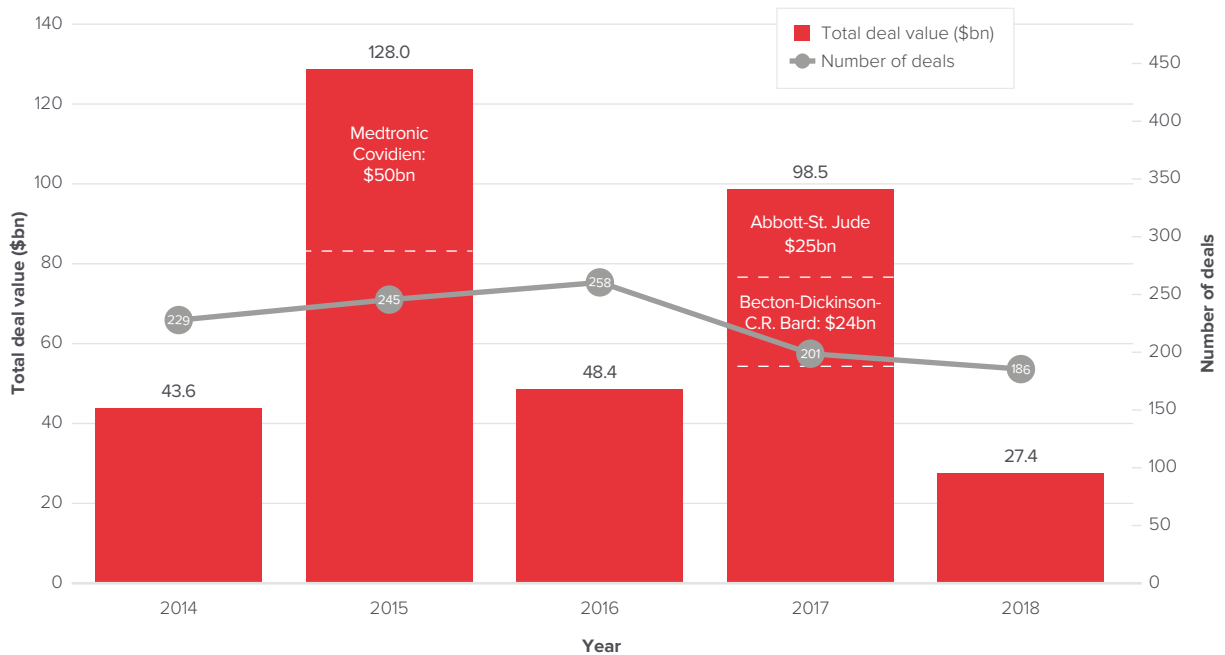
Medtechs saw little advantage in scale in 2018

In 2018 the lowest amount was spent on mergers and acquisitions in the medtech sphere than in any year since 2013. And the fewest deals – just 186 – have been closed than at any point since 2009, in the wake of the global financial crisis.

The total value of M&A deals last year came to \$27.4bn, a precipitous decline from 2017's figure of nearly \$100bn. And underlining medtech's lack of interest in large, transformative deals is the fact that four of the top 10 transactions were private equity buys.

Medtech M&As closed over the last 5 years

Source: Evaluate* January 2019



Private equity firms seem to be stepping into the gap left by the larger medtechs, who are put off by high valuations and an increasing focus on portfolio synergies when choosing which groups to buy. Roche's two billion-dollar-scale deals are examples of this. The cancer diagnostics specialist Foundation Medicine and the electronic health record analysis company Flatiron Health both had technology that dovetails with the Swiss group's oncology ambitions.

But medtech's choosiness does not mean it is doing more smaller deals in place of fewer large ones.

While the number of mergers worth more than \$1bn has dropped sharply, from 19 in 2017 to just seven last year, the number of smaller tuck-in deals has also fallen. 34 acquisitions known to be worth less than \$100m closed in 2018, compared with 50 the year before. This analysis only includes those deals with disclosed values, so the real numbers will be different, but it is hard to argue with the trend showing a decreasing number of smaller deals since 2010.



Number of deals closed by size bracket

Source: Evaluate® January 2019

Completion date	\$0-10m	\$10-100m	\$100m-1bn	\$1bn+
2014	18	43	47	8
2015	18	49	32	18
2016	21	46	31	12
2017	14	36	32	19
2018	9	25	39	7

Note: only includes deals with known value.

By contrast, the number of deals in the \$100m-1bn bracket has remained remarkably steady in the same time period, and 2018's figure is squarely mid-range for the decade.

It is true that merger trends are cyclical to some degree – a year in which several megamergers close will be followed by a quieter one as buyers are preoccupied and the number of targets reduced. But that is hardly the whole story behind the startling drop in both the number and scale of transactions from 2017 to 2018.

For one thing, the device sector remains awash with easy venture funding, meaning that the larger private groups that wish to put off a trade sale can do so with relative ease.

Private equity has also been flash with the cash. Four investment groups – Platinum Equity, Altaris Capital Partners, Veritas Capital and TPG Capital – feature as buyers in the list of 2018's top 10 largest M&A deals. There were no such deals in the top 10 in 2017 and only one the year before. Two of the groups bought were subsidiaries divested by large conglomerates, and a third, Analogic, was in real trouble when Altaris swooped on it.

Arguably this presages another round of similar deals in around five years' time, with private equity's business model usually requiring an investment exit horizon in that timeframe.

Top 10 deals closed in 2018

Source: Evaluate® January 2019

Completion date	Acquirer	Target	Value (\$m)	Vantage coverage
July 31	Roche	Foundation Medicine	2,400	Roche hopes to lay a Foundation for growth
October 2	Platinum Equity	LifeScan subsidiary of Johnson & Johnson	2,100	J&J sheds another medtech business
April 30	Danaher	Integrated DNA Technologies	2,000	-
April 6	Roche	Flatiron Health	1,900	Roche spends \$2bn for faster oncology work
November 9	Stryker	K2M	1,400	Stryker gets its purse out again, but integration is key
June 22	Altaris Capital Partners	Analogic	1,070	Analogic succumbs to a take-under
July 11	Veritas Capital	Value-based care division of GE Healthcare	1,050	Twilight of the medtech conglomerates
January 23	Weigao Group	Argon Medical Devices	844	Shandong Weigao looks outside China with Argon buy
February 14	TPG Capital	Exactech	737	Private equity buyout trend continues with Exactech
February 28	Stryker	Entellus Medical	662	Stryker noses out growth with Entellus buy

Meanwhile, there are two big reasons to hope for an uptick in activity to come: Siemens Healthineers and GE Healthcare. The first of these two huge imaging companies has already split from its pan-industrial parent and the second is about to, and part of the reasoning behind these moves is that the more specialised groups could be freer to buy. 2019 could be big.



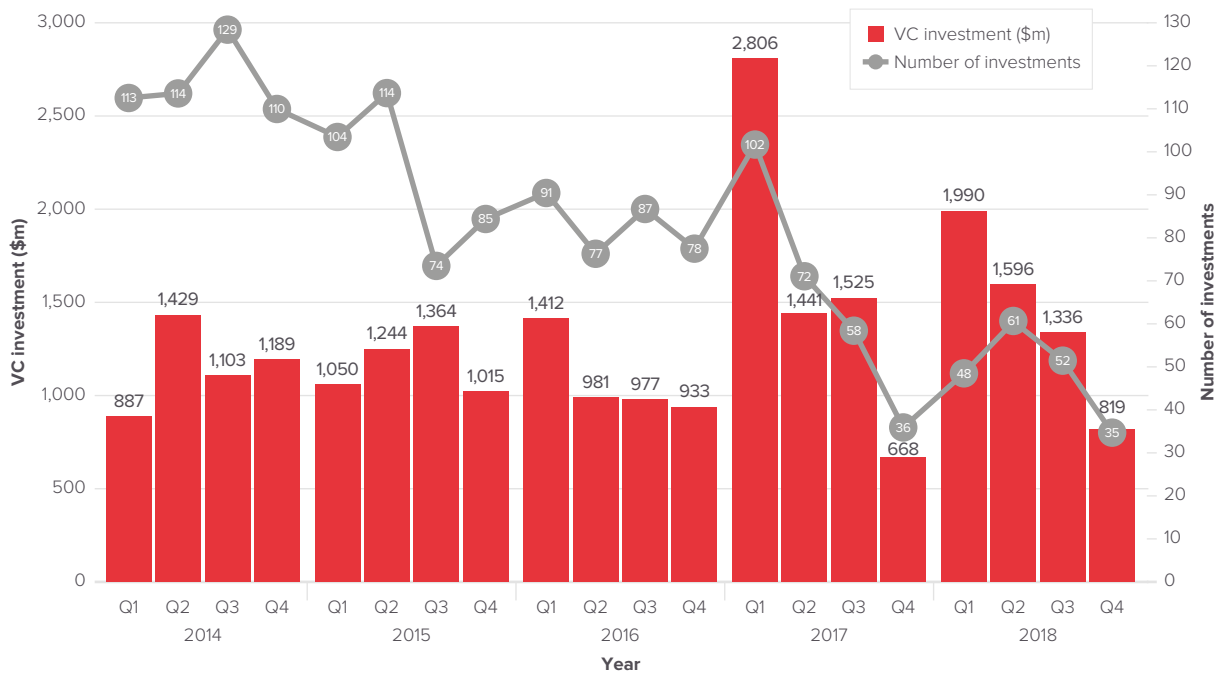
Fewer than 200 medtech VC rounds closed in 2018

If big medtechs are becoming more demanding when evaluating potential takeout targets, the same is true of investors. For the first time, the number of venture funding rounds closed in a year has dropped beneath 200.

The 196 VC deals done in 2018 is the lowest number for more than a decade. The amount raised in total, though, is holding fairly steady: at \$5.7bn it is higher than ever before with the exception of 2017's total. Given Verily's \$1bn investment in early 2019 – the first one-shot billion-dollar deal closed by a private medtech – it appears that the coming year might also leave 2018 in the dust.

Quarterly medtech VC investments

Source: Evaluate[®] January 2019



Grail led the 2018 charge, with a second tranche of its series B worth \$315m and a \$300m series C taking the first and second places. Helix is a consumer genetics company, selling products including a \$160 test resulting from a collaboration with the Mayo Clinic, designed to allow healthy individuals insight into health and disease risks and mutations associated with hereditary genetic conditions.

Oxford Nanopore's \$140m round in March underscored its unicorn status, and was followed by a \$66m equity investment by Amgen in October. But the group is expected to take orders worth just \$75m in 2018, and its plans to disrupt the sequencing market will take some doing.

Sequencing technologies are popular with venture investors because they are relatively cheap to develop and are often lightly regulated; meanwhile advances in machine learning mean that data can be sifted rapidly to provide meaningful, usable results. Roche's \$2.4bn takeover of one such group, Foundation Medicine, will not have been lost on VCs either.



Top 10 VC rounds of 2018

Source: Evaluate[®] January 2019

Date	Round	Company	Investment (\$m)	Focus
January 11	Series B (second close)*	Grail	314	Sequencing-based in vitro diagnostics
May 21	Series C	Grail	300	Sequencing-based in vitro diagnostics
September 27	Series D	Butterfly Network	250	Portable ultrasound
February 14	Series E	Heartflow	240	Cardiac imaging and blood flow analysis
November 28	Series E	Auris Health	220	Endoscopy
March 1	Series B	Helix	200	Sequencing-based in vitro diagnostics
January 31	Series E	Insightec	150	Ultrasound therapy and magnetic resonance imaging
June 14	Undisclosed	Mevion Medical Systems	150	Proton therapy
March 26	Undisclosed	Oxford Nanopore Technologies	140	Sequencing-based in vitro diagnostics
August 28	Series D	Outset Medical	132	Portable dialysis

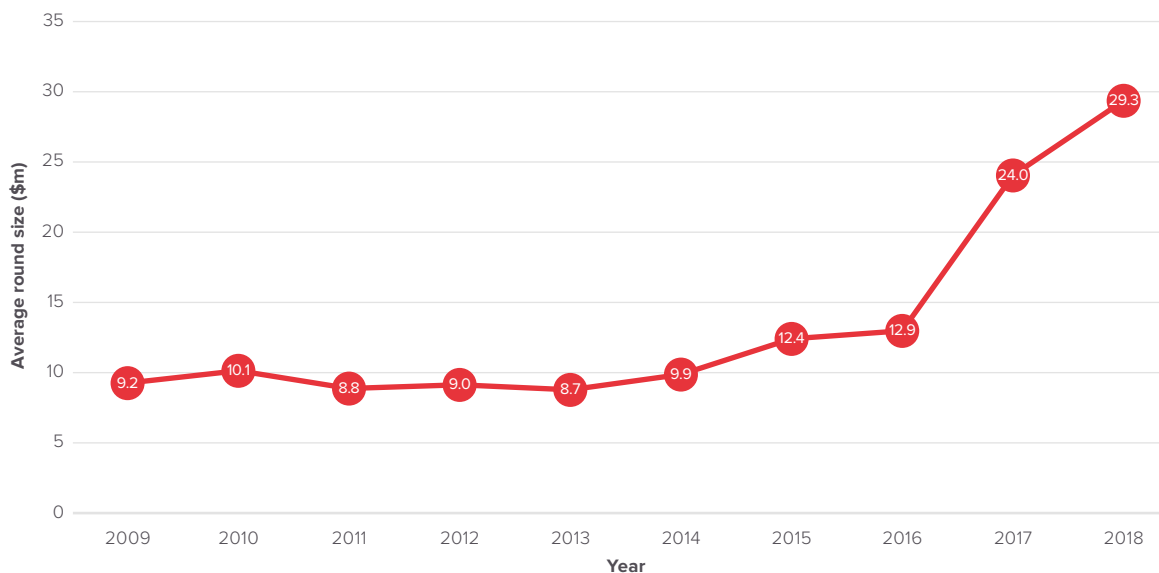
*Grail's series B raised \$1.2bn in total. Source: EvaluateMedTech.

And these groups are immensely popular as takeover targets. Philips alone has bought 10 companies specialising in imaging, informatics and other software since mid-2016, and GE Healthcare bought Nvidia for similar technology. Imaging technologies have also been popular investment targets. This sector has moved rapidly in recent years from a fairly staid area where the most that could be hoped for was incremental improvements to established imaging machines to more mobile, advanced and combined technologies, again boosted by artificial intelligence.

The paucity of VC deals this year has pushed the average size of a medtech funding round to nearly \$30m. Verily's monster round in January means the chances of this average figure decreasing in 2019 are approximately nil. The chances of traditional device makers displacing data-driven diagnostics companies in terms of appeal to VCs are probably about the same.

Average size of medtech VC rounds (\$m)

Source: Evaluate[®] January 2019





Medtech IPOs rocket as stock markets falter

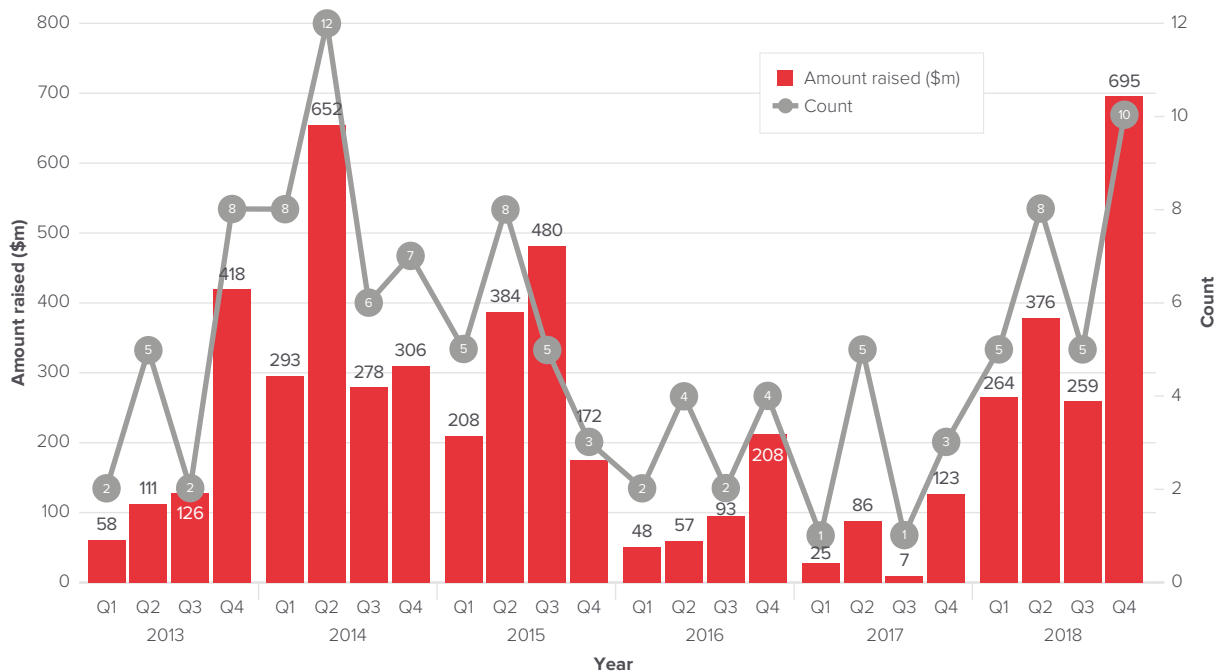
Last year saw the largest healthcare flotation in history – that of Siemens Healthineers, raising \$5.1bn. But excluding this highly anomalous deal from Vantage’s analysis of medical device company IPOs gives a clearer picture of the underlying trends in the sector, and allows something even more interesting to emerge.

Remarkably, considering the severe slide in share prices at the end of last year, the fourth quarter of 2018 set a new record. A total of \$695m was raised by device companies going public, more than any other three-month period since Vantage started tracking medtech listings in 2013.

The graph below excludes both Healthineers’ IPO and the \$1.9bn listing of Convatec in 2016 in order to better focus on smaller companies raising growth capital.

Quarterly medtech IPOs

Source: Evaluate* January 2019



Note: 2018 total excludes Siemens Healthineers’ IPO

The bumper fourth quarter was spurred by the second and third largest offerings of the year: those of the liquid biopsy group Guardant Health and neuromodulation specialist Axonics, both in October and both on the Nasdaq.

The former company has done rather better than the latter. Guardant’s share price has doubled since its debut, buoyed by a third quarter beat-and-raise. A partnership with AstraZeneca under which its Guardant360 test will be developed as a companion diagnostic for the lung cancer drug Tagrisso will also have helped, and expectations are building that the FDA will approve Guardant360 for cancer-agnostic diagnosis in early 2019.



Axonics, however, saw little change in its stock. This still puts it ahead of most in the class of 2018: 28 companies went public last year, and only 12 of them have seen their shares appreciate in value since.

Top 10 medtech IPOs of 2018

Source: Evaluate* January 2019

Date	Company	Amount raised (\$m)	Offering price	Share price change to YE18	Exchange	Focus
March 16	Siemens Healthineers	5,125	€28	27%	Frankfurt	Diagnostic imaging
October 4	Guardant Health	273	\$19	98%	Nasdaq	In vitro diagnostics
October 31	Axonics Modulation Technologies	138	\$15	1%	Nasdaq	Neurology
March 23	Medartis	130	SFr48	15%	SIX Swiss Exchange	Dental; general & plastic surgery; orthopaedics
October 17	Si-Bone	124	\$15	39%	Nasdaq	Neurology; orthopaedics
May 3	Inspire Medical Systems	124	\$16	164%	NYSE	Anaesthesia & respiratory
February 8	Huami	110	\$11	(11%)	NYSE	Patient monitoring
June 28	Neuronetics	108	\$17	14%	Nasdaq	Neurology
June 22	Electrocore	78	\$15	(58%)	Nasdaq	Neurology
July 19	Establishment Labs	77	\$18	52%	Nasdaq	General & plastic surgery

And Inspire Medical Systems has appreciated the most, with its stock up 164% over eight months. The company, which makes systems to treat patients with sleep apnoea, raised its full-year guidance when it reported its third quarter results in November, aided by the insurance company Aetna deciding to covering Inspire therapy. The group is not yet profitable, but its net loss has narrowed from 2017.

The partial float of Healthineers might have grabbed the headlines last year, but the reanimation of the medtech IPO market after the moribund performance in 2017 is an even more compelling story.



Approvals of high-risk devices drop as de novos take off

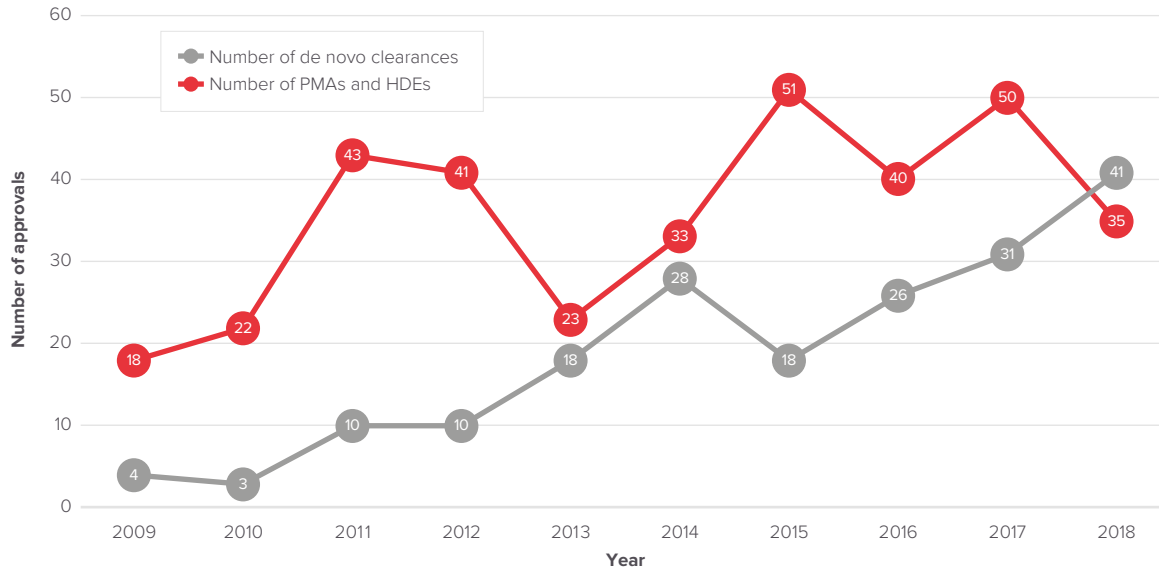
At first glance, the fact that the US FDA has only approved 35 novel medical devices via the PMA and HDE routes last year is rather alarming: it is a huge drop from 2017's figure of 50. However, this fall was matched by a corresponding increase in FDA clearances of low-risk devices.

The US regulator is seeking to encourage device makers to use the de novo route for their innovative products, and it seems to be working: for the first time the number of de novos exceeded the number of approvals by the more established PMA and HDE pathways. This newer approval pathway is speeding the path to launch for devices – but perhaps not as much as might be expected.

PMA (premarket approval) is the means by which high-risk, or class III, medical devices – those that sustain or support life or are implanted – are approved. HDE (humanitarian device exemption) is awarded to a device if it treats a condition that affects fewer than 8,000 individuals in the US per year. De novos are used for safer class I or II devices, those that would usually receive market clearance via the 510(k) route, but which are so unlike previously approved devices that a predicate cannot be found.

Medtech approvals, 2009-2018

Source: Evaluate® January 2019



The de novo pathway is designed to be a fast and simple route by which medtechs can get innovative devices to market, and its growth in popularity suggests that this aim has been achieved. Previously developers of low-risk devices for which a predicate was unavailable generally had to submit a PMA; now they can go straight to the de novo route.



However, while de novos are approved more rapidly than PMAs, the difference is not enormous. The de novos granted in 2018 took an average of 13.4 months to traverse the FDA, whereas PMAs and HDEs, despite the riskier nature of the devices here, only took around six weeks longer.

2018's approvals by therapy area

Source: Evaluate[®] January 2019

Device classification	PMAs/HDEs		De novos	
	Number of approvals	Average approval time (mths)	Number of approvals	Average approval time (mths)
Cardiology	13	19.4	3	6.5
In vitro diagnostics	6	11.4	13	18.3
Ophthalmics	4	6.8	-	-
Anaesthesia & respiratory	3	12.8	3	11.8
Diabetic care	3	15.9	-	-
Neurology	3	13.5	4	11.3
General hospital & healthcare supply	-	-	3	14.5
Average		14.7		13.4

Note: this includes only the categories in which at least three devices were approved this year.

The more interesting question is what might happen in the future. One possibility is that the de novo pathway in particular could see a lot more action.

The FDA wants to redouble its efforts to ensure that unsafe devices are caught before reaching the market, and in a series of announcements that coincided with an investigation into dangerous implants by the International Consortium of Investigative Journalists the FDA said that it would tighten regulations.

Its actual concrete proposals were somewhat tepid, but in future device makers might have to use more recent predicate devices in their 510(k) submissions. The agency expects that this will push more groups towards the de novo route.

Tightening rules mean that the record set for PMAs – 51 in 2015 – might stand for some time to come.



Looking forward to 2019

The opening weeks of 2019 have seen a certain stability return to global stock markets, which has helped the biopharma and medtech sectors regain lost ground. The question is whether this renewed optimism will be long lived, and the answer to this largely lies in macro issues from beyond the sectors.

A sustained pick up in M&A would certainly help biopharma, however. The big takeouts of Celgene, Loxo Oncology and Tesaro helped to pique investor excitement, though whether deals will continue to materialise remains to be seen; much depends on sellers' willingness to accept lower valuations.

There is also an expectation that more buyouts will emerge in medtech, with the \$3.4bn purchase of Auris Health by J&J getting 2019 off to a strong start. Siemens Healthineers is already independent from its parent and GE Healthcare soon will be, meaning that two new potential buyers will emerge in an industry left short of them by successive waves of consolidation.

One thing is all but certain for the medtech industry in 2019: the average size of a VC round will continue to creep higher. Verily, Google's sister company, closed a \$1bn round in January, and there is no sign that venture investors are returning to small, early deals. Similarly, in drug development, well stocked venture funds will continue to deploy capital this year, though few expect 2018's heady heights to be reached.

The state of the IPO markets will depend much on broader equity trends, and so far in 2019 there are few signs of cooling investor appetite. This can change very quickly, of course, and with the October rout still fresh in memories, those chasing a public listing are no doubt keen to move quickly.

The issue of drug pricing will also remain live this year, and many big pharma executives have warned that price hikes will be harder and harder to push through. If volume is the game, then offering clear innovation will become ever more important. Few big companies boast well-stocked pipelines, however, so perhaps those hoping for an uptick in takeovers this year have another reason for optimism.



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