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# The Next Big Patent Cliff Is Coming, And Time Is Running Out To Pad The Fall

by Jessica Merrill

Blockbusters like Stelara, Eliquis, Prolia and Ibrance are poised to lose US exclusivity over the next five years; pressure is mounting for industry to replenish the portfolio with the next high-growth brands.

The pharmaceutical industry is in the midst of a steady period of moderate growth, but financial pressure will build toward the middle part of the decade as many key blockbuster brands face loss of exclusivity (LOE). The window for launching new growth drivers to fill the expected revenue gap is narrowing.

Investors are growing wary about the period from 2025-2030, when many big brands will lose market exclusivity in the US and Europe and face generic or biosimilar competition for the first time. Big pharma companies generally appear to be on their back foot for now, without the pipeline to make up the deficit, which may put more pressure on drug makers to rely on business development as the tool to fill it.

Industry watchers forecast that from 2022-2030, the industry's top drug companies will lose more than $200bn.

"It's a huge amount," ZS Associates principal Maria Whitman said in an interview. "Clearly, the pipelines are not prepared for this."

The top 10 pharmaceutical manufacturers combined have more than 46% of their revenues at risk during that time frame, and five companies have more than 50% of their revenues at risk, according to ZS Associates.

Factoring in analyst consensus estimates for projected pipeline drugs in 2022-2030 hardly moves the needle. "They are really only reducing the total revenue loss by a couple of percentage points,

from 46% to 44%, and you still have three companies losing over 50% of their revenues," Whitman said.

However, drug makers can sustain the lifespan of a brand through lifecycle-management strategies, and biologics typically experience less erosion from biosimilars than small molecules do from generics. Business development activity could also offset LOEs if drug makers are able to bring in new assets that can reach the market in the second half of the decade.

LOEs will affect most big biopharma companies, but some will feel more pressure than others. *Pfizer Inc.*, *Novartis AG*, *Merck & Co., Inc.*, *Eli Lilly and Company* and *Bristol Myers Squibb Company* are poised to face steep patent cliffs. *Roche Holding AG*, which already cycled through big LOEs in 2020 with biosimilar competition to three blockbuster-sized drugs, now appears well-positioned for the foreseeable future, after the anticipated launch of Lucentis (ranibizumab) biosimilars in the US later this year. *Sanofi* is also largely protected from losses, with its core growth driver Dupixent (dupilumab) protected in the US until 2031 with a possible patent term extension.

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"Approximately one-third of large biopharma's 2025 estimated revenue will be impacted by LOE revenue erosion between 2024 and 2030," SVB Leerink analyst Geoff Porges forecast in a December 2021 research note. SBV Leerink analyzed 19 US and European biopharma companies that have marketed products facing loss of exclusivity between 2021 and 2029.

"Eighty-four percent of the companies have at least 20% of expected 2025 estimated total revenues impacted or at risk of LOE erosion by 2030 and 58% have at least 30% of 2025 estimated total revenue at risk or impacted by LOEs," Porges said. His analysis showed that Bristol, *Amgen, Inc.* and Pfizer will face the biggest impact from LOE erosion with 47%, 29% and 28% of 2025 estimated total revenue likely to be eroded by 2030.

"Companies facing the biggest impact from LOE erosion typically have several prominent products that not only make up a significant portion of expected 2025 revenue, but also face relatively quick erosion of those franchises because of competitive or commercial circumstances," he added.

## From Humira To Keytruda

*AbbVie Inc.* will usher in the start of the next big patent cliff, with the loss of the mega-seller Humira (adalimumab) in the US beginning in 2023. Biosimilars to Humira launched in Europe in 2019, which has already frayed at the brand's sales, though Europe already was a substantially

smaller market for Humira revenues compared to the US.

*Johnson & Johnson* will have to navigate a challenging period around the same time, with the company's top-selling drug Stelara (ustekinumab) expected to lose patent protection in the US in 2023, followed by Simponi (golimumab) in 2024.

Later in the decade, Pfizer is headed over the cliff with the potential US loss of the rheumatoid arthritis drug Xeljanz (tofacitinib) in 2025, the blood thinner Eliquis (apixaban) in 2026, and the cancer drugs Ibrance (palbociclib) and Xtandi (enzalutamide) in 2027.

Pfizer has been trying to prepare for this period of LOEs, vowing to be an active deal maker to replenish the portfolio with late-stage drugs. Earlier this year, CEO Albert Bourla said Pfizer is aiming to sign deals that will add $25bn of risk-adjusted revenues to the top line by 2030, and it has significant fire power to get deals done from the success of its COVID-19 vaccine and therapeutic.  Pfizer recently bought one late-stage asset, and potential revenue patch, with the $6.7bn acquisition of *Arena Pharmaceuticals, Inc.*, which could deliver the selective sphingosine 1-phosphate receptor modulator etrasimod for ulcerative colitis and other immuno-inflammatory conditions to the market soon. (Also see "*Pfizer Buys Arena For $6.7bn In Bid To Diversify In Inflammation & Immunology*" - Scrip, 13 Dec, 2021.)

Bristol markets Eliquis with Pfizer but will experience other losses as well. This year, it is already under pressure, facing the loss of Revlimid (lenalidomide) in Europe and Japan and on a volume-limited basis in the US. Its first immune checkpoint inhibitor, Yervoy (ipilimumab), could lose exclusivity in 2025 followed by Opdivo (nivolumab) in 2028. The company has been launching a steady stream of new drugs that it hopes will grow into bigger brands later in the decade to fill the gap as its current blockbusters mature. (Also see "*Bristol's Growth Plan Faces First Test In 2022*" - Scrip, 4 Feb, 2022.)

At Merck, meanwhile, the entire plotline is pivoting on its checkpoint inhibitor Keytruda (pembrolizumab) and how the company will reduce its dependence on the big anchor brand before it faces LOE in 2028. Recent pipeline setbacks in chronic cough and HIV have only put more pressure on the company to show investors how it can successfully prepare for the loss. (Also see "*Merck's Gefapixant CRL Dashes Hopes For Another Near-Term Growth Driver*" - Scrip, 24 Jan, 2022.)

## Not All LOEs Are The Same

Estimating the timeline of an LOE is not an exact science, and the expected life of a brand drug can be unexpectedly lengthened or shortened based on the outcome of patent litigation, Patent & Trademark Office patent reviews and delayed biosimilar or generic launches.

Oral small molecule drugs typically erode quickly following a generic entry while biologic drugs

usually retain a greater amount of market share post biosimilar entry. That's partly because biosimilars are harder to make and there are fewer competitors and because the US market at least is still relatively new compared to generics. Although there have been several successful biosimilar launches in the US, most notably in cancer, the next big patent cliff will be more heavily weighted to biologic drugs.

The launch of Humira biosimilars in the US next year will pose an unusual case because there are so many biosimilars expected to enter the market, and it is still unclear how competitive they will each be against such a legacy brand. (Also see "*A US Biosimilar Turning Point Approaches, With Work To Do*" - Scrip, 17 Feb, 2022.) AbbVie expects to retain a majority of the US adalimumab revenues in 2023, forecasting biosimilar erosion of around 45%. (Also see "*AbbVie Says Rinvoq Holding Up, Humira Erosion Will Continue Into 2024*" - Scrip, 2 Feb, 2022.)

While many big brands are poised to lose exclusivity over the remainder of the decade, many could have a prolonged tail and remain steady contributors to the top line, as has been Johnson & Johnson's experience with Remicade (infliximab) and Sanofi's experience with Lantus (insulin glargine).

"When we think about the scale, it is a little bit different in the erosion curves from what we saw in the 2000s and the patent cliffs we saw in prior times," Whitman said.

EY partner Arda Ural also agreed. "We have seen the movie before in 2012 – now it is a different version of it, but we will start to see that similar impact," he said in an interview. That earlier wave of LOEs was also notable for the loss of blockbuster small molecule brands like Pfizer's Lipitor (atorvastatin), Lilly's Lexapro (olanzapine) and Bristol Myers Squibb's Plavix (clopidogrel). (Also see "*Bye Bye Lipitor: 2011 Presents A Big Opportunity For Generic Drugs*" - Pink Sheet, 10 Jan, 2011.)

"The monoclonal antibodies are now facing the next patent cliff and we will see that impact starting in 2023 onwards," he added.

## Replenishing The Portfolio

Big losses put more pressure on pharmaceutical companies to refill the pipeline. An analysis of the top 25 biopharma companies by EY suggests the industry could be approaching a challenging period because the portfolio replenishment rate – the ratio of incremental sales from products launched in the last five years to losses in sales from patent expirations over the same period – is expected to fall by 50% from 2020 through 2026.

In other words, more sales are at risk from upcoming patent expirations than are expected to be generated from new products. That comes even as the cost of R&D across the industry has increased. The top 25 biopharma companies have increased R&D spending as a percent of sales

from 14.4% to 17% over ten years, according to EY. (Also see "*Up, Up And Away: A Comparison Of Industry R&D Spend Now Versus 10 Years Ago*" - Scrip, 17 Mar, 2022.)

That extra research spending is showing results when it comes to innovation, but new drug launches generally tend to address smaller indications, take longer to ramp up and don't always translate into big commercial winners. Pipeline growth in 2021 was nearly twice that for the previous year, pushing the number of products under active development over 20,000 for the first time, according to the *Pharma R&D Annual Review 2022* from Pharmaprojects (part of Informa Intelligence). (Also see "*COVID-19 Factor Wanes But Pharma's R&D Pipeline Hits Record Heights*" - Scrip, 31 Mar, 2022.)

The expectation is that big pharma will rely heavily on M&A and business development to fill the deficit, especially because drug makers have the cash they need to do deals. The challenge remains finding the right assets, at a value investors won't consider overpriced. (Also see "*EY: Don't Expect Mega-Mergers To Return, But 'Never Say Never'*" - Scrip, 10 Jan, 2022.)

"It comes down to each company's risk profile and the CEOs tenure and how they value their pipeline. It is very unique case by case," Ural said.

Several factors have made deal-making more challenging for big pharmaceutical manufacturers recently, including the high value for assets, the cash-rich financing environment for biotechs, an onslaught of innovation that has made due diligence overwhelming, and the fact that more emerging biopharmaceutical companies are launching drugs independently.

"Big pharma, they are trying to figure out how do we actually value and assert risk assessment onto potential valuations," Whitman said. "I do think that big pharma is at a moment where they have to get more sophisticated in selecting and choosing."

## On The Positive Side

JP Morgan analyst Chris Schott remains optimistic, however. He said after reviewing company performance following historical big patent losses, he is reassured about the industry's financial prospects as it cycles through this period.

"Our analysis suggests that investor concerns around major patent expirations are likely overdone based on several factors," Schott said. Historically, stocks experienced modest underperformance into LOEs followed by outperformance coming out of the events and companies on average saw multiple expansion from 9-10 times earnings per share pre LOE to 17-19 times post LOE, he added.

"With six to seven years until core LOE events, we see a clear opportunity for both EPS upside and out year multiple expansion as the street gets more clarity on post LOE growth trends via

both internal pipeline development and external business development," he said.