

A long wooden pier extends from the foreground into a calm lake. The sky is a deep, vibrant red, and numerous white arrows of various sizes and orientations are scattered across the sky, pointing in various directions. The overall scene is surreal and evocative, suggesting a path forward or a journey.

Pharma & Biotech 2015 in Review

Lisa Urquhart and Jonathan Gardner – March 2016



Pharma and Biotech 2015 in Review

What a difference a few months make. Before the cold chill set into the market at the beginning of 2016 many were predicting more good times for the sector, especially as much of 2015 echoed the exuberance of a super-charged 2014.

Until the autumn share prices continued to set highs, the IPO window remained wide open, VCs revelled in their returns, and if there were suspicions that the good times could be stalling all one had to do was look at Pfizer's record-breaking move on Allergan.

Many had also seen the continued magnanimity of the FDA in approving new medicines as a sign that improved productivity in the market would persist in driving valuations.

Since then all has changed. A brief year-end rally has been replaced by further stock price slides, wiping out a whole year's worth of gains for the Nasdaq biotech index.

The sentiment issues facing the industry – criticism about high drug prices, the gradual closing of the tax inversion loophole, and the feeling that company valuations are still too high – remain. Add to this the worsening macro-economic environment, and it is unlikely that the current volatility in the market will subside quickly.

There had always been dissenting voices about the robustness of the current bull run, but in 2015 they began crystallising around pricing. First in the spotlight was Valeant, which drew criticism for the price hikes for the heart drugs Nitropress and Isuprel, but 2015 will perhaps be best remembered for Martin Shkreli bursting onto front pages with the 5,000% price increase for the generic toxoplasmosis drug Daraprim.

While the industry was quick to distance itself from a seemingly unapologetic Mr Shkreli, his actions had catapulted price gouging into the consciousness of the US public and the political arena.

The first big fall in the market came in mid-September after the presidential hopeful Hillary Clinton vowed to take on this sort of price-gouging in the industry. Then came a slowdown in China and falling oil prices.

One company that perhaps summed up the switch in fortunes in 2015 is NantKwest. The oncology group managed to float in July, raising \$223m, and then saw a 39% share price jump on its first day of trading bumped its market cap up to \$2.6bn.

However, despite the fairytale beginning, the happily ever after proved more elusive, as the shares were more than 50% below their IPO price three months after floating. In November the group was forced to undertake a \$50m share buyback programme – highly unusual for a lossmaking biotech – to shore up its flagging stock price.



That said, the year was not without its positives. Companies continued to push scientific innovation, and the fever around CRISPR replaced the previous year's excitement over CAR-T therapies. However, both technologies are very much in their infancy in terms of producing working therapeutics.

The venture capital haul topped an already impressive total for 2014, and until the very end of the year VCs were able to get exits. However, the trend for larger rounds to fewer recipients continued, again raising fears that the lack of funding for the industry's smaller players could choke off innovation.

The FDA continued approving new products, and 2015 saw a record-breaking 57 new drugs hit the US market, the highest total this century. That said, the sales potential of this expanded cohort was still below the forecasts for the class of 2014, which included future blockbusters Harvoni, Opdivo and Keytruda. But even so, the number of drugs moving through pipelines gave hope to industry observers.

Since the end of 2015 the volatility in the market has left the industry falling into two distinct camps: those who believe that fundamentals remain strong and that the markets will recover, driven by the need for new medicines, aging western populations and the development of paradigm shifting treatments. Then there are the bears, who see the current woes as the beginning of a larger shift in the industry, where outside pricing pressure and over-stretched valuations are finally coming home to roost, and believe that at best 2016 will remain an uncharacteristically quiet year, with valuations falling even further as macro-economic factors weigh on global markets.

Certainly, companies like Axovant, Agios Pharmaceuticals and Blueprint Medicines, which managed to float despite not having any projects in clinical development, now look like a market operating at the height of folly. As such the current conditions could be the start of a shakeout of biotech unicorns.

Either way, the current correction in stock prices means that for the first time in years bargains can be had, presenting an ideal time for the cash rich to Hoover up discounted companies. Perhaps when we return to look at 2016 it might be remembered as the year of M&A.

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



Investor infatuation tempered

Despite a shaky finish, when broadly assessing the full-year returns in 2015 the sector was on a winning streak, with biopharma-specific indices all ending the year in the green.

But it was a year of two halves as pricing and sustainability issues took the air out of the biotech bubble in the latter part of 2015, with a now-famous tweet from the Democratic presidential candidate Hillary Clinton knocking nearly a fifth off the value of the Nasdaq biotechnology index in one turbulent week in September. This served as a precursor to the early 2016 market collapse, which now finds biopharma broadly having given away all its gains since mid-2014.

Andy Smith, chief investment officer of Mann Bioinvest, also believes that there could be further misery for investors: “We have further to go.”

Indices

Source: EvaluatePharma[®] January 2016

Stock Index	% Change in 2015
NASDAQ Biotechnology (US)	11%
S&P Pharmaceuticals (US)	3%
Dow Jones Pharma and Biotech (US)	4%
S&P 500	(1%)
DJIA	(2%)
Dow Jones STOXX Healthcare (EU)	16%
Thomson Reuters Europe Healthcare (EU)	0%
Euro STOXX 50	5%
FTSE-100	(5%)
TOPIX Pharmaceutical Index (Japan)	33%

Nonetheless, when measured by gains from the arbitrary January 1 to December 31 period, investors came away winners in 2015, although as usual the average figures hide companies that saw their shares decline.

Within traditional big pharma’s sphere, it is hard to believe that Eli Lilly was the biggest riser two years in a row, but the returns do not lie. From January 2014 through to the end of 2015 the Indianapolis-based group rose an incredible two thirds, with the one-year gains of 2015 amounting to 22%. Lilly was particularly bedevilled by the patent cliff of 2011 and 2012, losing Zyprexa and Cymbalta along the way, and thus had to fight its way back from a low base. The progress of Trulicity and Cyramza, along with the promise of baricitinib, ixekizumab and the great mystery, its Alzheimer’s disease project solanezumab, are helping to drive Lilly along.



Big Pharma Companies: Top Risers and Fallers in 12 Months

Source: EvaluatePharma[®] January 2016

Top 3 Risers	Share Price (Local Currency)			Market Capitalisation (\$bn)	
	YE 2014	YE 2015	Change	YE 2015	12M Change
Eli Lilly	\$68.99	\$84.26	22%	93.4	16.6
Bristol-Myers Squibb	\$59.03	\$68.79	17%	114.8	16.8
Sanofi	€ 75.66	€ 78.60	4%	115.2	(12.1)
Top 3 Worst Performers					
AbbVie	\$65.44	\$59.24	(9%)	96.8	(7.4)
Novartis	\$92.66	\$86.04	(7%)	230.3	18.3
Merck & Co	\$56.79	\$52.82	(7%)	147.6	(14.3)

Bristol-Myers Squibb's rise is not as surprising, as its cancer immunotherapy Opdivo is now the poster child for innovation in the pharma sector. Sanofi, on the other hand, rebounded well in 2015 following a tumultuous 2014. Selecting a new chief executive, signing some licensing deals and declaring itself ready for more dealmaking seems to have brought the French group back into investors' favour.

Big pharma fallers were led by AbbVie – which had been among the top risers in 2014 as it tried to acquire Shire – along with Novartis and Merck & Co.

In spite of being in some of the sector's most popular therapy areas, hepatitis C, immunology and oncology, AbbVie had a hard go of 2015 on the public exchanges. A desperate-looking takeout of Pharmacyclics and fears about Humira biosimilars have to be weighing heavy on AbbVie.

Novartis's position atop pharma sales rankings did little to prevent it from having a bad year, as its Alcon ophthalmology business struggled while its heart failure drug Entresto failed to meet launch expectations. Generic competition for its top-seller, Gleevec, emerged when Sun Pharma announced that it had launched its version in early February 2016, and this also served as a factor in Novartis's troubles.

Merck & Co's presence on the top fallers list is more surprising, given that it too has a leading immuno-oncology agent – but looming generic competition for Zetia and Vytorin, along with a steep loss in revenue for its European Remicade business, cannot be helping.

Other Big (>\$25bn) Pharma Companies: Top Risers and Fallers in 12 Months

Source: EvaluatePharma[®] January 2016

Top 3 Risers	Share Price (Local Currency)			Market Capitalisation (\$bn)	
	YE 2014	YE 2015	Change	YE 2015	12M Change
Novo Nordisk	DKr260.3	DKr399.9	54%	124.1	30.5
Regeneron Pharmaceuticals	\$410.25	\$542.87	32%	55.5	14.6
CSL	A\$86.68	A\$105.31	21%	40.3	(1.0)
Top 3 Worst Performers					
Valeant Pharmaceuticals International	\$143.11	\$101.65	(29%)	34.7	(13.4)
Baxter International*	\$39.82	\$38.15	(4%)	20.9	(18.9)
Shire	\$212.54	\$205	(4%)	40.5	(1.3)

*Corrected for spinout of Baxalta



Among other large cap pharma companies outside the universe of big pharma, pricing and payer matters helped to define one winner and one loser. Novo Nordisk got the better of Sanofi in the increasingly competitive long-acting insulin space. Valeant, meanwhile, was punished by investors after a series of allegations about its relationships with speciality pharmacies that were accused of manipulating prescriptions to Valeant's benefit.

The remaining two risers in this category are Regeneron and CSL. The former continues to benefit from strong sales of Eylea, while the latter has established a strong niche in blood products and vaccines, and now its cholesterol-lowering project CSL112 is seeing increased attention.

The remaining two major fallers are Baxter International and Shire. Baxter's spin-out of its biopharma business precipitated a re-rating, while Shire's pursuit of that spin-out – Baxalta – was unpopular with its investors.

Other Notable Risers and Fallers in 12 Months

Source: EvaluatePharma[®] January 2016

Top 5 Risers	Share Price (Local Currency)			Market Capitalisation (\$m)	
	YE 2014	YE 2015	Change	YE 2015	12M Change
Incyte	\$73.11	\$108.45	48%	20171.9	7820.6
UCB	€ 63.20	€ 83.23	32%	18172.2	2589.3
Alkermes	\$58.56	\$79.38	36%	11911.6	3348.3
Anacor Pharmaceuticals	\$32.25	\$112.97	250%	4984.7	3601.3
Galapagos	€ 16.00	€ 56.76	255%	2489.7	1875.2
Top 5 Worst Performers					
Puma Biotechnology	\$189.27	\$78.40	(59%)	2543.0	(3163.1)
Avalanche Biotechnologies	\$54.00	\$9.52	(82%)	245.2	(968.2)
Zafgen	\$30.84	\$6.29	(80%)	171.3	(529.0)
Synta Pharmaceuticals	\$2.65	\$0.35	(87%)	48.5	(240.1)
Celladon	\$19.53	\$1.47	(92%)	35.2	(420.0)

Related EP Vantage Comment and Analysis

Top 5 Risers	
Incyte	Winners and losers – An ASH bloodbath
UCB	UCB far from rehabilitated, despite divestment and study success
Alkermes	Alkermes' approval injects new life into antipsychotic market
Anacor Pharmaceuticals	Anacor shows the power of positive phase III data
Galapagos	Galapagos turns the tables on AbbVie, courtesy of Gilead
Top 5 Worst Performers	
Puma Biotechnology	Asco – Puma might have to rely on extended follow-up
Avalanche Biotechnologies	Avalanche crashes down as gene therapy disappoints
Zafgen	Zafgen's fate hangs on outcome of two part-completed studies
Synta Pharmaceuticals	Synta will have to go back to find the future
Celladon	Celladon spoils the gene therapy party



Among the mid- and small-cap companies, it was primarily clinical and business development that defined the biggest risers and fallers. For example, Incyte and Galapagos were on a roll because of expectations for their assets Jakafi and filgotinib – the former crashing out in pancreatic cancer in February 2016. On the negative side of the ledger, Avalanche, Zafgen, Synta, and Celladon all faced clinical setbacks.

Zafgen and Synta may have been punished more severely by having the misfortune of facing failure just as the broader biotech market was imploding.

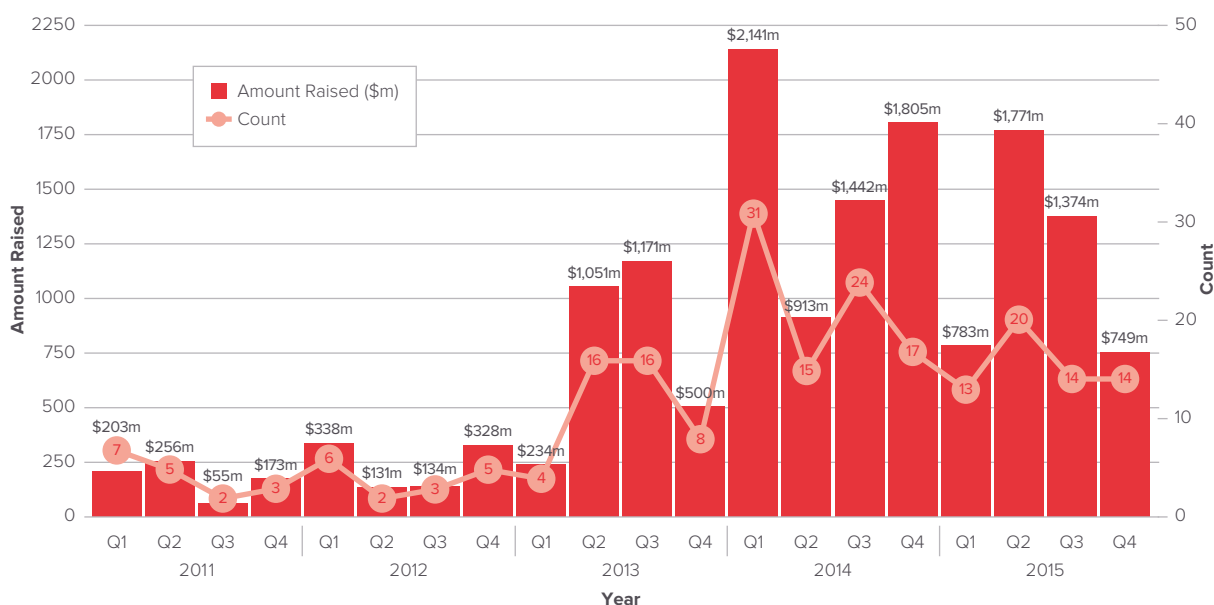


IPO – Volatility the order of the day

It was always going to be hard to beat 2014, a year that will be remembered not only for the IPO window remaining open, but for expanding this to the size of a bi-fold door. As such, while flotations were lower in 2015 they did at least manage to get away – right up until the fourth quarter when things slowed significantly.

Biotech Initial Public Offerings by Quarter on Western Exchanges (excluding Medtech)

Source: EvaluatePharma[®] January 2016



During the year there were 61 IPOs reported across western exchanges – all the more remarkable given the wobbles in the market. The companies that did reach the market raised a total of \$4.68bn, down from the record haul of \$6.3bn in 2014.

IPO Annual Totals (Western Stock Exchanges)

Source: EvaluatePharma[®] January 2016

Year	Total Amount raised (\$bn)	US IPOs	EU IPOs	Total IPOs*	Avg. amount raised (\$m)
2015	4.68	46	13	61	76.7
2014	6.30	73	13	87	72.4
2013	2.96	40	3	44	67.2
2012	0.93	12	4	16	58.2
2011	0.69	12	5	17	40.4

*includes IPOs on other western exchanges



The tendency for investors to back big floats was seen by the average size of float nudging up to \$76.7m, just as the number of IPOs in the year fell from 87 in 2014 to 61 in 2015. The number of companies raising more than \$100m remained relatively stable compared with 2014, despite the fall in the absolute number floating.

IPOs Raising More Than \$100m (Western Stock Exchanges)

Source: EvaluatePharma[®] January 2016

Year	No. raising >\$100m	Average discount/premium
2015	17	(5%)
2014	18	(12%)
2013	7	(13%)
2012	2	(18%)
2011	2	(24%)

Unsurprisingly, the beneficiaries of investors backing the industry's big stories were all US companies predominantly listing on Nasdaq. NantKwest hauled in \$208m and attracted a 16% premium to its original pricing range, while the controversial Axovant managed to persuade public investors to hand over \$315m for a company built around GlaxoSmithKline's old Alzheimer's project RVT-101. Some called the float the definitive sign of a biotech bubble.

Once again European companies were under-represented in the top ranks. However, Adaptimmune's decision to list on Nasdaq, rather than its home market of the UK, ensured its place in the top rankings.

But in a sign that the European IPO window had finally opened – a long way behind the US – many European companies chose to float on European exchanges. Notable European floats included Belgium's Mithra Pharmaceuticals, which raised \$97m, and France's Abivax, which raised \$49m.

Top 10 Biotech IPOs on Western Stock Exchanges in 2015

Source: EvaluatePharma[®] January 2016

Company	Amount raised	Offering price (\$)	Range	Discount/premium	Exchange	YE2015 Share Price Change Since Float	Date
Axovant	\$315m	15.00	\$13-\$18	(3%)	NYSE	20%	June
NantKwest	\$208m	25.00	\$20-\$23	16%	Nasdaq	(31%)	July
Adaptimmune	\$191m	17.00	\$15-\$17	6%	Nasdaq	(29%)	April
Spark Therapeutics	\$161m	23.00	\$19-\$21	10%	Nasdaq	97%	January
Aimmune Therapeutics	\$160m	16.00	\$14-\$16	7%	Nasdaq	15%	August
Blueprint Medicines	\$147m	18.00	\$17-\$19	0%	Nasdaq	46%	April
REGENXBIO	\$139m	22.00	\$14-\$16	47%	Nasdaq	(25%)	September
ProNAi Therapeutics	\$138m	17.00	\$15-17	6%	Nasdaq	(12%)	July
Seres Therapeutics	\$134m	18.00	\$16-18	6%	Nasdaq	95%	June
Global Blood Therapeutics	\$120m	20.00	\$14-16	33%	Nasdaq	62%	August
Average across top 10 IPOs	\$171m			13%		24%	
Average across all 61 IPOs	\$76.7m			(5%)		8%	



Haircuts – the discounts companies accept on their IPO ranges – were some of the lowest in the last five years, indicating that valuations were being pitched more realistically. However, in what looked like a sign of the hardening economic climate at year end, the discount to IPO price range jumped to 17% as companies tried to squeeze themselves through what looked to be a closing IPO window.

The third and fourth quarters saw an equal number of companies floating on the public exchanges – 14 in each period. The difference was that the fourth-quarter entrants raised just half that of the third quarter, pointing to smaller companies willing to accept less money and bigger haircuts just to get away.

There were signs that the window was swinging shut in October, when the UK's Shield Therapeutics and Apellis were among the victims of turning sentiment, and both were forced to pull their float plans. There were also no biotech IPOs on Nasdaq during December.

Shield did eventually manage to get away in 2016, but at a much reduced price, and Apellis decided not to risk the markets at all, instead opting for a further venture capital round to get its rare disease treatments closer to market.

Genghis Lloyd-Harris, a partner at Abingworth, believes that getting IPOs away in 2016 will remain tough: "Although the IPO window is not hermetically sealed you better have outstanding insider support to get an IPO away in the US."

For those who did manage to float in 2015, their time on the public markets has not been easy, with many now trading below their offer price.

The companies that did not get their IPOs completed before the end of last year now face the choice of waiting until the markets improve or relying heavily on insiders. But as Renaissance Capital analysts point out the question will be whether private investors will be willing to accept only modest premiums to their last venture round.

As such it looks like, rather than finding their exits through IPO in 2016, venture investors might want to turn to the cleaner exit route of sales.

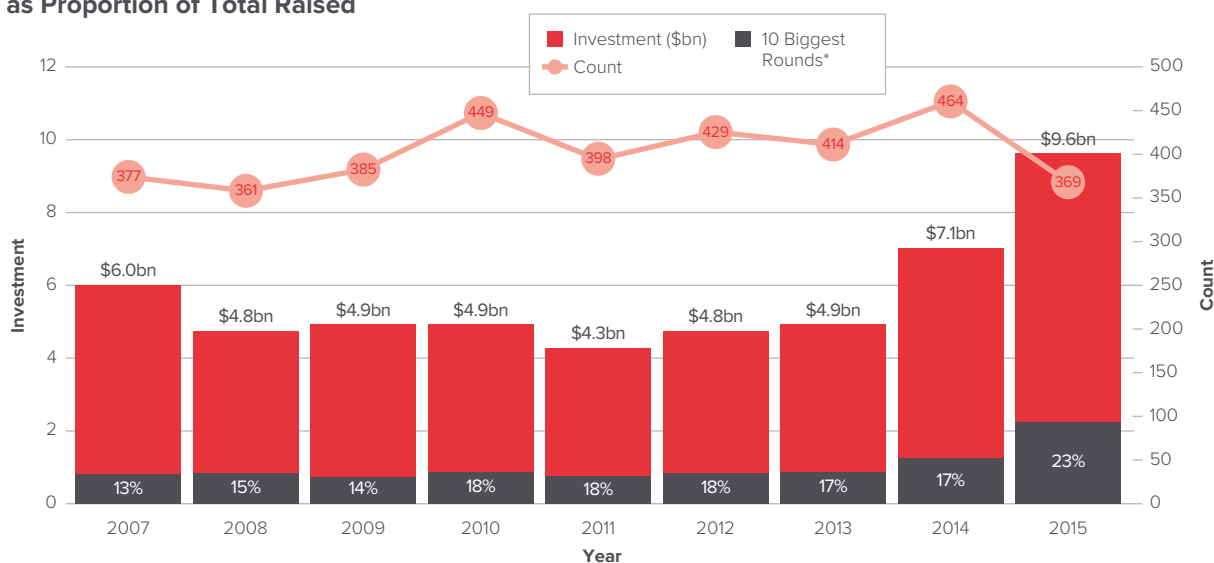


Venture funding focuses on the lucky few

In the venture capital world, a shift toward megarounds was evident in 2015, with the top-10, triple-digit raises hoovering up nearly one quarter of all the funds available for development-stage biotechs. Indeed, a marked drop in VC rounds and rise in amount raised can clearly be seen, as the top three rounds, led by Moderna's jaw-dropping \$450m series D, totalled more than \$1.1bn.

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

Source: EvaluatePharma* January 2016



*10 biggest rounds as a proportion of the total amount raised

As a sign of how venture capital was distributed at the trough and the peak of the biotech market, the \$9.6bn total of 2015 was double that of 2008, but only eight more rounds were completed.

As with IPOs and secondary offerings, it might very well have been a case of raising money when the environment was favourable. However, the presence of crossover investors participating in pre-IPO rounds could also be a factor in the size and distribution of VC rounds as private biotechs sought to tap the public exchanges before the window swung shut.

This is the conclusion of Sander Slootweg, managing partner of the venture capital group Forbion Capital Partners: "Money was abundant. The public markets were wide open. People were assuming that by building interesting companies they could flip them to the public markets."



Top 10 Rounds of 2015

Source: EvaluatePharma[®] January 2016

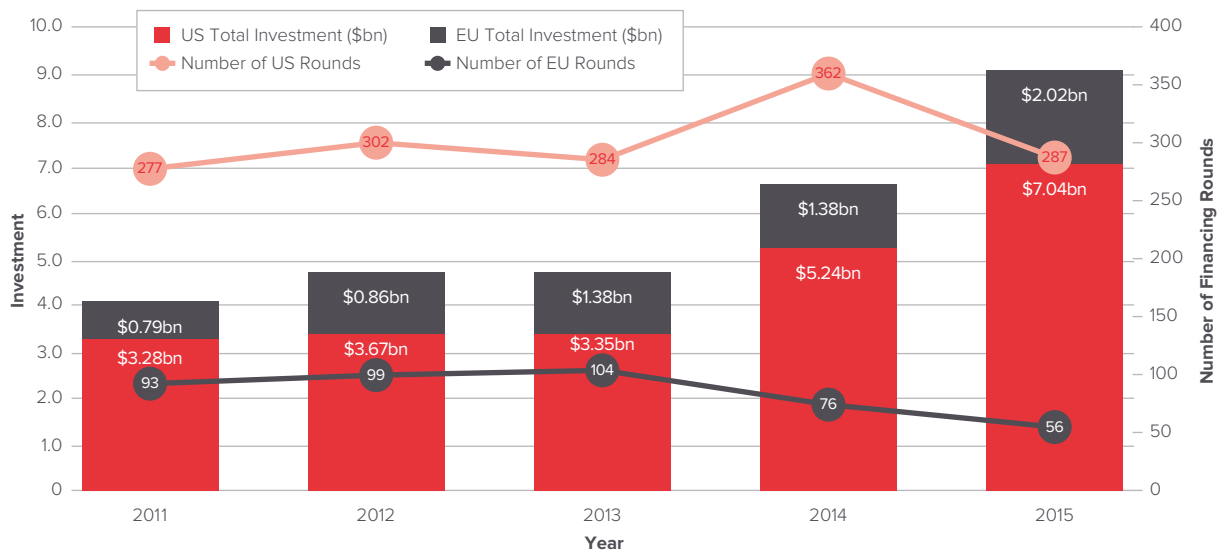
Company	Investment (\$m)	Round	Date
Moderna Therapeutics	450.0	Series D	January
Acerta	375.0	Series B	May
Immunocore	320.0	Series Undisclosed	July
Stem CentRx	250.0	Series Undisclosed	August
Denali	217.0	Series A	May
TauRx Pharmaceuticals	135.0	Series Undisclosed	October
Nabriva Therapeutics	120.0	Series B	April
Editas Medicine	120.0	Series B	August
Mereo BioPharma	118.0	Series A	July
CureVac	110.0	Series F	November

How skewed to the top end was 2015? To make the top 10 last year a biotech needed to raise more than \$100m; by comparison, in 2014, six of the top 10 rounds were below \$100m. To make the top five in 2015 a company needed to raise more than \$200m.

Looking at regional differences, it is not surprising that European companies constituted a small fraction of the disclosed venture capital rounds and money. The European story is similar to the other side of the pond, with EU rounds on average being even bigger than their American counterparts, an average of \$36m to \$24m.

US vs. EU VC Funding

Source: EvaluatePharma[®] January 2016





2015 also confirmed a funding trend that has been present for a couple of years: the slow decline of the A round in favour of the later-stage companies at their B and C raises. Among those that disclosed information on their rounds, B rounds constituted nearly one third of all VC financing available while A rounds represented less than one fifth, a substantial shift from the situation in 2011, when A rounds raised the most money.

Presumably, the investment consortia represented by venture capitalists have become more risk averse and exit focused. In the top 10 alone, series B rounds of Acerta, Nabriva and Editas combined were \$615m.

Venture Capital Investment Rounds

Source: EvaluatePharma[®] January 2016

Financing Round	Total Investment (\$m)					Total Finance Deals					% Investment per Financing Round				
	2015	2014	2013	2012	2011	2015	2014	2013	2012	2011	2015	2014	2013	2012	2011
Seed Capital	123	135	135	190	140	26	28	51	48	47	1%	2%	3%	4%	3%
Series A	1,858	1,466	1,341	1,185	1,270	100	125	132	134	122	19%	21%	27%	25%	29%
Series B	3,088	2,430	1,034	1,092	1,047	90	125	72	94	74	32%	34%	21%	23%	24%
Series C	1,567	948	900	794	510	55	61	52	53	35	16%	13%	18%	17%	12%
Series D	1,192	722	447	673	362	30	29	29	29	17	12%	10%	9%	14%	8%
Series E	546	233	489	195	404	14	16	17	11	15	6%	3%	10%	4%	9%
Series F	148	67	205	140	49	5	7	5	10	2	2%	1%	4%	3%	1%
Series G	49	128	62	210	127	3	3	3	2	2	1%	2%	1%	4%	3%
Series H	-	208	-	-	-	-	2	-	-	-	-	3%	-	-	-
Series I	2	93	-	-	-	1	1	-	-	-	0%	1%	-	-	-
Series Undisclosed	1,150	632	330	272	431	46	67	53	48	84	12%	9%	7%	6%	10%
Total	9,723	7,063	4,945	4,751	4,341	370	464	414	430	398					

The second and subsequent investment rounds are becoming ever more crucial for companies moving to their endgames. In 2015 there were no exits among companies whose last venture finance round was an A. The historical data series shows the importance of the B and C rounds most of all, with these constituting more than 40% of the exits in 2011-15.

With biotech off the boil so far in 2016 it will be interesting to see how this affects venture investment, especially given the well-documented presence of crossover funds that are in it to support an IPO.

Mr Smith of Mann BioInvest believes that many of these relatively new entrants to the biotech funding space could now withdraw in light of the market downturn: "Crossover funds did a lot of private investments in the hope these companies would IPO; some of them did and now their investments are locked into falling markets, which is absolutely not what you want."



Investors who are interested in backing high-quality research and technology might not be discouraged, but their numbers could dwindle if the exit sign is growing dim.

Mr Sloomweg says his advice to early-stage biotechs looking to raise money in the current environment is to plan a different exit. "I would say the assumption has to be to build a company for a trade sale rather than an IPO," he states.

In preparing for an IPO, he says a company might need a seasoned management team and a broad pipeline. When building toward a trade sale, he says, "You can have a virtual or semi-virtual infrastructure."

Last Venture Financing Round Before Exit

Source: EvaluatePharma® February 2016

Year	Seed Capital	Series A	Series B	Series C	Series D	Series E	Series F	Series G	Series Undisclosed
2011	4	18	29	15	12	7	1	2	39
2012	4	15	18	21	13	11	2	1	13
2013	6	8	10	25	13	11	3	2	6
2014	0	6	20	17	8	5	1	1	6
2015	0	0	8	4	6	5	3	0	4

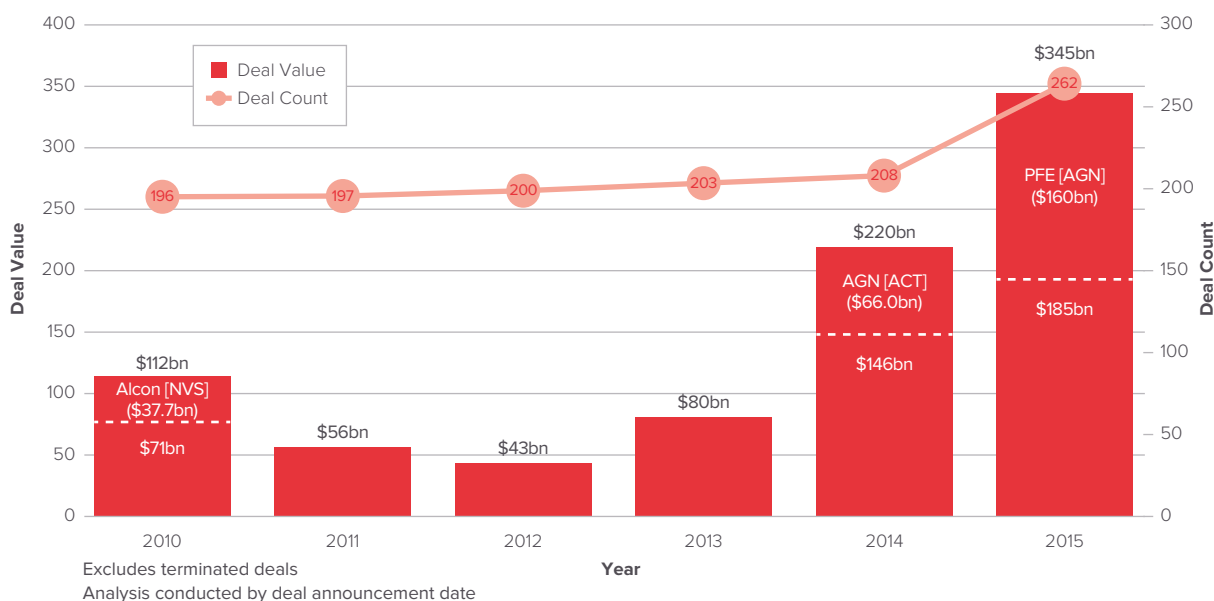


M&A – Pfizer to the rescue

When 2014 concluded, it seemed hard to believe that the year's M&A tally could be exceeded, but it was, and quite easily, thanks to the usual megamerger suspect, Pfizer. The yet-to-be-concluded \$160bn acquisition of Allergan established a new record, and one that could very well be difficult to top should valuations continue to retreat.

Pharma and Biotech M&A Activity

Source: EvaluatePharma* January 2016



The deal beats any previous single transaction from the traditional big pharma sector, signifying not only the vast changes in the companies that achieved big cap status in the biotech boom, but also showing how acquisitive speciality pharma groups like Allergan managed to climb their way up the valuation tree.

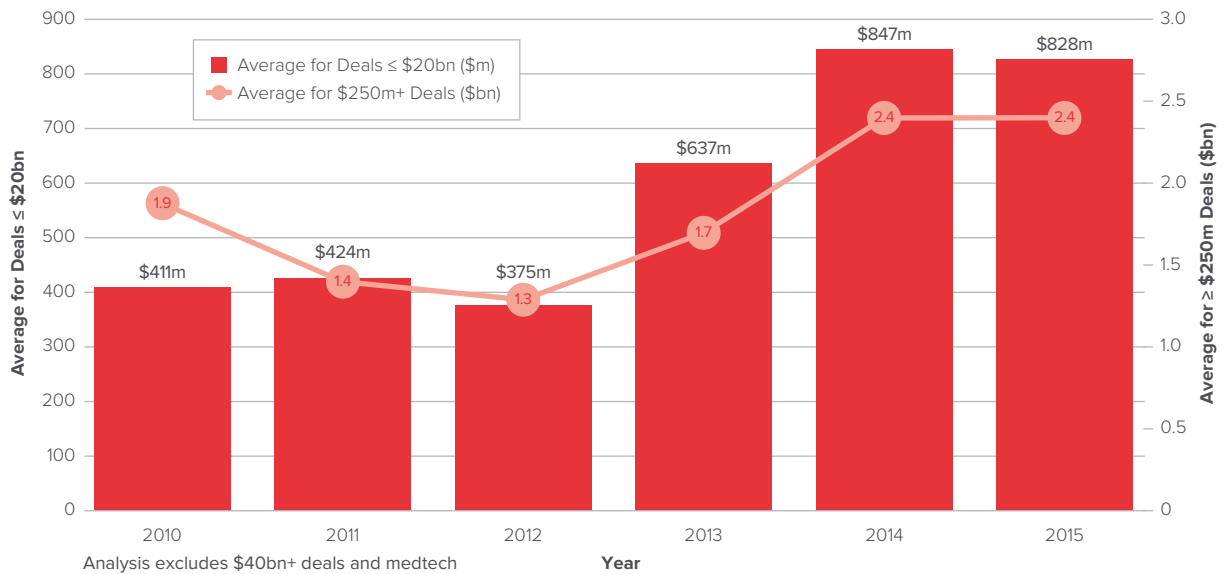
In total the biopharma sector spent \$345bn over 262 deals, the deal count also being the biggest total in at least the past nine years.

The cooldown in transactions aimed at reducing tax expenditures did nothing to slow M&A, and even excluding the big Pfizer-Allergan deal \$185bn in acquisitions took place, a total that a decade ago might have seemed unthinkable.



Average M&A Deal Values Per Year

Source: EvaluatePharma[®] January 2016



Looking beyond the big noise of Pfallergan, one can see a strong signal that 2015 looks a little more like 2014. Averaging the values of deals of between \$250m and \$40bn yields \$2.4bn for both years. Looking at averages for deals of \$20bn or less, 2014 looks a little richer at \$847m to 2015's \$828m.

This is borne out by the ranking of top deals. Pfizer-Allergan rules along with Allergan's pre-Pfizer disposal of its generics unit, but 2015 numbers 3 through 5 are \$17.6bn, \$17.0bn and \$11.4bn, while corresponding deals in 2014 were \$16.0bn, \$9.5bn and \$8.3bn. These trends might point to a peak in M&A valuations that coincided with the top of the biotech market.

Biggest Pharma and Biotech M&A Deals Announced in 2014 and 2015

Source: EvaluatePharma[®] January 2016

Year	Acquirer	Target	Deal status	Value (\$bn)
2015	Pfizer	Allergan	Open	160.0
	Teva Pharmaceutical Industries	Generics business of Allergan	Open	40.5
	AbbVie	Pharmacyclics	Closed	17.6
	Pfizer	Hospira	Closed	17.0
	Valeant Pharmaceuticals International	Salix Pharmaceuticals	Closed	11.4
2014	Actavis	Allergan	Closed	70.5
	Actavis	Forest Laboratories	Closed	28.0
	Novartis	Oncology business of GlaxoSmithKline	Closed	16.0
	Merck & Co	Cubist Pharmaceuticals	Closed	9.5
	Roche	InterMune	Closed	8.3



Should the early 2016 re-rating continue, it will be interesting to watch how big pharma business development strategies change. Prized assets might be less expensive in coming months, so one hypothesis holds that deal activity will pick up even if total dollar amounts do not.

On the other hand, the view being taken by some big pharma chief executives is that biotech leaders and investors believed the hype in the heat of the biotech bull rush, and as a result their companies are simply overpriced. This school is best exemplified by Roche's Severin Schwan and Sanofi's Olivier Brandicourt, the latter of whom recently said, "We're not sure that the expectation of boards and shareholders of this company may actually be realistic even after recent price falls."

Mr Sloatweg, of Forbion Capital Partners, believes that the valuation imbalance is not universal. "There are certain subsectors where people have inflated expectations, like immuno-oncology. I think there will be a huge shake-out. In other areas, the valuations are realistic."

He also believes that valuation is not the only factor at work in M&A decision-making. "The underlying need of larger players to fill pipelines – I think that's more the driver."

It would be unfortunate for the sector if an unintended consequence of the enthusiasm for biotech during 2012-2015 translated into a suppression of deal making in future.



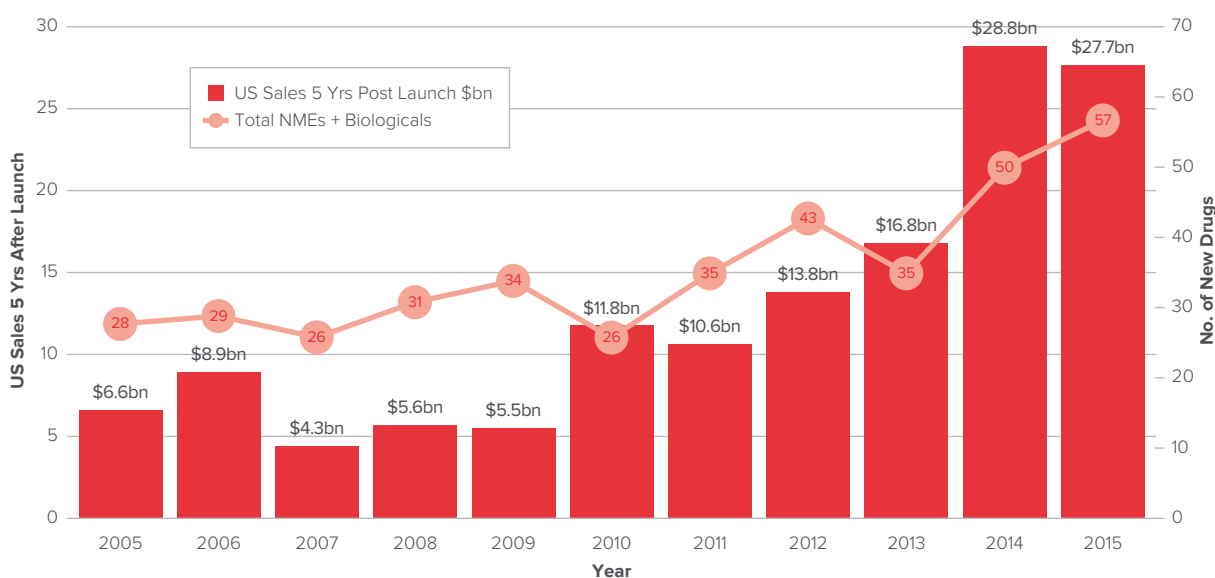
R&D engine continues in fifth gear as productivity gains increase

The markets may have been in turmoil, but one thing in which biotech investors found comfort was the number of new drugs approved by the FDA in 2015. This jumped from an unprecedented 50 in 2014 to 57 in 2015, providing investors with some justification for ever-increasing valuations.

The analysis below tracks these approvals and pairs each year's cohort with their actual or forecast fifth-year sales. The consecutive three year rises in forecast sales indicate that not only is the industry successfully moving drugs through the pipeline, but the quality of these drugs also remains high.

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

Source: EvaluatePharma[®] January 2016



2010 Prevnar 13 (PFE) Victoza (Novo N) Prolia/Xgeva (AMGN)	2011 Xarelto (J&J/BAY) Eylea (REGN/BAY)	2012 Eliquis (BMS/PFE) Stribild (GILD)	2013 Sovaldi (GILD) Tecfidera (BIIB)	2014 Opdivo (BMY) Harvoni (GILD)	2015 Orkambi (VRTX) Entresto (NVS)
--	--	---	---	---	---

As the analysis includes approvals of small molecules, biologics, vaccines, allergenic and tissue derived products, as reviewed by the FDA's Center for Drug Evaluation (CDER) and Center for Biologics Evaluation and Research (CBER), it provides a comprehensive overview of US approvals.



Driven by the approvals of the likes of Vertex's Orkambi and heart failure drug Entresto, the fifth year sales potential of the 2015 cohort is an impressive \$27.7bn, but still behind the class of 2014, which included the launch of Harvoni and Opdivo, whose sales have been significantly upgraded, making 2014 a year that is unlikely to be surpassed anytime soon.

Once again FDA schemes to get drugs to market faster provided momentum for approvals, albeit in a roundabout way, as companies purchased priority review vouchers (PRV) to speed the regulatory process. Gilead bought one for its once-daily HIV drug Genvoya, while Sanofi used the same tactic to get its rival PCSK9 drug Praluent to the market a month ahead of Amgen's Repatha. Despite this short advantage analysts, at least, believe Repatha will capture most sales, leaving Praluent out of the five biggest drugs approved in 2015.

What is interesting about 2015's crop of big sellers is the indications they are approved in. 2014 was all about immuno-oncology and hepatitis C, with Opdivo and Harvoni leading the sales pack. In contrast, 2015 was made up of drugs in less hyped disease areas, including Vertex's Orkambi for cystic fibrosis patients and Novartis' Entresto in heart failure.

However, in a sign of just how tough the reimbursement climate is becoming, early indications show both are substantially below their forecast launch trajectories.

Top Five Approvals of 2015

Source: EvaluatePharma[®] January 2016

Product	Pharmacology Class	Company	Approval Date	US Sales 2020 (\$m)
Orkambi	CFTR corrector	Vertex Pharmaceuticals	02-Jul	2,855
Entresto	AT1 antagonist & neprilysin inhibitor	Novartis	07-Jul	2,482
Repatha	Anti-PCSK9 MAb	Amgen	27-Aug	2,118
Genvoya	NRT inhibitor, HIV integrase & CYP3A inhibitor	Gilead Sciences	05-Nov	2,033
Ibrance	CDK 4 & 6 inhibitor	Pfizer	03-Feb	1,824

Looking to 2016, although the five year sales forecasts again fall short of the industry's most recent productive period, there are still plenty of potential blockbusters moving through pipelines. And some products have already been approved, including Actelion's Upravi and Merck & Co's grazoprevir/elbasvir, now named Zepatier.

After setbacks with portfolio projects bitopertin and onartuzumab Roche looks like it is making all the right moves to regain its biologics crown, by having two of biggest forecast launches in 2016.



The Biggest Biologics Slated for Launch in 2016

Source: EvaluatePharma[®] January 2016

Product	Company	Therapy Area and/or Pharmacology Class	Phase	WW Sales 2020 (\$m)
Ocrelizumab	Roche	MS therapy; anti-CD20 MAb	Phase III	2,758
Atezolizumab	Roche	Anti-cancer agent; anti-PD-L1 MAb	Phase III	2,491
Dupilumab	Sanofi	Dermatology treatment; IL-4 alpha MAb	Phase III	1,867
Empliciti	Bristol-Myers Squibb/AbbVie	Multiple myeloma treatment; SLAMF7 MAb	Approved	1,086
Ixekizumab	Eli Lilly	Psoriasis therapy; IL-17A MAb	Filed	1,034

With atezolizumab, the group will finally join the immuno-oncology race by potentially having the industry's first approved PD-L1 in either non-small cell lung cancer or bladder cancer. But it is multiple sclerosis product ocrelizumab that has investors most excited. The group is also set to share in some of the predicted success for small molecule leukaemia treatment Venetoclax, although there may be some lingering safety concerns following previous incidents of tumour lysis syndrome.

Sanofi has had its fair share of issues including battling with lower sales of both its diabetes franchise and slow uptake of some of its new drug launches, so the fact that it has one drug in the top five is a positive. Dupilumab, an antibody treating atopic dermatitis, is forecast to be approved by the end of the year. However, the drug will eventually face competition from other interleukin-targeting antibodies like AstraZeneca's tralokinumab.

AbbVie too could use an approval as it wrestles with biosimilar threats to Humira, its biggest product, and a regulatory green light for Empliciti could be imminent with a PDUFA action date of February 29.

The Biggest Small-Molecule Agents Slated for Launch in 2016

Source: EvaluatePharma[®] January 2016

Product	Company	Therapy Area and/or Pharmacology Class	Phase	WW Sales 2020 (\$m)
Zepatier	Merck & Co	Hep C therapy; NS3/4A & NS5A inhibitor	Marketed	1,953
Obeticholic Acid	Intercept Pharmaceuticals	Liver therapy; FXR agonist	Filed	1,581
Venetoclax	AbbVie/Roche	Leukaemia treatment; Bcl-2 inhibitor	Filed	1,387
Emtricitabine/Tenofovir Alafenamide Fumarate	Gilead Sciences	HIV therapy; NRTI	Filed	1,318
Upravi	Actelion	PAH; prostacyclin receptor agonist	Marketed	1,080

Although a hepatitis C product is set to be the biggest small molecule drug launched in 2016, it is not a Gilead drug. Instead Merck & Co and Intercept have been left to be the hepatology champions of the year. Merck achieved its marketing authorisation for Zepatier in January and Intercept is aiming to get its obeticholic acid product first approved in the relatively small indication of primary biliary cirrhosis, with the eventual aim of expanding the drug into the much bigger and more lucrative non-alcoholic steatohepatitis setting.



Some of these drugs, will however, not make it to market this year, and some are cautioning that the current volatility in the market might have an impact on long-term pipeline productivity. Mr Smith of Mann Bioinvest warns that R&D spend might slow down among smaller companies.

“The last thing you want to do if you are a company that has raised money is spend it. So what we might see is companies going into hibernation, we will see them delaying their clinical trials, or slowing down trials, or not starting trials, because they don’t know how long this retrenchment will go on for.”

However, the full implications of this scenario will not hit productivity for a few years. What drugs launching now are more likely to encounter is a toughening reimbursement climate. Sustaining, or even commanding, the prices that underlie all of these forecasts could become more challenging. And as *EP Vantage* has previously argued until the reimbursement outlook becomes clearer pharma and biotech could be in for more volatile times in spite of the clear R&D wins.



Stormy horizons

At the end of last year there were still plenty of bulls predicting the good times would continue into 2016. The gloomy start to the year has proved them wrong, and trying to predict what the rest of the year ahead holds from the vantage point of only a few volatile months is a risky, if not foolhardy enterprise.

Attempts at crystal ball gazing have been made even more difficult by the fact that it was not pricing and reimbursement, or drug failure that eventually burst the biotech bubble. Instead it was the wider macro-economic environment, including China's stalling growth, the fall in oil prices and the continued crisis in the Middle East that did what logic had failed to accomplish.

"The thing about investor behaviour in a period where share prices are going up is the illogical expectation that because share prices have gone up a lot for the last five to eight years they will continue to go up for much longer than that," says Mr Smith of Mann Bioinvest.

But with the air now out of the bubble, the industry is left facing not only a period of uncertainty, as valuations find their level, but other issues that will be harder to ignore in a downward market.

The noise around the pricing debate has not gone away, and while the eventual winner of the US presidential elections will have little or no influence on drug prices, the subject will continue to weigh on sentiment.

Pharmacy benefit managers, however, do have influence and they will carry on flexing their muscles in negotiating lower prices, especially among drug classes with high competition, or products that offer only incremental benefits. Even drugs with clear advantages, but high prices, could see pushback, or more pay for performance reimbursement deals.

Politically, while the threat of a Grexit has all but subsided, there is now an even more serious danger of a Brexit. The effects of the UK leaving the European Union are hard to predict, but it will do little to ease jittery international markets.

The coming year will also see more biosimilar entrants knocking at the door of the US healthcare system, and despite the doomsaying by originators, their uptake might be surprising, especially if payers like Express Scripts have anything to do with it.

Venture capital funds, who last year invested record amounts of money, are almost certainly going to be less active in the coming year. The closing of the IPO window has robbed them of exit opportunities, and the US has only seen five IPOs since the start of the year across all sectors. What might give industry watchers hope is that four have been in healthcare.

With so many uncertainties Mr Lloyd-Harris of Abingworth is predicting a much quieter time in the sector, as smaller companies who have raised money hunker down and cut their cash burn. "The mindset among companies now is 'cash is king and who knows when we will be able to raise money again.'"



However, this might have a knock on effect of increased collaborations within the industry and licensing deals, with heavy R&D development elements.

And while some argue that valuations of some companies are still too high. Cheaper stock prices do mean buying opportunities, either for big pharma, who largely sat out the recent wave of record breaking M&A, or cash-rich larger biotechs.

So the market might expect a wave of M&A, but perhaps not until the expectations of owners fall into line with the reality of their share prices. Traditionally, a pickup in M&A has also heralded an opening in the IPO window; however, if this does not materialise, then the industry could be heading for uncharted waters.

As such, the only winners in 2016 might be large, revenue-producing , cash-rich companies wanting to pick up assets.

For everyone else, the defining feature of success might be the amount of cash raised while the sun shone on much of 2015.

Report authors: **Lisa Urquhart and Jonathan Gardner**

Established in 1996, Evaluate Ltd is the trusted leader in high quality life science sector analysis and consensus forecasts to 2020. Evaluate's team of expert analysts transform life science information into insights so companies can perform well.

EvaluatePharma® delivers exclusive consensus sales forecasts and trusted commercial insight into biotech and pharmaceutical performance.

 [@EvaluatePharma](https://twitter.com/EvaluatePharma)

EvaluateMedTech® sets a new standard in commercial analysis and consensus forecasts of the global medical device and diagnostic industry.

 [@EvaluateMedTech](https://twitter.com/EvaluateMedTech)

EvaluateClinical Trials® delivers unique clinical trial intelligence expertly curated to efficiently analyse the global clinical trial landscape.

 [@EPClinicalTrial](https://twitter.com/EPClinicalTrial)

EP Vantage an award winning editorial team, provides daily commentary and analysis with fresh perspectives and insight into current and future industry trends.

 [@EPVantage](https://twitter.com/EPVantage)

Evaluate Custom Services provides customised solutions to help you access, analyse and manage the information you need to support effective decision-making.

The Evaluate services enable the life science community to make sound business decisions about value and opportunity.

www.evaluate.com

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 Japan

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