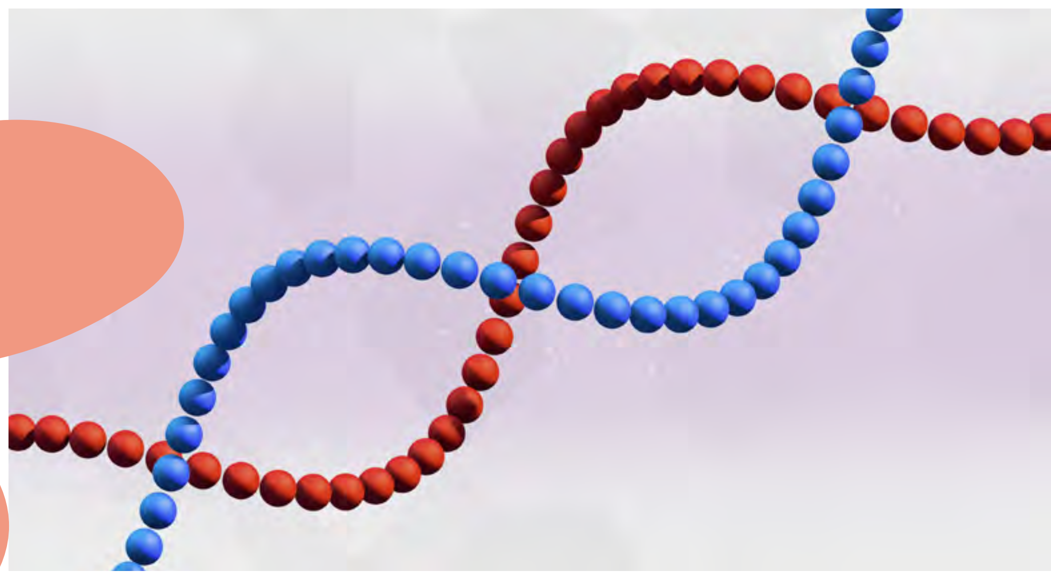
PHARMA & BIOTECH 2014 IN REVIEW



March 2015

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It is extraordinary that the preface to EP Vantage's 2013 pharma and biotech year in review could largely be repeated for the 2014 edition. Twelve months on the song remains the same, only with the volume turned up.

One year ago we commented that stocks had set record highs, the IPO and M&A markets were exhibiting rude health and the venture capital industry was looking in better shape versus previous years. These statements remain true, after a year when even more money was raised by many more companies on stock exchanges that continue to test new highs. Takeovers were pursued to a level not previously seen for a decade, and a big pharma megamerger did not even contribute to the tally.

Once again this progress was achieved alongside regular interjections of "is this the moment the bubble bursts?" The year certainly contained a couple of moments when air escaped. In spring the cost of Gilead's newly launched hepatitis C pill Sovaldi came under widespread criticism, and concerns about the sustainability of drug prices infected the wider US biotechnology market. This caused the flagship Nasdaq Biotechnology Index to fall to its lowest point all year, and pricing fears were responsible for a couple of the hisses heard throughout the year.

Federal Reserve Chairman Janet Yellen managed to puncture the rally in July with her description of smaller biotech stocks as

"substantially stretched", and another hiccup came when the tax inversion craze became the next political football, sparking fears that US lawmakers would move to spoil the M&A party. The collapse of AbbVie's bid for Shire for this very reason caused another deflation in October, and the rush by US companies looking for shelter from the taxman has since subsided.

However, none of these concerns ultimately discouraged investors, who by the end of 2014 had pushed the NBI and other global healthcare indices to new heights. Drug developers of all sizes are now basking in valuations not enjoyed for many years, propelled by unchecked enthusiasm for high-risk and novel technologies at one end of the spectrum, and at the other by growing confidence in the ability of established manufacturers to regenerate their pipelines and launch commercially successful new products.

The ability and willingness of western healthcare systems to pay for innovation, and the perceived growing power of payers, will remain a potential pin prick this year. As will the ability of those operating at the very cutting edges of medicine – CAR-T companies and gene therapy, for example – to prove that they are worth their huge valuations. And of course there are the numerous geo-political rumblings capable of causing more widespread deflation.

At the same time the adage of "what goes up must come down" is widely accepted. So it is not surprising that the life science sector, and in particular US biotech, is making the most of the good times. The start of 2015 has seen management teams, bankers and venture capitalists alike scramble to fill their coffers – it is estimated that in January US biotech companies raised more than $3bn in secondary offerings, for example.

In the midst of the furious financing it is easy to read much of this activity as opportunism and reckless risk taking – and it is certain that not all investors will emerge from the bull market with a profit. However, for many management teams raising cash now simply represents good business sense. Because it is inevitable that at some point the money will once again slow.

2014 could well end up as the crescendo before a quieter period – it is hard to see the records set by IPOs and M&A deals being beaten. But the volume has only got louder in the first few months of the year, so maybe this amp does go up to 11.

Unless stated, all data are sourced to EvaluatePharma® and were accessed in January 2015.

INVESTOR INFATUATION UNTEMPERED

Healthcare stocks of all sizes continued to prove popular with investors last year, with all major indices moving higher in the US, Europe and Japan.

The US continued to set the pace, and the ongoing biotech rally is clear in the performance of the NBI. While the index might not have repeated 2013's 66% advance it ended the year at double the previous peak set at the height of the genomics bubble in 2000.

In Europe healthcare stocks easily outpaced wider markets, which are still more concerned with sluggish economic growth and the rumblings of political unrest further east.

Percentage Change in Selected Stock Indices Over 2014

Stock Index	% Change in 12 Months
Nasdaq Biotechnology (US)	34%
S&P Pharmaceuticals (US)	19%
Dow Jones STOXX Healthcare (EU)	18%
TOPIX Pharmaceutical Index (Japan)	16%
DJIA (US)	8%
Euro STOXX 50 (EU)	1%

Last year, big pharma really reaped the rewards of convincing investors that R&D productivity problems were in the rear view mirror; this has been achieved to varying levels of success on a company-by-company basis, but enough are generating strong earnings growth and undertaking important new drug launches to encourage a broader sector re-rating.

"I would like to think it's the renaissance of their pipelines" that has driven re-valuations, says Andy Smith, chief investment officer of Mann Bioinvest. "But it could also just be that patent expiries have slowed. It's probably a combination of the two factors."

Add in the FDA's ever-improving reputation as a co-operative regulator, and many of the world's largest drug makers ended 2014 enjoying valuations not seen for some time. Eli Lilly, for example, was the year's best performing big pharma stock, and its shares are now at the highest level since mid-2004. This was achieved while the company fell off one of the sector's steepest patent cliffs, and despite the fact that much of its late-stage pipeline has yet to prove itself clinically or commercially.

Investors also managed to ignore the biosimilar threats to Humira, AbbVie's $14bn anti-rheumatic and the world's biggest-selling drug, and focus instead on the potential of its hepatitis C contender Viekira Pak. With sales of the Sovaldi competitor forecast to peak at $3.4bn in 2016, by contrast, and the company's efforts to broaden its horizons via a takeover of Shire thwarted, the company will be hoping its $21bn move on Pharmacyclics this year will be enough to keep shareholders happy.

Big Pharma Top Risers and Fallers in 2014

	Share Price (Local Currency)			Market Cap ($bn)	
Top 3 Risers	**YE 2013**	**YE 2014**	**Change**	**YE 2014**	**12M Change**
Eli Lilly	$51.00	$68.99	35%	76.8	19.4
AbbVie	$52.81	$65.44	24%	104.3	20.2
AstraZeneca	$59.37	$70.38	19%	88.9	14.3
Top 3 Worst Performers					
GlaxoSmithKline	£16.12	£13.76	(15%)	107.6	(18.4)
Sanofi	€77.12	€75.66	(2%)	127.3	(12.0)
Pfizer	$30.63	$31.15	2%	196.3	(2.2)

AstraZeneca came out the takeover battle with Pfizer in a much better shape, but much like Lilly its pipeline now needs to deliver. For its part Pfizer is under pressure to deliver a much-trailed restructuring – its recent $17bn move on Hospira is unlikely to satisfy investors for long.

Sanofi and GlaxoSmithKline represented the rare retrenchments of 2014, and are still troubling investors with concerns about future growth that many of their peers have managed to shrug off.

Other Big Cap Risers and Fallers in 2014

	Share Price (Local Currency)			Market Cap ($bn)	
Top 3 Risers	**YE 2013**	**YE 2014**	**Change**	**YE 2014**	**12M Change**
Allergan	$111.08	$212.59	91%	63.3	30.3
Actavis	$168.00	$257.41	53%	68.2	23.8
Shire	$141.29	$212.54	50%	41.8	14.2
Top 3 Worst Performers					
Takeda	¥4,825	¥4,997	4%	36.5	(2.4)
Baxter International	$69.55	$73.29	5%	39.7	2.0
Bayer	€69.55	€73.29	11%	118.7	3.5

Outside big pharma – a group that we classify as companies with a market value of more than $25bn and which includes 21 global drug makers – share price performances were even more remarkable last year. Not one of these stocks ended 2014 in negative territory.

"Big biotechs" like Gilead, Celgene and Biogen Idec have now firmly established themselves as hugely capable cash generators, and as the launches of profitable speciality drug franchises like Sovaldi and Tecfidera progressed last year, investors rushed to value these companies and their peers ever more highly.

The bidding war for Allergan helped this stock to become the cohort's best performer, while AbbVie's failed attempt boosted Shire. It is notable that the victorious party for Allergan, Actavis, was also richly rewarded by the markets for its fervent deal making; investor enthusiasm for M&A moves is showing no sign of waning.

Other Notable Risers and Fallers in 2014 (ranked on market cap)

	Share Price (Local Currency)			Market Cap ($m)	
Top 5 Risers	**YE 2013**	**YE 2014**	**Change**	**YE 2014**	**12M Change**
Vertex	$74.30	$112.31	60%	28,574	11,206
Actelion	€75.35	€115.30	53%	13,810	3,768
Bluebird Bio	$20.98	$91.72	337%	2,876	2,377
Santhera	CHF 3.72	CHF 85.05	2186%	444	428
Cellectis	€2.30	€12.23	423%	432	368
Top 5 Fallers					
Aegerion	$70.96	$20.94	(70%)	595	(1,480)
Exelixis	$6.13	$1.44	(77%)	281	(848)
Active Biotech	SKr 69.50	SKr 18.80	(73%)	194	(618)
Cyclacel	$4.02	$0.70	(83%)	16	(59)
Cytos Biotechnology	CHF 3.05	CHF 0.23	(92%)	7	(96)

Top 5 Risers	**EP Vantage Comment and Analysis**
Vertex	Traffic Transports Vertex back onto the right track
Actelion	Selexipag hit puts Actelion back on the buyout radar
Bluebird Bio	Bluebird sings sweet music to the ears of investors
Santhera	As Duchenne winds change, PTC and Santhera score surprise wins
Cellectis	Pfizer partners with Cellectis, but why not buy the company?

Top 5 Fallers	**EP Vantage Comment and Analysis**
Aegerion	Daily Market Movers (31 Oct 2014)
Exelixis	Exelixis wiped out after Comet-1 crash lands
Active Biotech	With EU knockback laquinimod's irrelevance is all but assured
Cyclacel	Cyclacel and Neovacs enter the graveyard shift
Cytos Biotechnology	Cytos bows out as asthma drug bombs

M&A hunger also played a part for smaller companies, and Actelion for one can partly thank its 2014 stock market success on bid rumours.

However, much like Vertex Pharmaceuticals it also benefited from success in franchise building. The former added Opsumit to its pulmonary hypertension line, with selexipag looking good as another follow-on, while Vertex is looking to expand on its cystic fibrosis play of Kalydeco with VX-809.

Bluebird Bio provided a prime example of investors' willingness to embrace risk – shares in the gene therapy player surged at the end of the year on very early data in just eight patients. Santhera, which scored a surprise success with idebenone in Duchenne muscular dystrophy, demonstrated the ongoing enthusiasm for orphan disease plays. Finally Cellectis thrived last year with investors' interest for all things CAR-T related, a field that has fuelled wild dreams and some even wilder valuations.

It is within these realms that fears of a bubble mostly reside. "You've got companies that have tested a gene therapy in three or four patients and they have three or four-billion market caps. That's just not real," says Mann Bioinvest's Mr Smith.

"You've got an island of overvaluation. Big pharma, diagnostics, even some smaller and earlier-stage companies are still reasonably good value. But you've got a glaringly sore spot in the middle that is high pressure and is going to burst at some point."

Genghis Lloyd-Harris, a partner at Abingworth, a London-based venture investor, agrees.

"There are frothy components," he says. "But part of the strong performance and build-up has been catching up on a lost period. And this bull market has got the solid underpinnings of companies like Gilead with 30% growth – where can you get that growth in any industry in the world?"

While by and large the direction of the markets was up last year, there were of course notable disasters.

Losing out were companies like Exelixis, which tumbled after trials of its lead prostate cancer project missed expectations. Aegerion Pharmaceuticals failed to build a convincing commercial case for its struggling high-cholesterol treatment Juxtapid, while Active Biotech experienced yet more trouble for the multiple sclerosis therapy laquinimod.

Ending the year really down and out were Cyclacel, which saw its entire pipeline downgraded as a result of the failure of sapacitabine in acute myeloid leukaemia, and Cytos Biotechnology. The long-suffering Swiss biotech finally decided to go out of business after its asthma vaccine CYT003 failed in phase II.

One of the worries about the ongoing rally is that many of the more exuberant runups in valuation have been driven by generalist investors piling in on red-hot areas.

"No generalist investor investing in these companies ever thinks they are going to fail, and they will be rudely awoken when they do, and that's what's going to lay to a retreat," says Mr Smith. "Will one phase III failure do it? No. Two or three? Probably not. But historical rates of clinical success being as they are means that there will be a string of failures."

IPO PANDEMONIUM

Enthusiasm was not only on display for established public companies last year; new issues were embraced to a level not seen since the bubble at the turn of the millennium.

The impressive haul of 2013 was more than doubled, as companies raised on average even larger sums. Encouragingly this upswing was also seen in Europe, where 13 biotechs went public.

IPO Annual Totals (Western Stock Exchanges)

Year	Total Raised ($m)	US IPOs	European IPOs	Total IPOs*	Average Raised ($m)
2014	6,301	73	13	87	72
2013	2,956	40	3	44	67
2012	931	12	4	16	58
2011	687	12	5	17	40

*Includes Australian IPOs

It is said that the European IPO market takes longer to respond to any recovery than the US, and this has certainly been the case. However, these figures mask the extent to which European drug developers have moved to tap US investors – seven of 2014's US listings were conducted by companies based on the continent, including Forward Pharma, last year's third-biggest IPO.

The Belgian company raised money through an American Depositary Share scheme, a route chosen by several European groups.

David Stueber, managing director of BNY Mellon's depositary receipts business, says he has an "active pipeline" of European biotechs exploring this option.

"I get a call every other week from a lawyer or banker exploring an ADR listing – everyone wants to come to the US for valuation reasons," he says.

It is also notable that the largest IPO haul last year was netted by a UK company – the allergy treatment developer Circassia. But it was without doubt US investors that led the charge for new issues.

The majority of the 10 most lucrative flotations below were US companies on Nasdaq, and several were conducted at a substantial premium to the originally proposed share price and upsized to meet huge demand.

The CAR-T players Juno and Kite provided the most outstanding examples of investor exuberance. They now sport $3.6bn and $2.7bn valuations respectively, despite scant clinical data to support their very early pipelines. Kite even managed to fit in a secondary offering that raised a further $216m before the end of the year.

Top 10 Biotech IPOs on Western Stock Exchanges in 2014

Company	Amount raised	Offering price	Range	Discount/ premium	Exchange	2014 YE change since float	Date
Circassia	£200m ($332m)	310p	250p-310p	11%	LSE (main market)	(10%)	March
Juno Therapeutics	$304m	$24	$21-23	45%	Nasdaq	118%	December
Forward Pharma	$235m	$21	$20-22	0%	Nasdaq	(1%)	October
FibroGen	$168m	$18	$16-19	3%	Nasdaq	52%	November
Bellicum	$161m	$19	$15-17	19%	Nasdaq	21%	December
Dermira	$144m	$16	$14-16	7%	Nasdaq	13%	October
Kite Pharma	$128m	$17	$12-14	31%	Nasdaq	239%	June
Versartis	$126m	$21	$19-21	5%	Nasdaq	7%	March
ZS Pharma	$123m	$18	$15-17	13%	Nasdaq	131%	June
Ultragenyx	$121m	$21	$19-20	8%	Nasdaq	109%	January
Average across top 10 IPOs	***$184m***			***14%***		***68%***	
Average across all 87 IPOs	***$72m***			***(12%)***		***34%***	

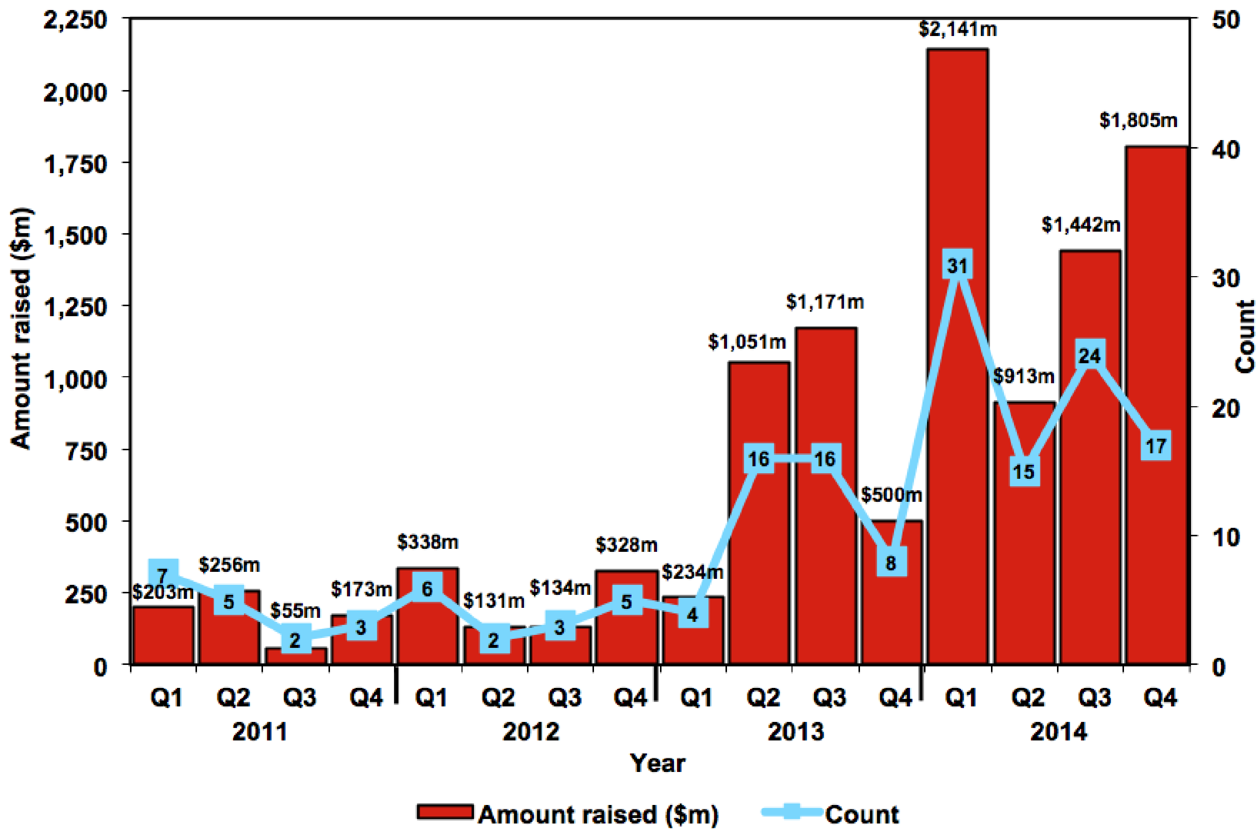
These top 10 IPO candidates also raised considerably more money than the average float last year, and their shares performed very strongly after the event – Circassia notwithstanding. This is perhaps not surprising from a cream-of-the-crop cohort – the average across all 87 IPOs conducted last year paints a slightly less rosy picture.

But it is clear that as the year progressed more and more companies were encouraged to brave the markets; a look at the last few quarters reveals the extent of the uptick in these issues.

The flow of companies jumping through the IPO window does not appear to be waning. And the huge $1.8bn haul registered in the fourth quarter of last year, by a relatively small number of issuers, suggests that there are still some private companies left that can attract sizeable public valuations.

The extent to which they can maintain and justify these valuations will determine for how long the window remains open.

Initial Public Offerings by Quarter on Western Exchanges



VENTURE CAPITAL CASHES OUT

Venture capital firms have been a major beneficiary of the IPO boom, which for them has opened up an exit route that had remained closed for so long.

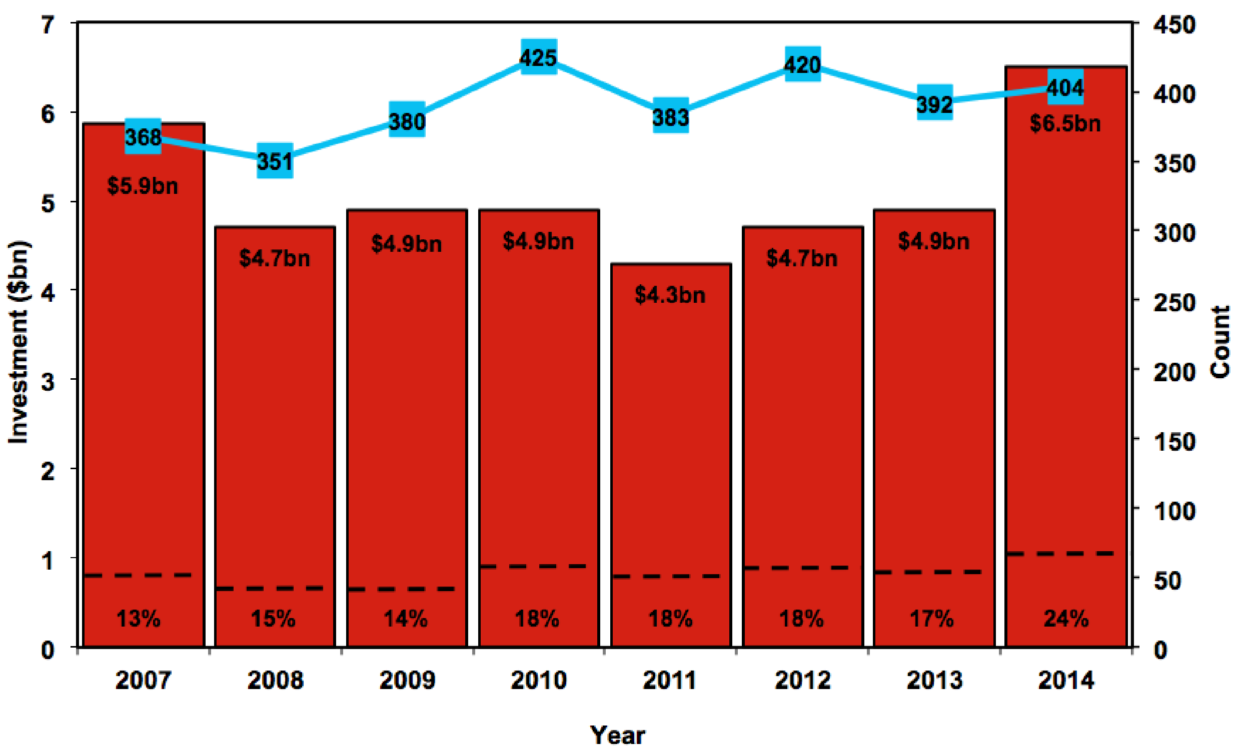
"[Venture firms] are really locking in profits now, and the fact that you can do all the secondaries and follow-ons means there is real liquidity in stocks. So in this market IPOs have been real exits, to some extent," says Abingworth's Mr Lloyd-Harris.

This has allowed the VCs to demonstrate to their own investors – called limited partners – that the cogs of their business model are turning. As a result last year the venture sector saw a healthy rise in new funds being raised, in both the US and Europe.

"Some venture firms have raised a lot more money than they expected – which suggests growing interest from the limited partner base," says Stephen Bunting, managing partner at Abingworth.

This in turn translated into a substantial uptick in the money the VCs invested in private drug developers. These data only comprise companies developing human therapeutics – diagnostics and medtech firms are excluded, for example.

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



The graph above also shows how an increasing share of the VC money is going to ever fewer companies. Despite these newly buoyant times re-financing risk remains, particularly in Europe, and over the past few years venture firms have responded by forging ever larger and stronger syndicates.

“Don’t think the next time you want to raise money the bull market will still be there. It will always be important to have a strong syndicate, and people around the table able to sign big cheques,” says Mr Bunting.

However, last year the top line was also heavily influenced by the growing presence of crossover investors; these are funds that invest in both private and public companies and are typically brought in to help shepherd a private company to market. The huge funds raised by the likes of Juno and Spark Therapeutics, which respectively raised $134m and $73m in their pre-IPO rounds, were boosted by this investor class.

These funds are likely to remain active and a big influence on this sector while the IPO window remains open. Of the companies that raised the 20 biggest VC-backed rounds of last year, three are already public, three more are rumoured to be moving that way, while two recently shelved their IPO plans; crossover funds will likely have been active in all of these companies.

Elsewhere, outside these close-to-market investments, the picture of venture capital investment is less pretty. For many start-ups, early-stage funding remains relatively hard to come by, although this always has and always will represent the riskiest stage of drug development.

But for those working in hot therapy areas or with technology that has captured the imagination of investors, there is undoubtedly plenty of money around. This situation was exemplified by RNA researcher Moderna’s $450m venture round in the opening days of 2015, a feat that rewrote the rule books on what can be achieved by an early-stage biotech with a promising technology.

Biggest VC Rounds of 2014

Company	Investment	Financing Round
NantWorks	$250.0m	Series B
Intartica Therapeutics	$200.0m	Series H*
Juno Therapeutics**	$134.0m	Series B
Adaptimmune	$104.0m	Series A
Paratek Pharmaceuticals***	$93.0m	Series I*
Cell Medica	£50.0m ($80.4m)	Series B
Naurex	$80.0m	Series C
NantWorks	$75.0m	Series Undisclosed
BeiGene	¥450.0m ($75.0m)	Series A*
Glycotope Group	€55.0m ($74.9m)	Series Undisclosed

*Series assumed, **Floated, ***Aquired by Transcept Pharmaceuticals

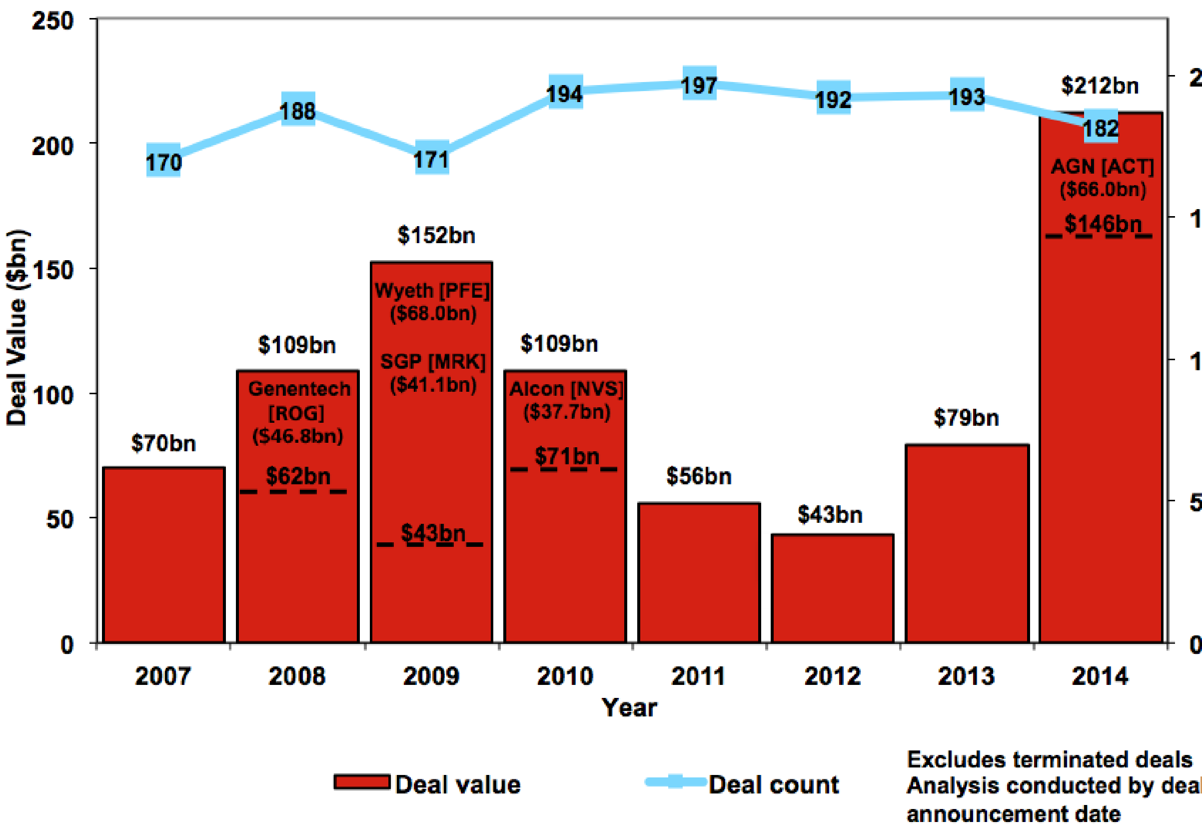
M&A MANIA

M&A proved another lucrative exit route last year, for all types of investor. Acquisitions worth more than $200bn were announced, a remarkable figure reached even in the absence of a traditional, big pharma mega-merger.

Still, the $66bn that Actavis paid for Allergan is certainly in the valuation territory of such transactions, coming within a whisker of Pfizer's $68bn takeover of Wyeth in 2009. That year, which also saw Schering-Plough swallowed by Merck & Co, saw deals worth $152bn announced. With last year's total far exceeding this, the gluttony of 2014 is laid bare.

This analysis only includes transactions struck by pharma and biotech companies, excluding medtech, for example.

Pharma and Biotech M&A Activity



The quest for targets that could help lower tax bills drove much of the activity in the first three quarters of the year, only for activity to dim in the wake of moves by the US to limit the appeal of inversions and other such financial engineering. This derailed several transactions; most notably AbbVie's move on Shire, but with investors continuing to react enthusiastically to corporate activity deal making remained firmly on the agenda of many a company.

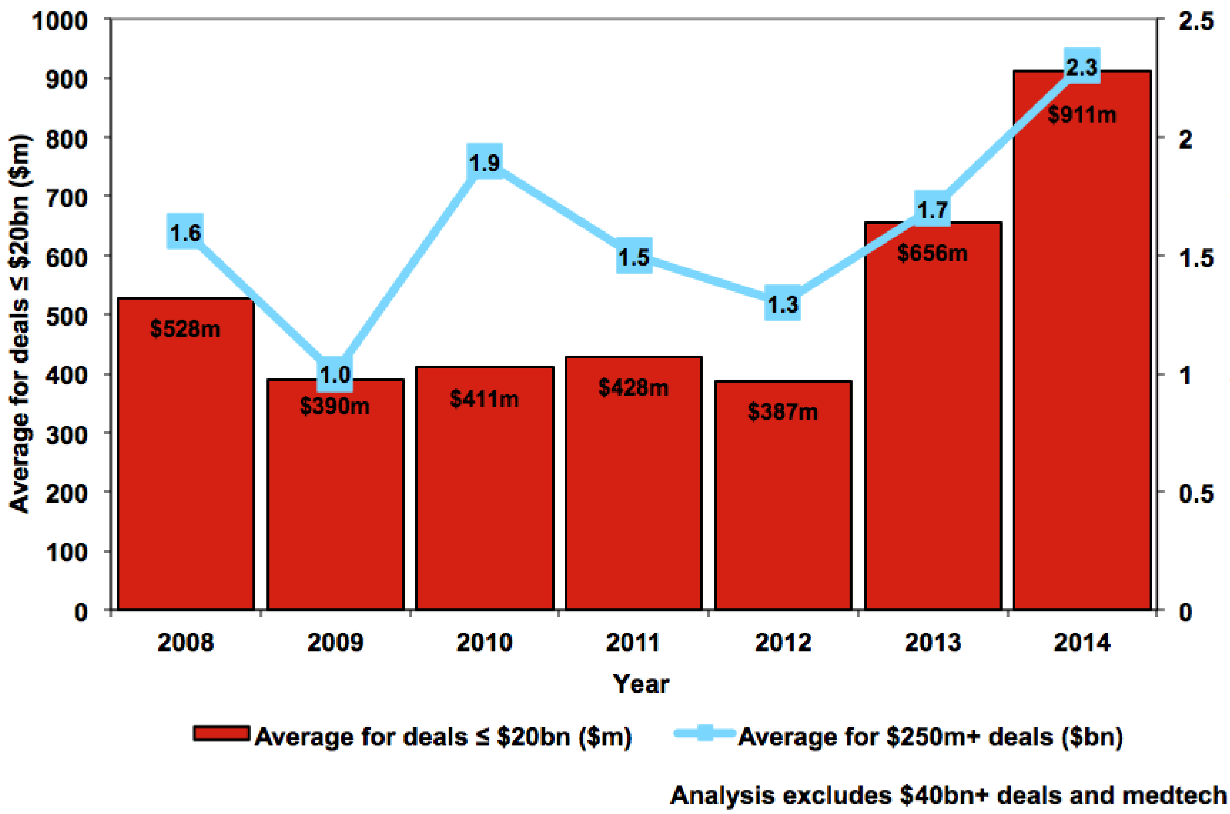
Looking at the annual run rate it is notable that, despite no apparent uptick in the number of deals being struck, the total value of transactions announced still soared.

The top line was inflated by a couple of large transactions – as well as Allergan, Actavis also bought Forest for $28bn, while the Novartis and Glaxo asset swap cost them each, respectively, $16bn and $7bn for oncology and vaccine franchises.

But soaring valuations also played a role, forcing buyers to write ever-larger cheques, a phenomenon that applied across all deal sizes.

A look at average deal values cut a couple of ways indicates just how far premiums have jumped. The analysis below removes the skewing effects of the very biggest takeovers of the past few years, namely Allergan and the big-ticket takeouts of Genentech, Wyeth and Schering-Plough.

Average Deal Values Per Year



This suggests that by 2013 valuations had returned to pre-crash levels, only to accelerate further across 2014. For followers of biotech stock indices, in particular the NBI, this will come as little surprise. Rising stock markets mean that many more companies have now crossed the blockbuster market-cap threshold.

The bull run "is also being sustained by M&A activity – companies are signing big deals", says Abingworth's Mr Lloyd-Harris. "Big pharma are fairly discerning and if they are willing to pay these sorts of up-fronts, it suggests a sensible foundation."

Growing valuations have also fed through to the private sphere, strengthening the arms of these companies at the negotiating table; having the option of going public is another boon to them.

"The market for private acquisitions and deals has gone up – big pharma has returned to top-line growth, but they still need to sustain that," says Mr Lloyd-Harris. He points to the $1.8bn takeover of Alios by Johnson & Johnson last year, widely regarded as the largest-ever takeout of a venture-backed private biotech.

All of which points to ever more expensive forays for those with acquisitive ambitions in the coming year. This was amply demonstrated by Bristol-Myers Squibb, which in February 2015 agreed to pay $800m up front for Flexus Biosciences – a company with only preclinical assets.

Top Five Pharma/Biotech M&A Deals in 2014 and 2013

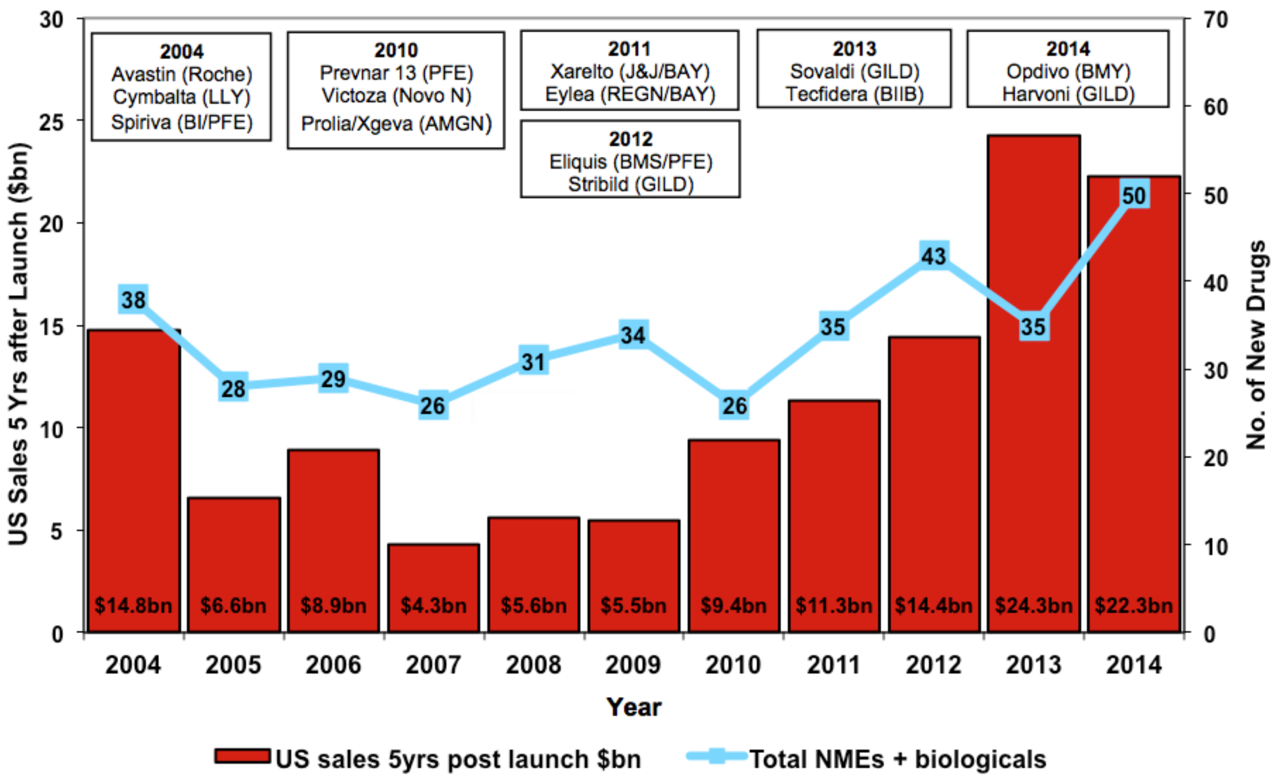
Year	Acquiring Company	Target company or business unit	M&A deal status	Deal value ($bn)
2014	Actavis	Allergan	Open	66.0
	Actavis	Forest Laboratories	Closed	28.0
	Novartis	Oncology business of GlaxoSmithKline	Closed	16.0
	Merck & Co	Cubist Pharmaceuticals	Open	9.5
	Roche	InterMune	Closed	8.3
2013	Amgen	Onyx Pharmaceuticals	Closed	10.4
	Valeant Pharmaceuticals	Bausch + Lomb	Closed	8.7
	Perrigo Company	Elan	Closed	8.6
	Actavis	Warner Chilcott	Closed	8.5
	AstraZeneca	Diabetes business of Bristol-Myers Squibb	Closed	4.3

PRODUCTIVITY GAINS EVIDENT

One of the main reasons cited to explain investors' growing willingness to buy into ballooning valuations is the sector's improving R&D productivity. Evidence can be found to suggest that this is more than a perception – in the last few years there has been an overall uptick in the number of novel compounds approved by the FDA, for example, several of which have gone on to enjoy huge commercial success.

The analysis below tracks these approvals and pairs each year's cohort with their actual or forecast fifth-year US sales, and the picture that emerges is one of an industry emerging from a disappointing trough.

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



This analysis looks at products approved by both FDA departments – the small molecules and biologicals reviewed by the FDA's Center for Drug Evaluation and Research (CDER), and vaccines, allergenics and tissue-derived therapeutics reviewed by the Center for Biologics Evaluation and Research (CBER) – and therefore provides a full picture of the US regulator's output.

The 50 new compounds that received a green light last year represented a huge haul for the industry. And although their sales potential might not reach that of 2013, the class of 2014 provides little evidence that the sector's strong run of drug approvals is coming to an end.

Various FDA efforts to ensure speedy approvals, particularly in areas of unmet need, have also helped improve the sector's image. Last year agents with the relatively new breakthrough therapy designation reached the market in an average four months –

measured from the date of submission to the FDA – adding to the image of a sector with an efficient production engine.

The table below lays out last year's most commercially valuable approvals, as forecast by sellside analysts. It is notable that every one of these products had breakthrough therapy designation; this also suggests that companies can win strong pricing power for products deemed to meet unmet needs, and explains the industry's inevitable focus on drugs that meet these criteria.

Biggest Five Approved Drugs in 2014

Product	Pharmacology Class	Company	Approval Date	US Sales 2019 ($bn)
Opdivo	Anti-PD-1 MAb	Bristol-Myers Squibb	December 22	3.61
Harvoni	Hepatitis C nucleoside NS5A & NS5B polymerase inhibitor	Gilead Sciences	October 10	2.52
Keytruda	Anti-PD-1 MAb	Merck & Co	September 04	2.22
Viekira Pak	Hepatitis C NS3/4A protease, hepatitis C NS5A & hepatitis C non-nucleoside NS5B polymerase inhibitor	AbbVie	December 19	1.60
Ofev	Tyrosine kinase inhibitor	Boehringer Ingelheim	October 15	1.08

Looking into this year, the omens also look good in this regard. Several potential blockbusters are waiting in the wings, three of which, Pfizer's breast cancer pill Ibrance, Novartis's psoriasis therapy Cosentyx and Sanofi's long-acting insulin Toujeo have already received green lights.

Regulatory reviews of the cholesterol-lowering PCSK9 antibodies promise to be among the most keenly awaited events of 2015 – this should happen around mid-year – and any signs of setback would prove damaging for the companies involved, and perhaps even beyond.

The progress of Novartis's LCZ696 will also be very closely watched; given the huge sales expectations attached to this heart failure project.

It is highly unlikely that all of these products will reach the market this year as planned. For the sector's reputation to remain unblemished, however, a good proportion of these highly valued products need to pass muster. Indeed, a handful of high profile regulatory setbacks could be all it takes to prompt a wider retrenchment in confidence.

The Biggest Products Slated for Launch in 2015 – Biotechnology Drugs

Product	Therapy Area and/or Pharma Class	Company	Current Phase	Annual Sales WW ($bn) 2020
Praluent (alirocumab)	Anti-hyperlipidaemic; anti-PCSK9 MAb	Sanofi	Filed	2.11
Evolocumab	Anti-hyperlipidaemic; anti-PCSK9 MAb	Amgen	Filed	1.84
Toujeo	Long-acting insulin	Sanofi	Approved	1.64
Bosatria	Bronchodilator; anti-IL-5 MAb	GlaxoSmithKline	Filed	1.12
Cosentyx	Psoriasis treatment; anti-IL-17A MAb	Novartis	Approved	1.10

The Biggest Products Slated for Launch in 2015 – Conventional Drugs

Product	Therapy Area and/or Pharma Class	Company	Current Phase	Annual Sales WW ($bn) 2020
VX-809 + Kalydeco	Cystic fibrosis; CFTR corrector + potentiator	Vertex	Filed	4.74
LCZ696	Heart failure; AT1 antagonist & ARNI	Novartis	Phase III	4.06
Ibrance	Breast cancer; CDK 4 & 6 inhibitor	Pfizer	Approved	3.08
Uptravi	PAH; Prostacyclin agonist	Actelion	Filed	1.21
Venetoclax	CLL; Bcl-2 inhibitor	AbbVie	Phase III	1.06

ENDGAME IN SIGHT?

Trying to predict what might cause the bubble to burst will be a persistent preoccupation for followers of pharma and biotech in 2015. The huge surge in activity seen in the IPO and M&A markets and soaring valuations are simply not sustainable, the argument goes; the sector's seeming inability to break out of a boom-and-bust model certainly supports this logic.

Regulatory disappointments could provide a trigger, but so too could commercial ones. Payers are increasingly flexing their muscles when it comes to high-priced products that offer only incremental improvements in efficacy; companies attempting to launch new offerings in the respiratory and insulin markets already are struggling with reimbursement, for example. This is widely expected to start happening in other fields, and any push-back in oncology, the huge value-driving therapy area for the sector, would be a jolt for many.

The battle that broke out in hepatitis C last year demonstrated the fight that companies can expect to face in justifying huge price tags even when their new drugs represent substantial steps forward. The rebates that Gilead and AbbVie had to offer to secure coverage spooked many an investor, and the harsh realities of the ever-more aggressive market threatens to hold further shocks in the coming months.

Still, many believe that it will take more than worries about drug prices to turn back a rising tide that has so far proved far more persistent than previous advances.

"It probably won't be driven by drug pricing issues per se, as we've had a couple of pricing scares already and recovered. And Gilead might be offering a 40% discount on Sovaldi, but they are still charging triple what Pharmasset were planning," says Mr Lloyd-Harris.

"Previous bubbles, which are not strictly analogous, were pricked by unexpected things."

His colleague Mr Bunting agrees. "This is a very different bull market from what we've had before. Interest in the sector has increased slowly and steadily after a drought of 12-13 years.

"Is it overblown? I'm sure there are examples where that is the case. But in 2000 and 1992 the markets became overblown very quickly and fizzled out in months. That was a very different dynamic with only one outcome, and that was one hell of a mess."

The intrinsic vagaries of drug development are another ongoing risk, which many investors appear happy to ignore. The huge valuations being assigned to very early-stage companies operating in largely unproven areas like gene therapy or CAR-T technologies remain highly susceptible to clinical setback and failure, which could easily infect investor confidence in other areas of drug research.

"Life is punctuated by its successes, not by its disappointments," says Mr Smith of Mann Bioinvest. "As soon as the first patient has some serious adverse effect related to a gene therapy product, for example, you wait and see what happens. Something will happen sooner or later."

He says his fund has started reducing its exposure to biotech investments.

Shocks could also originate from outside the sector. Currency shifts are already having an impact on earnings guidance, a "Grexit" from the Eurozone is still possible, the situation with Ukraine and Russia remains unstable and unrest in the Middle East is only likely to deepen and spread.

"We haven't seen the sector tip back in the last few years because nothing has pushed it. If valuations continue to march up, plus some significant geo-political uncertainty, that might lead it to happen," says Mr Smith.

At the same time, however, interest rates remain at record lows, providing a boost to corporate activity, and politicians and central banks the world over remain intensely focused on pulling every lever possible to keep the financial markets on an even keel.

And within the pharma and biotech sector, ever-larger amounts of money are being raised and frantic deal-making in hot areas continues apace, none of which does the industry's image of rude health any harm.

Indeed, many believe that although life will calm down the fallout of any slowdown will not be as damaging as previous crashes, particularly as companies are raising far more money than they have ever been able to before – meaning that the sector should be sustained for longer in the next downturn.

"The next decade is probably going to account for 20-25% of everything we've ever achieved in medical research and therapeutic drug development because the science base is there, and now the money has arrived as well. We also have some very experienced executives who know what they are doing – that adds value because inexperience tends to lead to inappropriate placement of capital," says Mr Bunting.

"We are in a good situation right now because of those things."

When and how quickly the biotech bubble bursts will be determined by the events of the coming year. But while the markets remain overwhelmingly receptive to M&A deals and fund raisings, companies will continue to make the most of the good times.

Report Author: Amy Brown

EDITORIAL TEAM

Lisa Urquhart
Editor
LisaU@epvantage.com
@LisaEPVantage

Amy Brown
News Editor
AmyB@epvantage.com
@AmyEPVantage

Jonathan Gardner
Deputy News Editor
JonathanG@epvantage.com
@JonEPVantage

Jacob Plieth
Senior Reporter
JacobP@epvantage.com
@JacobEPVantage

Elizabeth Cairns
Medtech Reporter
ElizabethC@epvantage.com
@LizEPVantage

Joanne Fagg
Content Manager
JoanneF@epvantage.com
@JoEPVantage

FOR GENERAL QUESTIONS ON THIS REPORT, CONTACT

Christine Lindgren
Vice President, Marketing
Christine.Lindgren@evaluategroup.com
+1 617 573 9458

http://www.evaluategroup.com/PharmaBiotech2014inReview

Evaluate – Headquarters – Evaluate Ltd, 11-29 Fashion Street, London E1 6PX United Kingdom
Tel: +44 (0)20 7377 0800 – Fax: +44 (0)20 7539 1801

Evaluate – North America – EvaluatePharma USA, Inc., 15 Broad Street, Suite 401, Boston, MA 02109 USA
Tel: 1-617 573-9450 – Fax: 1-617 573-9542

Evaluate – Japan – EvaluatePharma Japan KK, Tokyo, Japan
Tel: +81 (0) 80 1164 4754

www.evaluate.com