



# EP Vantage 2016 Preview

Lisa Urquhart, Jonathan Gardner & Edwin Elmhirst – December 2015



## Foreword

Let the good times roll. Sceptics burned by a downturn in sentiment over the summer and looking for a sign that the biopharma sector's incredible momentum is about to falter will not find much evidence in 2016. Research and development productivity is forecast to continue at a high pitch while patent expiries remain less of a worry for many companies than expected, even with the advent of US biosimilars.

The year is expected to see the launch of as many as 12 new drugs that are forecast to achieve blockbuster sales by 2020, sustaining the torrid pace established in 2013. At the other end of product lifecycle, pharma companies have few immediate concerns as only six billion-dollar sellers face loss of market exclusivity – and one of them, Humira, is not expected to go up against immediate competition.

With that picture in mind it is surprising to see how investor sentiment around the biopharma sector has cooled. The sentinel Nasdaq biotechnology index is well off its mid-2015 record, as policymakers' closer questioning of drug pricing and tax avoidance has put the brakes on investor enthusiasm.

It is possible that continued scrutiny of pricing is the one factor that could keep denting investor sentiment, and cause further cooling of the sector.

Erosion of market valuation has not been sufficient to make buyers out of big pharma players, even though many will ultimately need to refill their pipelines through acquisitions. Only Pfizer took the plunge last year and made a major acquisition in 2015.

In 2016 we can expect big pharma to continue being active in smaller M&A, of course, but unless valuations continue to decline these companies' acquisition strategies will be about focusing business lines and, among smaller companies, bulking up to keep from being acquired themselves.

That said, companies like AstraZeneca, Sanofi and Gilead, which need to accelerate their pipelines, might buck the trend and buy big in 2016.

Even though investors are less keen, the sector has been on a winning streak for several years now – long enough to make one wonder what it will take to bring it to an end.

A safety scare for one of the big money-makers, more assertive action from payers or a series of major regulatory stumbles are among the possibilities. Signs of payer activism have emerged, but for now they are limited. Biopharma is still a good place to be.

Report authors | Lisa Urquhart & Jonathan Gardner



## Top 10 Companies in 2016

Pfizer to the pfore.

Novartis and Pfizer have been duking it out as the top companies by sales ever since the latter's Lipitor lost patent protection in 2011, and in the absence of M&A activity 2016 would have seen the fight continue. However, Pfizer's pending acquisition of Allergan will change that picture significantly, assuming it goes through in 2016.

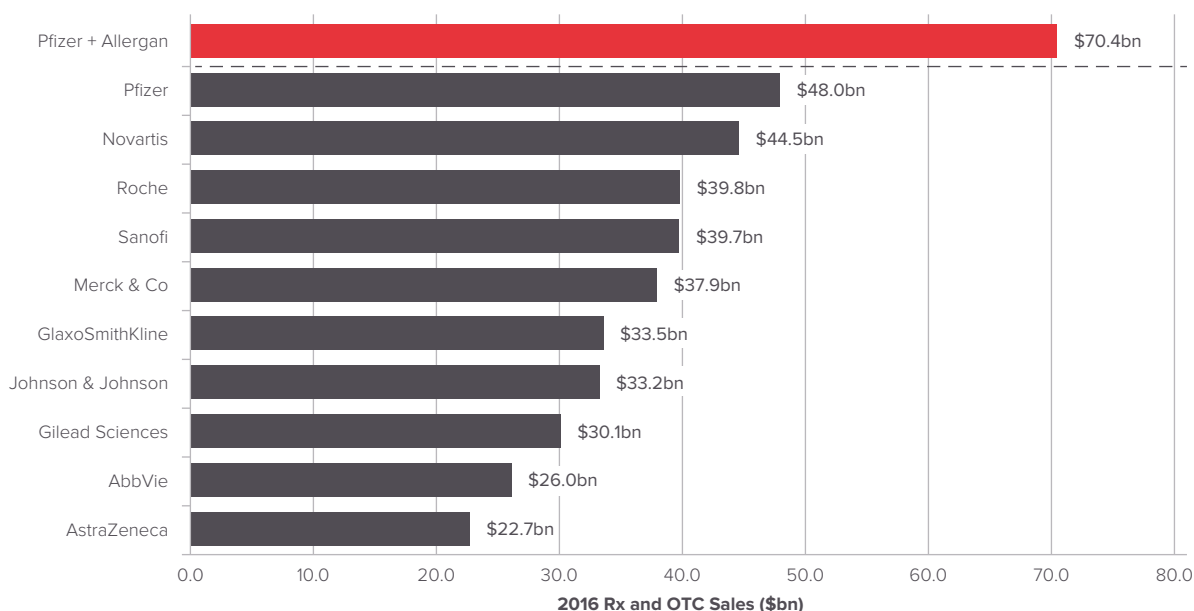
With \$70.4bn in prescription and over-the-counter sales the Pfizer-Allergan combination would put the title for biggest company well out of the reach of Novartis in 2016, and indeed any other big pharma company unless they too are willing to combine.

Still, without any major mergers Novartis looks pretty secure in that second spot, helped along by the launch of its heart-disease pill Entresto and durable sales from franchises like Gilenya, Tasigna and Afinitor. The Swiss group is being held back a bit by its less innovative divisions, with the Alcon ophthalmology business in particular having an off period right now.

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### Top 10 Companies by 2016 WW Rx and OTC Sales

Source: EvaluatePharma\* 20 November 2015



Roche will hold on to its number three position, but only just. Having been knocked around in the diabetes game for some time, number four Sanofi will come on strong in 2016 as launches of Praluent and dupilumab, along with growth for Aubagio and Lemtrada, continue to make themselves felt. Merck & Co is secure in the fifth spot, but for sixth place a close race between GlaxoSmithKline and Johnson & Johnson will probably be fought. More bad news from the UK group's respiratory franchise, or good news from J&J's Imbruvica partnership with AbbVie, could change this picture.



Gilead Sciences looks well-established now as the main company that has moved up from mid-cap biotech into the realm of big pharma, thanks to its hepatitis C franchise, but this is maturing. Gilead might want to seek to diversify through an acquisition which could push it up the ranking.

AbbVie and AstraZeneca round out this list – these two present different pictures of growth, with Astra slipping down the rankings thanks to patent expiries while AbbVie’s sales are expanding thanks to its takeout of Pharmacyclics and its cancer drug Imbruvica.

## Top 10 drugs in 2016

While there has been change among the industry’s biggest players for 2016 with the emergence of Pfallergan, little has altered among the biggest selling drugs.

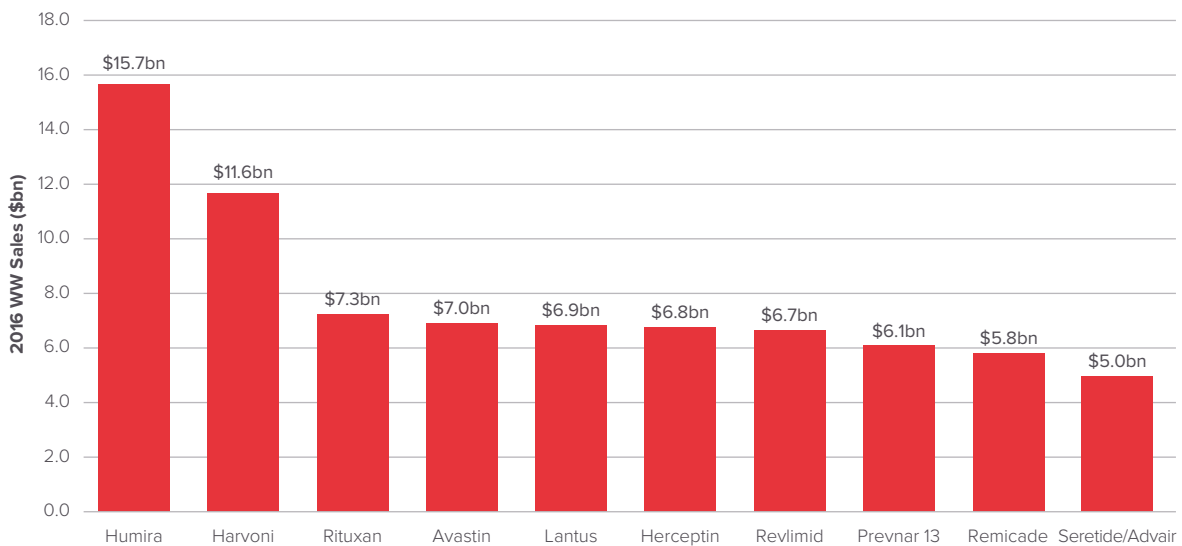
And although the likes of tenofovir, atezolizumab and their fellows will be making great leaps towards the top in coming years, they will have a long way to go to unseat the sector’s biggest sellers – although in 2016 there will be a theme of emerging competition to biologics as biosimilars near the market.

Once again in 2016 the honour of biggest seller will go to Humira – with \$15.7bn in revenues forecast for 2016 it is expected to outsell its nearest rival by an estimated \$4.1bn, a sum not far off the total sales of Glaxo’s Seretide/Advair. But the sheer scale of Humira sales point out what is at stake for AbbVie now that Amgen has submitted its lookalike product, ABP 501, to the FDA.

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### Top 10 Drugs by 2016 WW Sales

Source: EvaluatePharma\* 20 November 2015





Most companies would be happy to have just one product in the top 10. Roche is in the fortunate position of having three, with its oncology antibodies Rituxan, Avastin and Herceptin forecast to pull in a combined \$20bn in 2016. While Roche is not as dependent as AbbVie on a single product, its previously unassailable drugs are now all at risk of biosimilar competition. Indeed, Remicade's low position in the pecking order could be partly due to the fact that the drug is already seeing biosimilar competition in Europe.

Talking of competition, Sanofi's Lantus will retain its position in the top 10, although its sales are forecast to slip to \$6.9bn from \$7.4bn in 2015. The entry of Lilly's biosimilar Basaglar has a great deal to do with this, along with Novo Nordisk's long-acting insulin Tresiba.

### **Payers forcing the pace**

A small-molecule agent in the top 10 that is facing strong pricing pressure is Advair, sales of which are expected to halve between now and 2020. Forecasts for Advair have come down rapidly as pharmacy benefit managers like Express Scripts began to flex their muscles in drug classes where there is existing competition and therefore an opportunity to prioritise one drug over another in return for price decreases.

Earlier this year, Glaxo was forced to slash the price of its flagship drug in an effort to get it back onto formularies. While this is a tragedy for Glaxo, it is also worrying as a potential signal for the rest of the industry that its pricing power might be collapsing.

Despite an impressive-looking 2016 forecast, Harvoni sales are also falling back from the \$14bn expected in 2015, but for very different reasons. The shifting market for hepatitis C drugs means many warehoused patients have now completed treatment. This along with competition from an array of new projects will dent its dominance, but its first full year's sales set a benchmark that will not soon be matched.

With all this talk of competitive pressures, there are still agents in the top 10 that will see growing sales. Revlimid has secured a strong position as a frontline multiple myeloma treatment, while Prevnar 13 has locked up a huge lead in the pneumococcal vaccine space. Expect these two agents to climb up the top 10 rankings in coming years.



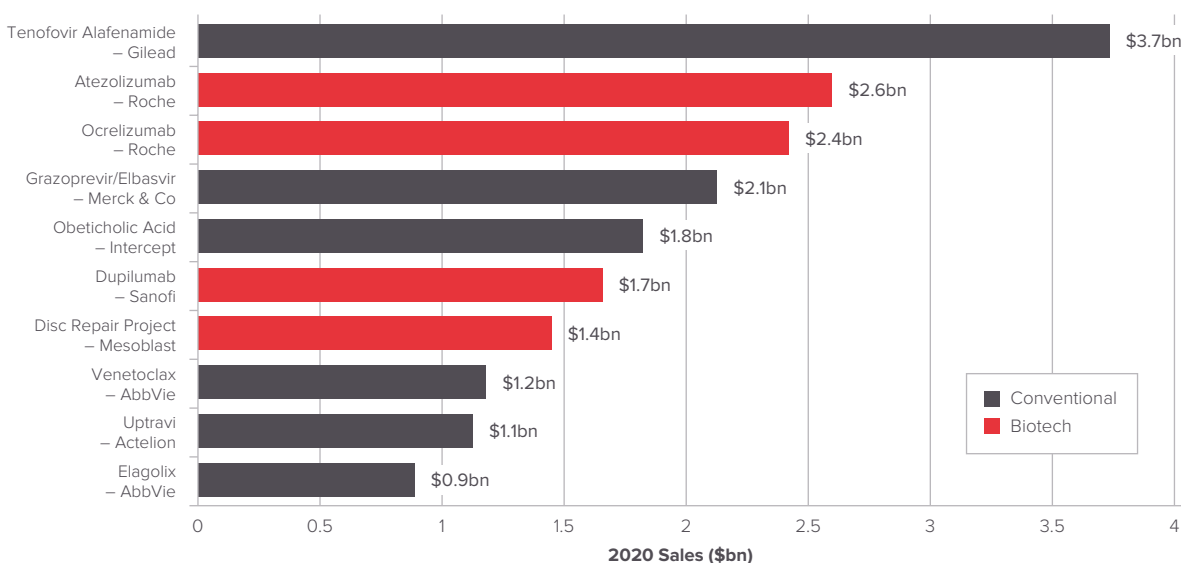
## The big launches of 2016

The seemingly non-stop procession of forecast blockbusters is in many ways a result of the patent cliff panic of around five years ago. 2016 is set to be every bit the equal of 2013 and 2015, with no therapy category clearly dominating.

The analysis below is based on a consensus of equity analysts' expectations, collected by EvaluatePharma.

### Biggest Launches 2016

Source: EvaluatePharma\* 20 November 2015



The biggest forecast launch is that of an antiviral. Gilead Sciences has been so heavily invested in hepatitis C in recent years that it is easy to forget its strength in HIV. The upcoming year will be a return to form, as tenofovir alafenamide, already part of the California-based group's Genvoya, will make a single-molecule launch. On the strength of reduced toxicity, compared with many of Gilead's combination therapies, this prodrug is now forecast to hit \$3.7bn in worldwide sales in 2020 and outsell all of the group's HIV offerings except Stribild.

Roche at last joins the immuno-oncology chase with its entry atezolizumab, with first approval for the PD-L1 antibody likely to come in non-small cell lung cancer or bladder cancer. The third biggest launch by forecast 2020 sales also belongs to the Swiss group, with its multiple sclerosis project ocrelizumab helping it to branch out from its strong suit of cancer-fighting agents.

Hepatology is also due to make a strong showing in 2016, with Merck's hepatitis C doublet grazoprevir/elbasvir slated to start building toward \$2.1bn in sales, while Intercept Pharmaceuticals expects to get obeticholic acid (OCA) off the ground in the relatively small indication of primary biliary cirrhosis. Non-alcoholic steatohepatitis (NASH) is set to become a much bigger contributor to OCA sales over time.



AbbVie has two entries in the top launches, in its blood-cancer candidate venetoclax (partnered with Roche) and endometriosis agent Elagolix. It is just as well that the Illinois-based group has some new projects coming on stream with the emerging biosimilar threat to Humira, the biggest-selling product in the world.

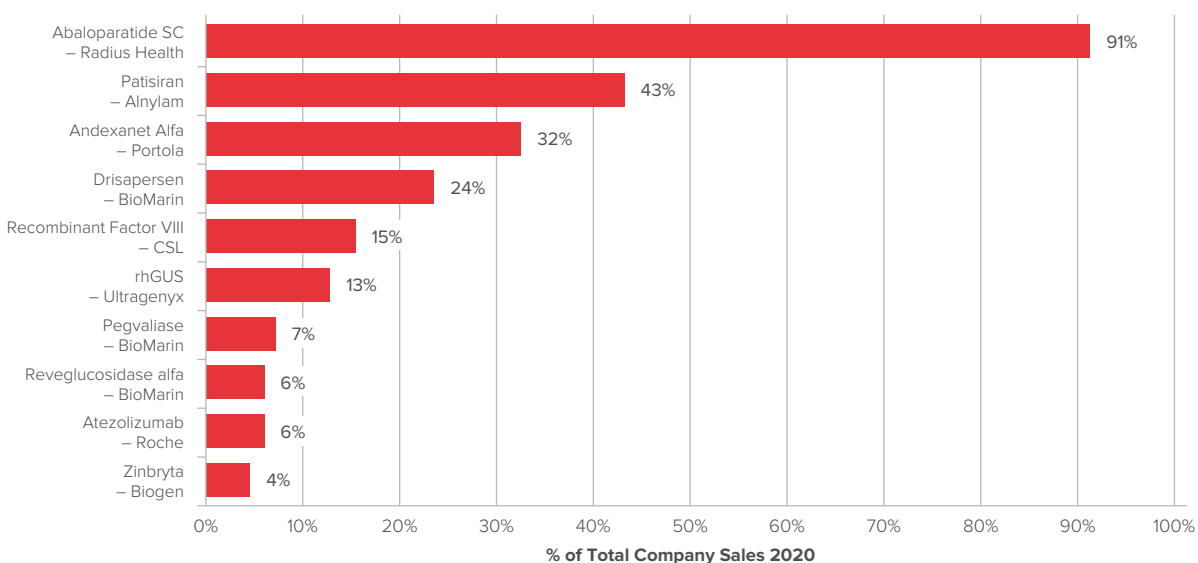
Other potential blockbuster launches worth noting are Sanofi's dermatitis antibody dupilumab; the pulmonary hypertension pill Upravi, an extension to Actelion's franchise built around Tracleer.

## Top launches by company sales in 2016

As big as Gilead's new HIV drug tenofovir alafenamide is predicted to be, it will not move the needle for the group the way launches for smaller companies do. Acadia, OPKO Health, Intercept Pharmaceuticals, Radius Health and Neurocrine Biosciences, by contrast, are set to launch products responsible for all or nearly all of their total sales.

### Top 2016 Biotech Launches by % of Company 2020 Sales

Source: EvaluatePharma<sup>®</sup> 20 November 2015



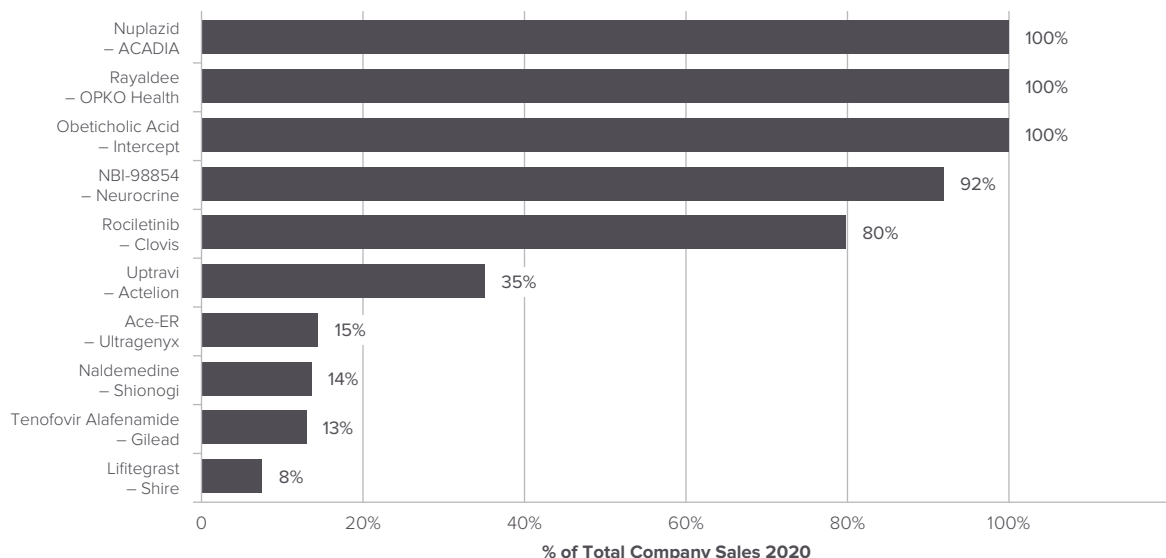
In the case of the first three, Nuplazid, Rayaldee and OCA respectively would constitute 100% of the company's sales in 2020, and for Neurocrine and Radius, NBI-98854 would account for 92% and abaloparatide SC, 91% of the company sales, respectively. All but Neurocrine and Radius are due FDA decisions in the first half of 2016.

One established company also has much at stake in this analysis. BioMarin makes three appearances, although its most significant hoped-for 2016 launch, drisapersen, looks in doubt after an FDA advisory committee gave it a sceptical review in November. This demonstrates how much BioMarin's pipeline of enzyme replacement projects still matters.



## Top 2016 Conventional Launches by % of Company 2020 Sales

Source: EvaluatePharma\* 20 November 2015



In ranking launches this way, the top three biotechnology launches go to companies that are pre-revenue, with Alnylam Pharmaceuticals receiving 43% of its forecast 2020 sales from patisiran and Portola Pharmaceuticals 32% from andexanet alfa. The top five conventional drug launches are also for pre-revenue companies, with Clovis Oncology deriving 80% of its forecast revenue from rociletinib.

One money-making company has a significant launch waiting. Actelion can expect its pulmonary hypertension franchise extender Upravi to generate 35% of its 2020 sales as Tracleer sales diminish.

## Biggest-selling drugs going off patent in 2016

Like drug launches, patent expiries are a natural part of the lifecycle of the healthcare industry, and in 2016 some companies are going to be hit harder than others.

Humira may be 2016's best-selling drug, but how long it will retain this top ranking is wide open to debate. The drug technically loses a key US patent in December 2016, and biosimilar makers are already circling. Merck & Co and Pfizer both have phase III versions of the arthritis MAb in development, and last month Amgen submitted its Humira lookalike, ABP 501, to the FDA.

That said, the biosimilar pathway in the US has not been entirely cleared of debris, giving Rick Gonzalez, AbbVie's chief executive, the confidence to be adamant about keeping biosimilar competition in the US at bay until at least 2022. The fact that Humira makes up 62% of AbbVie's sales must provide extra motivation for keeping biosimilars off the market for as long as possible.





Consensus, however, begs to differ with Mr Gonzalez's predictions, with sales forecast to peak at \$18.8bn in 2018 and then fall to \$16.2bn in 2020.

Payers are keen to see more biosimilar competition. Express Scripts believes that it could save \$250bn from the use of just 11 biosimilar products between 2019 and 2024, giving an idea of how the wind might be changing – and changing faster than some companies and analysts predict.

## Biggest Selling Drugs Going Off Patent in 2016

Source: EvaluatePharma\* 20 November 2015

Product	Company	2015 Sales (\$m)	% of 2015 Company Sales	Forecast 2016-17 CAGR
Humira	AbbVie	14,090	62%	+5%
Seretide/Advair	GlaxoSmithKline	5,577	17%	-23%
Crestor	AstraZeneca	4,918	21%	-45%
Zetia	Merck & Co	2,522	7%	-58%
Benicar	Daiichi Sankyo	1,847	25%	-30%
Epzicom/Kivexa	GlaxoSmithKline	1,191	4%	-17%
Zostavax	Merck & Co	836	2%	+5%
Kaletra	AbbVie	729	3%	-49%
Iressa	AstraZeneca	564	2%	+4%
Invanz	Merck & Co	535	2%	-34%

### Small molecules losing big

Other more clear-cut small-molecule losers include Daiichi Sankyo's Benicar, which made up a quarter of 2015 sales. The Japanese group has struggled to come up with replacement drugs for its portfolio champion and its best effort so far, drug-thinner Lixiana, is a late entrant to the market and is hindered by a black-box warning.

Another company also struggling to find replacements for its aging pipeline is Glaxo, which has two products coming off patent next year. Seretide/Advair loses exclusivity in 2016, further adding to Glaxo's misery around the already declining franchise, and it will also see reduced sales of the HIV drug Epzicom.

With Glaxo eschewing the idea of major M&A, like Daiichi it could be facing a long hard slog to get both sales and investor enthusiasm back up again.

Perhaps the biggest patent event of 2016 is the industry waving goodbye to one of its last remaining heavyweights, Crestor. Along with Lipitor, this drug represents a simpler, more nostalgic time for the pharma industry – of primary care drugs, produced relatively cheaply and most importantly servicing a huge patient population.

Crestor, sales of which peaked at \$7.07bn in 2011, has earned Astra over \$50bn since its launch in 2003 and it is expected to contribute 21% of Astra's 2015 sales.

Crestor's loss of exclusivity will finally see AstraZeneca get out of the patent expiry woods. But even post-patent Crestor will remain one of Astra's biggest-selling products, raking in \$1.48bn in 2020, showing its importance and Astra's difficulty in filling the hole it leaves.

Indeed, with such a big sales gap to fill the company's allergy to large acquisitions might have to be reversed in 2016.



## Top 5 companies by patent risk in 2016

Patent expiries for Astra’s Crestor and Glaxo’s Seretide/Advair put them firmly in the top five companies by patent risk in 2016, while the loss of three drugs, including the cholesterol-lowerer Zetia, gives Merck & Co its entry in the chart.

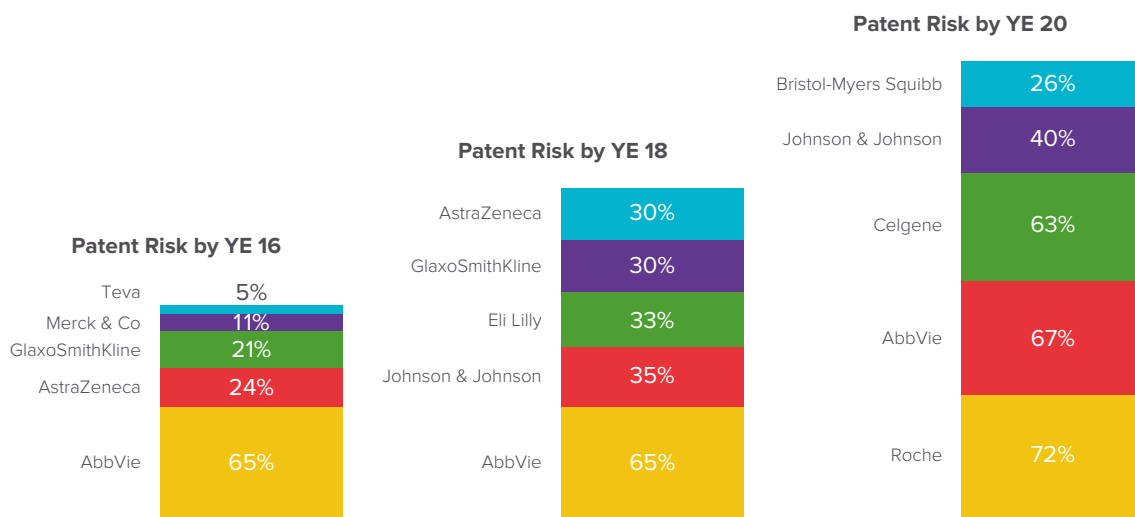
Once again the cash cow Humira is AbbVie’s greatest strength and its greatest weakness, but there is little likelihood of a challenger being launched in the US in 2016.

Like AbbVie, the massive erosion of both J&J’s and Roche’s sales by 2018 and 2020 respectively will come from the US biosimilar threat to some of their biggest names. For J&J it is the 2018 patent expiry of Remicade, while Roche’s Avastin, Herceptin and Rituxan are all set to lose patent protection by the middle of 2019. Roche is, however, already starting the lifecycle management fightback with a variety of strategies that include developing its own second generation of products with better efficacy and working on formulations to make administration easier or more convenient.

### Top 5 Companies by Patent Risk

Source: EvaluatePharma 20 November 2015

% of 2015 Sales from Drugs Coming Off Patent in 1/3/5 Years



Alongside individual strategies and the already painful patent dance, some analysts are speculating that originators will use old-fashioned delaying tactics to keep lookalikes off the market for as long as possible. Analysts at Bernstein have highlighted the potential use of citizen petitions, picking court venues known to be slow and adding patents to ongoing litigation as additional hurdles to biosimilar entry.



While Celgene does have this option with Revlimid, the patent expiry of the small molecule in 2019 could hit it hard. This could explain Celgene's efforts to shore up its pipeline through M&A, as seen by its \$7.2bn purchase of Receptos in July and various collaborations around immuno-oncology. One bet that it will be hoping pays off is its \$450m deal to use Astra's PD-L1 antibody durvalumab in combination with a number of its pipeline products.

### **More than zero**

These figures, however, assume that the sales of all the drugs in our list will fall to zero when their patents expire. How much Roche, AbbVie and other originators will lose to generics is still unknown, but one of the lessons from Europe, where biosimilars are more common, is that discounts can vary widely.

Price cuts are running at 30-40%, but in Norway the discount for Remsima, a generic version of Remicade, has hit 80% thanks to the negotiating stance of the government.

As well as payers driving costs down, competition could also see discounts increase greatly. While a number of the industry's biggest names are looking at the loss of some of their biggest products next year, the full impact will in many cases not be felt until long after 2016.

On paper it looks as if 2016 will be another strong year for the sector. R&D productivity continues to be strong and most of the big patent expiries of the year are unlikely to impact originators any time soon.

However, clouds are forming on the horizon. The US Federal Reserve has announced its first interest rate rise in seven years, signalling the end of the cheap money that has been driving transactions in the sector.

And as we have said previously, regulatory or clinical setbacks for some of our brightest hopes could cast shadows over the industry's ebullience. Even for those drugs that do make it to market, the growing power of payers will increase their commercialisation risk.

All of this could negatively impact investor sentiment, which has already resulted in the Nasdaq biotechnology index coming off the historic high it hit earlier this year, yet further.

The industry is entering interesting times and any significant missteps by pharma companies, either over big clinical programmes or pricing, could tip the balance.

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**Evaluate Headquarters**

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

**Evaluate North America**

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

**Evaluate Japan**

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