Pharma, Biotech & Medtech Half-Year Review 2019

Amy Brown, Elizabeth Cairns and Edwin Elmhirst – July 2019

Evaluate Vantage

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As 2018 drew to an end a notable lack of merger and acquisition activity among biopharma companies was probably one of the biggest grumbles heard about the sector. Those complaints would be hard to make now, midway through 2019.

The first half of the year delivered two mega-mergers – Bristol-Myers Squibb's $74bn swoop on Celgene and Abbvie's $63bn takeout of Allergan – that set up 2019 as a record M&A year. Still, the huge sum of dollars committed to biopharma M&A masks a substantial slowdown in the number of these transactions being announced.

The medtech sector finds itself in a similar situation, with the takeovers closed so far this year worth more than the whole of 2018 – but with far fewer deals in the first half of 2019 versus the same period last year.

This is also being seen in the drug licensing deal market, which saw a big drop in the second quarter of 2019. This trend can be partly explained by easy access to financing – with other fundraising options on the table, smaller drug developers are not as beholden to deep-pocketed partners to push promising projects forwards.

This is supported by the data on biotech IPOs and venture financing. Demand for new biotech issues from equity investors showed no sign of diminishing over the first quarter. And in the venture world, the boom of 2018 might be over but the private space is still flush with cash.

As for medtech, the trend towards fewer, bigger deals is more prevalent than ever. The year kicked off spectacularly with Verily's $1bn funding round, the largest the medtech sector has ever seen, and twice the size of the biggest-ever VC deal for a biotech.

This is not the only measure by which the medtech sector has surpassed biopharma. On the stock markets, listed medtechs in each size bracket outperformed their biopharma peers, with increases in share prices steeper, and the falls fewer and less precipitous. Medtech has long held a reputation as a safe if unglamorous sector in which to invest, and while it has seemed pretty safe so far this year, it has been anything but dull.

The regulatory space also contains few areas of concerns, and though the US could see a slight downtick in the number of novel drug approvals this year, this seems unlikely to signal a serious tightening in the regulatory climate.

Still, the spectre of drug price controls in the US remains a topic of concern for investors, and the share price performance of some of biopharma's bigger beasts is far from impressive. These pockets of pessimism are hard to square with areas of huge exuberance – and huge valuations – in some of the more innovative and high-risk biopharma spaces. As the remainder of 2019 unfolds, perhaps the haves and have-nots will diverge even further.

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

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

Biopharma big caps stay buoyant, while small caps provide the action

With a couple of notable exceptions most of the world's biggest biopharma companies managed to register share price gains in the first half of the year. Partly helped by resurgent global stock markets, US drug makers shrugged off something of a nosedive in the second quarter to end the first half largely in the black.

Other healthcare indices rose too, with a 12% jump in the Thomson Reuters European Healthcare index being of particular note. However, Japanese drug stocks have not grown as strongly as others. Alongside ongoing price cuts to Japanese drugs, the wider market has suffered from the rising trade tensions in the region sparked by the recent hostility between the US and China.

Share price indices

Stock index	6 month % change
Nasdaq Biotechnology (US)	13%
S&P Pharmaceuticals (US)	5%
Dow Jones Pharma and Biotech (US)	5%
S&P 500 (US)	17%
DJIA (US)	14%
Dow Jones Stoxx 600 Healthcare (EU)	14%
Thomson Reuters Europe Healthcare (EU)	12%
Euro Stoxx 50 (EU)	16%
FTSE-100 (UK)	11%
Topix Pharmaceutical Index (Japan)	2%

A couple of mega-mergers marked the first half, and it is notable that the two buyers – Abbvie and Bristol-Myers Squibb – ended the period as the big cap segment's worst performers.

In a dramatic reversal of fortune, Lilly, which was one of the top risers in the first quarter, found itself near the bottom of the table by the halfway mark. Disappointing readouts from key trials of Trulicity and Taltz were partly to blame, while a lowering of full-year revenue forecasts also dealt a blow.

On the upside, Roche continued to defy expectations: despite the ever-present threat of biosimilars, strong sales of Hemlibra and Ocrevus helped to divert investors' attentions.

The powerhouse that is Keytruda kept Merck & Co in the top flight, while Astrazenca delivered a strong set of annual results and pledged a return to sustainable growth.

Big pharma: top risers and fallers in H1 2019

Source: EvaluatePharma®, July 2019

	Share price	Market capitalisation ($bn)	
	6-mth change	H1 19	6-mth change
Top 3 risers			
Roche	13%	234.8	24.3
Merck & Co	10%	215.9	17.2
Astrazeneca	11%	108.3	12.1
Top 3 fallers			
Abbvie	(21%)	107.5	(31.2)
Bristol-Myers Squibb	(13%)	74.2	(10.7)
Eli Lilly	(4%)	107.6	(15.0)

Outside the big pharma sphere, but still among the larger drug stocks, South Korea's Celltrion was one of the first half's biggest disappointments. A decision to halt production at its main facility weighed on its shares, as did price cuts for its biosimiliars, Truxima and Herzuma.

Elsewhere, Regeneron's shares are hit by slowing sales of it's cash cow, Eylea, and concerns about the future. Biogen is causing similar worries among its investor base; confirmation that its Alzheimer's candidate, aducanumab, had failed wiped almost a third from the stock's value in February, and the big biotech must be among the least loved names of the sector.

Other big drug stocks ($25bn+): top risers and fallers in H1 2019

Source: EvaluatePharma®, July 2019

	Share price	Market capitalisation ($bn)	
	6-mth change	H1' 19	6-mth change
Top 3 risers			
Celgene	44%	65.2	20.4
Allergan	25%	54.9	9.8
Jiangsu Hengrui Medicine	25%	43.5	15.4
Top 3 fallers			
Biogen	(22%)	45.3	(15.3)
Regeneron Pharmaceuticals	(16%)	33.7	(6.0)
Celltrion	(9%)	23.1	(1.6)

Outside the big cap space, Daiichi Sankyo was the star of the first half, largely boosted by a $1.35bn licensing deal with Astrazenca. The companies hope that the Japanese group's antibody-drug conjugate will prove itself a "better" Herceptin.

Galapagos was already benefiting in the first half from progress made with its Gilead-partnered rheumatoid arthritis project, filgotinib; a huge collaboration announced between the two in July will surely mean that the Belgian biotech ends the year as one of 2019's best performers.

Sarepta gained more fans as it continued to lead the Duchenne muscular dystrophy space, with a rival Pfizer gene therapy project failing to put up much competition.

On the downside, the decision by 44 US states to launch an investigation looking into alleged price fixing among big pharma and generic companies wiped tens of billions off the market caps of those named in the investigation. Of the larger groups, Mylan and Teva were hit hard, though both are also grappling with their own financial issues.

Sumitomo Dainippon Pharma has been on a particularly long losing streak. Alongside two complete response letters in the past 10 months, the group has also been hit with a failure in stroke, and the discontinuation of napabucasin in a phase III study in pancreatic ductal adenocarcinoma.

Mid cap ($5-25bn): top risers and fallers in H1 2019

Source: EvaluatePharma®, July 2019

	Share price	Market capitalisation ($m)	
	6-mth change	H1 19	6-mth change
Top 5 risers			
Aurora Cannabis	97%	7,799	2,603
Daiichi Sankyo	60%	35,784	13,711
Galapagos	41%	6,987	1,948
Sarepta Therapeutics	39%	11,268	3,573
Bausch Health Companies	37%	8,875	2,414
Top 5 fallers			
Biocon	(60%)	4,328	(801)
Sumitomo Dainippon Pharma	(42%)	7,281	(5,050)
Teva Pharmaceutical Industries	(40%)	10,083	(6,715)
Mylan	(31%)	9,815	(4,313)
Hisamitsu Pharmaceutical	(30%)	3,627	(1,495)

The most dramatic movements are always to be found among the smallest of the sector, and the first half provided plenty of action. Array's rise is thanks to its $11.4bn takeout by Pfizer, though others have progressed without the attention of a suitor.

Arqule attracted interest after presenting promising data on its BTK inhibitor ARQ 531 at the European Hematology Association meeting, while Sosei was also up on hopes for the Novartis-partnered asthma triplet, QVM149.

Ziopharm did not even need data; the group's shares got a bump after it got the nod to start clinical trials of its personalised T-cell receptor project.

Meanwhile, the first-half fallers were led by Inflarx, which plummeted after the spectacular failure of its lead project, the anti-C5a MAb IFX-1, in hidradenitis suppurativa.

Novavax, Aptinyx and Solid Biosciences were also all hit by clinical trial flops, while Insys Therapeutics was a casualty of the US opioid scandal. The company filed for bankruptcy in June after settling claims it paid doctors kickbacks to prescribe its pain drugs.

Small cap ($250m-$5bn): top risers and fallers in H1 2019

Source: EvaluatePharma®, July 2019

	Share price	Market capitalisation ($m)	
	6-mth change	H1 19	6-mth change
Top 5 risers			
Arqule	297%	1,308	1,006
Array Biopharma	225%	10,336	7,300
Ziopharm Oncology	212%	947	681
Sosei	196%	1,621	1,080
Voyager Therapeutics	190%	1,003	697
Top 5 fallers			
Inflarx	(92%)	82	(861)
Insys Therapeutics	(91%)	22	(238)
Novavax	(85%)	133	(571)
Aptinyx	(80%)	121	(433)
Solid Biosciences	(79%)	185	(765)

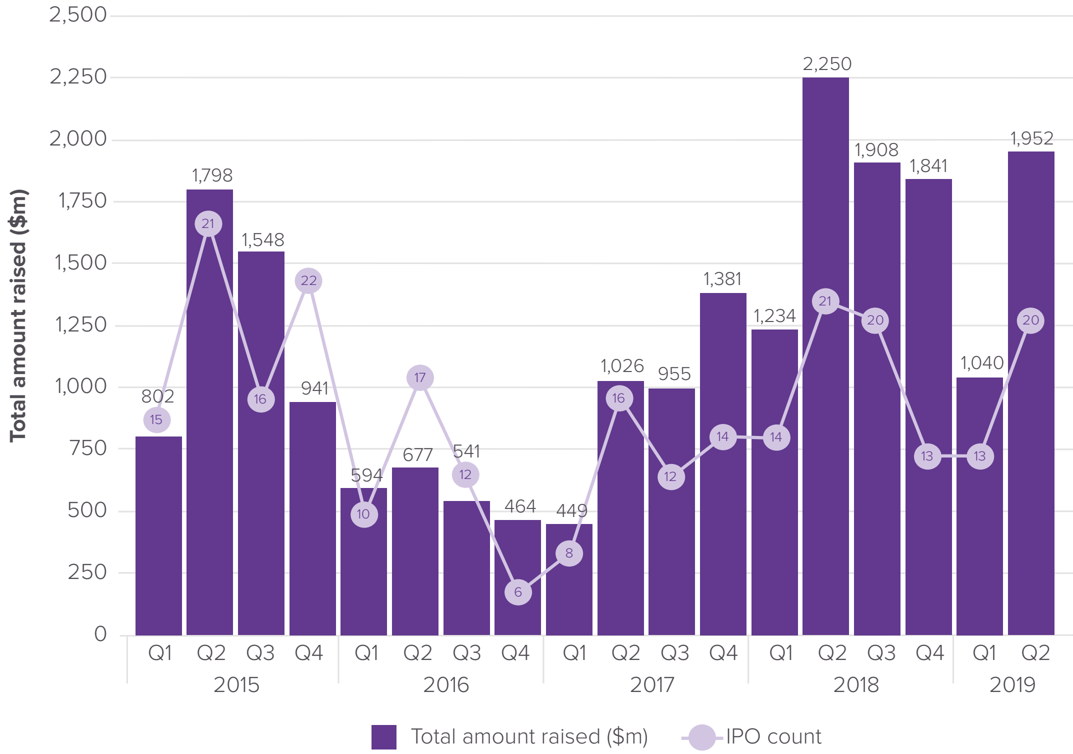
Back to business for biotech flotations

As stock markets have rebounded so has demand for fledgling drug companies. The second quarter of 2019 saw 20 biopharma flotations, EvaluatePharma data show, a reassuring bounce back after a notable slowdown at the start of the year.

Almost $2bn was raised by these early-stage outfits in the second quarter, according to this analysis, which encompasses all first-time flotations on western exchanges of companies involved in the development of human therapeutics. It excludes pure-play medtech and genomics firms, for example, and provides a picture of investor appetite for the riskiest end of the healthcare sector.

Biotech initial public offerings by quarter on Western exchanges (excludes medtech)

Source: EvaluatePharma®, July 2019



A look at the pricing of these IPOs shows that this year's new issues, for the most part, have been able to achieve the valuations that their bankers pitched. This is another sign of investor interest in these companies, and represents something of a recovery from six months ago.

The analysis below looks at the average discount or premium – the difference between a company's initially proposed offer price and the one it finally floated at. This climbed back to close to zero over the second quarter, a statistic that could embolden others to seek a market listing.

Only two of the 20 second-quarter new issues floated on an exchange other than Nasdaq, indicating that the IPO scene remains a US-led story.

Premium/discount of float price to initially proposed IPO price range

Source: EvaluatePharma®, July 2019

Nasdaq IPOs only; Calculated from mid-point of initial range

A look at some of the individual companies going out also underlines the strength of investor demand. Ten companies raised more than $100m in the first half, led by Bridgebio's monster $349m IPO.

It seems unlikely that 2019 will match last year's record of 31 biopharma firms raising more than $100m, but the IPO window is still firmly propped open.

Bridgebio is also notable for the reception it received: as well as selling more shares for a higher price than initially planned, the genetic disease researcher's valuation ballooned by almost a third once its stock was trading. The company is now capitalised at $3.5bn; with three phase III projects and a broad pipeline, the California firm at least has several shots on goal.

Stoke Therapeutics, which is focused on genetic diseases, and the targeted oncology play Turning Point also carried out very well-received offerings. Not all are managing to retain investor interest, however, with Alector, a neurodegenerative disease researcher, struggling to stay in positive territory.

More established biotechs are not exactly flavour of the month and perhaps the fledgling end of the sector is benefiting from a loss of confidence elsewhere. If this is true, it is even more important that these new issues live up to expectations, which in some areas look almost impossible to achieve.

Top 5 H1 2019 biotech IPOs on Western exchanges

Source: EvaluatePharma®, July 2019

Company	Primary focus	Amount raised ($m)	Premium/ (discount)	Chg since float to end Q2
Bridgebio Pharma	Genetic diseases	348.5	13%	59%
Gossamer Bio	Immunology and inflammation	317.4	0%	18%
Turning Point Therapeutics	Targeted oncology treatments	191.3	6%	126%
Alector	Neurodegenerative disease	176.0	0%	(1%)
Stoke Therapeutics	Genetic diseases	142.0	20%	62%

Venture investing dips again for biopharma

The venture capital world is far from quiet, but the sums involved are certainly getting smaller. Young drug developers raised $3bn over 91 rounds in the second quarter of 2019, according to EvaluatePharma – the smallest quarterly haul in two years.

Looking behind the figures, it seems as if a dip in the number of $100m-plus rounds has largely driven the top-line decline. Biontech's huge $325m series B in July shows that mega financings are far from a thing of the past, but they might be seen less frequently this year.

Over the first half of 2019 there were 13 rounds that tipped $100m, and 53 that tipped $50m. A similar second half would mean an annual drop in both of these categories, although 2018 was a record-breaker never likely to be matched.

Annual biopharma venture investments

Source: EvaluatePharma®, July 2019

Date	Investment ($bn)	Financing count	Avg per financing ($m)	No. of rounds ≥$50m	No. of rounds ≥$100m
H1 2019	6.6	189	36.4	53	13
2018	17.3	415	44.1	129	38
2017	12.1	442	29.9	72	16
2016	9.7	442	23.4	48	13
2015	11.0	514	22.5	56	13

Looking at the number of financings taking place, it appears that 2019 could register a big decline, not only on last year but in comparison with the past five years.

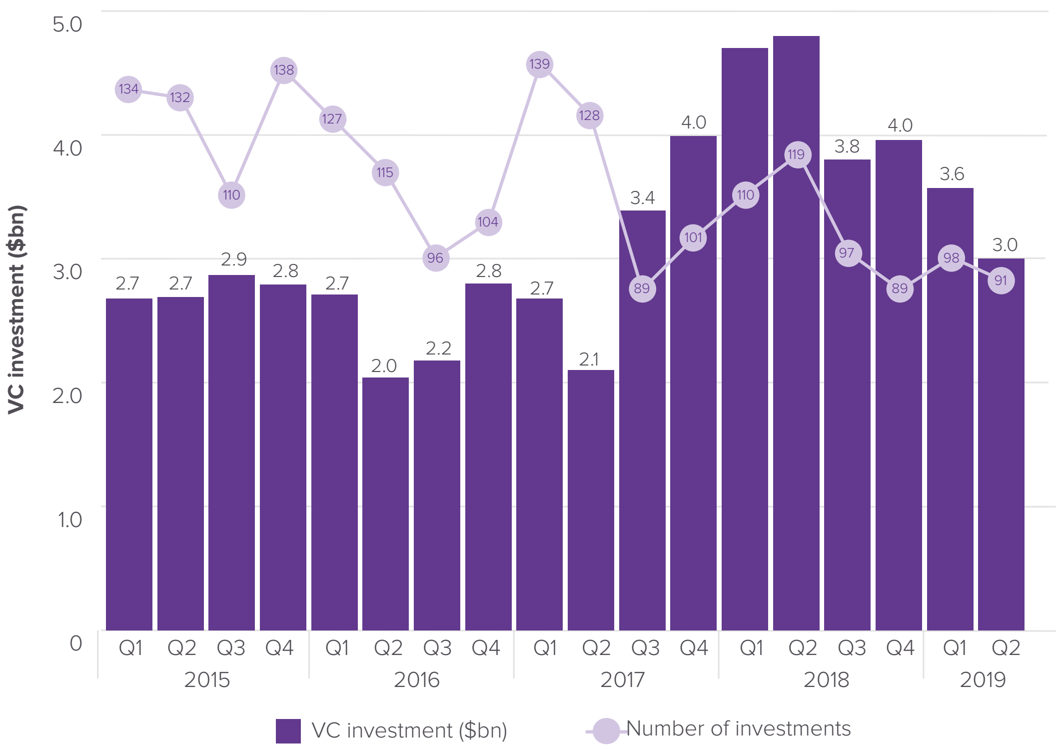
On the other hand, perhaps 2019 will see a return to a more typical shape: the graph below shows that the second quarter tends to be the quietest, with the exception of last year.

The slew of financing news in July suggests that activity could pick up again. As well as Biontech, Revolution raised a $100m series C and Lepu Biotechnology got $131m from Chinese investors.

This analysis includes only developers of human therapeutics, excluding sectors such as medtech or diagnostics.

Global quarterly biopharma venture investments

Source: EvaluatePharma®, July 2019



It seems certain that the peak of early 2018 has passed, so the next question is the depth of any retrenchment. Few considered the recent excesses sustainable but, equally, no one wants to see the money wells dry up.

The steady stream of financing news from the venture world makes a serious downturn look unlikely, in the immediate future at least. And the IPO market remains welcoming to fledgling drug stocks, which should help retain the interest of private investors in this space.

Equally, there are few signs that public or private investors are backing off from the highest-risk propositions. For example, the gene therapy researcher Asklepios BioPharmaceutical – Askbio for short – is barely in the clinic, but managed to attract a huge $235m in April.

Still, one implication of the trend for ever bigger rounds is that fewer start-ups have been funded each year. It is still hard to know whether a winning investment strategy will emerge: much more cash to fewer companies, or smaller sums for more. Either way, the sun is still shining in the venture world, and the message to start-ups seems to be: let's make hay.

Biopharma set for a big dealmaking year – on dollar terms at least

Over the first half of the year drug developers pledged to spend a total of $173bn on mergers and acquisitions, an eye-watering sum that already beats the last three full years on total deal spend. In fact, in only two of the last 10 years did the sector splash out more than this on takeovers.

The multi-billion takeouts of Celgene and Allergan, for $74bn and $63bn respectively, are almost entirely responsible for the figure; the presence of a mega-merger in any year will always give a top-line boost.

Biggest M&A deals announced in H1 2019

Source: EvaluatePharma®, July 2019

Date announced	Acquirer	Target	Status	Value ($bn)
Jan	Bristol-Myers Squibb	Celgene	Open	74.0
June	Abbvie	Allergan	Open	63.0
June	Pfizer	Array	Open	11.4
Jan	Eli Lilly	Loxo Oncology	Closed	8.0
Feb	Roche	Spark Therapeutics	Open	4.8

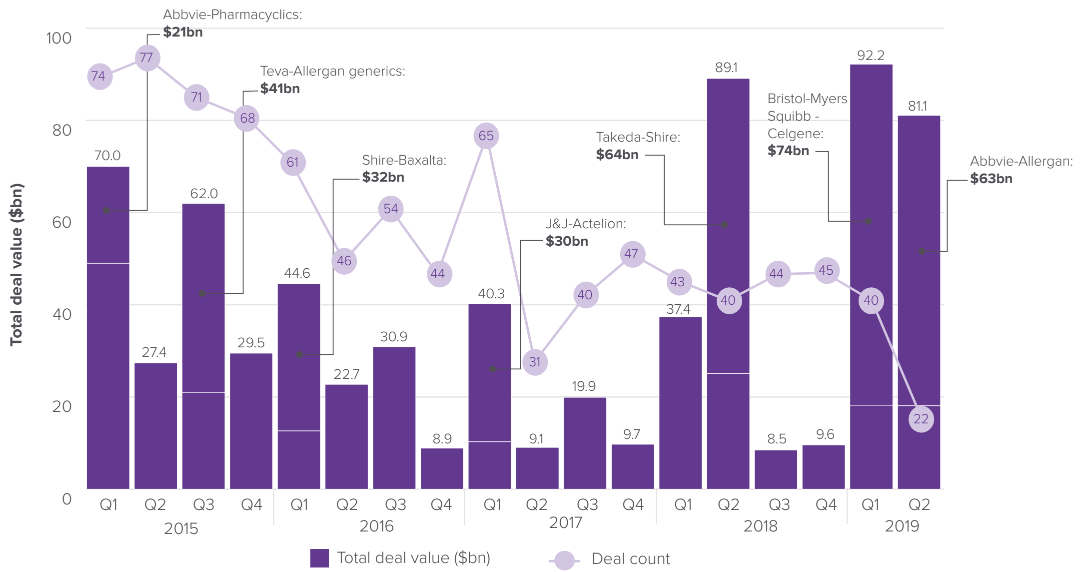
A look at the volume of deals happening tells a different story, however; transaction volume has been low for a while, but a big drop-off seems to have happened last quarter.

EvaluatePharma counts only 22 company takeovers in the second quarter, the smallest quarterly count for at least a decade. Having four large drug makers distracted by two huge deals could provide something of an explanation, but this analysis does seem to point to a sluggish level of underlying M&A activity.

This analysis looks only at drug makers, and excludes medtech companies or genomics specialists, providing a focused look at the high-risk end of the sector.

Pharma and biotech M&A transactions announced each quarter

Source: EvaluatePharma®, July 2019



Deal bankers lucky enough to get a slice of the mega-merger action are unlikely to be concerned by the latest quarter's slowdown, but no one will want to see this level of activity over the remainder of the year.

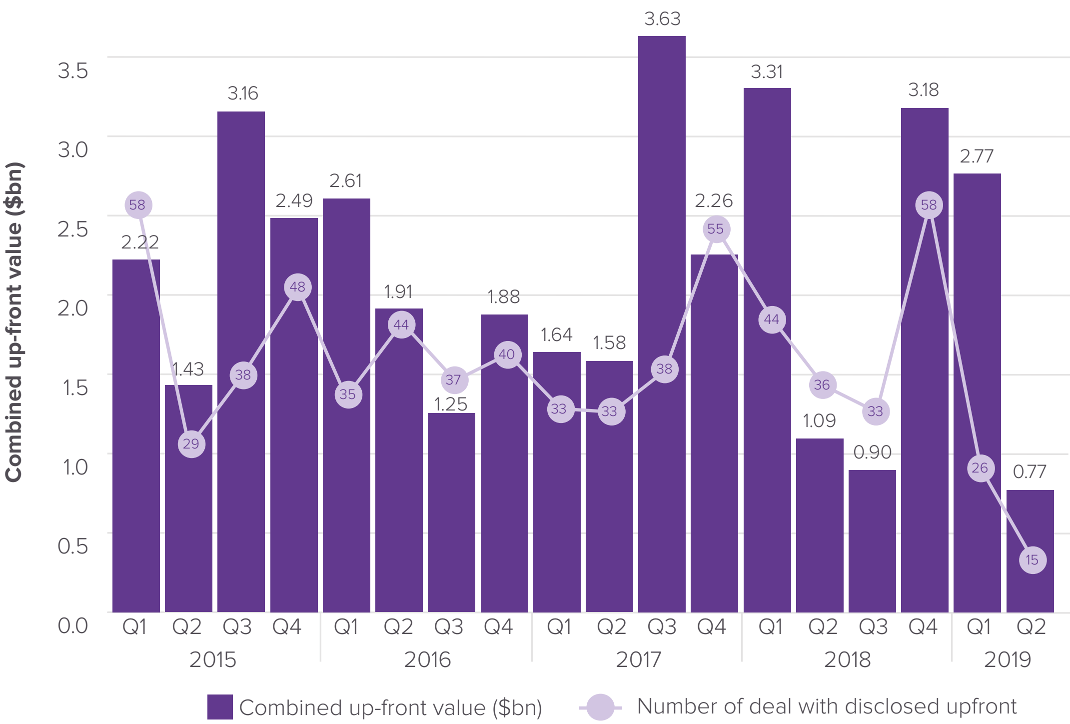
Lack of appetite for some of the sector's more unrealistic valuations has been blamed for the slowdown in deal making, and perhaps this factor is still at play. At the same time, however, the takeouts of companies like Array Biopharma and Loxo Oncology show that when big players want an asset, they are willing to swallow huge price tags.

But deals of this size are the exception rather than the rule. It is the smaller deals that tend to drive the volume of M&A activity in any given year, so a slowdown at this end of the transaction scale must be responsible.

An important factor to consider here is the willingness of equity and venture investors to fund young drug developers, which can lessen the need to make a deal. This availability of capital is presumably also having an impact on the licensing deal market, which has also registered something of a slowdown.

Licensing deal up-fronts

Source: EvaluatePharma®, July 2019



The first quarter of 2019 saw 26 licensing deals with up-front fees worth $2.8bn disclosed. The huge $1.4bn up front that Astrazeneca paid to access Daiichi Sankyo's antibody-drug conjugate, trastuzumab deruxtecan, gave the top-line a big boost, masking a pretty low number of deals.

The second quarter then saw a further slump in activity, and the lowest up-front total in at least five years.

This analysis looks only at transactions where an up-front fee was disclosed, so will understate the sector's total licensing deal activity. The trends overall will be largely similar, however. By including only up-front fees and ignoring the headline-grabbing "biodollar" values, which will almost never be paid out in full, these numbers arguably paint a more accurate picture of biopharma's spending on these sorts of moves.

Of course July saw the huge Gilead and Galapagos collaboration, under which the US biotech paid $4bn to effectively to access the Belgian company's entire pipeline. This is without doubt one of the largest licensing deals that the biopharma sector has seen; it is also notable because the initial payment exceeds the total sum of all up-fronts paid out in biopharma licensing deals over the first half of 2019.

This transaction will give 2019's total spend on up-fronts a huge boost, and take the tally closer to what has typically be seen in the last few years.

However on transaction volume, both the licensing deal market and the M&A scene seem quiet. Those pitching ideas are competing with offers of cash from numerous sources, and these analyses clearly show which camps are winning the business.

Novel drug approvals head for a down year

A couple of huge years for novel drug approvals have raised the bar substantially for FDA watchers, but the tally for 2019 so far suggests that a down year could be in the making. At the end of June the US regulator had rubber-stamped 18 first-to-market products – a disappointing run rate compared with the last five years.

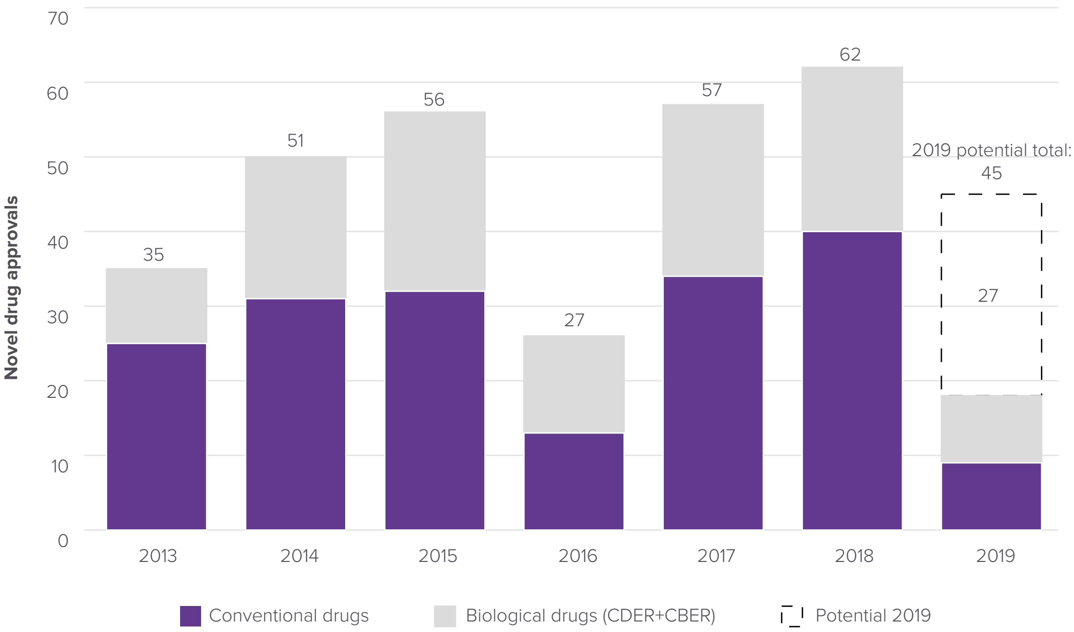
Of course the annual numbers do fluctuate, and with few signs of a serious tightening of the regulatory climate there seems little reason to believe that a more conservative era is beginning at the FDA. Still, an *Evaluate Vantage* analysis has identified only a further 27 novel projects awaiting judgement by the close of 2019.

The chart below shows that, if all of these are green-lit, 45 novel agents will have reached the US market by the end of this year. This would represent something of a slowdown versus the last couple of years, though to be fair it certainly would not be the kind of dip that should cause alarm.

With a new FDA commissioner settling in after a period of some upheaval perhaps this is to be expected, though industry watchers will not want to see a further deceleration over the remainder of the year.

Annual FDA novel drug approvals

Source: EvaluatePharma®, July 2019



The most high-profile green light so far this year probably goes to Novartis's gene therapy Zolgensma, for the inherited degenerative childhood disease SMA. With a price of $2.1m a year the product is not only a scientific breakthrough, it also stands as the most expensive drug in the world.

However, in terms of commercial potential, Abbvie's new psoriasis biological Skyrizi is probably the most valuable new arrival. The sellside reckons that this anti-IL-23 antibody could generate annual sales of more than $3bn by 2024.

As for the big approvals still possible this year, Abbvie will be hoping its Jak inhibitor, upadacitinib, follows Skyrizi onto the market. With two big launches under way and a mega-merger to complete, the big biotech is undergoing something of a transformation this year.

Elsewhere, as Bristol-Myers Squibb looks to close its takeover of Celgene, the company will want to see one of the latter's key partnered assets, luspatercept, secure approval for anaemia resulting from myelodysplastic syndromes and beta-thalassaemia. The sellside reckons that revenues could breach the blockbuster threshold in 2024.

Biggest approvals of 2019

Source: EvaluatePharma®, July 2019

Product	Company	Mechanism/use	2024 sales ($m)
Approved so far			
Skyrizi	Abbvie	Psoriasis	3,196
Vyndaqel	Pfizer	Heart disease caused by transthyretin mediated amyloidosis	2,108
Zolgensma	Novartis	Spinal muscular atrophy	1,569
Mayzent	Novartis	Relapsing multiple sclerosis	1,312
Balversa	Johnson & Johnson	Advanced or metastatic bladder cancer	1,150
Potential approvals			
Upadacitinib	Abbvie	Rheumatoid arthritis	2,517
Brolucizumab	Novartis	Wet age-related macular degeneration	1,178
Lumateperone	Intra-Cellular Therapies	Bipolar depression	1,122
Luspatercept	Celgene	Transfusion-dependent beta-thalassaemia	1,082
Tenapanor	Ardelyx	Irritable bowel syndrome with constipation	694

Big cap medtech comes roaring back

Welcome to the big time, Exact Sciences. The cancer testing company has made the leap from mid cap to big cap, its market value having climbed to more than $15bn in the first six months of 2019 on the back of an 87% share price increase.

This makes it the biggest riser in a cohort that has seen enormous success so far this year – only one big-cap medtech, the heart pump maker Abiomed, has seen its stock fall in value. And comparing the gains in this sector to those in big cap biotech and pharma belie the medtech industry's reputation for stolidity.

Overall big cap medtech is a pretty good place to be. The share price indices that give a broad idea of the sector's health have escaped the doldrums in which they were trapped throughout 2018, and as usual US-listed stocks are outpacing those in Europe.

Share price indices

Stock index	6 month % change
Thomson Reuters Europe Healthcare (EU)	13%
Dow Jones U.S. Medical Equipment Index	20%
S&P Composite 1500 HealthCare Equipment & Supplies	18%

And a quiet merger scene – many of the big M&A deals so far this year have involved private equity buying rather than big medtechs – means share price movements can be attributed to other factors.

Exact Sciences has gone from strength to strength in recent years, with sales of Cologuard, its faeces test for colorectal cancer, soaring from $1.8m in 2014 to $454m last year. But it has yet to turn a profit, and its net loss has widened.

More recent data are not encouraging either, with the first quarter of 2019 bringing a net loss of $83m, more than twice as great as in the same period in 2018.

Investors are nonchalant, driving the group's share price ever skywards, and short interest in the stock has rarely breached 10% over the past year, Nasdaq figures show.

Large cap ($10bn+) medtech companies: top risers and worst performers in H1 2019

Source: EvaluateMedTech®, July 2019

	Share price	Market capitalisation ($bn)	
	6-mth change	H1' 19	6-mth change
Top 5 risers			
Exact Sciences	87%	15.2	7.5
Dentsply Sirona	57%	13.7	5.4
Straumann	39%	13.6	3.7
Steris	39%	12.6	3.6
Danaher	39%	102.3	30.0
Top 3 worst performers			
Abiomed	(20%)	11.8	(2.8)
Siemens Healthineers	1%	41.6	(0.4)
Terumo	3%	21.8	0.9

If its backers are hoping that Exact might be acquired, as single-product companies often are, the moment might have passed. Few buyers exist that could snap up a company with a $15bn valuation, and excitement is building around liquid biopsies that might, sooner or later, come to edge Cologuard out. The company saw a rare blip when the blood testing group Guardant Health's statement that it was going to trial its Lunar assay as a screen for colorectal cancer caused a 10% drop in Exact's shares.

Abiomed, maker of the Impella range of temporary heart pumps, suffered a significant selloff in March after a previously halted US trial of Abbott's potential competitor, the Heartmate PHP, was restarted. This precipitous decline seems a little overdone considering that Abbott's device is not expected to go on sale in the US before 2021.

The drop might also reflect Abiomed shareholders' disappointment that a takeover has not materialised. In many ways the company makes a likely candidate for an acquisition, being specialised, fast-growing and profitable. It is also largely free of competition, or at least it will be for the next two years, and its stock went on a tear across 2018, ending the year up 73%.

Perhaps the recent contraction in its value might lure a buyer. In the meantime medtech investors might want to reflect on the similarities between Abiomed and Exact Sciences, and wonder why it is the profitable company that has suffered.

Smaller listed medtechs might not have had quite such a successful time as the larger companies during the first half, but they still performed pretty well overall. Most of the stock fluctuations can be attributed to excitement around technological promise, with diagnostics to the fore in both the mid and small cap groups.

Outside the big caps the trophy goes to Guardant Health, whose efforts to develop its various liquid biopsy platforms have grabbed headlines throughout 2019. Its market valuation has more than doubled this year, and at the halfway point its share price was up more than 350% from the price at which it floated last October.

The battle for dominance of the liquid biopsy space is still in its early stages, but as one of the companies to have a test well established on the US and European markets, Guardant is one of the best positioned to win out.

Other significant risers and fallers in H1 2019 (ranked on market cap)

Source: EvaluateMedTech®, July 2019

	Share price	Market capitalisation ($bn)	
	6-mth change	H1 19	6-mth change
Top 5 risers			
Guardant Health	130%	7.9	4.7
Novocure	89%	6.1	2.9
Getinge	83%	4.0	1.7
Natera	98%	1.9	1.1
Accelerate Diagnostics	99%	1.2	0.6
Top 5 fallers			
Inogen	(32%)	3.5	(1.0)
Transenterix	(21%)	3.5	(1.0)
Asahi Intecc	(43%)	3.1	(2.3)
Ambu	(46%)	1.5	(1.2)
Livanova	(40%)	0.3	(0.2)

Novocure, in second place, reaped the rewards of May's FDA approval of its cancer therapy device, NovoTTF-100L. The system uses electrodes placed against the patient's skin to emit alternating electric fields, which the company says enter cancer cells and attract and repel charged proteins during cancer cell division, disrupting the growth of tumours.

The approval, in combination with Lilly's Alimta and platinum chemo for the first-line treatment of unresectable locally advanced or metastatic malignant pleural mesothelioma, was the first for this form of mesothelioma in more than 15 years, according to Novocure.

Investor excitement about many of the smaller medtechs' technology is unchecked, but these groups will have to deliver on their promises.

Big device deals are back

Six months into 2019 and the medtech sector has already surpassed 2018's M&A total. Deals worth more than $29.5bn have been closed so far this year, swelled by Johnson & Johnson's purchase of the surgical robotics group Auris Health and the sale of its healthcare records company Athenahealth to private equity: both these transactions weighed in at more than $5bn.

Even so, the total is far short of 2017's, which almost cracked $100bn. The mean price paid, though, is creeping back up to 2017 levels: the 39 mergers with disclosed value were worth $755m each on average, more than twice as much as last year.

Medtech acquisitions of the past five years

Source: EvaluateMedTech®, July 2019

Deal completion date	Deal value ($bn)	No of deals	No of deals with known value	Average deal size ($m)
H1 2019	29.5	74	39	755
2018	26.8	206	86	312
2017	98.5	210	96	1,027
2016	48.6	261	110	442
2015	128.1	247	113	1,134

Much of the activity was at the top end. Eight multibillion-dollar deals have closed so far this year, more than in all of 2018, but the number of acquisitions worth less than $1bn is way down. 33 deals in this size bracket have been closed so far in 2019. Extrapolating this out to the next six months would give a 2019 total of 66, rather less than the 80 seen in 2018 or the 81 a year earlier.

A potential reason for this concentration of larger mergers is illustrated by the type of companies being bought. The four largest buys this year all concerned businesses that supply hospitals, a fairly commoditised space where competition is fierce and generally price-based. The need for large groups to build scale to broaden their offering and make themselves appealing to often cash-strapped customers is clear, and consolidation the answer.

No. of deals closed by size bracket

Source: EvaluateMedTech®, July 2019

Completion date	$0-100m	$100m-1bn	$1bn+
H1 2019	16	17	8
2018	39	41	7
2017	49	32	19
2016	66	32	12
2015	66	32	18
2014	60	47	8

Note: only includes deals with known value

The other notable point is the continuation of the trend of private equity increasingly involving itself in medical technology. Last year four of the top 10 transactions saw medtech companies or business units fall to private equity shops, and so far this year two such deals have occurred.

Flush with cash and the debt financing permitted by low interest rates, private equity is being more active in acquiring companies and carve-outs across many sectors, not just medtech. But heath tech groups can be particularly appealing: unlike natural resources, for example, the product supply is not finite, nor is it subject to increasing regulatory strictures.

The developed world's ageing population means demand for devices is only going up, and investment groups are often convinced that they can increase efficiency, curbing spending and making the kind of hard choices that might be better made away from the scrutiny that attends listed companies.

Top 10 deals closed in H1 2019

Source: EvaluateMedTech®, July 2019

Completion date	Acquirer	Target	Value ($m)	M&A focus
April	Johnson & Johnson	Auris Health	5,750	Endoscopy; general & plastic surgery
February	Veritas Capital and Elliott Management	Athenahealth	5,700	General hospital & healthcare supply; healthcare IT
February	Colfax	DJO Global	3,150	Orthopaedics; physical medicine
April	Fortive	Advanced Sterilization Products business of Johnson & Johnson	2,800	Endoscopy; general hospital & healthcare supply
February	Fresenius Medical Care	Nxstage Medical	2,000	Blood; nephrology
March	Montagu Private Equity and Astorg	Nemera	1,150	Drug delivery
February	3M	M*Modal	1,000	Healthcare IT
January	Sonic Healthcare	Aurora Diagnostics	540	In vitro diagnostics
June	Boston Scientific	Vertiflex	465	Orthopaedics
January	Boston Scientific	Millipede	450	Cardiology

Some acquisitions were motivated by their target's technology, rather than investment groups' solely financial considerations.

The dialysis giant Fresenius Medical Care closed its takeout of Nxstage Medical, a maker of portable and home-based blood filtration machines. The $2bn deal hit antitrust obstacles, as had been widely expected, but eventually closed in February after Fresenius divested Nxstage's bloodline tubing set business.

And Boston Scientific closed not one but two technology-specific bolt-on deals as it ramped up its inorganic growth strategy to better compete with its larger rivals. The acquisition of Millipede, which makes a device to repair the mitral valve, will enable Boston to go up against Abbott, though that company's MitraClip is well established on the market. And its purchase of spine implant developer Vertiflex will boost Boston's orthopaedics offering and allow it to square up to groups like Medtronic and Stryker.

There is, perhaps, an aspect of haves and have-nots to the M&A scene so far this year. The medtech market's fast growth and unfettered demand has attracted cash-rich investment groups, but hospital suppliers facing ongoing cost pressures have been forced to consolidate to survive.

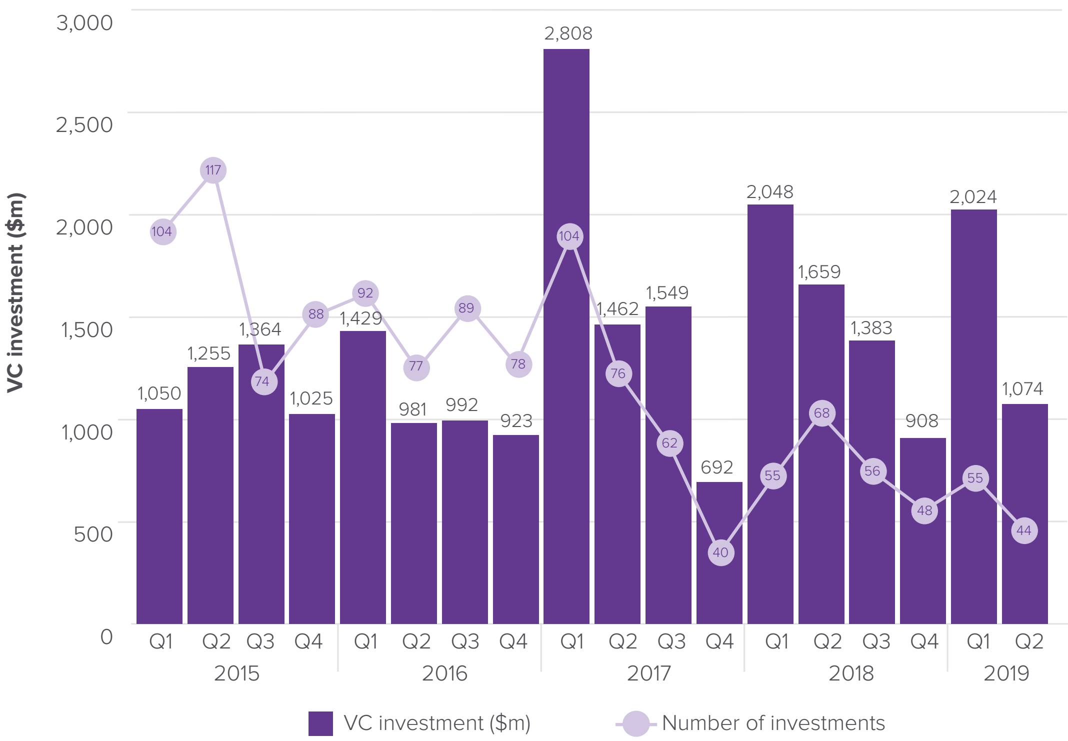
Medtech VC and the billion-dollar era

What is it about the final months of the year that prompts venture investors to think about spending? The first quarter of the past three years has seen private funding deals worth more than $2bn in total, meaning when the rest of us were saving for Christmas presents VC syndicates were gearing up to spend on companies developing promising medical technology.

And almost half of 2019's first quarter's total came from a single deal. Verily Life Sciences, the somewhat opaque health technology group that is sister company to Google, scooped the industry's first $1bn venture round on January 3. Nearly 10 times the size of the next biggest round so far this year, the deal underlines the growing faith financiers have in the value of data-driven healthcare.

Quarterly medtech VC investments

Source: EvaluateMedTech®, July 2019



If the richness of recent first quarters is one obvious trend in the above graph, the other is that the hoped-for recovery in the number of venture rounds done in each period is fizzling out. True, the 44 financings in Q2 of 2019 beat the previous low of 40 seen in Q4 2017, but the overall downturn over the past decade cannot be ignored.

It is perhaps surprising how early some of 2019's largest rounds were in the companies' development. Verily's blockbuster financing was only its second reported round, and Thrive, Archer and Pear Therapeutics made the top 10 table with A, B and C rounds, respectively. Overall, early investment in medtechs is falling alarmingly, as this analysis shows, but clearly some groups are able to tap into VC's largesse.

Thrive is a case in point. The groups is active in the hottest technological space in medtech, developing a liquid biopsy, CancerSeek, which is designed to not only diagnose cancer early but also to detect the organ of origin.

Top 10 VC rounds of H1 2019

Source: EvaluateMedTech®, July 2019

Date	Round	Company	Investment ($m)	MedTech Focus
Jan	Undisclosed	Verily Life Sciences	1,000	Diabetic care; ophthalmics; patient monitoring
May	Series A	Thrive Earlier Detection	110	In vitro diagnostics
Jun	Series D	Acutus Medical	100	Cardiology
Feb	Series E	Nuvaira	79	Anaesthesia & respiratory
Jan	Series D	Ablative Solutions	77	Cardiology
Jan	Undisclosed	Sophia Genetics	77	Healthcare IT
May	Series G	Pulmonx	65	Anaesthesia & respiratory
Jan	Series C	Pear Therapeutics	64	Healthcare IT
Jan	Undisclosed	PQ Bypass	60	Cardiology
May	Series B	Archerdx	60	In vitro diagnostics

Archer is also developing a liquid biopsy, but this is only one of the ways in which the group is applying its next-generation sequencing. It also has assays that run on tumour tissue samples, as well as companion diagnostics and tests that screen for inherited disorders in newborns.

Pear Therapeutics is applying novel computing-based technology to treating diseases in a different way. It is one of the emerging groups developing digital medicines – software, such as apps and computer games, that are regulated and prescribed as medical devices. Pear's Reset app, designed to help patients with addiction problems remain abstinent from drug abuse, gained FDA de novo clearance in September.

Advanced computing-based tech such as genetic sequencing, digital medicines and the kind of large-scale data crunching promised by Verily have one enormous advantage over other medical devices: they are cheap. Computing power is constantly dropping in price, and the development of software does not require dedicated laboratory facilities or hospital-based clinical trials.

This helps explain why medtech's heavy-hitters are outplaying biopharma's in terms of attracting venture financing. A comparison of the top three largest-ever rounds in the two sectors shows Verily and the liquid biopsy group Grail are way ahead of the only biotech group to crest $450m, the mRNA company Moderna.

This is not the whole picture, of course – biopharma attracts far more VC action overall than medtech. It is just that in medtech the distribution of the cash is extremely unequal.

Top VC rounds ever in medtech and biopharma

Source: EvaluateMedTech®, July 2019

Date	Round	Company	Investment ($m)	Focus
Medtech's top 5 VC rounds				
Jan 2019	Undisclosed	Verily Life Sciences	1,000	Diabetes care; surgery; healthcare IT; ophthalmics; patient monitoring
Mar 2017	Series B	Grail	900	In vitro diagnostics
Jan 2017	Undisclosed	Verily Life Sciences	800	Diabetes care; surgery; healthcare IT; ophthalmics; patient monitoring
Sep 2017	Series A	Shanghai United Imaging Healthcare	507	Diagnostic imaging
May 2017	Series E	Guardant Health	360	In vitro diagnostics
Biopharma's top 5 VC rounds				
Feb 2018	Undisclosed	Moderna	500	mRNA therapeutics
Aug 2016	Undisclosed	Moderna	451	mRNA therapeutics
Jan 2015	Series D	Moderna	450	mRNA therapeutics
Aug 2018	Series A	Samumed	438	Wnt pathway modulators
May 2018	Undisclosed	Acerta Pharma	375	Oncology

Few medtechs go public, but those that do do nicely

For companies wishing to go public the party is not over exactly, but somebody has turned the music down. Last year 29 medical device companies listed on stock exchanges; in the first six months of 2019, just eight medtechs went public.

At least the sizes of the offerings were respectable. Last year's total of $6.7bn was distorted by Siemens Healthineers' vast Frankfurt listing – without that, the total raised was $1.6bn. The first half of 2019 has already seen a total of $1.3bn raised through IPOs, so the few that did feel able to go out met with a receptive audience.

Just like last year, the largest single listing is European. The Swiss orthopaedics company Medacta Group stayed with its home exchange, raising SFr547m ($588m) in April. The founding Siccardi family has retained control of the company, with its free float amounting to about 30% of its shares.

IPOs by year

Source: EvaluateMedTech®, July 2019

Year	IPO count	Total raised ($m)	Average size ($m)
H1 2019	8	1,334	166.8
2018 (excluding Healthineers)	29 (28)	6,719 (1,594)	231.7 (56.9)
2017	10	241	24.1
2016 (excluding Convatec)	12 (11)	2,354 (406)	196.1 (36.9)
2015	21	1,244	59.2
2014	33	1,529	46.3

If Medacta is the winner in terms of float size the Australian group Next Science, which makes polymer gels that are designed to disrupt the structure of bacterial biofilms in an effort to help reduce reliance on antibiotics, beat all when it came to share price appreciation. Its stock rose 311% from its float in April to the end of June – but perhaps this is not the extraordinary achievement it first appears given that the company went out at a price of just one Australian dollar per share.

Indeed it is reassuring that these debutante companies are benefiting, overall, from the positive sentiment in the market that most of medtech has enjoyed so far this year. Five of the eight groups have seen their stock rise, and all but two of the companies managed to hit the values deal bankers had pitched.

H1 2019's medtech IPOs

Source: EvaluateMedTech®, July 2019

Date	Company	Amount raised ($m)	Offering price	Stock exchange	Discount/ premium	Share price change to Jun 28
Apr	Medacta Group	588	SFr104	Six Swiss Exchange	8%	(23%)
Jun	Adaptive Biotechnologies	345	$20	Nasdaq	25%	142%
Apr	Silk Road Medical	120	$20	Nasdaq	25%	142%
Mar	Shockwave Medical	111	$17	Nasdaq	13%	236%
May	Transmedics	105	$16	Nasdaq	0%	81%
Feb	Sequana Medical	32	€8.50	Euronext	(3%)	(25%)
Ap	Next Science	25	A$1	Australian Securities Exchange	0%	311%
Feb	Innotherapy	8	KRW18,000	Korea Exchange	(11%)	(37%)

One of the exceptions here is Innotherapy, which had to take an 11% haircut to get its tiny offering away and still saw its value drop 37% to mid-year – but the group is remarkable in another way.

The developer of bioadhesive surgical sealants is the only Korean float so far this year – remarkable considering seven companies went out on South Korean exchanges in 2018. This alone might count for the downturn in the number of flotations so far in 2019, though the US government shutdown that kicked the year off cannot have helped either.

Even so, half of the action, in terms of both number of listings and total cash raised, was outside the US. This is a huge difference from biopharma, where the IPO scene is still US-led, but par for the course in the medtech sector, where listings have been more or less evenly split between the US and non-US markets for the past three years.

For companies seeking growth capital, the IPO market is uncomfortably reminiscent of the VC situation. Those that can do a deal tend to succeed quite nicely – but the number of deals being done is falling.

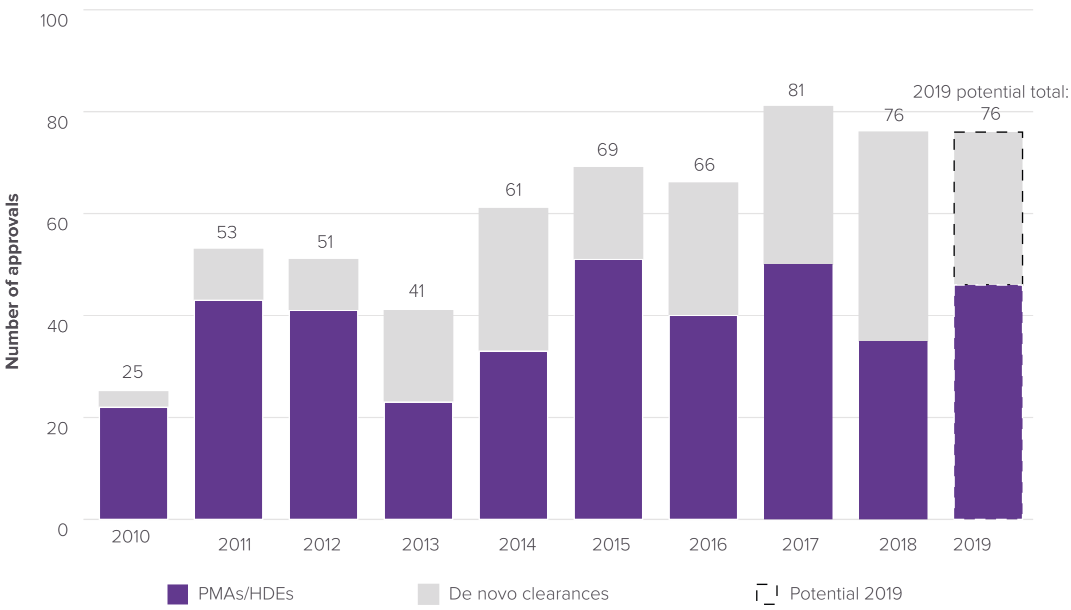
De novo device clearances fall out of fashion

The FDA's attempts to liberalise the medical device approval processes seem to have been stymied somewhat by the US government shutdown in early 2019. Consequently the number of approvals and clearances granted for innovative technologies is tracking exactly level with last year.

But a closer look at the figures shows a slightly unexpected finding. The number of de novo clearances – the route by which low-risk novel devices reach market – which has exploded in popularity in recent years, fell sharply in the first half. True, this trend could reverse in the remainder of 2019, but it does prompt questions about whether the FDA can achieve its aim of speeding up approvals of low-risk devices.

Medtech approvals

Source: EvaluateMedTech®, July 2019



The graph above shows projected figures for the entirety of 2019, assuming that the current rate of approvals continues until the end of the year.

The FDA intends to bring in changes that it expects will boost the popularity of the de novo 510(k) clearance pathway – requiring companies to use more recently approved devices as predicates, for example. But these changes have not been implemented yet, and in any case there are questions over exactly how effective they might be.

H1 2019's de novos by therapy area

Source: EvaluateMedTech®, July 2019

EvaluateMedTech classification	Number of de novos	Average approval time (mths)
Neurology	5	10.5
In vitro diagnostics	3	6.8
Anaesthesia & respiratory	1	18.8
Blood	1	11.3
Cardiology	1	10.3
Diabetic care	1	3.6
Gastroenterology	1	4.9
Orthopaedics	1	12.5
Wound management	1	13.2
Overall	**15**	**9.8**

As befitting neuroscience's status as one of the fastest-growing segments in medtech, most of the low-risk devices to reach the US market were for neurology applications. Neurosigma's Monarch device, which stimulates the trigeminal nerve to treat attention deficit hyperactivity disorder, is one such example – it is external rather than implanted, enabling it to be classified as low-risk.

The most populous therapy category among the high-risk devices, with 10 approvals, was cardiology – since implanted devices are automatically classified as high-risk this is to be expected. Boston Scientific's Lotus transcatheter aortic valve, Impulse Dynamics' Optimizer Smart heart failure device and Biotronik's Orsiro drug-eluting stent all fall into this category.

H1 2019's PMAs and HDE by therapy area

Source: EvaluateMedTech®, July 2019

EvaluateMedTech classification	Number of approvals	Average approval time (mths)
Cardiology	10	13.0
Orthopaedics	4	20.4
In vitro diagnostics	4	6.8
Neurology	2	8.0
Anaesthesia & respiratory	1	11.5
Gastroenterology	1	9.2
Obstetrics & gynaecology	1	7.5
Overall	**23**	**12.3**

Overall, with 15 de novo clearances, 23 PMAs (for 22 devices) and one humanitarian device exemption – for Novocure's NovoTTF-100L system for the treatment of mesothelioma – 38 innovative devices and diagnostics were ushered out to US patients in the first half of this year.

Should this pace be maintained in the second half, 76 new products will be made available – precisely the same number as last year.

On some measures the first half of 2019 has been more rewarding for medtech companies and their investors than it has for biopharma. Early indications are that the startling share price gains device makers enjoyed over the first half at least might settle down a bit, with the bellwether indices largely flat throughout July so far.

Life could become more volatile for drug makers in the coming months, with the Trump administration's long sought-after drug price reform still a big unknown. After calling off plans to ban the rebates paid to pharmacy benefit managers, the White House promised to come back with other measures; what these might look like will continue to preoccupy investors as the US heads into a presidential election year.

Takeover action always helps attract investors to a sector, of course, though it could be reasoned that a lot of the year's firepower has already been spent. With two mega-mergers in biopharma under way, and a quieter second half predicted for medtech, expectations for much more M&A perhaps ought to be tempered.

The volume of deals, in both biopharma and medtech, also looks unlikely to pick up, unless events from beyond healthcare close down the financial markets. With venture funds well stocked and public investors willing to buy new issues, the smaller end of these sectors looks well supported, financially speaking, heading into the second half.

Still, it could also be argued that life looks good only in certain areas. Start-ups in must-have areas like genetic therapies, targeted oncology and liquid biopsy are able to amass broad and deep investor backing, and support here seems almost bottomless. But, outside these white-hot spaces, companies must swim in shallower pools.

The biotech boom is over but isolated bubbles of hype still exist. As ever in the healthcare world, investors must stay alert for excessive claims, and unreasonable expectations.

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APR 2020