



Evaluate Pharma<sup>®</sup>

# WORLD PREVIEW 2022

## Outlook to 2028: Patents and Pricing

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15TH EDITION – OCTOBER 2022

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# FOREWORD

There has been little to celebrate in 2022 so far. Public biotech is still languishing after a harsh post-pandemic correction. IPOs are non-existent, M&A is sluggish, and pharma will face drug price negotiations in the lucrative US market before the decade is out.

Despite all this, *Evaluate's* World Preview to 2028 isn't all doom and gloom. Pharma's fundamentals remain good, even amid widespread geopolitical and economic turmoil. Global drug sales are forecast to continue their steady rise, notching up an enviable 6% CAGR between now and 2028. The looming patent cliff – the biggest in recent history – sounds foreboding. But it will likely shave just \$26 billion off the \$1.6 trillion total pharma sales forecast for 2028. Even this might be an over-estimate, given industry's skill in defending lucrative franchises. In 2028 AbbVie will be the second-biggest company by pharma sales, despite losing exclusivity on the world's biggest drug, Humira, next year.

Biotech, too, is well cushioned. Private funding continues to break records, pulling in almost \$13 billion for young drug developers in the first half of 2022. Private equity firms are bringing still more capital to the sector, anticipating its continued relevance – and a likely resurgence in M&A. Most of 2028's top 10 drugs are biotechnology-based, a reminder of where innovations originate.

As this World Preview went to press, Biogen/Eisai [reported positive phase 3 clinical data](#) for their keenly awaited Alzheimer's therapy lecanemab, setting up a potential FDA approval early in 2023. Confirmatory data, and/or good news from similar late-stage candidates at Roche and Eli Lilly, could inject confidence into a sector shaken over the last 12 months by negative readouts and a somewhat unpredictable regulator.

Learning to deal with uncertainty is an implicit message to biopharma from this year's report. We discuss how China has become a less predictable force in global biopharma, assess the possible – yet uncertain – implications of the new US drug pricing laws, and ask whether industry can, and should, continue to focus so heavily on rare diseases. Niche drugs dominate the pipeline, particularly in oncology. But, as the category grows, payers are pushing back. Meanwhile, new treatments for obesity (and, perhaps, Alzheimer's) promise a far wider impact on a much greater number of patients.

The world still needs better treatments yet is also more discerning in how it values them – and what it's prepared to pay. Industry should bear that in mind, even as drug sales continue their upward march. Notable among this report's forecasts is a significant drop in pharma's expected R&D spend growth to 2028. This might result from greater R&D efficiency. It could also signal challenges ahead.



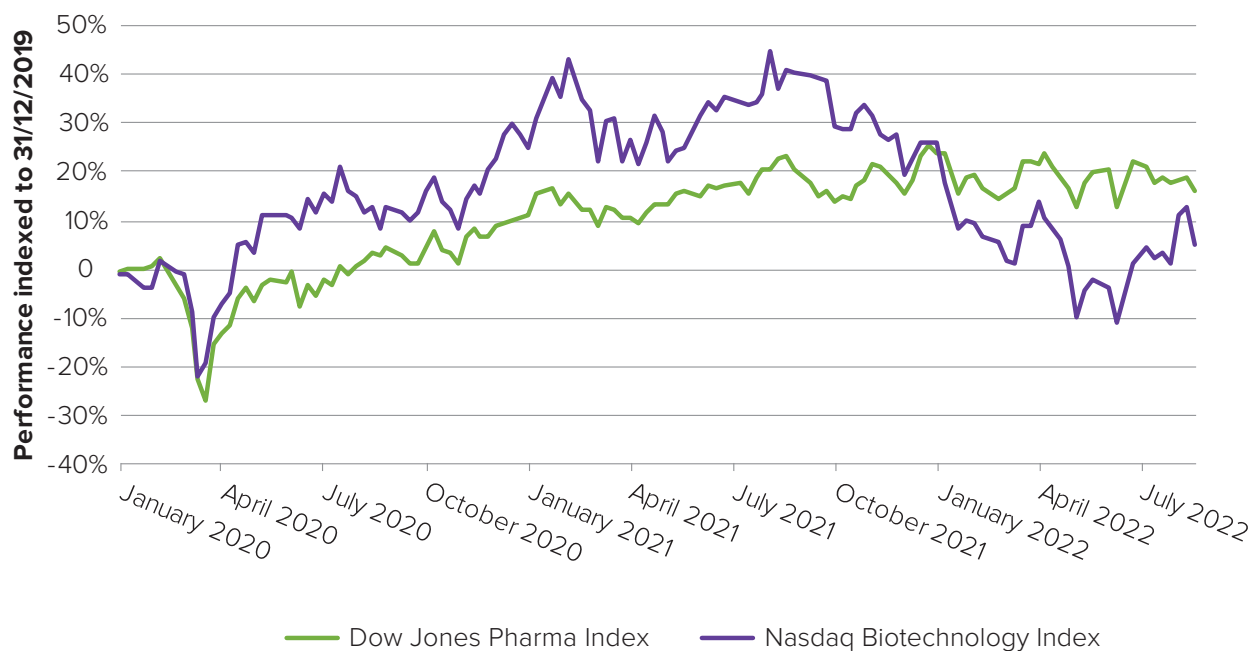
# 2022 World Preview to 2028: Patents and Pricing

► The Evaluate World Preview 2022 was written by Melanie Senior

Battered biotech is reviving. M&A is heating up as pharma companies face up to their patent cliff. Growth forecasts for drug sales continue skyward and PhRMA is squealing about drug pricing. Business as usual?

After pandemic exuberance, a return to sobriety and a chance to reflect on what just happened. Biotech boomed and bust in spectacular fashion, living up to and beyond its characteristic volatility. Big pharma had a smoother ride and is now back in vogue – not just relative to biotech, but as a defensive stalwart amid broader inflationary and macro-economic pressures. The Dow Jones index of US pharma stocks is up almost 30% since pre-pandemic. The Nasdaq Biotech Index in July 2022 gently rose past its pre-Covid levels – almost as if the 27-month rollercoaster ride never happened.

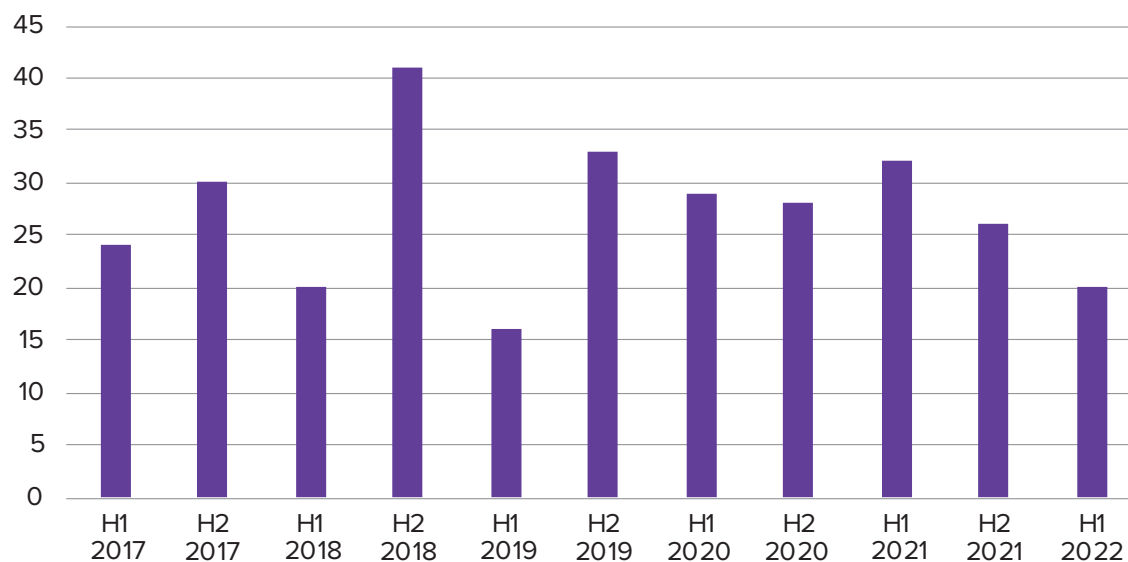
Figure 1: Pharma rises steadily as biotech peaks and falls





Almost. Damage has been done in biotech – to companies, and to confidence. That may endure, dampening future biotech upturns. So could other factors, including a tighter rein at the FDA. The agency [came under fire](#) for certain approval decisions during the pandemic, and new permanent commissioner Robert Califf may want to throw off accusations of being too close to industry. First-half approvals are well below 2020 and 2019 levels, while rejections, known as complete response letters, are up.

**Figure 2: FDA new drug approvals slow**



*CDER & CBER novel approvals – therapeutics only.*

*Source: Evaluate Pharma*

Meanwhile, big pharma hasn't exactly rushed to buy risky biotechs, even if these are cheap. Meaty licensing deals, too, are missing, and geopolitics have complicated China's increasingly prominent role in global biopharma. And there is now a timetable for the US government to negotiate the price of some drugs. It's not quite business-as-usual.

### **SCORCHED EARTH**

Seasoned biotech-watchers knew the correction would come; some cautiously welcomed a shake-out. Yet few expected such a hard, indiscriminate fall. Public companies, which swelled considerably during the pandemic, all faced a bloodbath of retreating capital, [a cluster of bad clinical news](#) and a stricter regulator, on top of the inflation, supply chain constraints and geo-political tremors affecting all industries. Layoffs and liquidations dominated newswires as management teams, spoiled by months of money growing on trees, were forced into unfamiliar cash-saving mode. A third of biotechs in the iShares Biotech ETF were, at the nadir, trading below their cash value, according to Refinitiv data.

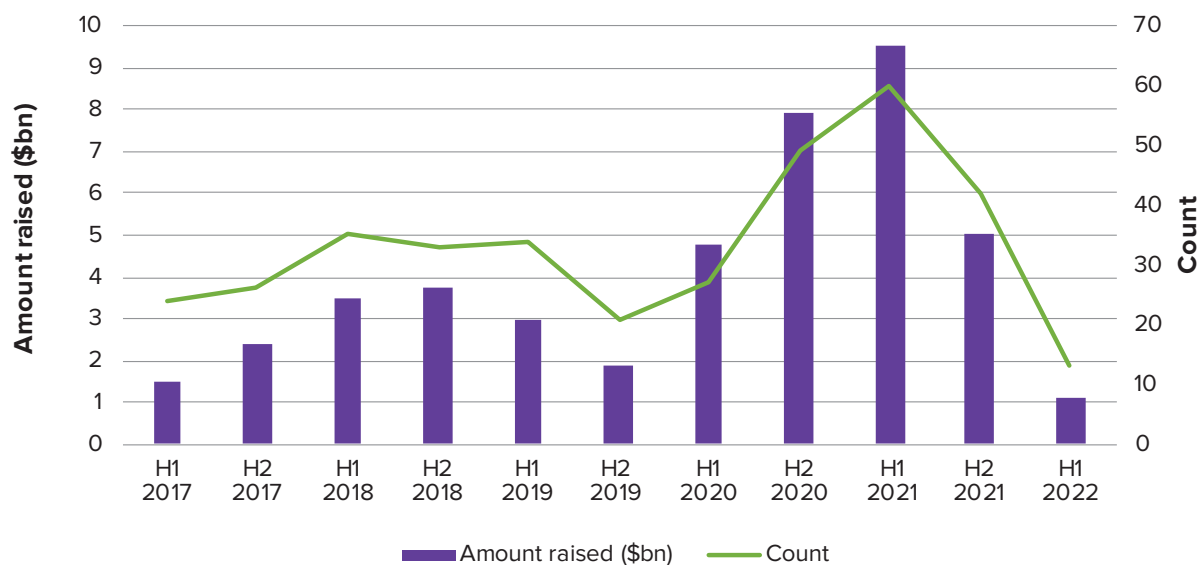
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One-time stars fell from grace: Novavax, whose long-delayed vaccine failed to make the cut commercially, is down 90% from pandemic peaks. Centessa, which drew in \$500 million in 2021 for its risk-lowering multi-asset strategy, has shed over three times that in market value, owing to clinical setbacks. Even Moderna, now touting a second-generation Covid-19 vaccine, is down nearly 70% from its heady peaks.

IPOs have fallen to a trickle: there were barely a dozen listings on Western exchanges during the first half of this year – a fraction of 2021’s (admittedly outsized) haul.

**Figure 3: IPOs virtually disappear in 2022**



Note: Excludes SPACs, secondaries. Pure-play drug developers only.

Source: Evaluate Pharma

Follow-on financings also collapsed in volume, according to Capital IQ data cited by the investment bank Torrey. Neither did M&A pick up the IPO slack as fast as investors hoped. The biggest deals focused on companies with marketed drugs that can quickly offset patent expiries, rather than riskier mid-stage firms that face cash crises. Pfizer’s \$11.6 billion acquisition of Biohaven was all about migraine drug Nurtec; Amgen’s \$3.7 billion Chemocentryx buy came with Tavneos, approved for a rare autoimmune disease. Merck & Co’s \$30 billion-plus Seagen acquisition, if it [gets over the line](#), will deliver four marketed drugs and a dozen in the pipeline. The paucity of big licensing deals also belies pharma’s cashpile and pipeline hunger.

Private biotech isn’t entirely protected: the malaise has seeped into late-stage rounds as valuations adjust to reflect the public-market reality, and investors hoard cash to support existing businesses through a potentially prolonged drought. No one likes down-rounds, so these are pushed out as far as possible, stalling existing projects and cancelling new ones. Slower start-up activity has the same deadening effect.

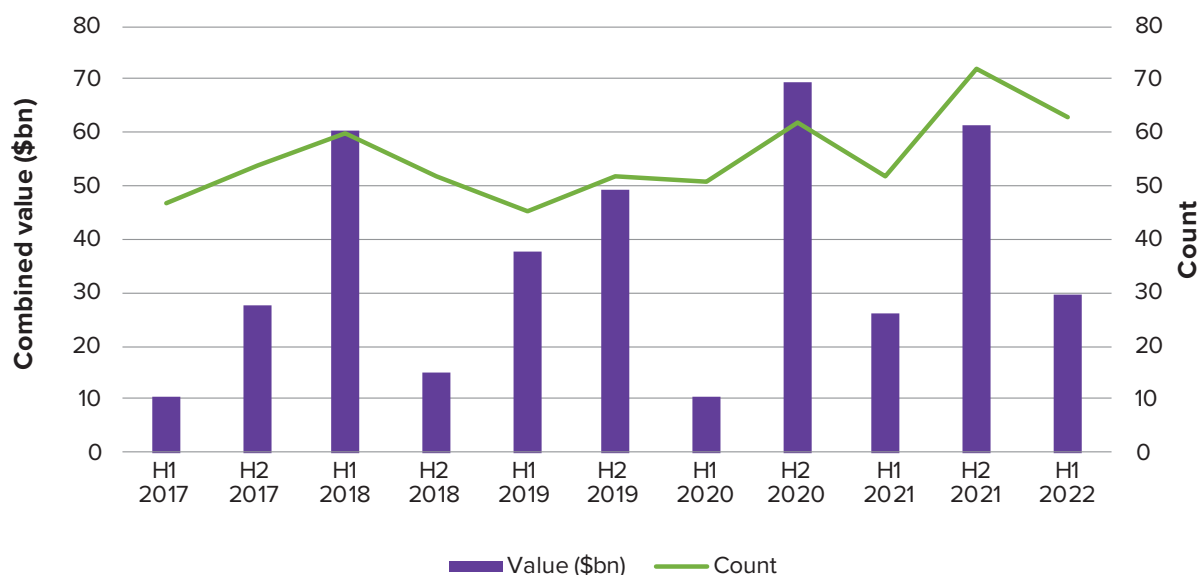


## GREEN SHOOTS

Since the mid-year, there have been signs of recovery. The NBI is up about 17% since a mid-year low, as a few stalwarts spot buying opportunities. That's also resulted in slightly fewer biotechs trading below their cash value, says Torreya, citing data from Capital IQ.

M&A is also reviving as big pharma wakes up to the potential sales losses facing it over the next decade (see Figure 7 “sales at risk” on page 14) and puts to work the estimated [\\$500 billion cash](#) at its disposal before it is inflated away. Pfizer, flush with Covid cash that will soon run dry, in August announced a \$5.4 billion takeover of Global Blood Therapeutics (GBT), whose next-gen sickle cell disease treatment is in phase 2. Two months earlier, Bristol Myers Squibb, with three blockbusters under threat and already slipping down the [sales rankings](#), forked out over \$4 billion for Turning Point Therapeutics and its mid-stage precision oncology candidate. In May, GSK bought the phase 1/2 stage vaccine-maker Affinivax for \$2.1 billion, just weeks after paying nearly \$2 billion for Sierra Oncology.

Figure 4: M&A: Coming to the sector's rescue



Note: Excludes Pfizer-GBT and Amgen-ChemoCentryx (August). Full company takeouts of pure-play drug developers only.

Source: Evaluate Pharma

A successful Seagen acquisition for Merck, facing a 2028 patent expiry for its \$17 billion (2021 FY sales) cancer behemoth Keytruda, could also trigger more buying action – unless the hawkish Federal Trade Commission (FTC) digs in its claws. Meanwhile, Merck revved up the licensing scene over the summer, paying \$290 million for Orion's phase 2 prostate cancer project in July, and \$150 million in August to co-discover new therapies using Orna Therapeutics' circular RNA platform.

Private investors have lots of money, and fixed, fund-linked timeframes within which to deploy it.



There's also some slack in the system. Deals ebb and flow; third-quarter 2022 M&A is shaping up and the full year may catch up to, or even surpass, prior years. Private investors have lots of money, and fixed, fund-linked timeframes within which to deploy it. Almost \$13 billion went into private biotechs in the first half of 2022, according to *Evaluate*. With the exception of 2021, that's more than in any half-yearly period since 2017.

**Figure 5: VC funding stays strong**



Note: Funding for pure-play drug developers only.

Source: Evaluate Pharma

Fresh funds are still emerging, too: China's Qiming, for instance, in July 2022 pulled in over \$3 billion for healthcare and technology investments.

Buoyant private funding won't restore public market sentiment. But perhaps there are silver linings: half-a-billion-dollar IPOs for preclinical companies, as seen in 2020/21, are not sustainable; a slowdown in company creation may simply re-balance what some say looked like over-supply. Importantly, pandemic constraints and the subsequent market rout have made all companies – including surviving biotechs – more resilient, and forced new, sometimes better ways of working.

Broader economic and geopolitical uncertainties mean it's too early to call the bottom of this cycle. But we've been starkly reminded that what goes up must come down.



## **PATENTS AND PRICING WILL HIT PHARMA. BUT NOT MUCH.**

Markets may rise and fall, but the fundamentals remain good for pharma. Global drug sales continue their steady rise, notching up an enviable 6% CAGR between now and 2028. Most of the top-selling drugs that year will be biologics, which is unsurprising given their higher price tags. Novo's diabetes drug Ozempic and AbbVie's psoriasis treatment Skyrizi will grow fastest in 2021-28 (at CAGRs of 15% and 21% respectively) while a waning pandemic may push Pfizer/BioNtech's Covid-19 vaccine Comirnaty off the list. Oncology will maintain its dominance, with neurology a distant, but strong second. (See figure 12 on page 18).

The sector faces an [historic set of patent cliffs](#) in the next 10 years, as mega-blockbusters including Humira, Keytruda, Opdivo and Eliquis lose protection. AbbVie's \$20 billion-a-year Humira will be first to fall next year.

Don't expect the lights to go out, though. AbbVie is adept at playing with pricing, and will vigorously defend its brand. It also has other drugs to help fill the gap, like Jak inhibitor Rinvoq and fast-growing Skyrizi. Merck has six years of breathing space with Keytruda and over a dozen indications to build defences around. In all, the at-risk sales from loss of exclusivity will be less than 7% of the total \$1.6 trillion in 2028. Actual expected industry-wide annual sales losses – given precise monthly patent expiry timings, and competitor launch mechanics – is just a quarter of that, about \$26 billion. (See figure 7).

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By then, pharma will face a less familiar foe: drug price negotiations with the US government. Against the odds, a bill was signed into law in August requiring federal-funded Medicare (which covers over-65s) to negotiate prices for 10 top-selling drugs by 2026, rising to 20 by 2029. This also demands rebates on any Medicare drugs whose prices rise faster than inflation, and caps beneficiaries' out-of-pocket spending in 2025. It's tough stuff: there are rules capping the maximum negotiated price, and punishment – in the form of an excise tax on prior year sales, rising from 65% to 95% – for manufacturers that refuse to negotiate. Those who negotiate but don't stick to the agreed price will also be penalised.

Passing the so-called Inflation Reduction Act (IRA) – which also contains policies to counter climate change and reform tax – was a [hard-won victory](#) for ruling Democrats (who, by using a procedure called budget reconciliation, didn't need any Republican votes). They've been seeking healthcare reform for years; several wanted even more sweeping change to state coverage. The idea is that the savings from drug spend help pay for the planned outlays around climate change. Republicans oppose the lot.

For pharma, the Act's bark might be worse than its bite. Industry lobby group PhRMA and various big pharma CEOs are screeching about its chilling effect on innovation and its punitive cost on the industry (an estimated \$270 billion over 10 years, according to Pfizer's CEO, [Albert Bourla](#)). But the scope of the price negotiations could have been much worse. Drugs with available generics or biosimilars, those less than seven years (for small molecules) or 11 years (for biologics) from approval or those that cost Medicare less than \$200 million in 2021 will be excluded. So the bill won't substantially eat into market exclusivity periods, which stand at five-to-seven years for small molecules, and 12 for biologics. Negotiations won't kick in for another four years (after the 2024 presidential election), and will apply only to 10 Part D drugs initially; the more expensive injectables and other hospital-administered products under Part B won't be subjected to negotiation until 2028. Pharma's top-10 best-seller list of (mostly) biologics are protected until then (the same year Keytruda goes generic). (See figure 11 on page 17).





Policy experts also say there is plenty of room for interpretation around key provisions, such as whether the number of drugs subject to negotiation will be cumulative. Legal challenges are highly likely as CMS sorts out the details.

This package is still a long way from European-style price negotiations, which in most markets apply at or soon after a new drug approval. Indeed, one consequence of the IRA may be higher launch prices, as companies squeeze as much as they can out of their products before eventual price negotiations and curb their chances of being fined for above-inflation year-on-year price increases along the way. The IRA may also provide another tailwind for developers of orphan drugs, since it protects them from price-capping measures.

The US Congressional Budget Office estimates that the provisions will reduce the number of drug approvals by about 10 over the next 30 years (for context: FDA has approved about 50 new drugs in each of the last few years). Industry fears a much greater impact.

If the bill does generate the hoped-for savings (about \$100 billion over 10 years, according to the CBO), it could presage further change: no government will be able to resist going back for more. Demographic trends, the long-term rise in drug approvals and the growing share of complex biologics and cell-based therapies make further US price controls of some sort look almost inevitable.

### **CHINA: A LESS PREDICTABLE FORCE**

China's emerging innovative biotech sector is increasingly intertwined with that in the West. Domestic Chinese firms want access to more generous Western payers, and Western players want new assets and a door into the world's second-largest market.

Biotech isn't directly in the firing line for now...but the moves are a reminder that China is unpredictable.

Geopolitical tensions have complicated, though not stopped, this two-way flow. The US has used [auditing rules](#) to clamp down on US-listed Chinese firms, and FDA [appears to have](#) tightened its criteria for accepting Chinese clinical data. Lilly/Innovent's PD-1 inhibitor sintilimab and Novartis/BeiGene's tizelulisumab have both been caught. In May 2022, FDA slammed a CRL on Hong Kong-based Hutchmed's cancer drug surufatinib despite two positive phase 3 studies and a US bridging trial in rare cancer subtypes, pancreatic and non-pancreatic neuroendocrine tumors. The agency wanted a multi-regional clinical trial with more US data – apparently to the surprise of many clinicians and patients. There are good scientific reasons for demanding more representative data, but such requests are usually signalled in advance.

A strict Covid-19 lockdown in Shanghai for two months during early 2022 disrupted clinical trial recruitment and patient management, forcing delays and contingency plans just as the rest of the world was opening up. Then the Chinese government spooked markets with a flurry of regulations under its “Common Prosperity” policy. Designed to reduce inequality and foster competition, the policy is the cloak for state interference to curb capitalist excess. Biotech isn't directly in the firing line, for now – real estate, fintech, edu-tech and social media are. Chinese biotech innovation will continue; companies adapt. Western-Chinese alliances [won't go away](#) either. But the moves are a reminder that China is unpredictable.



## IS INDUSTRY OVERWEIGHT IN RARE DISEASES?

Far more predictable is oncology's continued dominance of the product and pipeline league tables through 2028 – growing over twice as fast as anything else (See figure 12). Cancer is at the forefront of precision medicine; high prices, multiple per-product indications, drug combination potential and expedited regulatory review also make this an attractive space.

As genomics slices cancer into less prevalent subtypes, oncology medicines often classify as 'rare', which helps explain why FDA orphan drug approvals now match or outnumber those for more widespread conditions. The high prices achieved for rare diseases drugs – not just in cancer – are triggering concerns over their cumulative cost to health systems, especially given that evidence requirements for such medicines may also be lower than for non-rare drugs. Some, like the cost-benefit watchdog the Institute for Clinical and Economic Review, question whether the expedited approvals and other economic incentives such drugs enjoy under the US Orphan Drug Act and its European equivalent, may have swung the pendulum too far. ([Take a look at our Orphan Drug Report for a more in-depth analysis](#))

Research into rare diseases has generated important new therapies and therapy modalities, such as gene and cell therapies (see box, Gene & Cell Therapies: Not So Fast). It has also helped expand scientists' understanding of both rare and non-rare disease mechanisms. Over the next decades, there will be [more calls](#) for industry to turn these learnings from rare genetic conditions and oncology precision medicine to the vast unmet need in common, increasingly widespread conditions like obesity, Nash, cardiovascular disease and dementia. Some of these also increase cancer risk, and make us more vulnerable to infection, as the recent pandemic showed.

Already today, three of the top 10 most valuable R&D projects based on forecast 2028 sales are for chronic neurological conditions; another is for a non-rare cardiovascular condition (See figure 15: Top 10 R&D projects on page 21). Biogen's Alzheimer's drug Aduhelm, whose controversial 2021 approval presaged a commercial flop, hasn't stopped others from pursuing the space. The [FDA recently accepted](#) Lilly's donanemab for accelerated review, and phase 3 trials are under way of Roche's gantenerumab and Biogen/Eisai's [lecanemab](#). Karuna Therapeutics reported positive topline phase 3 data in August 2022 for the schizophrenia project KarXT, which, if approved, would end a multi-decade-long new treatment drought in this condition. (The company hopes to file in mid-2023).

Some question whether the expedited approvals and other economic incentives orphan drugs enjoy may have swung the pendulum too far.



## OBESITY HEATS UP

Meanwhile, a battle is brewing for share of the growing obesity market, as a new generation of more effective drugs arrive and payers loosen reimbursement strings. Novo Nordisk's Wegovy, a higher dose of diabetes medicine Ozempic (GLP-1 agonist semaglutide), is front of pack with forecast peak sales of over \$8 billion and a 2021-28 CAGR of almost 70%, according to *Evaluate*. But supply challenges and unexpectedly high demand hampered Wegovy's 2021 launch, [allowing Lilly to catch up](#). Its phase 3 contender, tirzepatide, a GLP-1/GIP agonist approved in May 2022 for diabetes as Mounjaro, may be even better at helping patients lose weight than Wegovy; Lilly has [recently launched](#) a head-to-head trial to find out for sure. Novo has another card up its sleeve, though: a combination of semaglutide with the amylin analog cagrilintide, whose [early phase 2 data](#) suggests it might trump Wegovy, both on weight loss and blood sugar lowering.

*Evaluate's* consensus-based forecasts put combined obesity sales in 2028 above \$11 billion, over four times the \$2.5 billion expected in 2022, with a 2021-28 CAGR topping 30%. Even that will be an underestimate, though, if tirzepatide is approved in obesity (current figures are risk-adjusted to capture pre-approval status).

The obesity pipeline has swollen to more than 20 phase 2 or 3 clinical candidates in 2022, more than double 2017's tally. The market's big, but so are trial size requirements (and thus costs). Patients also often need to pursue diet and lifestyle changes alongside treatment. Hence even the enlarged pipeline still contains fewer than a tenth of the number of candidates in development for Non-Hodgkin's lymphoma, for example, which accounts for under 5% of all US cancer diagnoses. Alongside Novo's Cagrisema combo, the obesity pipeline includes two GLP-1/glucagon receptor agonists from AstraZeneca (cotadutide, in phase 2 for Nash with obesity) and Altimmune (pemvidutide, phase 2 for obesity), and Pfizer's phase 2 oral GLP-1 agonist danuglipron.

*Evaluate's* consensus-based forecasts put combined obesity sales in 2028 above \$11 billion...with a 2021-28 CAGR topping 30%.

Obesity affects more than a third of US adults and over 10% of the world's population, yet the American Medical Association didn't recognize the condition as a disease at all until 2013. Payers have been reluctant to reimburse treatments that, until recently, didn't work very well anyway. Today, with Covid-19 having further highlighted the health risks and costs associated with obesity, most payers are unlikely to require further incentives to fund treatment.



## LONG-TERM HEALTH

In what many hope is now the aftermath of the Covid-19 pandemic, pharma looks in good shape. The sector didn't move up the reputational rankings as some hoped, but, amid economic, political, social and meteorologic upheaval, long-term demand for more, better healthcare looks gloriously certain. Biotech, though battered, will return more resilient. It might already be rising to its feet. And, as pharma's current batch of blockbusters reach the end of their lives, deals will accelerate.

The downward drift in expected R&D spend growth may look shocking, with 2021-28 CAGR less than half that of 2014-21 (See figure 14 below). That needn't mean less innovation, though. It might instead mean cheaper innovation, as digital and 'omics tools, in silico trials and more predictive toxicology methods (such as organs-on-chips and organoids) help accelerate drug R&D and increase success rates. Pharma used to boast about R&D as a percentage of sales. From now on, it will tout R&D efficiency.

US pricing laws are unlikely to curb this generation of blockbusters, or the next. Yet eventually they could slow drug price inflation, even as overall drug sales continue their upward march.

### Gene and cell therapies: not so fast

Gene and cell therapy companies sit at the sharp end of innovation – and risk. Many of the hundreds of pipeline programs are still early, and unproven. So these groups have been hard hit during the downturn, and may also be particularly vulnerable to a tighter FDA, which in September 2021 convened a two-day meeting to review the safety of certain gene therapy products.

Recent stumbles serve as a reminder of why such oversight is important – and that new treatment categories take time to become established. This summer, UniQure's phase 1b/2 AMT-130 for Huntington's disease threw up suspected, unexpected severe side effects (SUSARs) in two patients (and a possible third earlier), while the Israeli biotech VBL Therapeutics' phase 3 ovarian cancer candidate failed to meet its survival endpoints. Two children with spinal muscular atrophy reportedly died having received Novartis's approved Zolgensma; the Swiss group also in late August reported halting a phase 2b trial of its oral mRNA splicing modulator branaplam in Huntington's owing to neuropathic side-effects.

On the plus side, Bluebird Bio returned from the brink in August 2022 with a long-awaited FDA approval of beti-cel (Zynteglo) for beta thalassemia, a rare blood disease. The one-time treatment will cost \$2.8 million but may just about be cost-effective (albeit at the highest threshold), says ICER, since it will avoid a lifetime of blood transfusions estimated to be over twice as expensive still. BioMarin recently received a positive European CHMP opinion for haemophilia A gene therapy Roctavian, which, after an FDA snub in 2020, will also shortly be re-submitted in the US.

For now, the FDA has approved only a handful of gene and cell therapies, but there are almost two dozen gene therapies and over 10 cell therapies either filed or in phase 3, according to Evaluate Omnium. Adding phase 2 and phase 1 candidates multiplies the tally eight-fold. A few of these medicines, like Zolgensma, Roctavian and Sarepta's phase 3 SRP-9001 for Duchenne's muscular dystrophy are expected to sell more than \$1 billion.

Cell and gene therapies will save or improve many more lives, but their large impact will be on a small minority. Zynteglo, for example, is expected to treat about 200 patients in the US. These medicines will be largely protected from price-curbing measures in the recent US Inflation Reduction Act, meaning they'll remain a popular focus. Yet they should be developed alongside equally innovative treatments for more widespread diseases.



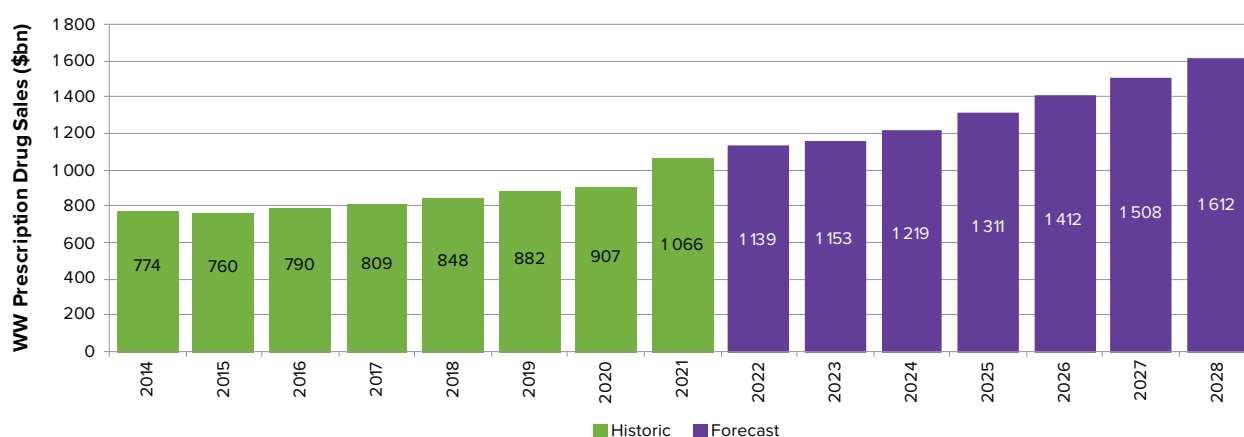
## Into the Detail....

**That's the context. Next, let's delve into the numbers as we extend our outlook into 2028.**

Sales of prescription drugs are forecast to grow 6% on an annualised basis out to 2028, according to *Evaluate Pharma's* consensus forecasts. These numbers are based on sellside analyst estimates, and include forecasts for R&D projects as well as products already on the market.

The huge boost that Covid-19 gave to the sector's top line in 2021 is readily apparent. Demand for pandemic products caused sales to surge 18% on 2020, the biggest year-on-year jump recorded by *Evaluate Pharma* this century. Future use of Covid-19 products, including vaccines, antivirals and antibodies, remains a big unknown. The course that the pandemic takes could still cause substantial changes to the sector's outlook, for example if the coronavirus surges back or dies out more quickly than expected.

**Figure 6: Worldwide total prescription drug sales (2014-2028)**



Note: 6.1% CAGR 2021-2028

Source: Evaluate Pharma® (Aug 2022)

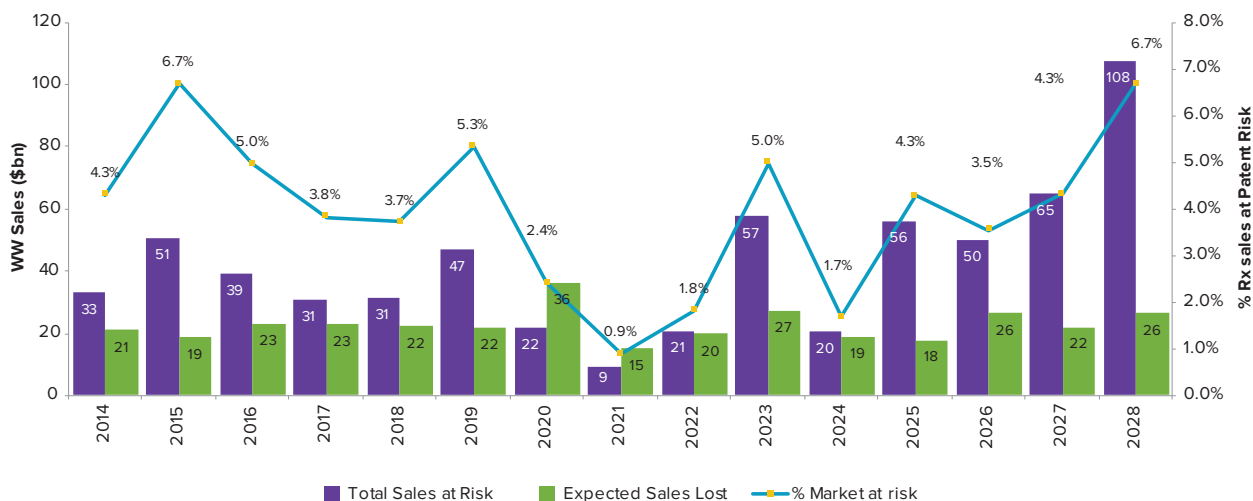
Recent drug price reform in the US could also cause long-term growth trends to shift downwards, according to industry. It remains unclear exactly what impact the new measures might have, however.

Patent expiry will become an even more pressing issue for the large drug makers as the decade progresses. A huge cliff awaits post 2028; affected companies could seek to mitigate lost sales through increased business development in the coming years.

The products and companies facing big losses in the coming years include Abbvie's Humira in 2023, and potentially Bristol Myers Squibb/Pfizer's Eliquis in 2026 and J&J/Abbvie's Imbruvica in 2027. Intellectual property for Eliquis and Imbruvica and many others is still being litigated, which might delay the launch of cheaper alternatives.



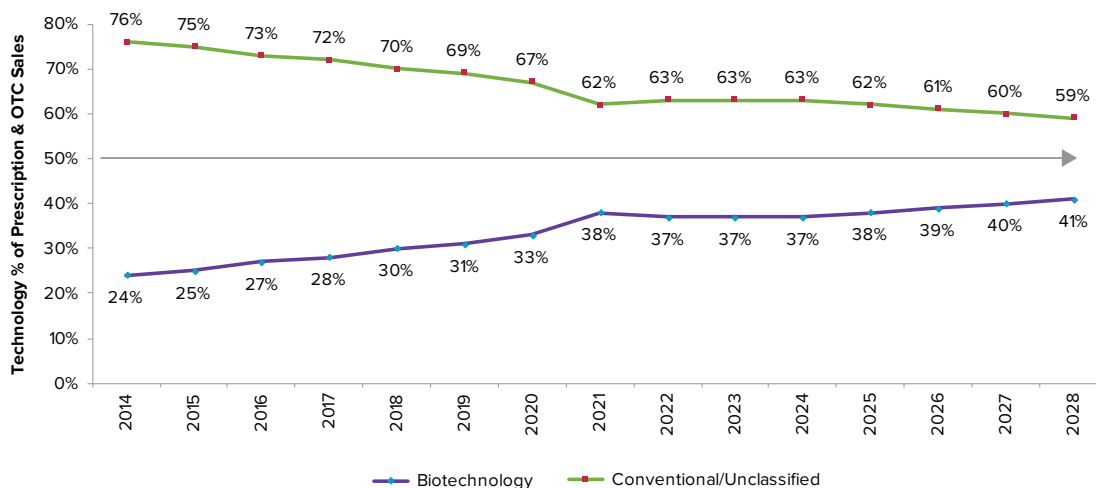
Figure 7: Worldwide sales at risk from patent expiration (2014-2028)



Source: Evaluate Pharma® (Aug 2022)

Total sales at risk refers to a product’s annual revenue in the year before loss of exclusivity. Expected 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.

Figure 8: Worldwide prescription drug and OTC pharmaceutical sales: biotech vs. conventional technology



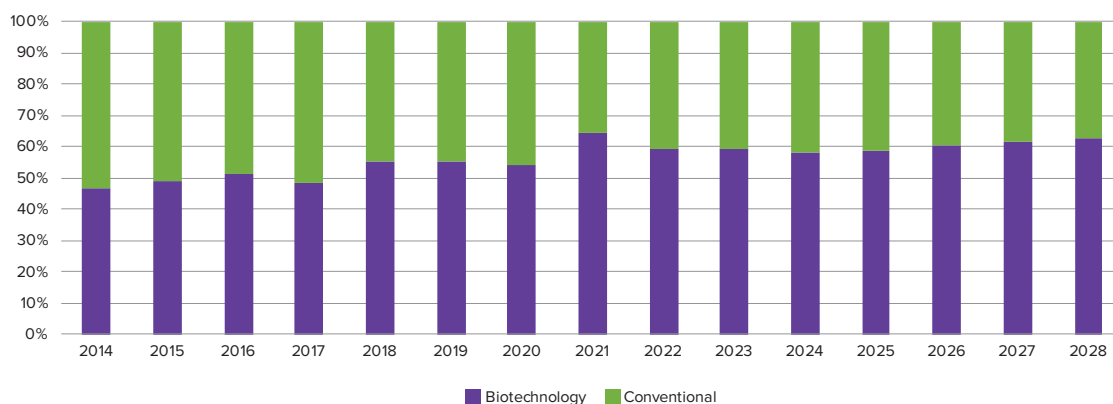
Source: Evaluate Pharma® (Aug 2022)



The importance of biotechnology-based products for industry continues to grow, although it is worth remembering that these are typically very highly-priced drugs. The sector's ability to grow so-called patent thickets around biologicals also means that these franchises tend to have greater longevity than small molecules, further boosting their dominance.

The big jump in 2021 in biotechnology products, from 33% to 38% of the overall market, is down to Covid-19 vaccines, which fall into the biotechnology classification.

**Figure 9: Biotech vs. conventional technology split in top 100 products (2014 – 2028)**



Source: Evaluate Pharma© (Aug 2022)

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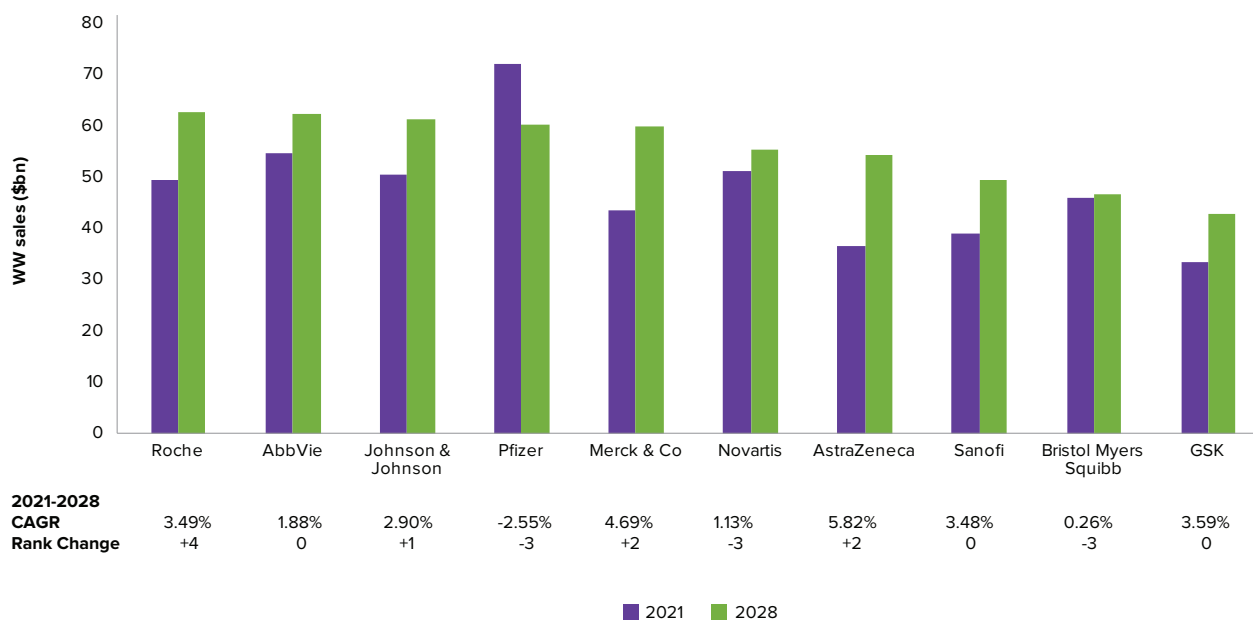
Merck’s anticancer agent Keytruda and Sanofi/Regeneron’s Dupixent, sold for various autoimmune conditions, are projected to be the biggest-growing biologics out to 2028. Abbvie’s rheumatoid arthritis drug Rinvoq and Vertex’s Trikafta, for cystic fibrosis lead the fastest-growing small molecules.

Roche is forecast to be the biggest drug maker by prescription sales in 2028, though not by much. Acquisitions and clinical hits or misses can quickly change a company’s outlook. For example, if Roche’s Alzheimer’s project gantenerumab succeeds, it is predicted to give the company’s top line a big boost. Many consider that “if” to be very big indeed, however.

Abbvie’s position is impressive considering that the company will start to feel the loss of Humira exclusivity in the US from 2023. Sales of biopharma’s biggest-selling drug are expected to peak at \$21 billion in 2022, to be replaced with growing contributions from the Jak inhibitor Rinvoq, psoriasis product Skyrizi and blood cancer drug Venclexta.

Pfizer, Novartis and Bristol Myers Squibb are all forecast to fall down the rankings in the coming years. Bristol is facing significant patent expiries of its own, while Pfizer’s fall will be largely due to the loss of Covid revenues.

**Figure 10: Worldwide prescription drug sales in 2028 (top 10 companies)**



Source: Evaluate Pharma® (Aug 2022)





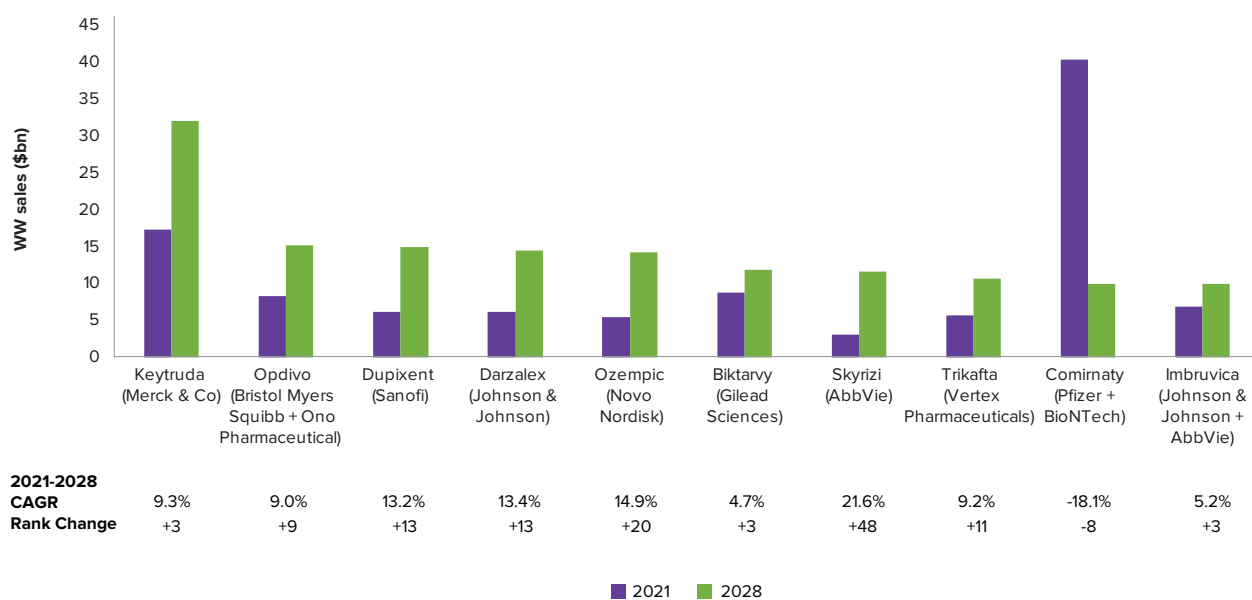
With Humira set to face biosimilars in the US next year, Keytruda’s turn at the top of the rankings begins. Sales of the Merck checkpoint inhibitor are expected to breach \$30bn in 2028; if these expectations are met it would set a new record for annual revenues.

Bristol Myers Squibb’s competing anti-PD-1 agent, Opdivo, is in second place in terms of 2028 sales, while several other similarly-acting drugs are also already in blockbuster territory, and still growing. This anticancer mechanism is set to make a huge contribution to the sector’s top-line growth in the coming years.

Pfizer and BioNtech’s Covid vaccine Comirnaty is for now seen among the top 10, although without clear visibility around where the pandemic is heading, this number could prove too high.

Abbvie’s new growth driver Skyrizi, for psoriasis, makes it into the top 10 for the first time, as does the cystic fibrosis drug Trikafta, sold by US biotech Vertex.

**Figure 11: Top 10 selling products worldwide in 2028**

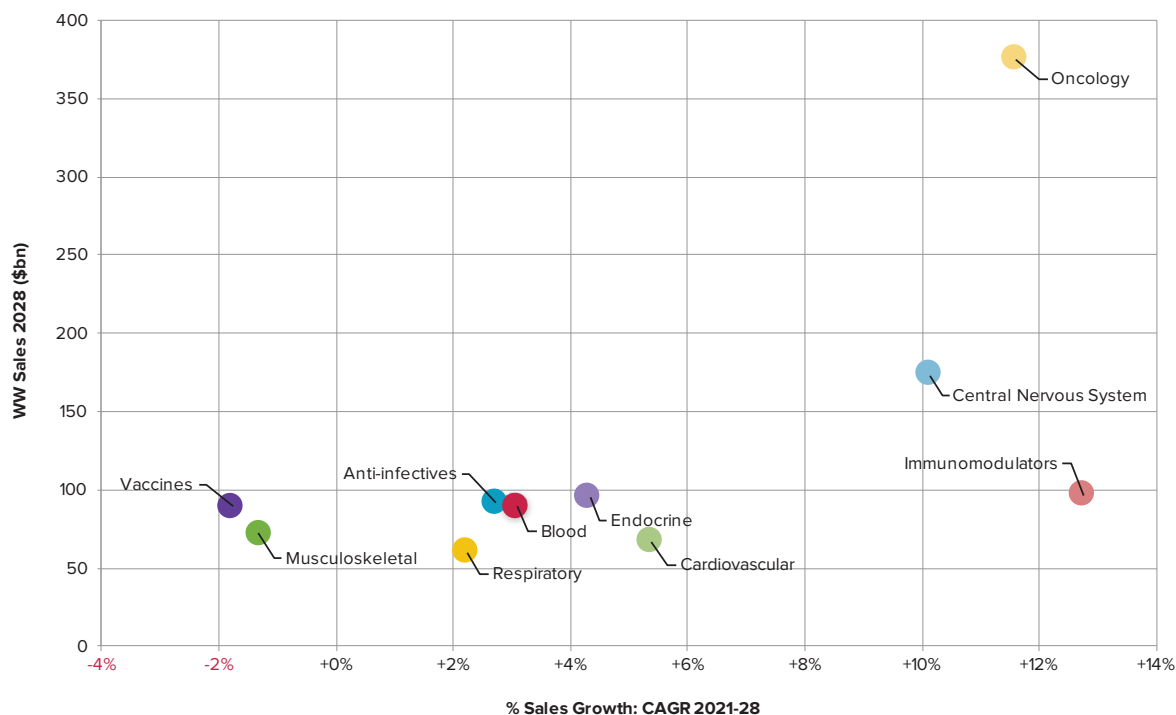


Source: Evaluate Pharma® (Aug 2022)



This graph demonstrates oncology's outsized contribution to growth of the sector's top line. Not only is this therapy area likely to generate the most sales in 2028 – more than double the next largest therapy area – its forecast growth rate is also one of the highest.

**Figure 12: Top 10 therapy areas in 2028, market share & sales growth**



Source: Evaluate Pharma® (Aug 2022)

Oncology is a more expansive therapy area than, for example, sensory organs, but this is not the only reason behind the huge level of sales that cancer drugs generate. Potentially lifesaving or extending therapies can command a high price, while substantial investment in this field means that relatively novel, and therefore patent protected, drugs dominate the landscape.

Immunomodulatory agents used in autoimmune conditions like psoriasis and atopic dermatitis are also seeing rapid uptick in demand. Growth in the CNS field, which includes both psychiatric medicines and treatments for neurological conditions, is being driven by new multiple sclerosis therapies as well as hopes for novel Alzheimer's projects. Alzheimer's remains a high-risk area of development, however.

Vaccines and the musculoskeletal field are projected to be among the sector's slowest-growing areas in the coming years. The former is due to the Covid tail, and the latter because of patent expiries in the anti-TNF class, most notably Abbvie's Humira.

## Evaluate Omnium

By applying machine learning to millions of data points from across the full clinical pipeline – including early phase and privately held assets – Evaluate Omnium identifies key risk and return correlations that uncover unique, highly accurate insights into asset development and commercial opportunity.

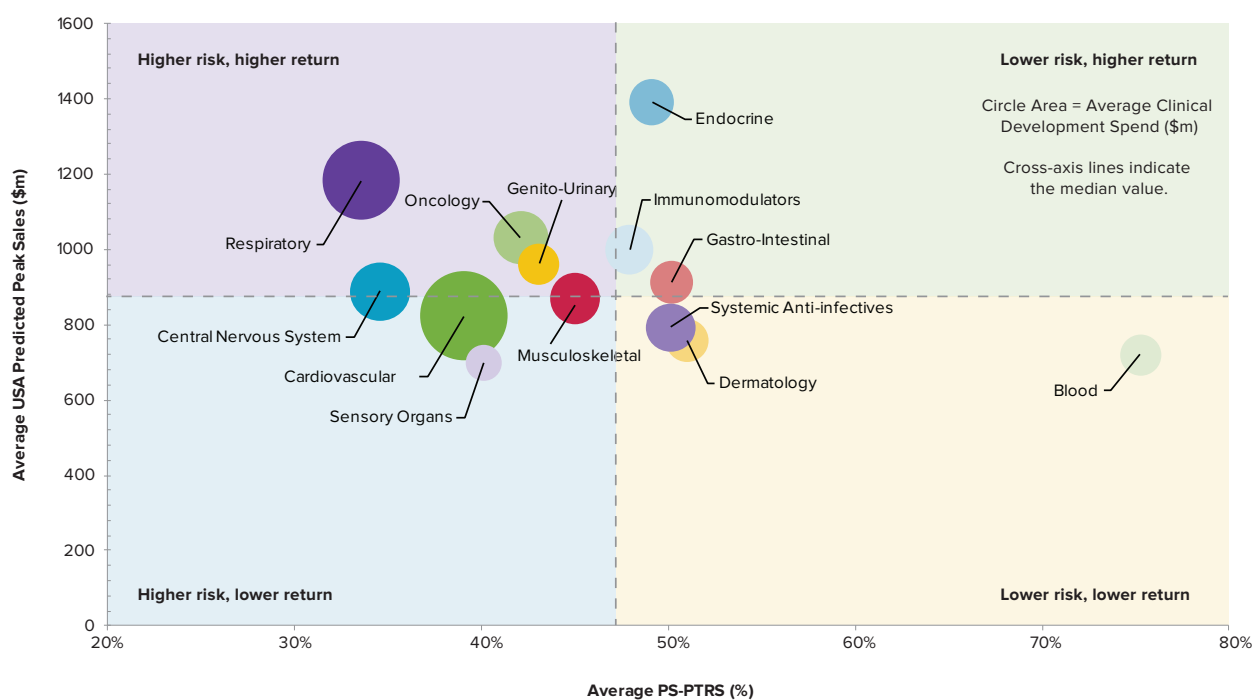


A look at predicted success rates also helps explain why developers are enthusiastically chasing oncology. Although this ranks as one of the highest-risk therapy areas, returns are also high.

Notably endocrine – which is mostly made up of type 2 diabetes drugs – has a higher return than oncology. Diabetes has seen a huge wave of successful, novel mechanisms come to market in the past few years, most recently the SGLT2 inhibitors. The bar for innovation is now extremely high in this space.

At the other end of the scale, a number of eye disease disappointments have likely dented the sensory organ area. Several gene therapies have had setbacks, while Novartis's Beovu, a next-gen anti-VEGF product, disappointed because of toxicity.

Figure 13: PTRS vs. predicted peak sales by therapy area of current US pipeline phase 3 assets



Source: Evaluate Omnium® (Aug 2022)

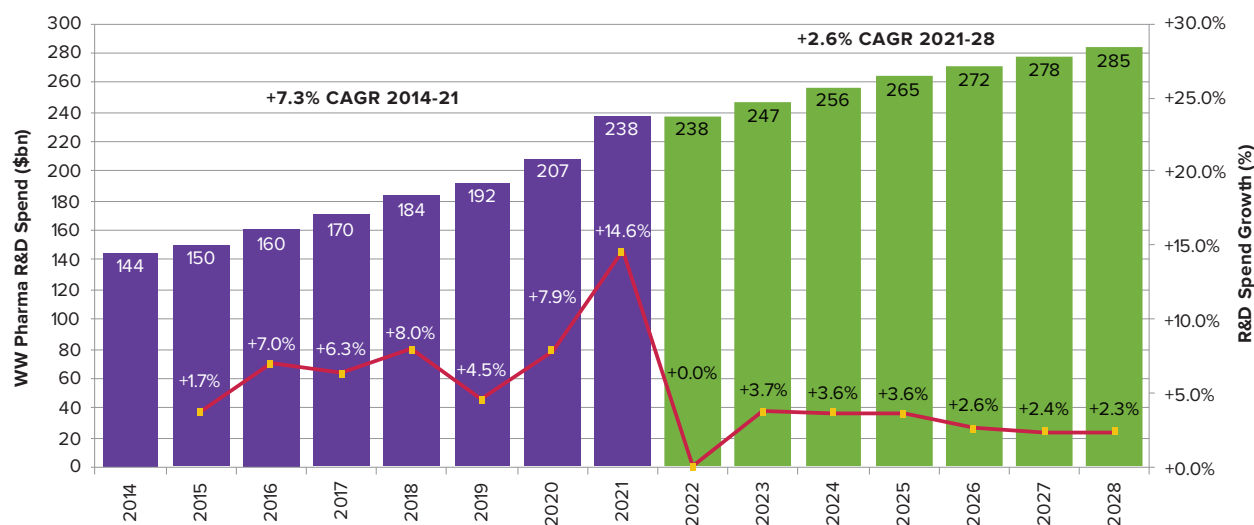


Moderate growth in the sector's R&D spending is forecast for the coming years, with annualised growth seen dipping to low single digits out to 2028. After the substantial Covid-prompted jump in 2021, perhaps a pullback should be expected.

Biopharma companies, particularly small developers, are likely to focus more sharply on cash conservation in the coming years, owing to the tightening of the financing climate. Clinical trial efficiencies are also improving, with increasing digitalisation of processes. If the promised advantages arrive, this should lower R&D bills.

Investors will have to hope that this apparent moderation in R&D spend does not signal a shrinking of the sector's late-stage pipeline.

Figure 14: Worldwide total pharmaceutical R&D spend in 2014 - 2028



Source: Evaluate Pharma® (Aug 2022)



Alzheimer's projects feature twice in the current list of most valuable R&D projects, despite the disappointing precedent set by Biogen's Aduhelm. Pivotal data due in the next 12 months will determine whether gantenerumab or donanemab make it to market.

Neither can projects from Apellis in eye disease and Mirati in lung cancer be considered safe bets. The former's clinical data have created uncertainty, while the latter's attempt to get to market via an accelerated approval path might be scuppered by rival Amgen, which could feasibly win a full approval for its competing Kras inhibitor Lumakras in the meantime.

Most of these projects still need to generate confirmatory pivotal results, despite already attracting lofty valuations. Epcoritamab in large B-cell lymphoma and KarXT in schizophrenia are arguably looking the most promising, having already demonstrated their potential, although full data packages have yet to emerge.

**Figure 15: Top 10 most valuable R&D projects (ranked by net present value)**

Rank	Product	Company	Phase (Current)	Mechanism of Action	WW Product Sales (\$bn) 2028	Today's NPV (\$bn)
1	<b>Gantenerumab</b>	Roche + MorphoSys	Phase III	Anti-beta-amyloid (Abeta) MAb	3.5	12.1
2	<b>Intravitreal Pegcetacoplan</b>	Apellis Pharmaceuticals	Filed	Complement factor C3 inhibitor	2.6	6.8
3	<b>Adagrasib</b>	Mirati Therapeutics + Zai Lab	Filed	KRAS G12C inhibitor	2.0	6.3
4	<b>Epcoritamab</b>	AbbVie + Genmab	Phase III	Anti-CD3 & CD20 bispecific MAb	1.7	5.1
5	<b>Donanemab</b>	Eli Lilly	Filed	N3pG-Aβ MAb	1.6	4.9
6	<b>KarXT</b>	Karuna Therapeutics + Zai Lab	Phase III	Muscarinic acetylcholine receptor (mAChR) M1 modulator	1.7	4.9
7	<b>SRP-9001</b>	Sarepta Therapeutics + Roche	Phase III	Micro-dystrophin gene therapy	2.2	4.6
8	<b>mRNA-1647</b>	Moderna	Phase III	Cytomegalovirus (CMV) mRNA vaccine	1.2	4.6
9	<b>Aficamten</b>	Cytokinetics	Phase III	Cardiac myosin inhibitor	1.2	3.7
10	<b>Tiragolumab</b>	Roche	Phase III	Anti-T-cell immunoreceptor with Ig & ITIM domain (TIGIT) MAb	0.8	3.4
<b>Top 10</b>					18.6	56.4
<b>Other</b>					235.8	543.6
<b>Total</b>					254.5	600.0

Source: Evaluate Omnium® (Aug 2022)



Evaluate provides trusted commercial intelligence for the pharmaceutical industry. We help our clients to refine and transform their understanding of the past, present and future of the global pharmaceutical market to drive better decisions. When you partner with Evaluate, our constantly expanding solutions and our transparent methodologies and datasets are instantly at your disposal, along with personalised, expert support.

Evaluate gives you the time and confidence to turn understanding into insight, and insight into action.

**Evaluate Pharma** offers a global view of the pharmaceutical market's past, present and future performance with best-in-class consensus forecasts to 2028, unique broker forecasts, and the application of proprietary methodologies to support highly robust, detailed and accurate analysis.

**Evaluate Omnium** provides a complete, dynamic view of development risk and commercial return across all phases of the clinical lifecycle – including early-phase and privately-developed drugs not covered by analysts' forecasts. With product-specific data including Predicted Peak Sales, Probability of Technical and Regulatory Success (PTRS), R&D Costs, Net Present Value, Time-to-Peak and more, Evaluate Omnium makes it easier than ever to quantify and compare risk and return across the full pipeline landscape.

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#### **Evaluate Headquarters**

Evaluate Ltd.  
3 More London  
London SE1 2RE  
United Kingdom  
T +44 (0)20 7377 0800

#### **Evaluate Americas**

EvaluatePharma USA Inc.  
60 State Street, Suite 1910  
Boston, MA 02109  
USA  
T +1 617 573 9450

#### **Evaluate Asia Pacific**

Evaluate Japan KK  
Holland Hills Mori Tower 2F  
5-11-2 Toranomon, Minato-ku  
Tokyo 105-0001, Japan  
T +81 (0)70 4131 0112