



Pharma Market Drivers Part Two: Ch-ch-changes

BY EDWIN ELMHIRST, AMY BROWN, MADELEINE ARMSTRONG AND LISA URQUHART | JUNE 2022



Introduction

Picture the scene. Roadrunner is being chased by Wile E. Coyote but cunningly hides behind a rock. Wile E. keeps running, right off the edge of the cliff, only to plummet to the ground after running on thin air for several seconds. For some of the biggest pharma players, there's a similar cliff looming. This one involves patent expiries, but running over the edge of it could result in a similar fate.

2028-2029 will see several of the biggest blockbusters on the market lose their exclusivity with up to \$115bn of sales at risk across those two years. Realistically, of course, it won't be as much as that but there are some big decisions to be made by several big pharma players about how to fill these pending gaps. In this report, we look at the scale of the challenge facing the market and consider the necessary activity to meet that challenge.

Who's running towards the cliff edge fastest? There are a couple of players more exposed than others and our freshness index provides a clear indication of which companies need to start investing, shopping and licensing to remain at the forefront of the industry.

This brings us neatly to the future. We've updated our forecasts to 2028 so we can take a good look not only at that patent cliff, but at which companies, drugs and innovations will be leading the way by then. Our consensus forecasts show a new number one leading the market with a few surprise fallers on the big pharma leader board.

All of which combines to give you a quick but insightful overview of the opportunities and challenges that face biotech, pharma and investors over the next few years. The stakes are high – and so is that cliff edge.



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The patent winter is coming

BY AMY BROWN AND EDWIN ELMHIRST

Biopharma is approaching the most painful period of patent loss for at least 30 years. Is M&A an answer?



The inevitable arrival of Humira biosimilars in the US next year means that Abbvie is hurtling towards biopharma's biggest-ever patent cliff. The anti-rheumatic is expected to sell \$18.6bn this year in the country, setting a new record for sales at risk.

But a bigger storm is coming for biopharma. A swathe of blockbusters could start to lose exclusivity from 2026, including the checkpoint inhibitors Keytruda and Opdivo, and the blood thinner Eliquis. The most painful period of branded sales erosion in at least 30 years is approaching, and a couple of developers look particularly exposed.

The chart below puts the scale of the losses in a 30-year context; this shows only US sales and patent expiries, so the drop in revenues globally for these

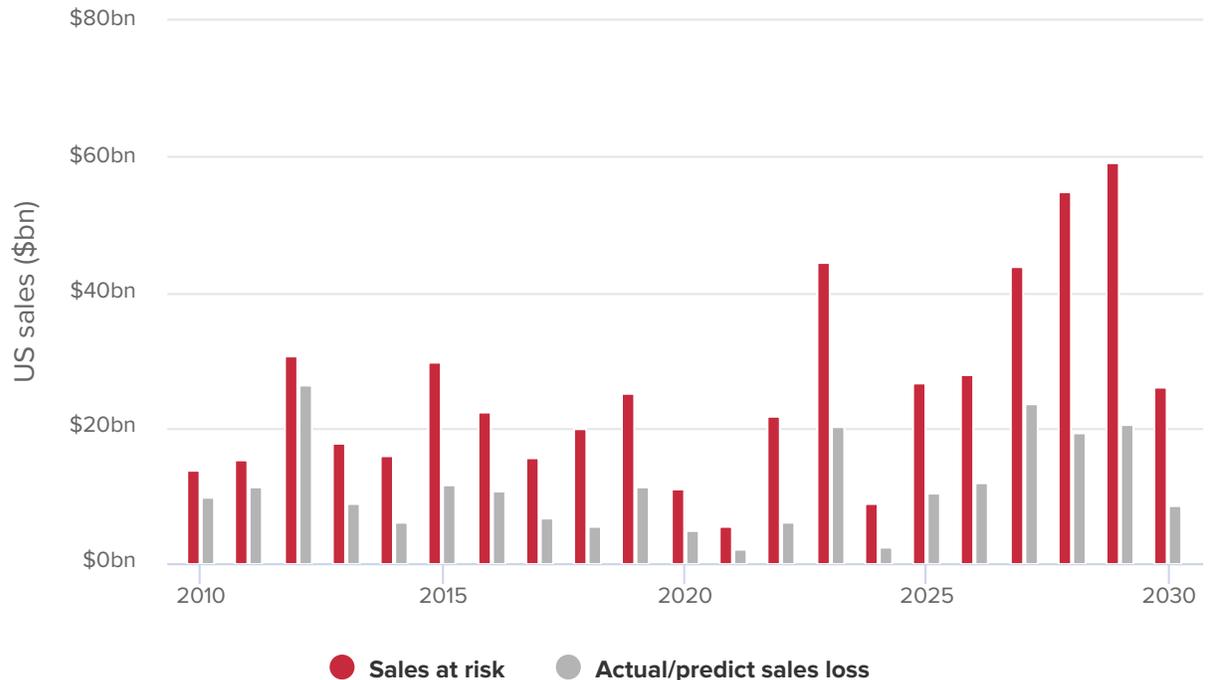
products will be much higher.

For clarity, sales at risk refers to a product's annual revenue in the year before loss of exclusivity. Actual or predicted loss is the difference between that sales at risk number and the first full year of sales post expiry, as reported by companies for historic expiries or computed by Evaluate Pharma's consensus for those still to happen.

The historic numbers in this analysis show that sales never drop as precipitously as these at-risk estimates suggest. Even small molecules, which see revenues disappear much more rapidly than biologicals, do not immediately drop to zero when copycats arrive.



The coming storm: a 30-year view of US patent expiries



Source: Evaluate

But it is clear that there is a lot at stake for biopharma in the coming years, even if the real rate of erosion is unknown.

BURNING QUESTIONS

Companies and investors are keen to know how quickly a major source of income will be lost, but in reality this is very hard to estimate, particularly for biologics. The burning question on Abbvie's recent earnings call was what Humira might sell in 2023, but opinions range widely, despite the close scrutiny.

The sellside is pencilling in US sales of \$10.9bn in 2023, according to Evaluate Pharma, while the company has issued guidance in the \$8.4-12.0bn range.

Another variable for expiries further out is the exact date of patent loss. Many of the products highlighted here are still being litigated, so could end up with longer life spans.

But these products will fall eventually. And what do large developers do when confronted with a revenue gap? They make acquisitions. This approaching wave of expiries is already being cited by those keen to see an uptick in M&A, and in many ways the need to replace sales provides a more convincing motivation for dealmaking than tumbling biotech valuations.

All of those named below will be feeling the pressure, in particular Bristol Myers Squibb and Abbvie, which appear more than once in the top 10. The likes of Merck & Co and Regeneron, meanwhile, face the loss of products that dominate their revenue streams.

The impending fall of these mega-blockbusters will be music to the ears of those advocating lower drug costs, of course. But developers will not give up without a fight, and it will require a significant strengthening of political will to weaken industry's



ability to weave the so-called patent thickets that protect these huge franchises. For now, it feels much more likely that these patents will get extended rather than falling unexpectedly.

Coming of age: the blockbusters approaching expiry		
Drug - manufacturer	Sales at risk (% of total for year)	Estimated US patent loss
Humira - Abbvie	\$18.6 (42%)	2023
Keytruda - Merck & Co	\$15.3bn (28%)	2028
Revlimid - Bristol Myers Squibb	\$8.7bn (40%)	2022
Opdivo - Bristol Myers Squibb	\$7.2bn (13%)	2028
Darzalex - J&J/Genmab	\$6.8bn (12%)	2029
Stelara - J&J	\$6.5bn (15%)	2023
Eylea - Regeneron	\$6.2bn (14%)	2023
Ocrevus - Roche	\$5.7bn (10%)	2029
Eliquis - Bristol Myers Squibb	\$4.9bn (18%)	2026
Trulicity - Lilly	\$4.3bn (8%)	2028
Imbruvica - Abbvie	\$4.2bn (10%)	2027

Note: sales at risk is annual US sales in the year before patent expiry.

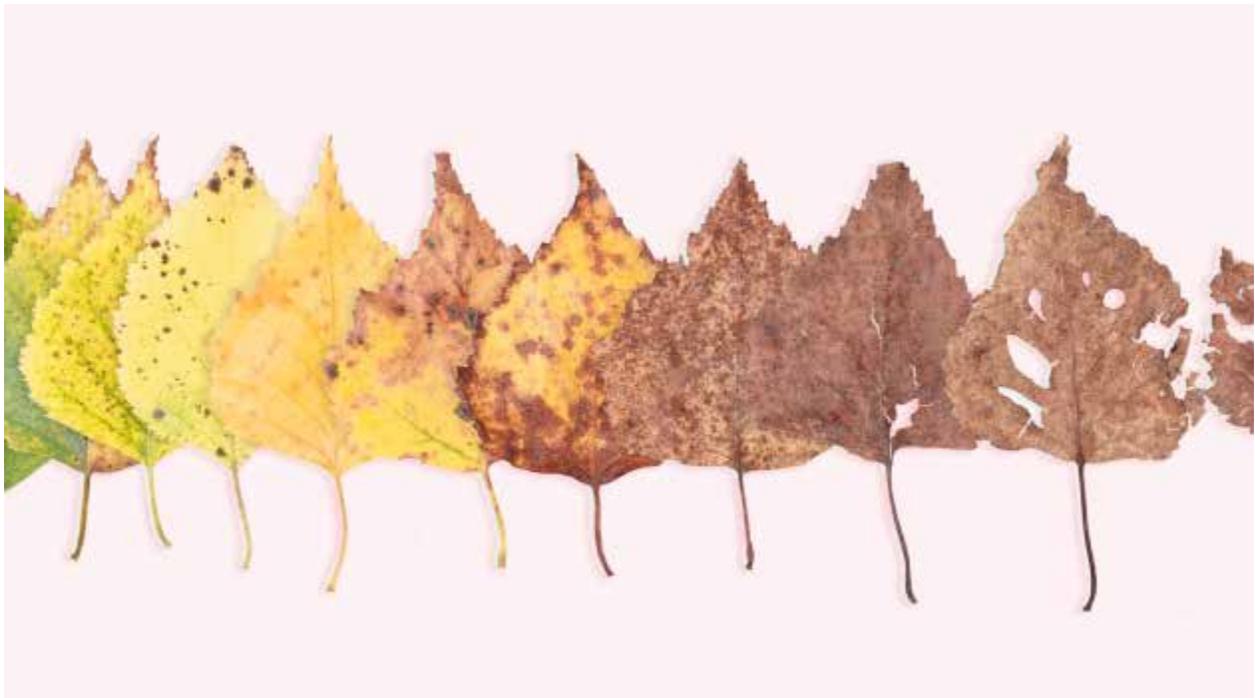
Source: Evaluate Pharma.



Bristol needs to get fresh

BY MADELEINE ARMSTRONG AND EDWIN ELMHIRST

Move over Amgen – Bristol Myers Squibb now looks like the big biopharma group most in need of revitalisation.



What was once fresh can soon become stale. This is universally true in biopharma, and at present Bristol Myers Squibb is the prime example of a group that has so far failed to find new blood to replace its ageing blockbusters.

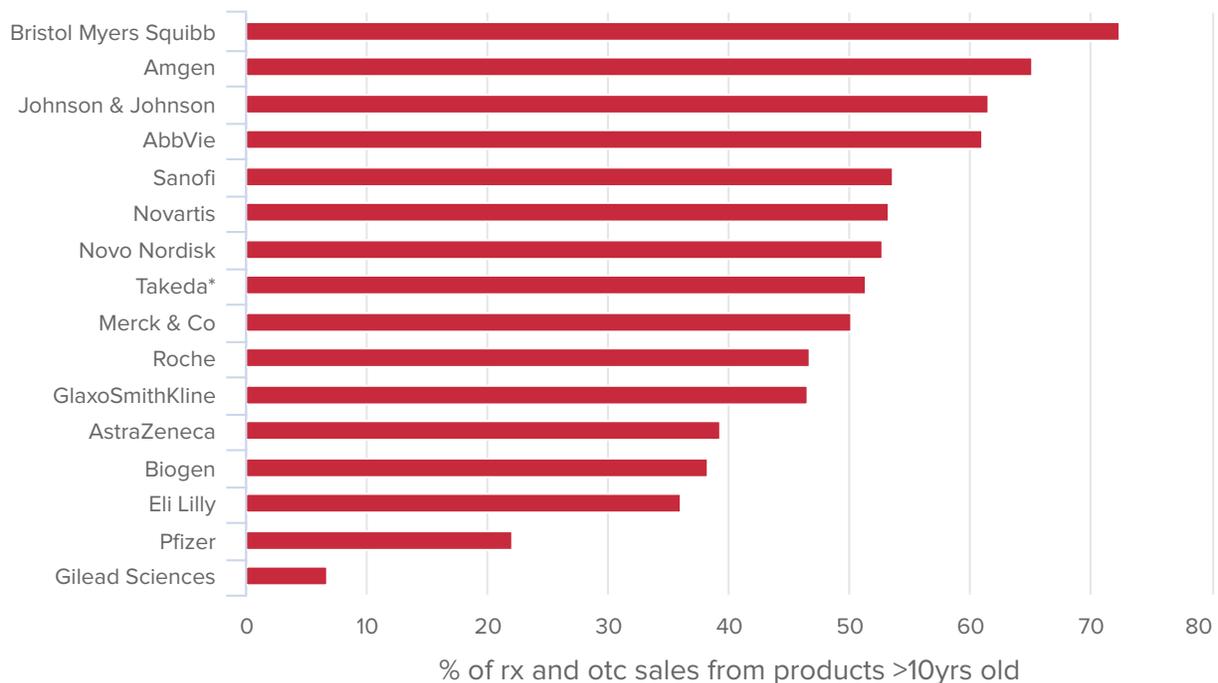
Evaluate Vantage's latest analysis of the freshness index, which looks at the proportion of a company's drug sales that come from products more than 10

years old, puts Bristol at the top of this list based on 2021 revenues. And the group's portfolio could soon look even more geriatric: these numbers do not include the PD-1 inhibitor Opdivo, which turns 10 in 2024.

The anticoagulant Eliquis reached this milestone last year, along with the CTLA4 inhibitor Yervoy.



Freshness index 2021



*Evaluate estimate

Source: Evaluate

The group's efforts to bring in fresh talent have not been a resounding success: witness the partnership with Nektar, [which Bristol finally walked away from last month](#). Bristol's current big hopes are the rare cardiovascular disease project Camzyos – gained via the \$13bn acquisition of Myokardia – and the Tyk2 inhibitor deucravacitinib. Both assets will have their work cut out to fill Eliquis and Opdivo's shoes.

ABBVIE LOOKS (SLIGHTLY) FRESHER

In previous years, Amgen and Abbvie were among the stales big biopharmas. Amgen has long been heavily reliant on its arthritis drug Enbrel, which was first approved in 1998 and, incredibly, is not set to go off patent in the [US until 2029](#).

Enbrel sales are already shrinking, though, leaving Amgen looking to the likes of Otezla – itself not too far off its 10-year anniversary – and the Kras inhibitor Lumakras, [early sales of which have disappointed](#).

Meanwhile, Abbvie has got slightly fresher but it is still booking a majority of its revenues from Humira, which is set to be challenged by biosimilars next year. Abbvie hopes to pick up the slack with the recent launches of Rinvoq and Skyrizi, which it reckons will bring in \$15bn between them by 2025.

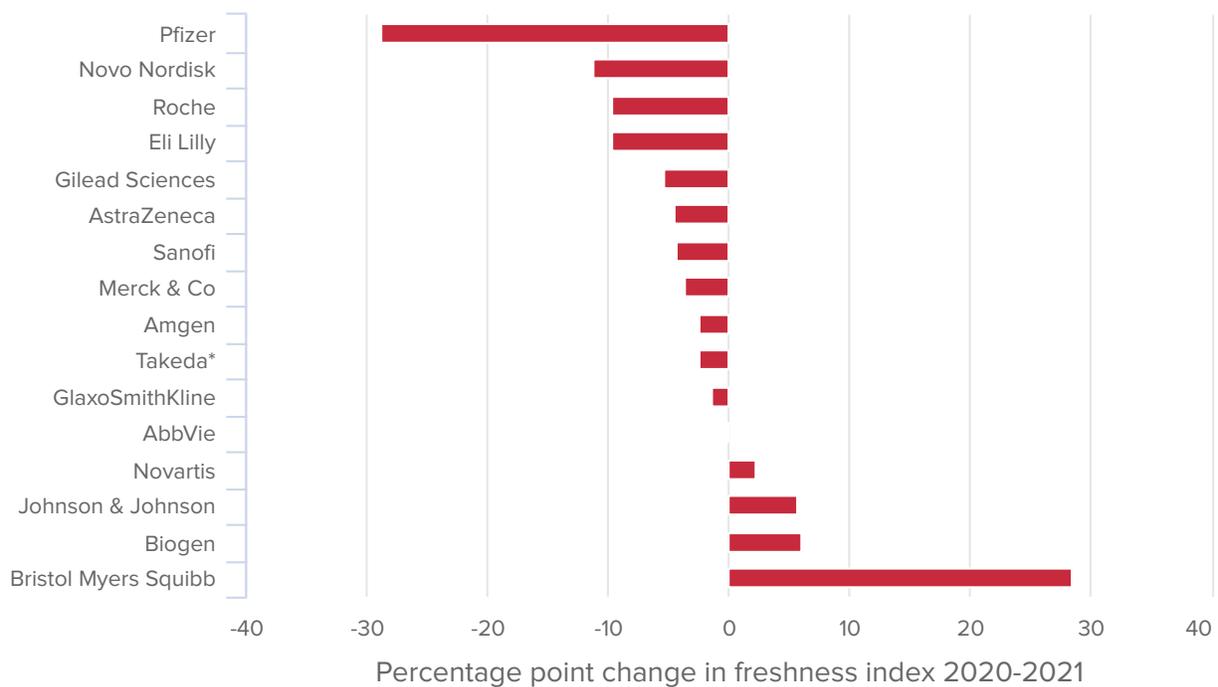
COVID BOOST

At the other end of the scale is Gilead, largely because of Biktarvy, its relatively youthful HIV triplet. But that company's plan to get into long-acting therapies, potentially the next big thing in HIV, took a knock with a [complete response letter for lenacapavir](#) following contamination concerns.

Meanwhile, Pfizer's reversal from stale to fresh was down to sales of its Biontech-partnered Covid vaccine Comirnaty. The chart below shows just what a huge swing the company experienced in 2021.



Change in freshness 2020-2021



*2021 value Evaluate estimate

Source: Evaluate

A look at current forecasts for 2022 suggests that this transformation might be short lived, with doubts growing about the longevity of Covid revenues for all companies involved.

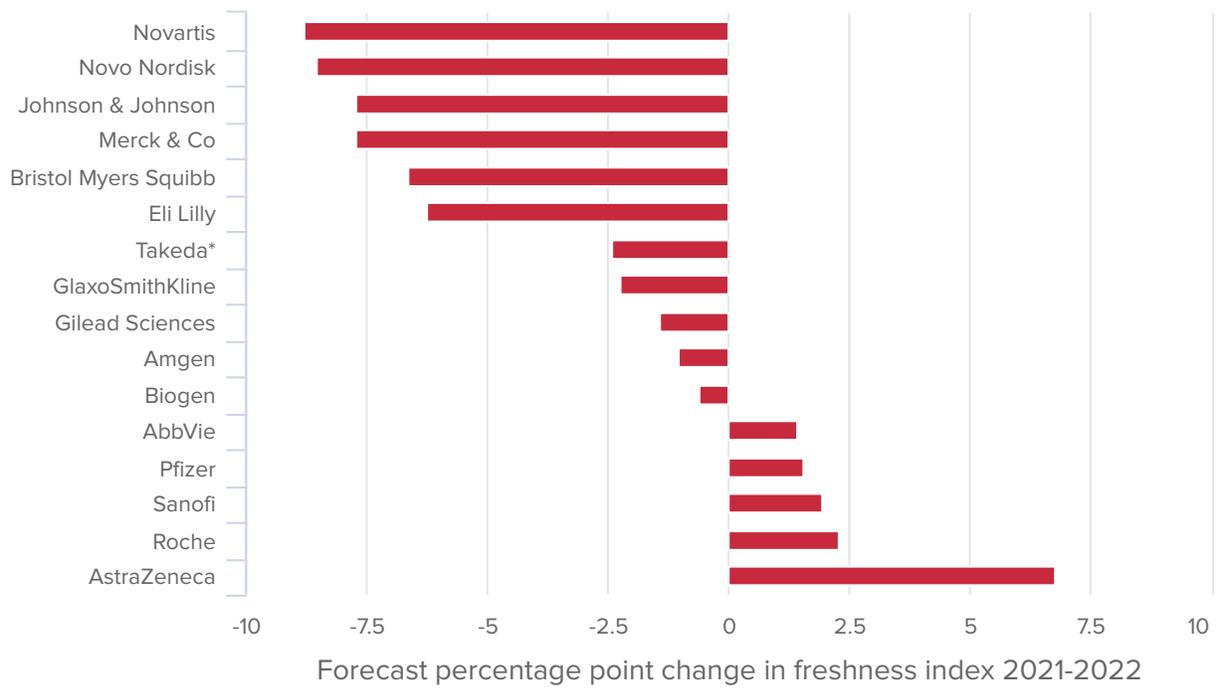
Other groups that look set to get staler include Roche and Astrazeneca, suggesting that even successful R&D teams cannot rest on their laurels. At least both groups are still expected to book less than half of their sales from ageing products this year, showing that everything is relative.

Merck & Co, meanwhile, looks fresh enough for now but will soon be facing a similar issue to Bristol: its mega-blockbuster Keytruda will have its 10th birthday in 2024.

Of course, freshness is not everything: old drugs can be highly profitable. But biopharma execs will want to soften the biggest impacts from patent cliffs, usually via deals. Bristol currently looks like the company under the most pressure to fill this void.



Predicted change in freshness 2021-2022



*2021 value Evaluate estimate

Source: Evaluate



Abbvie to become the biggest of pharmas in 2028

BY LISA URQUHART AND EDWIN ELMHIRST

New extended consensus forecasts from Evaluate Pharma show Roche edged out of first place by Abbvie as new blood replaces Humira.



Despite facing one of the steepest [patent cliffs in the industry's history](#) Abbvie is expected to rise up the rankings ahead of Roche to become the biggest pharma company by prescription sales in 2028, according to extended consensus forecasts from Evaluate Pharma.

Abbvie's gain contrasts with the slide down the rankings by Pfizer, Novartis and Bristol Myers Squibb, the last of which faces significant patent erosion of its own. Three of Bristol's blockbusters – Revlimid, Eliquis and Opdivo – could see cheaper copycats

arrive over the next six years.

ABBVIE'S TAIL WAGS THE DOG

While Abbvie will no longer enjoy \$20bn-plus sales a year from Humira after 2023, a fairly long tail of demand is expected for the anti-TNF rheumatoid arthritis drug. Those sales, plus growing contributions from the Jak inhibitor Rinvoq, psoriasis product Skyrizi and cancer drug Venclexta, are enough to create a very narrow lead over second-place rival Roche.



These numbers are of course based on estimates made by sellside analysts and collated by Evaluate Pharma. In Abbvie's case, maintaining this forecast

advantage will depend on the company's success in rolling out Rinvoq and Skyrizi in new indications.

Changing of the guard: the world's biggest drug makers in 2028		
Company	2028e Rx sales (\$bn)	2021-28 rank change
Abbvie	65.7	+1
Roche	65.0	+3
Johnson & Johnson	62.3	+1
Merck & Co	59.7	+3
Pfizer	57.1	-4
Novartis	55.2	-3
Astrazeneca	54.5	+2
Sanofi	50.8	0
Bristol Myers Squibb	44.3	-3
GSK	44.0	0

Source: Evaluate Pharma.

Given the paper-thin margin between Roche and Abbvie it is easy to see how their positions might switch, for example if biosimilar erosion of Humira is more severe than the market is currently forecasting. Conversely, some of Roche's longer-term success is based on the potential of [the novel immuno-oncology mechanism Tigit blockade, in which the company is heavily invested](#).

Recent events makes those future sales highly questionable. Tiragolumab [has now failed](#) in two of the 10 studies that make up the Skyscraper programme, casting doubt on the Tigit mechanism. It is just as well that Roche's multiple sclerosis drug Ocrevus, PD-L1 MAb Tecentriq and haemophilia product Hemlibra are forecast to grow strongly over the next six years.

Rapidly expanding oncology franchises are behind Merck & Co and Astrazenca's rise up the rankings. Annual sales of Astra's Tagrisso and Lynparza are expected to double between 2021 and 2028, while Merck's Keytruda is forecast to rake in \$30bn in 2028, [making it the biggest-selling drug of that year](#).

SLOW TO MIDDLING

Troubles with pipeline expansion have relegated GSK and Sanofi the lower half of the table. Neither managed to capitalise on the Covid vaccine boom and both are struggling to find new growth drivers.

In fact given GSK's current form the UK developer could see its position in the top 10 threatened by Lilly, the 11th big pharma company, which is currently projected to bring in \$38.9bn in prescription drug sales in 2028. The recently approved Mounjaro has delivered impressive results in both diabetes and obesity, and if the drug lives up to [the more optimistic expectations](#) Lilly could be catapulted up the rankings.

ON THE SLIDE

One big surprise is just how far down the list Pfizer sits; its name has historically been found among the top three. This shows that the sales bonanza Pfizer has enjoyed during the pandemic is expected to be fleeting, though it is also true that the spin-out of many older products into Viatrix in late 2020 shaved the company's top line.



Pfizer is fully expected to continue putting its Covid billions to work in the form of acquisitions and licensing deals. Novartis, flush from [the sale of its stake in Roche](#) and struggling to reinvigorate its revenues, might pursue this strategy too.

Bristol Myers Squibb's decline through the rankings seems inevitable, however. The company boasts one of the oldest pipelines in this list, with 72% of its 2021 revenues coming from [products that are more than 10 years old](#), and with age come patent expiries. So far the group's efforts to inject new blood into its pipeline have been less than successful.



Move over Humira, it's the cancer antibodies' turn at the top

BY EDWIN ELMHIRST AND AMY BROWN

Humira is set to lose its crown as the world's biggest-selling drug next year, ceding its position to Merck's anti-PD-1 MAb Keytruda.

With Bristol's similarly acting Opdivo in second place out to 2028, the top of the table will be dominated by these two checkpoint inhibitors until [their likely patent expiries at the end of the decade](#). The major Covid products – the vaccines Comirnaty and Spikevax and antiviral Paxlovid – sit among the top five for this year, but their reign is assumed to be brief. This newly extended view of consensus forecasts from Evaluate Pharma reveals therapies from a couple of non-big pharma names – Gilead and Vertex – in the top 10 in 2028. The cystic fibrosis

drug Trikafta is exactly the sort of product that many large developers would love to own, but Vertex's \$70bn valuation likely precludes an acquisition. Meanwhile the forecast success of Biktarvy in HIV shows that Gilead is still very good at developing antiviral drugs, despite its recent struggles in oncology. Skyrizi's predicted vault up the rankings helps explain why Abbvie is expected to become the biggest drug developer in 2028; Rinvoq sits just outside this table at number 11 ([Abbvie to become the biggest of pharmas in 2028](#), May 30, 2022).

Biggest selling drugs, 2028 reboot		
Drug (manufacturers)	2028 global sales (\$bn)	2021-28 rank change
Keytruda (Merck & Co)	30.9	+4
Opdivo (Bristol Myers Squibb/Ono)	15.7	+9
Dupixent (Sanofi/Regeneron*)	14.8	+12
Darzalex (J&J/Genmab*)	13.9	+12
Ozempic (Novo Nordisk)	12.0	+19
Biktarvy (Gilead)	11.6	+3
Skyrizi (Abbvie)	11.5	+46
Imbruvica (J&J/Abbvie)	10.1	+5
Trikafta (Vertex)	9.5	+15
Tagrisso (Astrazeneca)	9.4	+15

Note: sales include those also booked by global partners, where relevant; *partner books royalties.

Source: Evaluate Pharma.

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