



# Pharma Drivers 3: Blowin' in the wind

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BY AMY BROWN, EDWIN ELMHIRST, ELIZABETH CAIRNS & JACOB PLIETH | NOVEMBER 2022

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# Introduction

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There are some things in life you want to be consistent and predictable. Interest rates. Train timetables. The weather. And if you work in the pharma industry, the FDA. However, like leaves on the line or unexpected hail storms, there are factors in the regulatory environment that mean it is not always as easy to anticipate as one might hope.

Taking a new drug or medical device to market is a long, unpredictable process at the best of times. Clearing that final hurdle of regulatory approval remains one of the biggest challenges. In this eBook we look at some of the key regulatory issues, including the impact of Covid on approvals and what green lights might still emerge in 2022.

A late flurry at the FDA should mean that this year ends up less of a damp squib than the first half of the year suggested. However, 2022 will definitely be a slow year the US agency. For an industry still reeling from a brutal post-Covid market correction, an increasingly cautious FDA is the opposite of what is needed.

More approvals do not necessarily mean more revenues, of course, as you will also see in our review of quality versus quantity, included in this ebook.

Encouragingly, a number of big decisions have been delayed into 2023 rather than rejected outright. And our analysis of average regulatory timelines conducted earlier this year found no evidence of a pull-back throughout the pandemic. Whether that fallout has yet to be felt will be determined when we look back at the numbers in a few months' time.

The accelerated approval pathway is another focus of this ebook. Developers and the regulator have taken flak for foot-dragging on conversions. And while our analysis shows signs of improvement, this continues to be hot topic, and there is mounting evidence that the FDA is taking a stricter line.

The regulatory climate can make or break a novel project and its developer. It always pays to pay attention to which way to wind seems to be blowing.



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# How Covid failed to derail the FDA

BY JACOB PLIETH AND EDWIN ELMHIRST | MARCH 25, 2022

Average US review times match absolute approval numbers in remaining unaffected by the Covid pandemic.



Despite Covid-related delays to some FDA approvals – those of Jemperli and Breyanzi being two cases in point – average US review times showed no signs of dipping either during the pandemic or in the early months of the world’s subsequent opening up.

It was already known that the absolute number of novel US drugs approved actually [picked up slightly during the pandemic](#), and now an analysis of Evaluate Pharma data suggests no slippage in the time taken to review these, either on a standard or priority basis. The data will be of interest now that the FDA faces a challenge to its accelerated approval pathway.

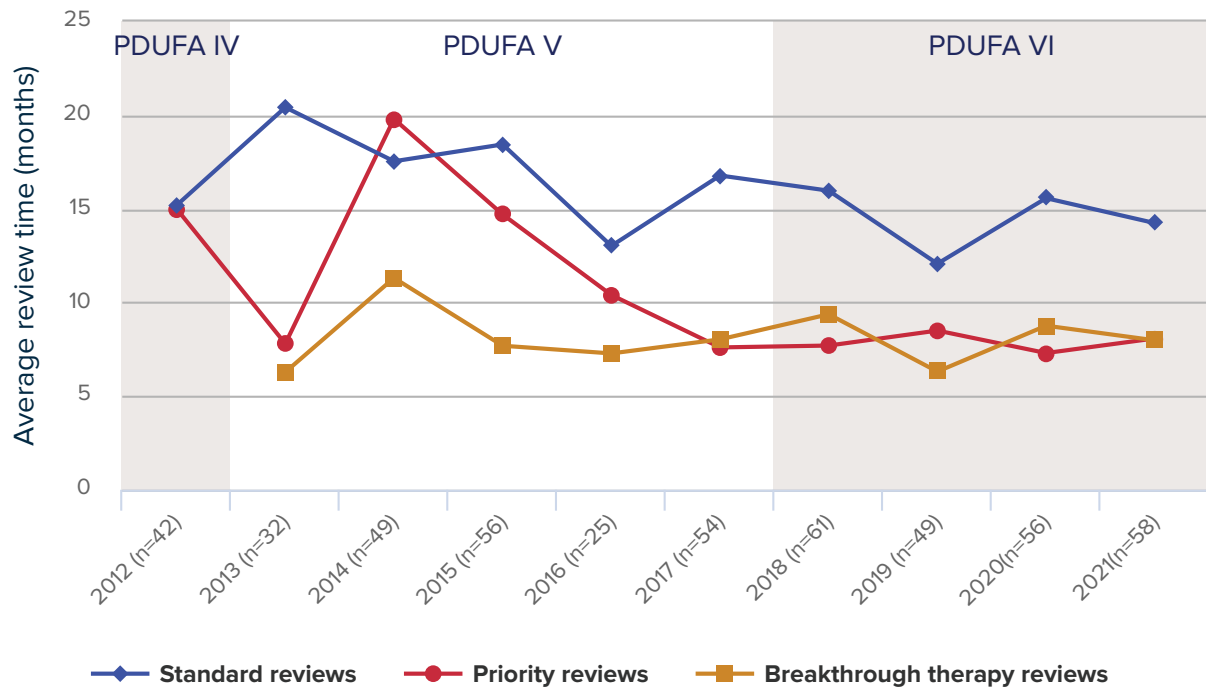
That challenge comes in the form of the [Accelerated Approval Integrity Act, unveiled earlier this month](#),

as questions persist over the FDA’s approval of questionable drugs like Aduhelm and Exondys 51. The measure seeks to put more pressure on the FDA to pull conditionally approved therapeutics whose makers do not swiftly confirm their benefit.

For now, however, the trend is clear: the 58 novel drugs greenlit last year by the FDA’s CDER and CBER were approved in an average review time of just under 10 months. This speed represents a steady upward trend over the past 10 years or so; in 2014, for instance, the average FDA review time was 17 months, according to Evaluate Pharma data. Though Covid was clearly a factor in 2020-21 the numbers suggest that, by and large, the FDA worked around the various problems it presented.



## CDER+CBER average approval times



Source: Evaluate

The chart above is complicated slightly by Pfizer/ Biontech's Covid vaccine Comirnaty, which was approved formally last August, some eight months after first becoming available under an emergency use authorisation. The numbers do not include Moderna's Spikevax, which was only approved two months ago, though like Comirnaty it has been available under EUA since December 2020.

Overall, as has already been reported, absolute US FDA approval numbers rose last year to 58 novel drugs, up from 49 in 2019, but down slightly on the year before that. Interestingly, despite variability in the number of drugs approved, the total sales these are expected to bring in is holding fairly steady.

Thus fifth-year US revenue, which for last year's crop of approvals means Evaluate Pharma sellside consensus for 2026 sales, stands at \$24bn for drugs approved in 2021, versus \$19bn and \$30bn for those greenlit in 2020 and 2019 respectively.

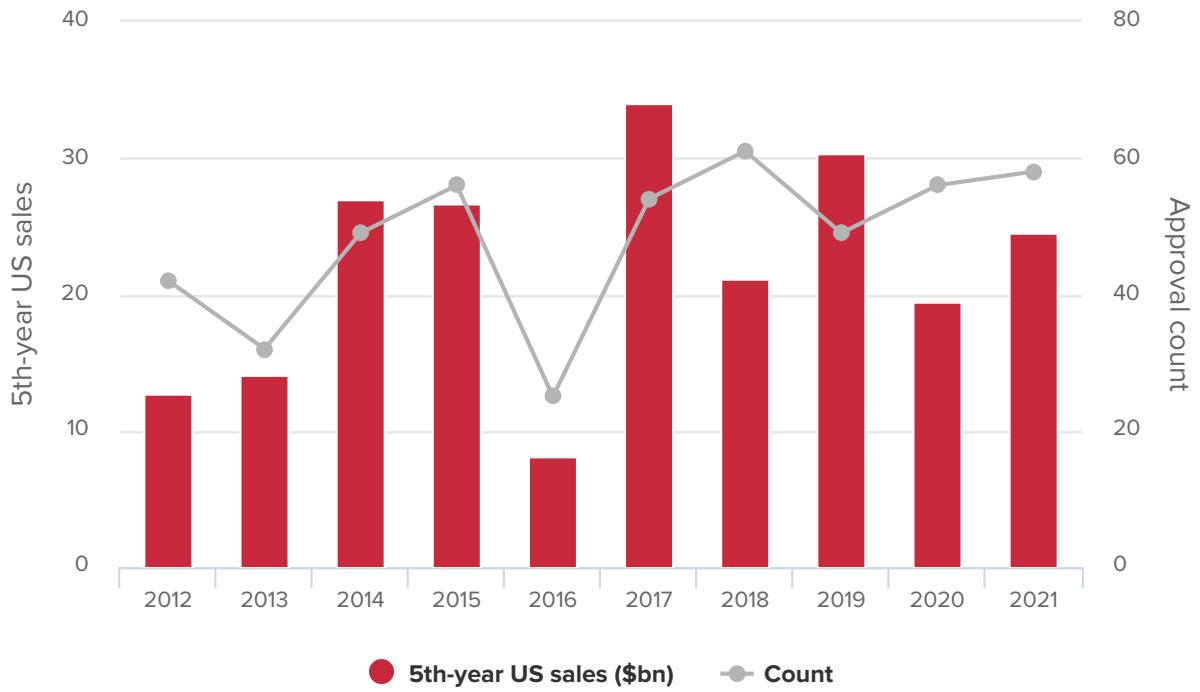
Still, there are a few caveats here, most notably the absence of significant contributions from Covid vaccines. Spikevax and Comirnaty alike are notable for being mega blockbusters – with combined global sales of \$106bn in 2021-22 – but by 2026 their revenues are expected to fall to the single-digit billions of dollars.

Other drugs approved last year expected to become 2026 blockbusters include Novartis's Leqvio, Argenx's Vyvgart, Bristol/Bluebird's Abecma and Amgen's Lumakras; the last two are hardly shoo-ins for billion-dollar sales generators.

Then there is Biogen's Alzheimer's drug Aduhelm, controversially approved on an accelerated basis last year. Aduhelm consensus sales forecasts have fluctuated wildly, along with its [prospects for broad US reimbursement](#), and for simplicity they have been omitted from this analysis.



## FDA novel approvals



Source: Evaluate



# Is biopharma getting better at accelerated approval conversions?

BY AMY BROWN AND EDWIN ELMHIRST | APRIL 14, 2022

Amid ongoing pressure to reform the FDA's fast-track pathway, signs emerge that the criticism is being heard.

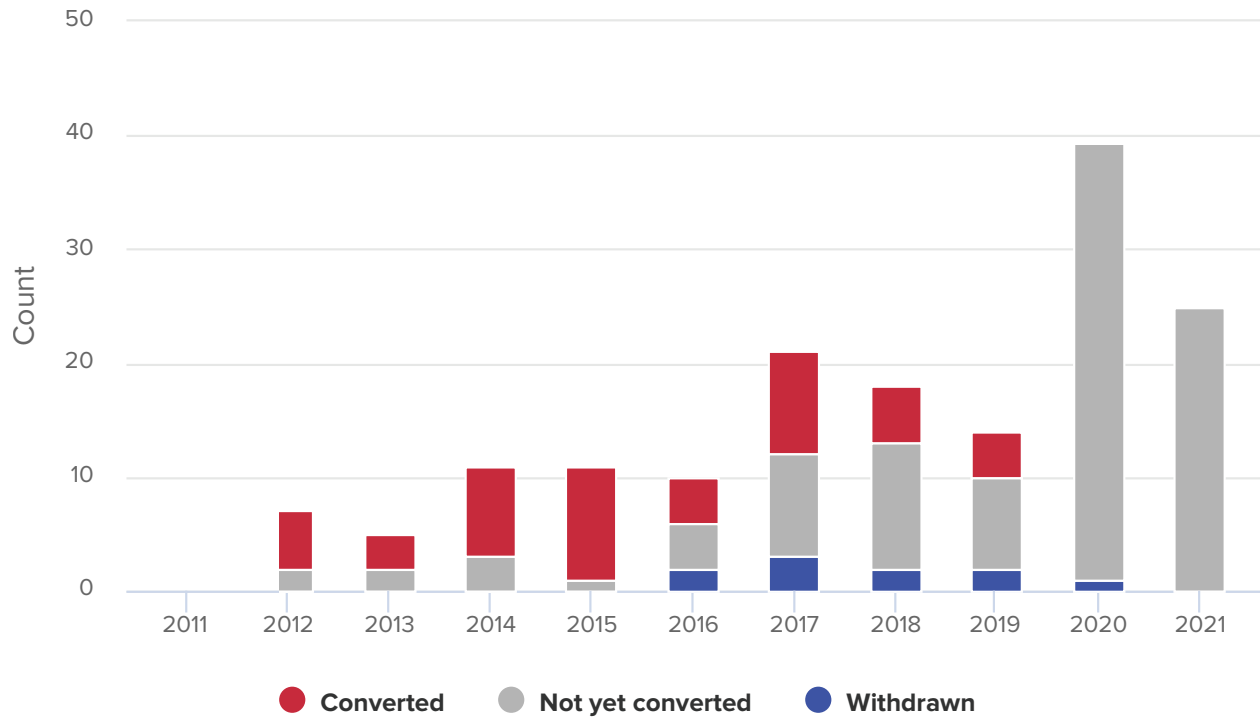


The FDA's accelerated approval pathway has been attracting mounting criticism, but change is on the way. [Bills seeking to reform the process](#) have been introduced as part of this year's reauthorization of the biopharma user fee bill, while the agency's new commissioner, Robert Califf, has made no secret of his desire to rectify weaknesses.

The latest stats on this area suggest that recent criticism as well as longer-standing admonitions have not fallen on deaf ears. More CDER accelerated approvals were converted to full approval last year than in any other, and a trend for faster conversions seems to be emerging.



## Accelerated approvals granted



Source: FDA

It is also notable that the conversions that happened over the past five and 10 years took a median of 3.1 years. This is much quicker than the five-year “expiration date” that has been proposed as part of one of the reform-seeking bills.

It could be argued that even three years is too long, although some drug trials will always take longer than others. Perhaps a time limit on accelerated approval is too blunt an instrument; still, it might discourage some of the more extreme cases of foot-dragging by sponsors in terms of running confirmatory trials.

It is the more egregious examples that have given this pathway a bad name, of course, and these are in the minority.

Aduhelm and Exondys 51 are frequently held up as cases in point. Biogen will start screening patients for the confirmatory study of the Alzheimer’s drug in May, almost a year after winning accelerated

approval, while the [confirmatory trial](#) of Sarepta’s Duchenne muscular dystrophy treatment is unlikely to yield data until 2026, 10 years after this drug’s green light.

Recent moves from the FDA suggest that the regulator’s patience is wearing thin. The agency seems to have decided that developers of PI3K inhibitors have been taking too long to prove their worth, for example, last month [denying MEI’s zandelisib access](#) to the accelerated approval pathway.

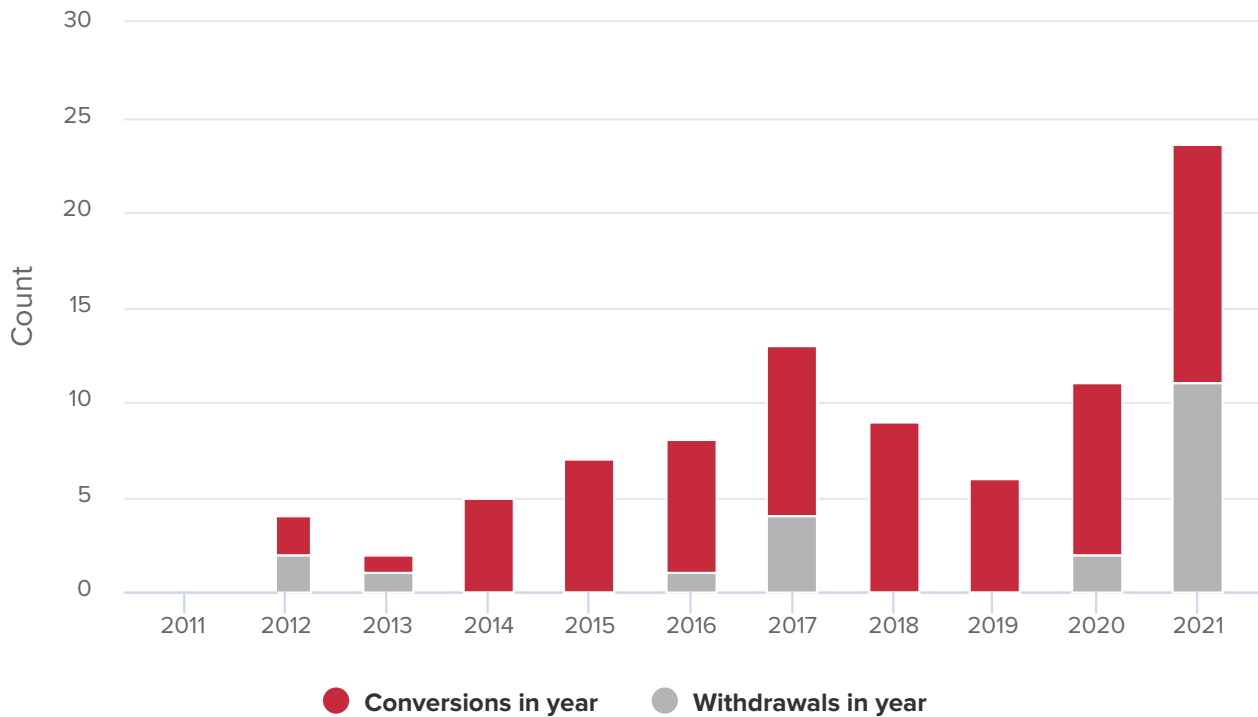
Another sign of a tightening up was last year’s [panel looking at “dangling” accelerated approvals](#) for various checkpoint inhibitors.

It is worth noting that 2020 was boosted by 16 accelerated applications by Merck & Co for alternative Keytruda dosing regimens. Even removing these, the 29 accelerated approvals represents a record high.





## Accelerated approval conversions and withdrawals



\*2021 value Evaluate estimate

Source: FDA

The chart above shows that a record number of conversions happened last year. This analysis, which considers CDER approvals only, is certainly encouraging, although a more sobering statistic is the number of drugs whose efficacy still needs confirming.

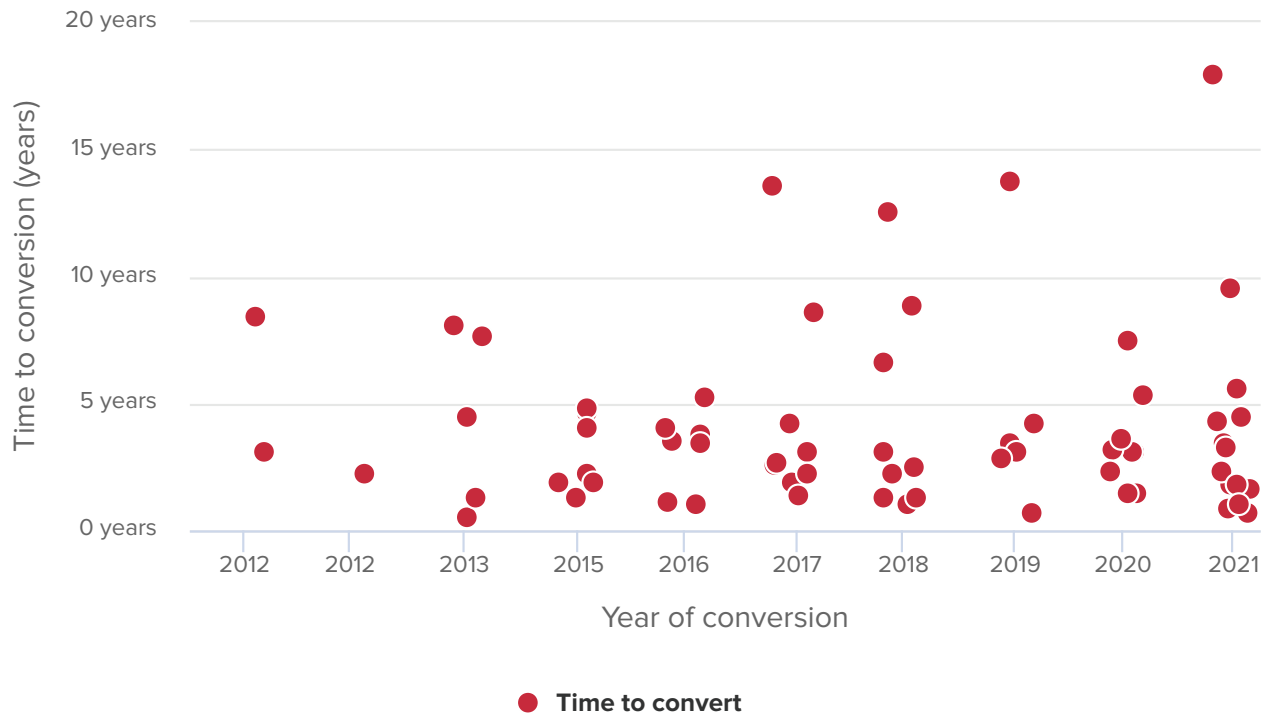
Of the 167 accelerated approvals granted in the past 10 years almost two thirds remain “dangling”. Meanwhile, the jump in withdrawals last year was largely a result of the FDA’s checkpoint inhibitor panel, which ultimately led to six of 2021’s exits.

The final chart here suggests that conversions are getting faster. Each dot is a conversion, showing the year full approval was granted and the time that this took to achieve. More recent years do seem to contain a higher density of faster approvals.

Pressure to improve on these statistics is only going to grow in the coming years, particularly if the use of the pathway continues to expand. Few would argue against more concerted efforts to purge the bad apples.



## Time to convert



Source: FDA

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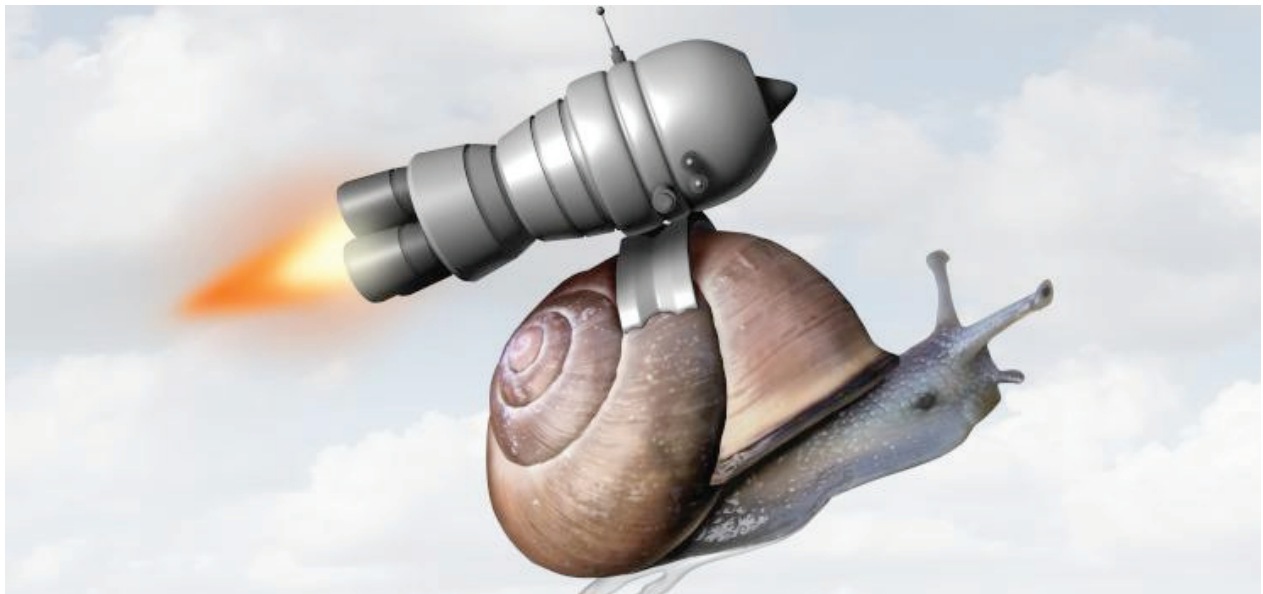
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# Brace for an end-of-year boost to drug approvals

BY AMY BROWN AND EDWIN ELMHIRST | SEPTEMBER 02, 2022

The first half of 2022 was slow on the regulatory front, but plenty of big decisions remain, however, delays will push some into 2023.



An apparent slowdown at the FDA has biopharma fretting. With the sector struggling to beat off a bear market, the last thing downtrodden developers need are regulatory worries.

Extreme concern is probably a bit premature, at least according to Evaluate Vantage's look at what remains on the cards for 2022. Several important verdicts are due in the final months of the year, with November looking particularly busy.

But the data do point downwards. The FDA's CDER and CBER divisions greenlit 19 novel medicines in

the first half of the year, the slowest six-month period since 2019. For this analysis imaging agents and reagents are removed from the agency's official lists of new drug approvals, to construct a tally of solely therapeutic agents.

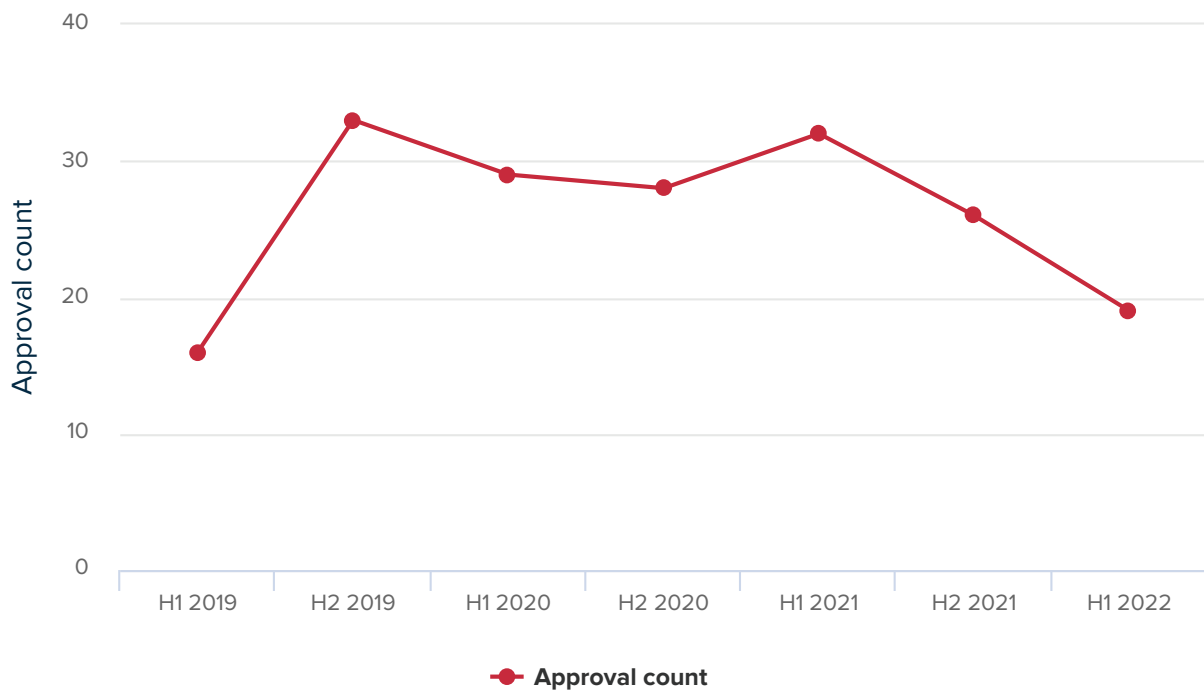
A number of reasons have been suggested for the apparent pullback. These range from staff shortages at the agency to a tightening of standards post-Aduhelm and the arrival of a new FDA commissioner. It could also just be a blip, of course, like 2016's, [when the annual tally dropped below 30](#).



Evaluate Vantage also identified 22 remaining approval decisions this year for listed developers being tracked by sellside analysts. This list will be far from exhaustive, as many companies keep regulatory progress under wraps, and there are always below-the-radar projects in the works.

If all 22 get a green light there will be 41 novel approvals in 2022 (data as of September). That would represent a slowdown on the last five years, and would also sit below the 10-year average of 48.

## CDER + CBER novel therapeutic approvals



Source: FDA and Evaluate Vantage

It is probably too early to know whether the FDA really is tightening up. Some believe that more complete response letters are being issued, but this is hard to track because the agency leaves disclosure up to developers. Ongoing pandemic travel restrictions have certainly delayed some decisions – the second half of 2021 also saw a drop on the previous six-month periods.

A separate consideration is whether new drug applications have fallen, but the agency only reveals that number sporadically. [Numbers disclosed to 2019](#) suggest that this is unlikely.

Whatever the reason, should investors be concerned if this slowdown is confirmed at year end? It is certainly a trend that no one would want to see worsening, given wider pressures on developers right now.

### ON THE CARDS

As for the big decisions, the verdict on Bristol Myers Squibb's deucravacitinib has long been one of this year's biggest. Whether chunky expectations can be met [will depend on the label](#).



November holds several key Pdufa dates including one for the haemophilia B gene therapy from Uniquire and its partner CSL.

December could be similarly busy, with decisions due on Mirati's adagrasib and TG Therapeutics' ublituximab, with a positive outcome far from guaranteed for either. By the end of the year a couple of followers in the anti-PD-(L)1 space are also hoping to arrive in the US: Novartis and Beigene with tislelizumab and Coherus and Shanghai Junshi with toripalimab.

Six of 2022's 10 biggest potential launches, as things stood back in February, have crossed the finish line. The remaining four are still in with a chance, with deucravacitinib and lenacapivir featuring among the most important still outstanding.

But several of the contenders in the list are looking shaky. TG's ublituximab, Provention Bio's PRV-031 and Mirati's adagrasib all have questions marks hanging over them. If the year does end with a whimper, it might start to feel like biopharma's years of excess really are ending, and not just on the stock market.

2022's biggest approvals still to come...			
Product	Company	Status	2028e sales (\$bn)
Intravitreal pegcetacoplan	Apellis	Delayed	2.6
Adagrasib	Mirati	Delayed	2.0
Deucravacitinib	Bristol Myers Squibb	Approved	1.6
Sunlenca (lenacapivir)	Gilead	Approved	1.6
Sparsentan	Travere Therapeutics	Delayed	0.9
...and those already across the finish line			
Mounjaro	Lilly	FDA approved for type 2 diabetes in May; CHMP positive opinion in Jul	7.4
Spikevax	Moderna	Full approvals in US & EU in Jan, to prevent Covid	4.1
Amvuttra	Alnylam	FDA approved for amyloidosis in Jun; CHMP positive opinion in Jul	2.4
Camzyos	Bristol Myers Squibb	FDA approved for cardiomyopathy in Apr; EU decision due Q4 2022	2.3
Vabysmo	Roche	FDA approved for AMD and DME in Jan; CHMP positive opinions in Jul	1.8

Source: Evaluate Pharma.

*This article has been amended to reflect the delay to Travere and Apellis's decisions, and Bristol's approval.*



# Novartis has the most new approvals, but Lilly's are worth more

BY EDWIN ELMHIRST AND ELIZABETH CAIRNS | SEPTEMBER 22, 2022

When it comes to big pharma's novel therapies, it is a case of quantity versus quality.



There are many growth strategies employed by big pharma, but ultimately the test of these businesses is bringing new drugs, and if possible new blockbusters, to market. On this metric Novartis leads the cohort, having launched 14 novel therapeutics over the past five years.

In terms of commercial potential, however, it is Eli Lilly that is set to reap the greatest value from its new arrivals. This is all the more remarkable considering Lilly has only had one first-time approval in the past 18 months: fortunately that product was

the metabolic disease asset Mounjaro, which arrived [backed by huge expectations](#).

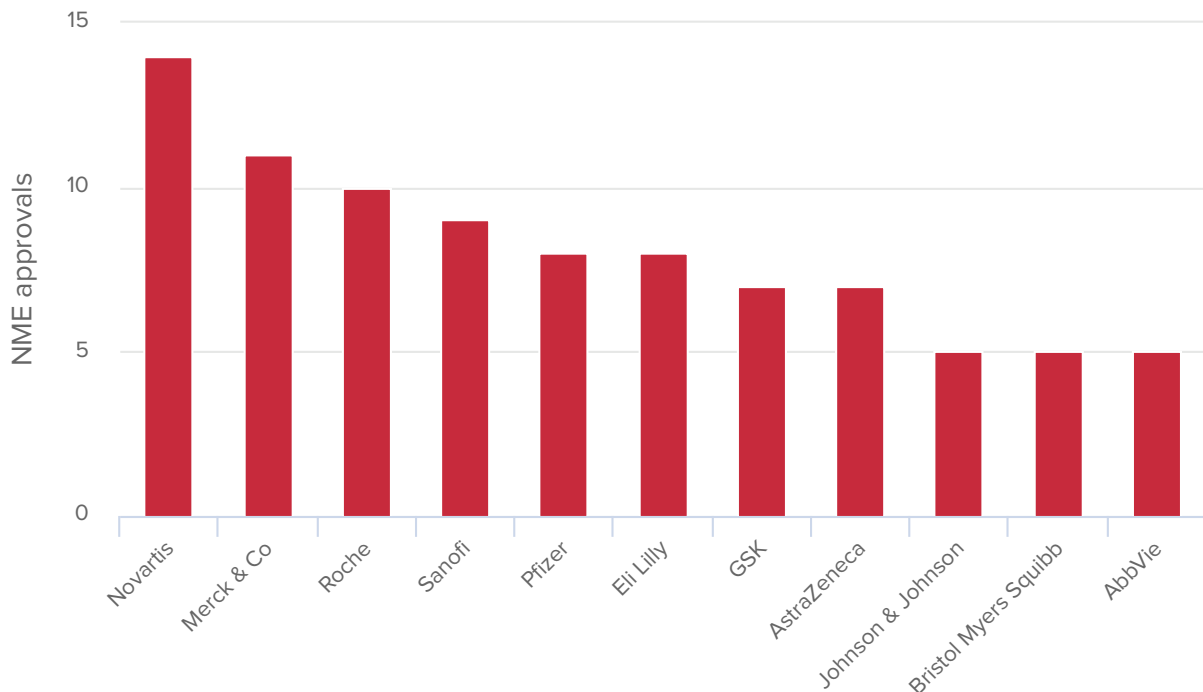
This might help explain why Novartis emphasised it is prioritising its pipeline to “focus on high value NMEs”, at an investor event held today ([Novartis starts the fight back](#), September 22, 2022). Quantity does not necessarily mean quality – when it comes to the value of big pharma's most recent arrivals, Novartis ranks thoroughly middle table, our analysis finds.



The analysis below captures only new molecular entities (NMEs) each of the 11 big pharmas owned at the time of the drugs' first approval, between the start of 2017 and the end of June 2022. Assets

acquired after approval are not counted; neither are subsequent approvals, when a drug adds another indication or setting to its label.

## Big pharma novel approvals 2017-H1 2022



Source: Evaluate Pharma

Novartis's total has been buoyed by three recent regulatory nods, for the PCSK9 Leqvio, the kinase inhibitor Scemblix and the radiopharmaceutical Pluvicto. Leqvio in particular is an important driver for the company; it is the third most valuable therapy ushered onto the market by a big pharma in the last 18 months, with a net present value of \$10.6bn.

But the most valuable of all the new market entrants is Lilly's Mounjaro, whose NPV sits at \$27.5bn. And it is largely thanks to this asset that Lilly punches

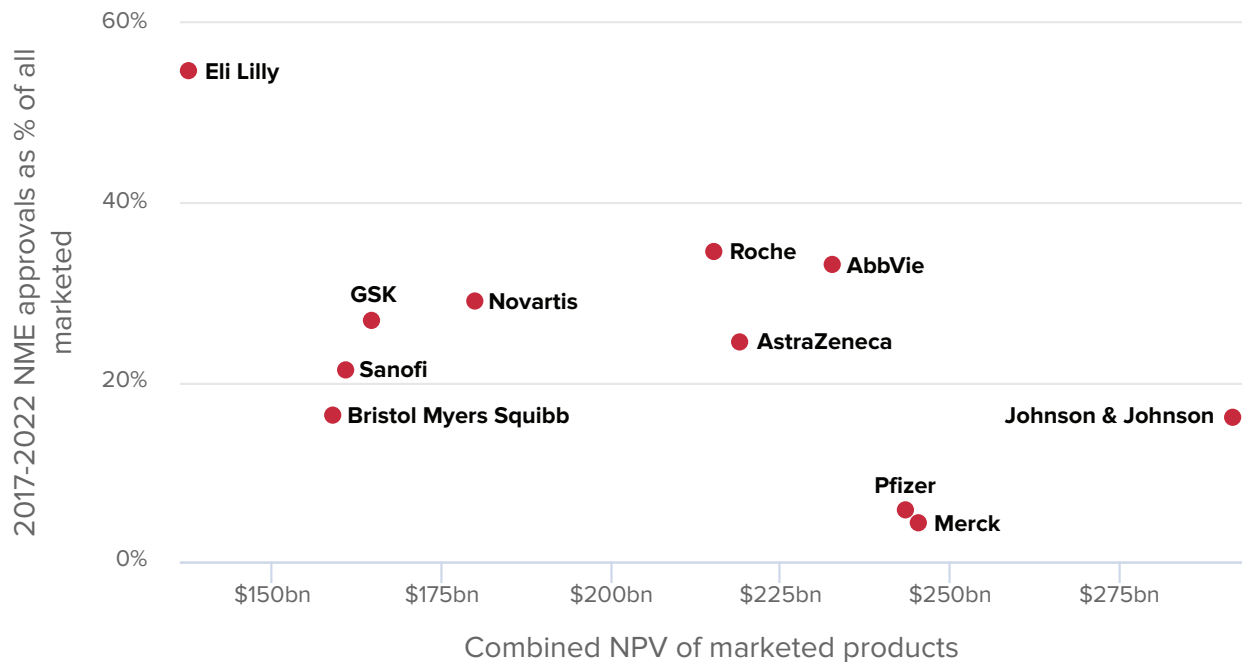
above its weight when the new arrivals are put in context.

The graph below looks at the combined NPV of each group's novel molecules as compared with the value of all their marketed products. Logically, a company would want this proportion to be as high as possible, on the grounds that newer drugs have longer patent lives and can remain productive cash cows for many years to come.



## A generous contribution?

### NPV of NMEs and marketed products



Source: Evaluate Omnium

And the winner here is Lilly, with the NPV of the eight drugs it has launched since 2017 making up more than half of the value of its total product offering. In fairness, the value of Lilly's entire franchise is relatively small; Johnson & Johnson, for instance, would have to launch a suite of incredible new drugs to hit a similar bar, simply because its overall sales are so much higher.

Conspicuous by their absence are the Covid therapies and vaccines. Since many were available under emergency authorisation in H1 rather than full approval, they fall outside the remit of this analysis. Next year, however, at least some of these products will probably appear here, with Comirnaty and Paxlovid potentially able to lift Pfizer from its position towards the bottom of the chart.



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