2016

Pharma and Biotech Half-Year Review

Amy Brown – August 2016

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The peak is in the past

If anything can be gleaned from the first half of 2016 it is that the peak is in the past. Any hopes that the declines of the second half of 2015 might be reversed must now be put to bed, and the highs of last July be consigned to the record books.

Concern about the pressures on drug prices continues to spook investors, who also have tepid economic recoveries in the west and the slowdown in China to grapple with. In Europe the impact of the UK's vote to leave the EU has yet to unfold and in the US, with the presidential race hotting up, the industry is bracing itself for a period of close scrutiny. Many expect drug pricing to become a big issue whichever camp ends up winning, although arguably a Democrat victory would spell more trouble for the sector.

Triggering the Top

All this has manifested itself in a sharp re-rating of share prices – by the end of June the Nasdaq Biotechnology Index had fallen 35% from its July 2015 peak. Fewer IPOs of fledgling drug developers are happening and those that get away are raising less than this time last year, while venture financing has also taken a tumble. M&A activity has dimmed, with several of the most enthusiastic consolidators of the last few years paying heavily for their profligate ways.

However, while all these indicators signal a slowdown, it should be remembered that this is a sector emerging from a spectacular bull run, which was for a time fuelled by almost unchecked investor exuberance. During that time huge amounts of money were raised and many research-stage, high-risk companies are now very well capitalised, and a vibrant cohort of newly public companies has emerged. Venture capital firms also benefitted and many raised substantial new funds, which remain to be tapped by start-ups. At the other end of the spectrum, investors to a certain extent still consider larger players a safe haven from macro-economic trends.

The bull run had to end sometime. But companies must now prove that valuations should not fall any further. This will require clinical and regulatory wins from across the sector, and in particular from the fields where investor excitement really drove valuations. Investors, meanwhile, will be on high alert for any evidence of a deepening downturn, and increasingly reluctant to be generous with their support in the face of any setback.

Pricing will remain the omnipresent issue, the life science industry's macro challenge. Concern around this issue will no doubt grow ahead of the US presidential elections in November, as uncertainties abound. The industry must hope that the reality ends up more benign than feared.

Unless stated, all data are sourced to EvaluatePharma and were compiled in July 2016.

Stock market jitters

A look at the pharma and biotech sectors on the financial markets reveals the flip side to the image seen this time last year. The Nasdaq biotechnology index lost 21% of its value across the first half of this year – at the mid-point of 2015 gains of the same magnitude had been made.

Stock Indices

Stock index	% Change in H1 2016
NASDAQ Biotechnology (US)	(21%)
S&P Pharmaceuticals (US)	3%
Dow Jones Pharma and Biotech (US)	(6%)
S&P 500	3%
DJIA	3%
Dow Jones STOXX Healthcare (EU)	(6%)
Thomson Reuters Europe Healthcare (EU)	(5%)
Euro STOXX 50	(13%)
FTSE-100	4%
TOPIX Pharmaceutical Index (Japan)	(10%)

The rout of the opening weeks of January, when the sector was meeting for its annual pow-wow at the JP Morgan Conference in San Francisco, was described by many as one of the most torrid times they had seen on the markets. True, the index has since recovered somewhat from the low point touched in February, but only just.

Given wider macro concerns that stretch from economic and political uncertainty to global unrest and terrorism, it is perhaps surprising that the broader indices have held up relatively well.

Big pharma as a group is being helped to a certain extent by its defensive qualities. Johnson & Johnson can probably thank its conglomerate structure for its sector-leading performance, although this would be to understate the substantial success of the company's drugs business in the last few years.

Big pharma companies: top risers and fallers in 6 months

Source: EvaluatePharma® July 2016

		Market capitalisation ($bn)	
Top 3 risers	Share price change	H1 2016	6 mth change
Johnson & Johnson ($)	18%	333.65	50.64
GlaxoSmithKline (£)	17%	111.90	11.78
Pfizer ($)	9%	213.54	14.21
Top 3 fallers			
AstraZeneca ($)	(11%)	76.36	(9.46)
Roche (SFr)	(7%)	229.63	(9.89)
Eli Lilly ($)	(7%)	86.93	(6.20)

GlaxoSmithKline, meanwhile, has been a big beneficiary of the drop in sterling, in the wake of the UK's surprise vote to leave the EU.

However, the smaller end of the sector has really suffered these last six months. No big drug maker worth more than $25bn, outside big pharma, has notched up gains. At the bottom of the pile sits Valeant, a shadow of its former self on the market, with its $7bn valuation dwarfed by its $30bn debt pile.

Following the former serial acquirer are high-risk biotechs selling high-priced products, which have been punctured by investors' concerns around drug pricing.

Other large cap (>$25bn): best perfomers and fallers in 6 months

Source: EvaluatePharma® July 2016

		Market capitalisation ($bn)	
Best performers	**Share price change**	**H1 2016**	**6 mth change**
Amgen ($)	(6%)	74.91	(8.10)
Astellas Pharma (¥)	(8%)	27.66	(1.09)
Shire ($)	(10%)	154.88	14.66
Top fallers			
Valeant Pharmaceuticals International ($)	(80%)	6.91	(27.77)
Alexion Pharmaceuticals ($)	(39%)	26.16	(16.82)
Regeneron Pharmaceuticals ($)	(36%)	36.03	(19.43)

At the other end of the sector gains can be found, and those able to pick winners in this market prove that there are still healthy profits to be made out there.

Genmab finally struck gold with Darzalex in multiple myeloma, partnered with J&J; the Danish biotech added a staggering $3bn in value over the first six months of 2016.

Tesaro has benefited from good old fashioned clinical success, with its Parp inhibitor niraparib smashing expectations in a phase III ovarian cancer trial.

Celator, meanwhile serves to remind the sector that tiny microcaps can, occasionally, beat the odds. The $1.2bn in market cap it added in the wake of its impressive leukaemia results rivals the value creation of some of the mid-caps.

Other significant movers in 6 months

Source: EvaluatePharma® July 2016

		Market capitalisation ($bn)	
Risers	**Share price change**	**H1 2016**	**6 mth change**
Genmab (Dkr)	32%	11.04	3.07
TESARO ($)	61%	3.85	1.76
Celator Pharmaceuticals ($)	1,615%	1.29	1.23
Fallers			
Endo International ($)	(75%)	3.47	(10.38)
Ionis Pharmaceuticals ($)	(62%)	2.81	(4.63)
Infinity Pharmaceuticals($)	(83%)	0.07	(0.32)

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Fallers	
Endo International	Daily Market Movers: Global Majors & Industry (6 May 2016)
Ionis Pharmaceuticals	Ionis safety blow boosts Alnylam
Infinity Pharmaceuticals	Dynamo puts Infinity into a tailspin

But fallers also exist here too. Endo, for example, is being punished for running a similar strategy to its once larger peer Valeant, while Ionis and Infinity are victims of clinical setbacks.

Picking winners will only get harder if equity markets take further tumbles, and investors become increasingly reluctant to reward anything other than unquestionable success.

IPO market slows

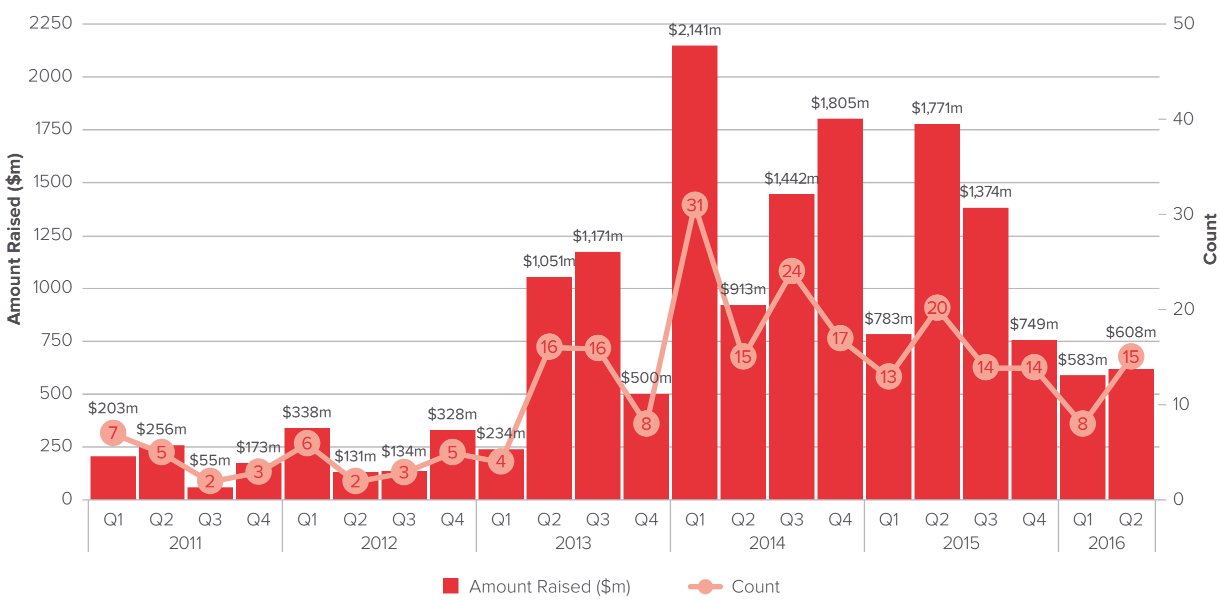
The poor state of the market has already had an impact on the IPO scene, with flotations dropping off substantially in the first quarter.

Only eight companies got away in the first three months of the year – the Nasdaq biotechnology index plunged 23% in January alone – and those that did were relatively big offerings able to weather the storm.

The second quarter managed something of a recovery in terms of the number of flotations. However, these were all relatively small and all had to offer substantial discounts to succeed.

Initial Public Offerings by Quarter on Western Exchanges

Source: EvaluatePharma® July 2016



News abounds of shelved IPO plans – BioCardia and PLx Pharma both scrapped US listing plans, while Gensight had to shift its ambitions back home, raising less than half it originally targeted in a Paris flotation.

The gene therapy company's chief finance officer, Thomas Gidoin, said rapidly deteriorating market conditions were making investors on both sides of the Atlantic much more cautious.

"When you talk to investors most of them are saying they will continue to invest in IPOs, but they will be very picky on the projects they chose, and they will only select the best stories with credible management teams and strong commitment from historic investors," he said.

He pointed to the poor performance of many 2015 IPOs and general market conditions as reasons for investor disquiet.

Another gathering trend is of existing investors having to take ever bigger stakes to persuade new shareholders to come on board.

Few expect this generally weakening picture to improve in the second half of the year.

Top 10 Biotech IPOs on Western Stock Exchanges in H1 2016

Source: EvaluatePharma® July 2016

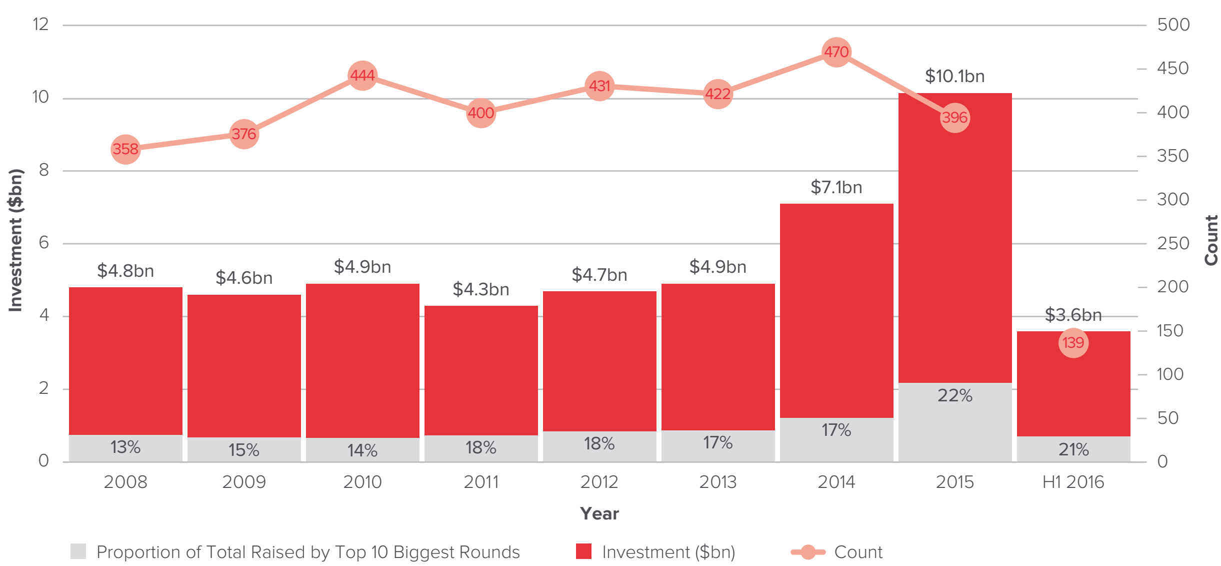
Company	Date	Amount raised ($m)	Offering price	Range	Discount/ premium	Exchange	H1 change since float
BeiGene	03/02/16	158	$24.00	$22.00-$24.00	4%	NASDAQ	24%
Intellia Therapeutics	06/05/16	113	$18.00	$16.00-$18.00	6%	NASDAQ	19%
AveXis	11/02/16	95	$20.00	$19.00-$21.00	0%	NASDAQ	90%
Editas Medicine	03/02/16	94	$16.00	$16.00-$18.00	(6%)	NASDAQ	53%
Corvus Pharmaceuticals	23/03/16	71	$15.00	$15.00-$17.00	(6%)	NASDAQ	(5%)
Selecta Biosciences	22/06/16	70	$14.00	$14.00-$16.00	(7%)	NASDAQ	(0%)
Reata Pharmaceuticals	26/05/16	61	$11.00	$14.00-$16.00	(27%)	NASDAQ	80%
Merus	19/05/16	55	$10.00	$14.00-$16.00	(33%)	NASDAQ	(20%)
Syndax Pharmaceuticals	02/03/16	53	$12.00	$14.00-$16.00	(20%)	NASDAQ	(18%)
Clearside Biomedical	02/06/16	50	$7.00	$14.00-$16.00	(53%)	NASDAQ	0%

Venture funding falls from peak

A look at the amount of venture financing raised so far this year also suggests that the peak has passed. It seems that 2015 was the boom year, and the total amount committed to private drug developers so far this year points to a level similar to 2014.

Annual VC Investments with 10 Biggest Rounds Shown as Proportion of Total Raised

Source: EvaluatePharma® July 2016



Many would consider a repeat of a year like 2014 to be not so bad. And it is certainly true that many venture firms are investing from plump new funds, raised in the last few years.

Nextech Invest, a Swiss-based, oncology focused VC firm just closed its fourth fund, at $64m, with participating investors from around the globe. “There is a lot of excitement around the paradigm change in drug development in the US and Asia. We saw some cautiousness with European investors, probably to do with the situation in Europe, and maybe to do with past performance,” said Alfred Scheidegger, founding partner.

Perhaps more worrying is evidence of a drop off in the number of financings. If this is confirmed across the full year it might be concluded that the trend of larger lumps of capital being focused in fewer hands is becoming more pronounced.

As can be seen in the above analysis, more than a fifth of the total amount raised sits in the hands of the top 10 companies, a proportion that has been increasing over the last few years.

"Companies don't just start with a scientific hypothesis, they start at a level which is much more advanced than 10 years ago. Certain scientific concepts reach a much higher degree of validation more quickly, which justifies putting more money behind them to reach the next inflection point," said Thilo Schroeder, a partner at Nextech.

Still, if fewer companies are getting backing, this is likely to disadvantage certain types of company, namely those in less favoured therapy areas or perhaps very early stage start-ups. Silicon Valley Bank, in a recent report on VC funding, also pointed out that larger rounds could supress M&A multiples down the road. Considering that a takeout remains the dream scenario for any VC investor, this is not a prospect to celebrate.

Another reason cited for the overall drop off in VC dollars is the withdrawal of crossover funds from the sector, as the IPO landscape becomes harsher. These investors typically top up substantial pre-float rounds and help a company transition from private to public hands, so any deterioration in the equity markets will naturally send them on their way.

Start-up drug developers will have to hope that this is the reason for the seeming retrenchment in venture financing this year, and that the underlying sector remains strong. However as the IPO window swings shut, M&A as an exit route will become only more important, making deal activity an ever more important indicator of sector health.

Biggest VC Rounds of H1 2016

Source: EvaluatePharma® July 2016

Company	Investment ($m)	Financing Round	Date
DalCor Pharmaceuticals	100.00	Series B	Apr
Hengrui Therapeutics	100.00	Series Undisclosed	Jun
MISSION Therapeutics	86.43	Series Undisclosed	Feb
Forty Seven	75.00	Series A	Feb
C4 Therapeutics	73.00	Series A	Jan
Kala Pharmaceuticals	68.00	Series C	Apr
NextCure	67.00	Series A	Jan
Aptinyx	65.00	Series A	May
Millendo Therapeutics	62.00	Series B	Jan
Zymeworks	61.50	Series A	Jan

M&A market struggles onwards

Venture investors hoping to find salvation in the M&A market will need to look closely. The number of takeover deals struck by pharma and biotech companies in the first half suggests a decline in activity – perhaps not surprising given the state of the markets and the withdrawal of a number of serial acquirers from the scene.

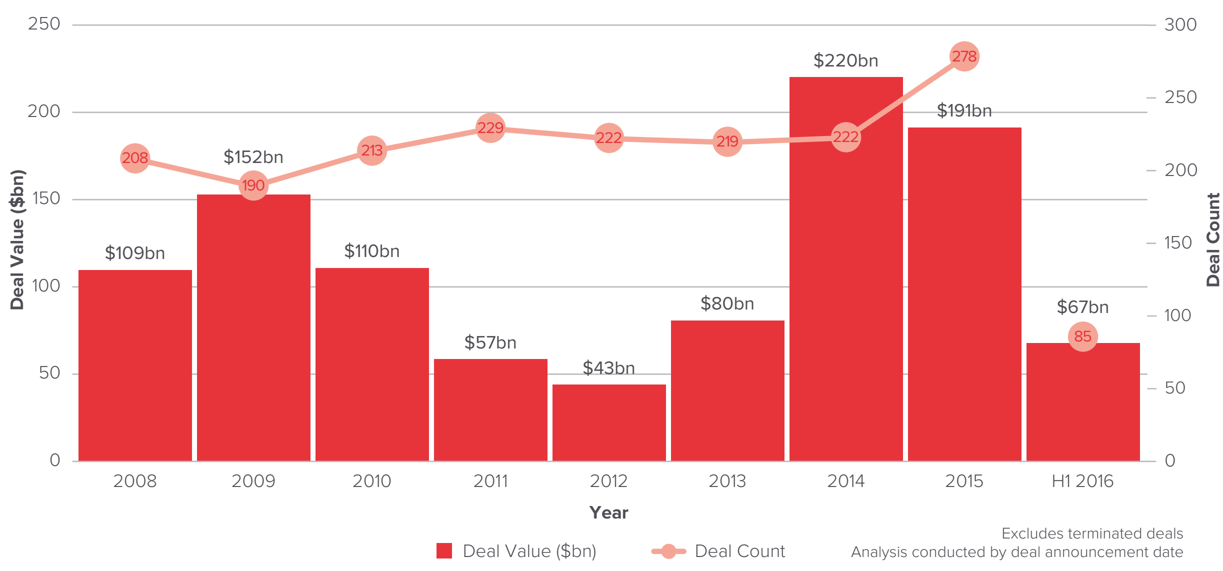
In fact, a closer look shows that the number of M&A deals being struck has dropped for the last four consecutive quarters. If this metric can be taken as a sign of the health of the deal landscape, then perhaps the omens are not good.

On the other hand, the $67bn spent by pharma and biotech companies in the first six months is a healthy tally for the half year stage. This figure was swelled by Shire's $32bn takeout of Baxalta, while the second quarter saw six deals of $1bn or more. And for those waiting for take-outs in the smaller end of the sector, Abbvie's $9.8bn Stemcentrx swoop and Pfizer's $5.2bn move on Anacor will lift spirits.

Pharma and Biotech M&A Activity

Source: EvaluatePharma® July 2016

2008 – Genentech (Roche) $46.8bn
2009 – Wyeth (Pfizer) $68.0bn
Schering-Plough (Merck & Co) $41.1bn
2010 – Alcon (Novartis) $37.7bn
2014 – Forest Laboratories (Actavis) $28.0bn
Allergan (Actavis) $70.5bn
2015 – Allergan generics (Teva) $40.5bn
2016 – Baxalta (Shire) $32.0bn



A look at average deal values shows these have fallen in the first half of the year. This finding is again not surprising given the dip in deal activity.

However the state of the financial markets could also have contributed to a drop in average deal value. This is not necessarily a bad thing – assuming sellers are willing to accept a return to more rational valuations more cautious acquirers could be drawn out in the coming months, and this could help drive deal activity.

And of course the year still has one big deal on the cards – Sanofi's on-going attempt to buy Medivation could still end up in an agreement. Although the French pharma giant remains the most likely buyer, speculation abounds that another party will still enter the fray.

Top 5 Pharma/Biotech M&A deals in 2015 and H1 2016

Source: EvaluatePharma® July 2016

Year	Acquirer	Target	Deal status	Value ($bn)
H1 2016	Shire	Baxalta	Closed	32.03
	AbbVie	Stemcentrx	Closed	9.80
	Mylan	Meda	Open	7.20
	Pfizer	Anacor Pharmaceuticals	Closed	5.20
	Jazz Pharmaceuticals	Celator Pharmaceuticals	Open	1.50
2015	Teva Pharmaceutical Industries	Generics business of Allergan	Open	40.50
	AbbVie	Pharmacyclics	Closed	20.77
	Pfizer	Hospira	Closed	17.00
	Valeant Pharmaceuticals International	Salix Pharmaceuticals	Closed	11.37
	Alexion Pharmaceuticals	Synageva BioPharma	Closed	8.39

Approvals still strong

Of course financial metrics are not the only way to judge the health of the sector – its track record in getting valuable new drugs to market is another important measure. Indeed, a successful spell of perceived high innovation played no small part in driving the re-rating of the last few years.

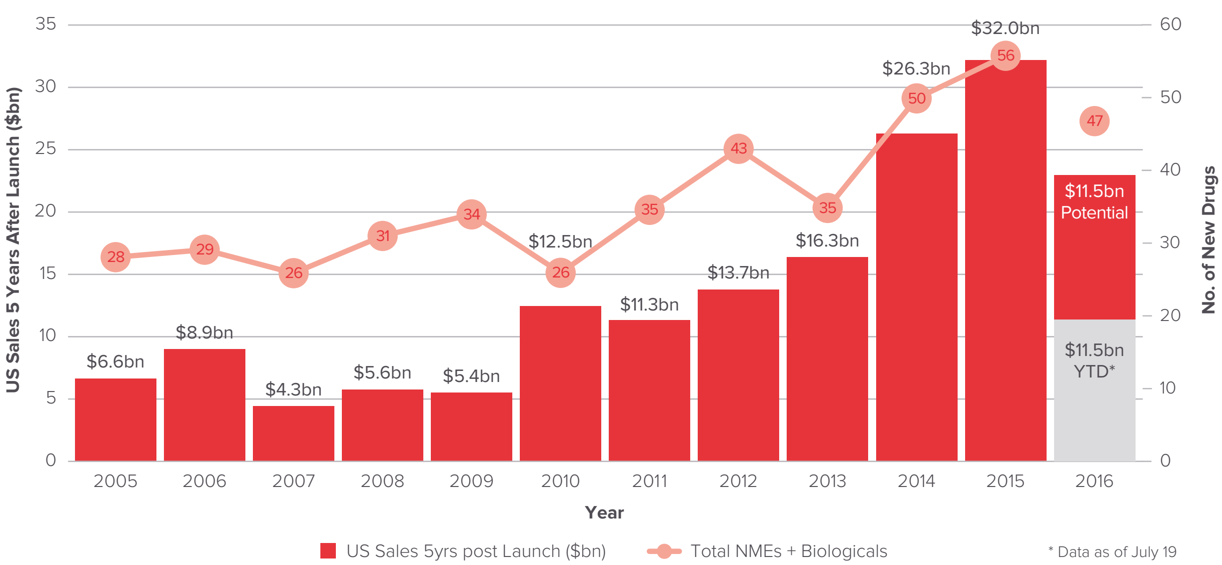
By mid-July the FDA had approved 17 NMEs and novel biologics, according to EvaluatePharma's count, a tally that points to a slower year than the last few. An analysis of the near-term pipeline reveals another 30 could still pass regulatory muster, making 47 in total.

Looking at the value of this cohort, by measuring fifth-year US sales estimates, also points to a slimmer year than 2015 and 2014.

FDA Approval Count vs. Total USA Product Sales 5 Years After Launch

Source: EvaluatePharma® July 2016

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)



* Data as of July 19

Still, these last two years not only saw a huge jump in the number of approvals, they also heralded the arrival of some substantial new products. Namely, Bristol-Myers' checkpoint inhibitor Opdivo, Gilead's hepatitis C combination Harvoni, and Vertex's cystic fibrosis combination Orkambi.

This year could also see some notable new arrivals, Roche's checkpoint entrant, Tecentriq, was given a green light back in May. And waiting for judgement is the Swiss pharma giant's Ocrevus, a product that promises to shake up the market for MS drugs in the next few years.

Regulatory approvals are always hard to predict, and it is far too soon to call a drop in productivity. However, with other indicators of the sector's buoyancy starting to deflate, it is even more important that drug companies keep delivering on innovation.

Top approvals of 2016 to July 19

Source: EvaluatePharma® July 2016

Rank	Product	Pharmacology class	Company	Approval date	US sales 2021 ($m)
1	Tecentriq	Anti-PD-L1 MAb	Roche	18/05/16	2,870
2	Zepatier	Hepatitis C NS3/4A protease inhibitor & hepatitis C nucleoside NS5A polymerase inhibitor	Merck & Co	28/01/16	1,455
3	Ocaliva	Farnesoid X receptor agonist	Intercept Pharmaceuticals	27/05/16	1,150
4	Venclexta	B-cell lymphoma 2 inhibitor	Roche	11/04/16	927
5	Taltz	Anti-IL-17A MAb	Eli Lilly	22/03/16	895

Top five potential approvals of 2016

Source: EvaluatePharma® July 2016

Rank	Product	Pharmacology class	Company	Approval date	US sales 2021 ($m)
1	Ocrevus	Anti-CD20 MAb	Roche	28/12/16	2,908
2	Dupilumab	Anti-IL-4 & IL-13 Mab	Sanofi	Rolling submission completed by YE	1,821
3	Baricitinib	JAK-1/2 inhibitor	Eli Lilly	January 2017	912
4	Abemaciclib	Cyclin-dependent kinase 4 & 6 inhibitor	Eli Lilly	Filing expected by YE	905
5	Tenofovir Alafenamide	Nucleoside reverse transcriptase inhibitor	Gilead Sciences	January 2017	758

Outlook for the second half and beyond

The various measures of the health of the life science sector at the half year stage might present a mixed picture, but it is clear that the boom has come to an end. While M&A activity and drug approvals remain buoyant, the reversal of the equity markets has had a clear impact on IPOs and venture financing.

There are no obvious triggers on the horizon to cause the financial markets to flourish once more, so it seems likely that these trends will deepen over the remainder of the year. One unknown remains the state of the M&A market and whether companies' appetite for deal making will dim and follow IPO and VC metrics downwards, or get a boost from more rational valuations.

Indeed differing opinions on valuation will no doubt challenge investors and dealmakers alike in the coming months, as sellers attempt to achieve the sorts of price tags enjoyed over the last few years. The heady days of unchecked investor exuberance are over, however, and it will be interesting to see the extent to which expectations fall in line with the new realities.

Meanwhile, the sector's lurking gremlin, drug pricing, will continue to stalk investors' nightmares. Both Donald Trump and Hillary Clinton have pledged to turn their attention to healthcare, and in the run up to the US presidential elections this will almost certainly harm sentiment towards the sector. Should the Democrats keep hold of the White House investors will take further flight – Mrs Clinton's pledges include granting Medicare the right to negotiate drug prices, the capping of out of pocket prescription costs and coming down hard on "pay for delay" deals. All of which could harm the industry's ability to keep raising prices in the US, one of the last markets where this remains even a vague possibility.

Still, the extent of the current downturn should not be over stated – many companies, public and private, and their investors remain well capitalised, having made hay while the sun shone. And the sector is a long way from plunging to the depths of the last recession.

According to the venture capitalists Mr Scheidegger and Mr Schroeder, there are many factors that make the industry more attractive than seven or eight years ago, such as faster time lines for drug development and more efficient capital structures, while fundamentals like an ageing population are not going to change.

"Private equity returned more capital than it raised in the last few years," Mr Schroeder said. And the life science sector "has a high independence from public markets because it's such an acquisition driven industry".

Assuming those returns keep flowing, that should be enough to keep investor interest alive in the coming years, particularly in a low interest rate environment.

Unfortunately, extracting profits will only get harder should stock markets continue to decline. To help avoid a protracted downturn developing, the industry must ultimately keep up its output of novel, innovative therapies, no matter the state of the markets, or the status of the debate around drug prices and affordability.

In particular, several of the more high risk fields that managed to raise substantial amounts of money over the past few years – CAR-T, gene therapies and gene editing, for example – need to deliver on their promises. For investors to be dissuaded that they bought into a bubble, these cutting-edge scientific spaces need to keep moving towards the market place. Otherwise investors will keep moving towards the door, and a look back at 2016 in its entirety will make for much more depressing reading.

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