2017

Pharma and Biotech Half-Year Review

Jonathan Gardner – July 2017

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Return to form

After the first half of 2017 biopharma investors are in a position to be exuberant: the threat of US price controls that have overshadowed the sector for a year have largely disappeared. The pricing debate has fizzled to proposals for regulatory relief, increased competition and value-based pricing, news of which sent the US biotech index by late June to its highest point since the end of 2015. Plans to reshape America's health insurance market and corporate taxes might still happen, even if the former does not contain the full repeal of the Affordable Care Act that Republican leaders have sought.

This year small companies have seized the opportunity to float, with IPOs exceeding $1bn in a quarter for the first time since 2015. Venture capital rounds are not quite on a pace to match 2015, although vigorous support remains. But lest one get the impression that the entire pharmaceutical ecosystem is in rude health, deal activity is at a nadir, and if not for Johnson & Johnson's $30bn takeover of Actelion things would look much worse. One could point to the macro issues of a lack of corporate tax reform and big pharma's inability to use overseas cash to fund domestic transactions as holding back M&A activity. However, big pharma still is confronting high biotech valuations, making them reluctant to take big acquisition risks.

If anything, the resumption of investors' enthusiasm for biopharma looks cautious. The first half of 2017 certainly saw no shortage of new drug approvals, suggesting healthy R&D productivity. On the other hand, private payers have talked tough about the costs of new drugs, and with the expected premier of one of the most complex oncology projects yet in Novartis's CAR-T therapy for leukaemia later this year, these discussions will not go away. Therapies costing thousands of dollars a year for common conditions like heart disease and hundreds of thousands of dollars for rare or life-threatening conditions like muscular dystrophy or cancer are taking a toll on health insurers, and they are rightly seeking some constraints, just as they do with hospitals, doctors and other medical professionals.

As long as there is a conflict between biopharma's overarching goals – generating returns by delivering heath-improving scientific innovation – and customers' desire to pay only for provably cost-effective therapies, the sustainability of 2017's recovery will always be in question. Novartis's cell therapy has captured the imagination of the sector and a larger public audience. Its approval and, more importantly, commercial uptake could be an important barometer for how pharma performs in the second half of 2017.

Unless stated, all data are sourced to EvaluatePharma and were compiled in July 2017.

Big cap biopharma back in favour

A big runup to the end of June helped push the Nasdaq Biotechnology Index to an 18-month high, and healthcare indices in general outperformed wider markets over the first half. Only a handful of companies have failed to move higher this year, marking Bristol-Myers Squibb, Astellas and Teva out as the first half's disappointing exceptions.

Share price indices

Stock index	H1'17 % change
NASDAQ Biotechnology (US)	17%
S&P Pharmaceuticals (US)	9%
Dow Jones Pharma and Biotech (US)	11%
S&P 500 (US)	8%
DJIA (US)	8%
Dow Jones STOXX Healthcare (EU)	7%
Thomson Reuters Europe Healthcare (EU)	17%
Euro STOXX 50 (EU)	6%
FTSE-100 (UK)	2%
TOPIX Pharmaceutical Index (Japan)	3%

Only Astrazeneca delivered a real trigger for its share price gain – results from the Pacific trial of Imfinzi in stage III, unresectable lung cancer in May prompted a 9% jump in the stock on the day. The impending Mystic study results will determine whether its rally continues.

Big pharma: top risers and fallers in 6 months

Source: EvaluatePharma®, July 2017

	Jun 30 share price	H1 chg	Jun 30 market cap ($bn)	H1 chg ($bn)
Top three risers				
Abbvie	$72.51	16%	115.4	13.6
Astrazeneca	£51.35	16%	85.1	15.8
Johnson & Johnson	$132.29	15%	356.4	42.9
Top three worst performers				
Bristol-Myers Squibb	$55.72	(5%)	91.8	(5.9)
Pfizer	$33.59	3%	200.5	3.4
Glaxosmithkline	£16.36	5%	101.7	7.2

Bristol-Myers, standing out as the lone big-cap decliner, has never recovered from last year's failure of Checkmate-026, the study that tried and failed to secure for Opdivo a position in first-line lung cancer. Further wins by Merck & Co with its rival checkpoint inhibitor Keytruda have consolidated its lead in the anti-PD-(L)1 antibody space.

Outside big pharma but still in the large-cap space more fallers can be found, dominated by Japanese companies. Shares in Japan's drug makers have been hurt this year by moves by the government to put a lid on rising medical costs.

Concerns about Teva's strategic direction and squeezed generic drug prices continue to hurt the Israeli company, which is still looking for a new chief executive. Interestingly, outside the top three, several big biotech beasts have also registered declines in the first half – Biogen, Shire and Gilead – albeit in the -2% to -6% range.

Other big drug stocks ($25bn+): top risers and fallers in 6 months

Source: EvaluatePharma®, July 2017

	Jun 30 share price	H1 chg	Jun 30 market cap ($bn)	H1 chg ($bn)
Top three risers				
CSL	AU$138.03	37%	47.2	12.3
Regeneron Pharmaceuticals	$491.14	34%	51.3	13.3
Takeda	¥5,709	18%	41.0	4.2
Top three fallers				
Astellas Pharma	¥1,375	(15%)	25.8	(7.8)
Teva Pharmaceutical Industries	$33.22	(8%)	33.4	(3.1)
Otsuka Holdings	¥4,790	(6%)	24.2	(3.1)

General investor enthusiasm for the sector is clearly not strong enough to erase concerns about the growth prospects for these majors. Regeneron stands out as a strong large-cap US performer, buoyed by the launch of the promising autoimmune drug Dupixent; consensus forecasts show royalties reaching $700m by 2022. There were also double-digit gains by Amgen and Celgene.

A look at the mid-cap space paints a more mixed picture for US biotech, with eight biotech climbers to five fallers.

Mid cap drug stocks ($25-5bn): top risers and fallers in 6 months

Source: EvaluatePharma®, July 2017

	June 30 share price	H1 chg	June 30 market cap ($bn)	H1 change ($bn)
Top five risers				
Vertex Pharmaceuticals	$128.87	75%	32.1	13.8
Ipsen	€119.85	74%	10.7	4.4
Zydus Cadila	Rs526	48%	8.3	2.9
Jazz Pharmaceuticals	$155.50	43%	9.3	2.8
Recordati	€35.52	32%	8.0	1.8
Top five worst performers				
OPKO Health	$6.58	(29%)	3.7	(1.5)
Lupin	Rs1,060	(29%)	7.4	(2.6)
Sumitomo Dainippon Pharma	¥1,533	(24%)	5.5	(2.2)
Hikma Pharmaceuticals	£14.70	(22%)	4.5	(1.1)
Dr. Reddy's Laboratories	Rs2,683	(12%)	6.9	(0.7)

Related EP Vantage Comment and Analysis

Risers	
Vertex Pharmaceuticals	Vertex investors toast birth of the son of Orkambi
Ipsen	Merrimack falls for $1bn oncology offer from Ipsen
Jazz Pharmaceuticals	Jazz keeps the narcolepsy market awake
Fallers	
OPKO Health	Pharma regulatory and clinical trial news over Christmas
Hikma Pharmaceuticals	Snippet roundup: Sighs of relief for Astra and Glaxo

The smaller end of the market has benefitted from substantial investor attention, in the US at least. Many of the risers detailed below have long been considered potential M&A targets. But as stock prices climb higher once again it is becoming increasingly hard to see how exuberant public market valuations can be met by more cautious industry buyers. Improving fortunes for Esperion's cardiovascular treatment, Puma's breast cancer candidate and Portola's blood thinner have all been reflected in substantial share price gains.

Of course there are always clinical failures and setbacks in biotech – Ardelyx and Trevena can attest to the pain of problems with a lead asset.

After a dismal 2016 many will welcome this buoyant mood. Those hoping to see a resurgence in takeovers, however, might question whether some of these valuations have departed too far from reality.

Small cap drug stocks ($5bn-250m): top risers and fallers in 6 months

Source: EvaluatePharma®, July 2017

	June 30 share price	H1 chg	June 30 market cap ($m)	H1 change ($m)
Top five risers				
Esperion Therapeutics	$46.28	270%	1,045	763
Puma Biotechnology	$87.4	185%	3,231	2,857
Portola Pharmaceuticals	$56.17	150%	3,203	1,945
Loxo Oncology	$80.19	150%	2,350	1,898
Immunomedics	$8.83	141%	974	271
Top five worst performers				
4D Pharma	£2.29	(68%)	188	(376)
Ardelyx	$5.10	(64%)	242	(430)
Trevena	$2.30	(61%)	134	(1,357)
Sorrento Therapeutics	$2.00	(59%)	153	(1,289)
Foamix	$4.64	(58%)	174	(418)

Related EP Vantage Comment and Analysis

Risers	
Esperion Therapeutics	Daily Market Movers: Global Majors & Industry (20 Mar 2017)
Puma Biotechnology	Puma pulls within sight of FDA OK
Portola Pharmaceuticals	Portola breezes past the FDA (Snippet)
Loxo Oncology	Asco – Loxo nudges ahead of Ignyta with tumour-agnostic therapy
Immunomedics	Activist investor puts Immunomedics phase III in play
Fallers	
Ardelyx	Ardelyx runs into problems with tenapanor
Trevena	Analgesic causes pain for Trevena (Snippet)
Foamix	Daily Market Movers: Global Majors & Industry (27 Mar 2017)

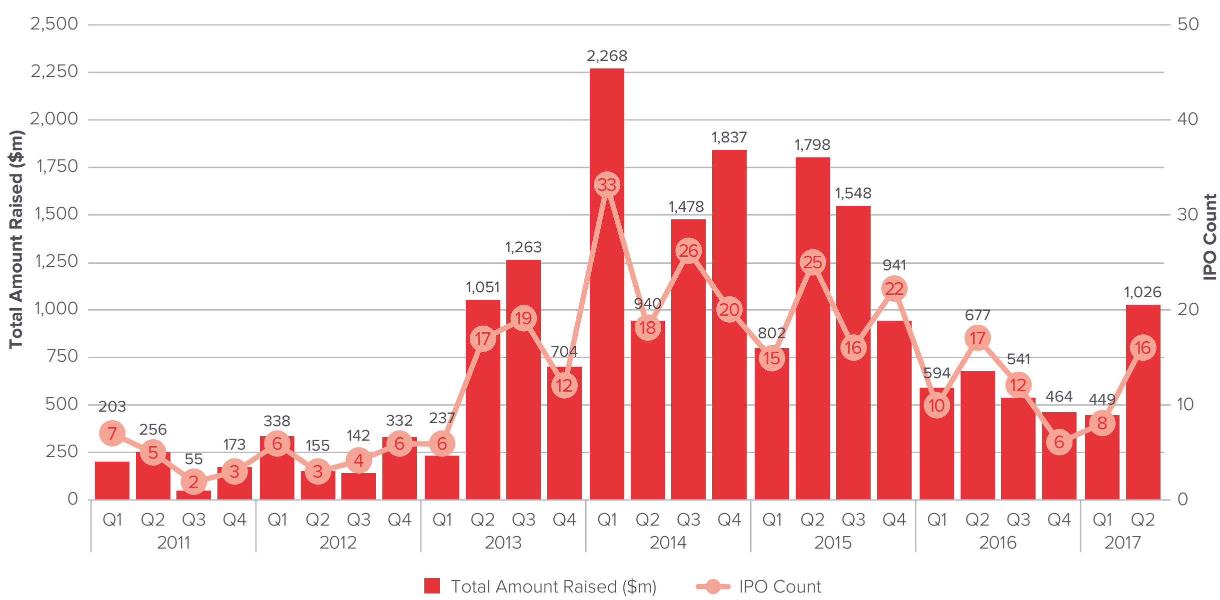
IPOs roar back

The second-quarter stock market surge for biopharma found a parallel in initial public offerings of development-stage companies, with new issues exceeding $1bn. This made for the strongest IPO quarter in nearly two years, a counterpoint to a first quarter so moribund it recalled pre-boom times.

The resurgence has been driven by the US, which in Biohaven's $168m float saw the biggest IPO of 2017 so far. It will not go unnoticed that the third quarter of 2015, the last time the $1bn mark was breached, came just after the peak of biotech's bull run, and that the Nasdaq biotech index last month hit its highest point since the end of 2015.

Biotech IPOs by quarter on Western exchanges (excludes medtech)

Source: EvaluatePharma®, July 2017



The first half was made up of two distinctly different quarters. 16 biotechs floated in the second quarter, only five of which did not involve US exchanges. In the previous three months Nasdaq was looking like a very unfriendly place, with half the first-quarter IPOs being done on European exchanges.

It will come as no surprise that non-US floats ended up at the bottom of the second-quarter table in terms of IPO size. Perhaps more worryingly, it was also non-US biotechs that accounted for the lion's share of post-float share price declines – four of seven – and collectively this cohort is off 13%.

Biotech IPO market by year

Source: EvaluatePharma®, July 2017

Year	No. of IPOs	Amount raised ($bn)	Avg. amount raised ($m)	No. raising >$100m
6M 2017	23	1.44	62	2
2016	45	2.28	51	3
2015	61	4.68	77	17
2014	87	6.30	72	18
2013	44	2.96	67	7
2012	16	0.93	58	2
2011	17	0.69	40	2

Though pre-IPO price haircuts are still commonplace, the fact that the second quarter suggested a relative equilibration of entrants might please biotechs in the flotation queue: two raised over $100m (the oncology player G1 Therapeutics in addition to Biohaven), yet the average amount raised, at $63m, outstripped the $51m average of 2016.

Renaissance Capital, a provider of IPO and pre-IPO analysis, found that across all sectors the second quarter of 2017 provided the most active US IPO market for two years. And it was tech and healthcare that drove this mini bull market, at the expense of natural resources companies.

Those hoping for continued resilience from biotech as the markets enter the summer lull will hope that this is just the beginning.

Hitting pause

However, it was not all good news. If it were not for Johnson & Johnson's takeout of Actelion, 2017 M&A stats would look very disappointing. As it is, the $30bn deal helps put 2017 on track to meet last year's combined values – but only if something else of similar scale materialises in the coming months.

Five-year M&A

Source: EvaluatePharma®, July 2017

Period	Combined deal value ($bn)	Deal count
H1 2017	49.3	85
2016	104.2	196
2015	188.9	289
2014	219.3	229
2013	79.5	226
2012	48.3	220

That might be a big task – a growing disconnection between biotech valuations and big pharma's willingness to pay for new technology is only one of a number of factors that is giving business development divisions some pause.

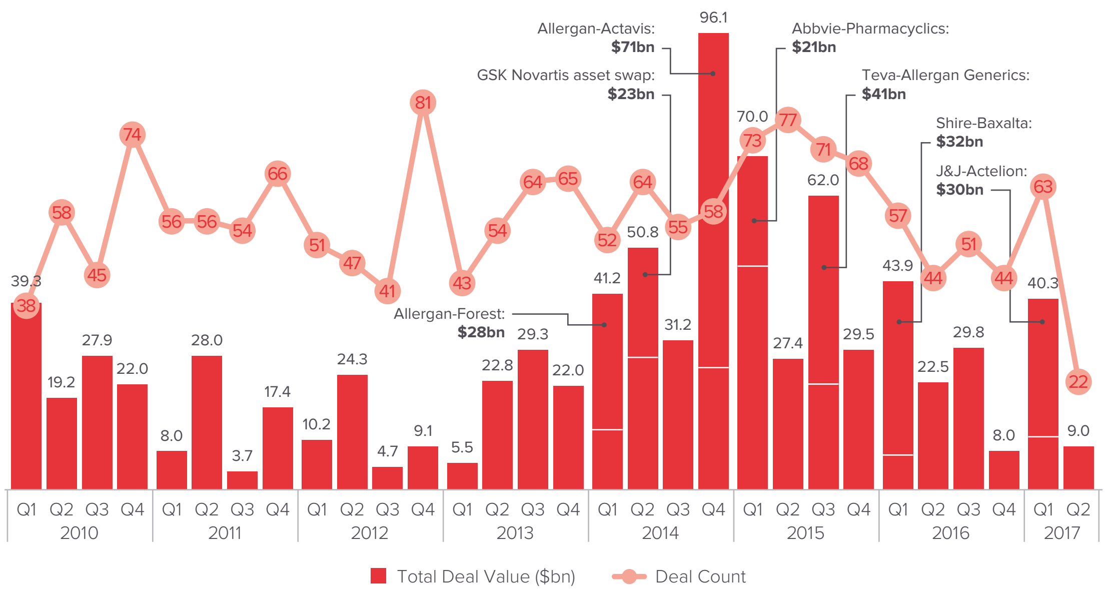
Washington DC's continuing twists and turns are calling into question proposed changes to the Affordable Care Act and the corporate tax cuts that health reform would enable. Until US big pharma has some clarity on whether it will be able to more cheaply repatriate overseas profits, it may be difficult to justify big transactions – and investors might punish any who jump the gun.

As a result, the first half of 2017 generated the lowest number of deals and total transaction value since 2013. But it is on a quarterly basis that the falloff in dealmaking can really be seen. The last three quarters have ticked along at around $8-10bn – excluding Actelion – although the number of transactions being announced has steadily been falling.

The second quarter's tally of 22 deals is probably the most worrying signal of these figures. It comes in substantially below the five-year average of 57, and if the trend continues this year could see a dramatic drop in transaction volume from 2015's peak.

Pharma and biotech M&A transactions announced each quarter

Source: EvaluatePharma®, July 2017



A look at last quarter's biggest acquisitions shows that generic consolidation has been a big contributor this year. Fresenius propped up values with two big deals, and if Stada Arzneimittel had managed to get its shareholders on board, its $6bn private equity-backed buyout would have been another notable transaction.

There have been biotech buys, of course, with Ariad's $5.2bn takeover in the first quarter and the True North acquisition in the second, by the Biogen-spin out Bioverativ.

Investors hope to see more as the year goes by, and if big companies like Gilead and Sanofi are on the M&A trail takeovers will happen. Biopharma dealmaking is not going away any time soon, but 2017 looks unlikely to be a bumper year for deal bankers.

Venture funding holding steady, with some shifts

Venture capital investment looks to be on track to at least match 2016's total, with a surprising trend away from the massive fundraisings that have been the hallmark of the previous two years.

It is hard to judge whether this reflects a simple regression to the mean, a lack of mature companies that would draw big rounds, or an increased interest in earlier-stage start ups. What is clear, however, is that while biotech has come off the boil since the 2015 peak, the investment climate remains more favourable for developers of human therapeutics than it was pre-boom.

Annual VC investments

Source: EvaluatePharma®, July 2017

Date	Investment ($bn)	Financing count	Avg per financing ($m)	No. of rounds ≥$50m	No. of rounds ≥$100m
H1 2017	4.50	209	22.9	9	3
2016	8.83	390	24.0	47	12
2015	10.72	472	23.6	56	13
2014	7.28	505	15.6	35	4
2013	5.11	447	12.7	13	3
2012	4.75	438	11.9	15	3
2011	4.35	413	11.7	11	3
2010	4.79	450	11.8	11	2

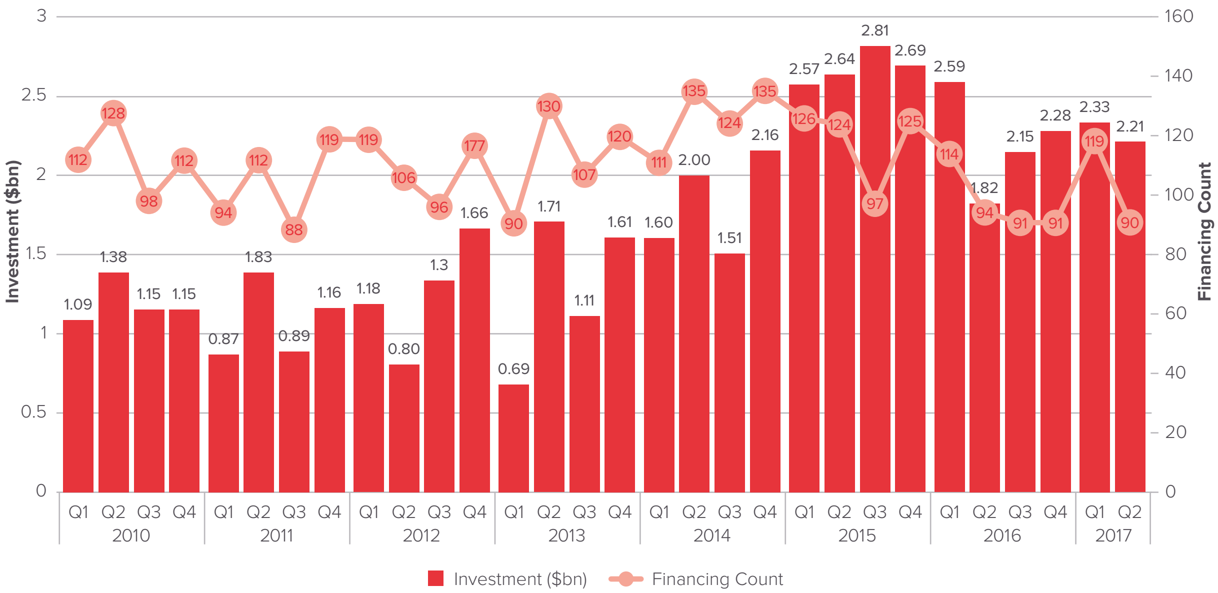
Venture financiers are on pace to match or exceed last year's total of $8.8bn in 390 rounds. But the average size per round has shown a small decline – to $22.9m from $24m in 2016.

The obvious explanation is a lack of rounds of $50m or more. There were just nine of these in the first six months, and if this pace continues the full-year figure would fall well short of the 47 recorded in 2016. These were the sorts of massive rounds that sparked worries that venture capitalists were bypassing earlier-stage companies in need of smaller tranches of funding.

One of the characteristics of venture investing in recent years has been the migration to big rounds and larger syndicates, and greater selectivity in support for seed and early-stage companies. The first half numbers suggest that trend is weakening.

Quarterly VC investments

Source: EvaluatePharma®, July 2017



Taking the second quarter in isolation provides some conflicting evidence, however. The number of rounds, 90, is one of the lowest quarterly totals recorded since *EP Vantage* began tracking venture financing, although the total for the quarter, $2.2bn, looks relatively strong.

That latter point could be down to a single financing from perennial chart-topper Intarcia Therapeutics, which hoovered up another $475m in April. The company is as late-stage as they come, as an FDA decision on its GLP-1 eluting implant is due by September.

Without that fundraising and that of Rubius Therapeutics, the second quarter would have looked rather pedestrian. Rubius landed a $120m series A in June, led by Flagship Pioneering with support from undisclosed institutional investors, to advance red-blood-cell based treatments for rare diseases and cancer.

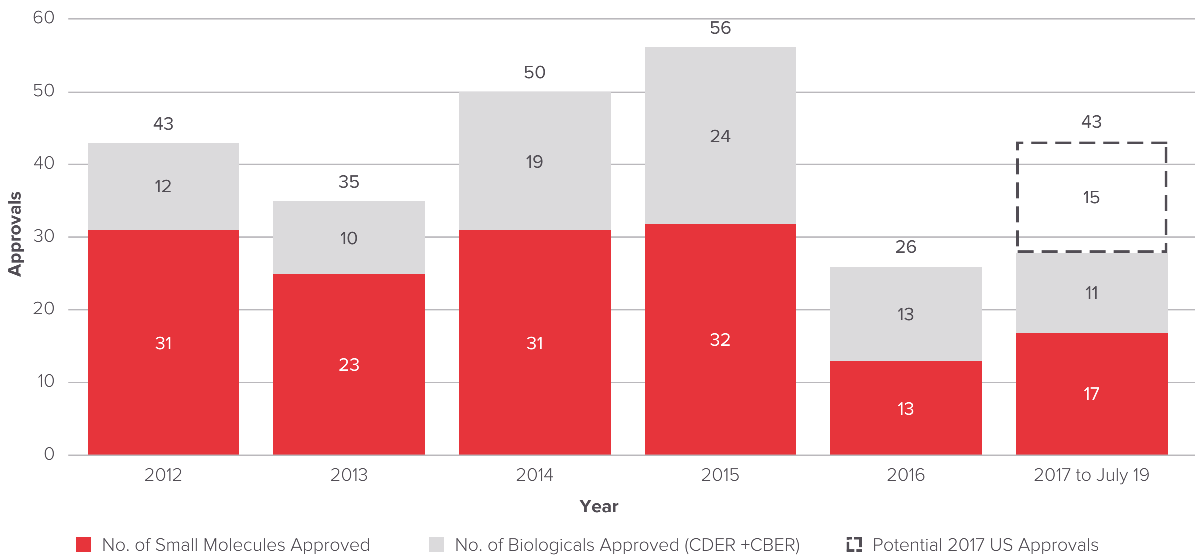
The clearest takeaway from venture funding in the first half of 2017 is that although it can no longer match the enthusiasm of 2015's peak of the biotech boom, the flow of money remains strong. The emphasis on early-stage or late-stage groups and preference for big rounds may be down to individual investors' strategies, meaning broad conclusions are difficult to make.

Approvals looking better

After a lull in 2016, FDA approvals look to be back on trend. As of July 19, 28 new drugs had been approved, exceeding the total of 2016 and putting this year on track for as many as 43 new chemical or biological approvals . This would be close to the typical total of the past five years and ought to put to rest any fears of a regulatory or innovative slowdown.

CDER + CBER novel approvals 2012 – July 19 2017

Source: EvaluatePharma®, July 2017



The allure of oncology shows no sign of weakening, as the year has seen the launch of Novartis's Rydapt and Kisquali, Boehringer Ingelheim's Bavencio and Astrazeneca's Imfinzi – the last two demonstrating the particular pull of immuno-oncology. That latter factor is also confirmed by what is likely to be the big biopharma event of the year, the FDA's decisions on the CAR-T treatments tisagenlecleucel-T from Novartis and axicabtagene ciloleucel from Kite Pharma.

But it has not been all oncology, as new immunomodulators have taken a big role this year. That includes Astra's Siliq in psoriasis, Sanofi and Regeneron Pharmaceuticals' Dupixent in atopic dermatitis, Roche's Ocrevus in multiple sclerosis and Regeneron's Kevzara in rheumatoid arthritis.

Nor has it been all clear sailing: Eli Lilly and Incyte missed with Jak inhibitor Olumiant in rheumatoid arthritis, and Astra with ZS-9 in hyperkalaemia, the latter because of manufacturing issues. That was also the case for decisions on two biosimilars, Pfizer's epoetin alfa and Coherus Biosciences's pegfilgrastim.

Beyond the CAR-T projects, the remainder of the year has some big events that should push this year's totals well past 2016's. These include approval decisions on Johnson & Johnson's Plivensia in rheumatoid arthritis, Novo Nordisk's once-weekly diabetes shot semaglutide and Pfizer's leukaemia drug Besponsa.

The rest of 2017

Though the key biotech share index has regained strength, it would be hard to ascribe that wholly to the underlying health of the sector. External factors – politics and economics – ran down valuations in 2016 and early 2017, and the lifting of the political threat has had much to do with the late June rally.

Still, it is hard to deny the signs of health. IPOs could be dismissed as a product of the rally, but a continuing flow of funds into private groups means venture financiers have not cooled to the risk of biopharma failure. A more troubling sign perhaps is the lack of M&A activity.

Since big pharma is not thought to have stopped looking for takeover targets, this trend suggests a divergence of opinions about biotech valuations.

As long as big pharma is sceptical of the surging market caps of potential targets M&A deal-making will remain subdued. For now, this is not a problem. As long as small companies can attract significant cash from public and private investors – and all the financing data suggests that this remains the case – their argument for holding out against what they perceive to be undervalued bids will remain strong.

The danger is that a few disastrous failures of recently floated companies puts a dampener on investor enthusiasm and erodes investor faith. This might be viewed as a positive in big pharma business development departments on the lookout for less expensive assets, but would be a negative when viewed through the lens of a startup needing capital to support its innovation.

The sector appears to have dodged a bullet on government pricing intervention, but the shadow of politics is ever present. The as-yet unresolved question of new reforms in US health insurance coverage also has some long-term implications for the industry. Rollbacks in Medicaid coverage for low-income people, bare-bones plans with less generous or non-existent drug coverage, and the “freedom” to go without health insurance coverage mean fewer buyers of pharma companies’ products. This may not have an immediate impact but surely will be felt over years if members of Congress and President Donald Trump have their way.

At a top level, a capricious president who speaks via Twitter only adds to the usual chaos of the market. This unpredictability can weigh heavily on shares, whether or not his tweets are specific to health policy. This additional level of volatility will not help biopharma investors make wise decisions in the second half of the year.

Report author: **Jonathan Gardner**

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Evaluate Headquarters
Evaluate Ltd.
11-29 Fashion Street
London E1 6PX
United Kingdom
T +44 (0)20 7377 0800
F +44 (0)20 7539 1801

Evaluate North America
EvaluatePharma USA Inc.
15 Broad Street, Suite 401
Boston, MA 02109, USA
T +1 617 573 9450
F +1 617 573 9542

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