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The State of Innovation in Europe

Introduction

Europe, and the many large pharmaceutical companies that call the continent their home, has a rich history of discovering essential medicines that have advanced human health globally. Yet, a growing number of leaders at these companies are voicing their concerns that Europe is becoming unfriendly towards innovation. In recent months, CEOs at Novartis, GSK, Sanofi, and Bayer have criticized policies either at the European Union level or within member (and former) member states, citing an environment that is uncompetitive with the US and China.

The main sticking points are measures designed to contain each country's expenditure on pharmaceuticals. In particular, the UK has come under fire for the expansion of its voluntary pricing agreement that aims to claw back spending above predefined thresholds. Innovators argue that the long-term consequence of such levies is to disincentivize innovation and will force R&D offshore, to the detriment of patients within Europe.

The pharmaceutical industry is very much global, and innovation is a critical export. Europe is losing ground at this level, with a declining stake in global R&D. As this white paper shows, Europe's innovative pipeline has reached a plateau, and is underexposed to high-growth areas such as oncology, cell and gene therapy. While investment is at all-time highs, this is targeted towards mature

companies, rather than entrepreneurial start-ups that are more at home in the US.

Pipelines and partnerships are the lifeblood of the pharmaceutical industry and dictate its future direction. With a declining stake in these, Europe runs the risk of the pharmaceutical industry being increasingly molded in the image of others. Emphasis on the US market opportunity is only increasing, biasing R&D towards high-cost innovations that are reimbursed by private healthcare. The rise of Chinese innovation and low-cost, fast-follower therapies threatens to squeeze Europe in the middle, where price controls have resulted in resistance towards new product launches.

European biopharmaceutical companies still have a hugely important role to play in the global innovation ecosystem. Europe may no longer match the US in scale, and find its position challenged by emerging markets, but it has a central role in partnering and possesses notable structural and scientific strengths. This paper reveals the current state of innovation in Europe, from pipeline constitution to emerging drug modalities, R&D alliances to financing trends. The narrative is supported by data and analysis from Citeline's proprietary, gold-standard industry sources, including Pharmaprojects and Biomedtracker.

The European Biopharmaceutical Industry in Stats #WeWontRest

Each year, the European Federation of Pharmaceutical Industries and Associations (EFPIA) publishes an annual factbook that is essential reading for any industry professional.[1] Some of the key metrics include a labor market of 840,000 skilled employees and €175bn trade surplus, showing the tremendous strategic importance of the pharmaceutical industry to the continent. Collectively, the region spends €41.5bn in R&D investment annually, a figure that has been rising at a compound annual growth rate (CAGR) of 4.0% since 2017.

At face value, these all look like impressive figures, although the report and EFPIA's accompanying lobbying activities strike a cautionary tone. "The sector has been severely hit by the impact of fiscal austerity measures introduced by governments across much of Europe since 2010," as described by EFPIA. Europe certainly has a long and storied history in the pharmaceutical industry, although this heritage is no guarantee of the future.

That 4.0% CAGR in R&D spend is eclipsed by an 8.5% growth rate in US R&D. While the US market accounts for around half of all pharmaceutical sales, 64% of newly launched product sales originate in the US. For Europe, which has a 23% share of the global market, drug launches progress much more slowly, capturing a comparatively lowly 17% of sales in the top five markets of France, Germany, Italy, Spain, and the UK.

While the equilibrium continues to tilt away from Europe and to the US, a new powerhouse in China is emerging. The local drug market has been growing at a double-digit rate for many years, and this has been accompanied by intense domestic

1. EFPIA (2022) The Pharmaceutical Industry in Figures. Available from: https://efpia.eu/media/637143/the-pharmaceutical-industry-in-figures-2022.pdf [Accessed 27 September 2022].

R&D activity. EFPIA estimates that R&D growth in China is running at an impressive 12.9% CAGR. If the current trajectory is maintained, China is on course to overtake Europe within the next 10–15 years purely in terms of spend, although other indicators point towards the crossover point being reached much earlier.

This rebalancing in Europe's position on the global stage has been a gradual process. Nathalie Moll, EFPIA Director General, points towards the first warning of a competitive decline being made in 1994 by the European Union.[2] Some of the statistics shared from Citeline's proprietary datasets later in this paper suggest that the process is now quickening. While this is not an existential threat, biopharmaceutical industry stakeholders must be mindful of the current state of innovation within Europe. For this reason, #WeWontRest has become a motto for the region, symbolizing the urgency with which drug developers, investors, regulators and policymakers must act to remain influential on the global stage. Past successes alone will not sustain the industry, and innovation is the essential component to protect Europe's future.

European Biopharmaceutical Pipeline

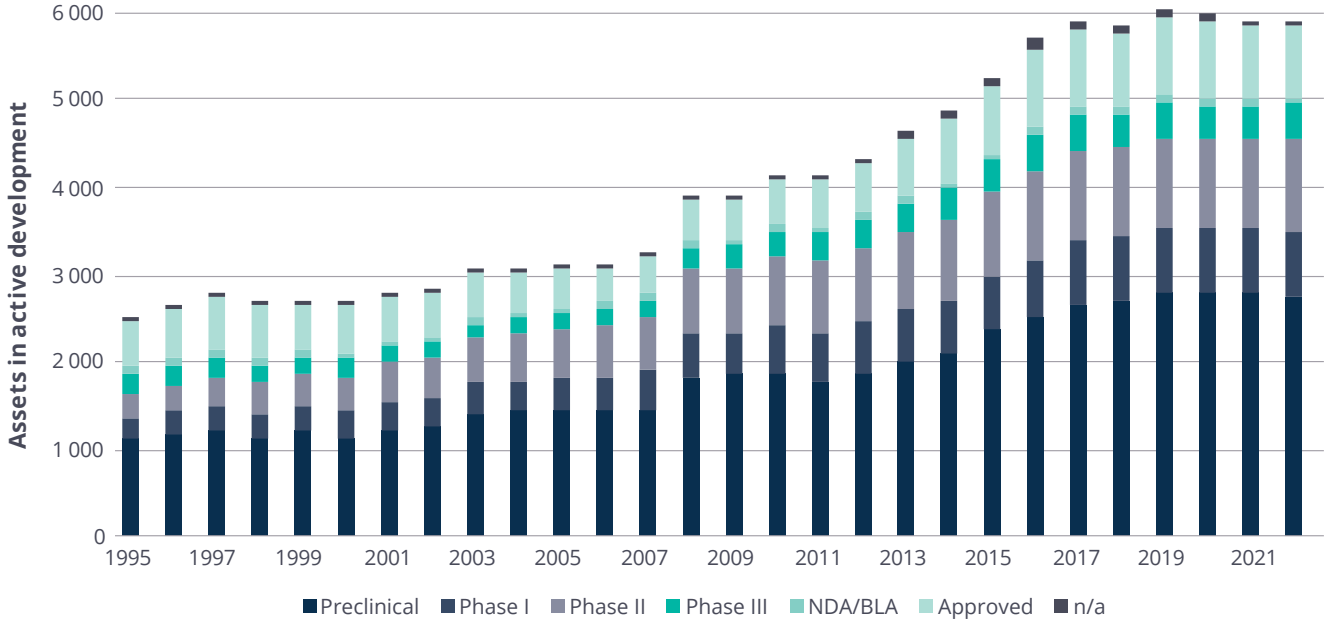
Growth has stalled after 6k ceiling reached in Europe

In line with its rich heritage, European biopharmaceutical companies have discovered or developed many of the medicines that have had most impact on global health. Buoyed by successes, drug developers have continued to increase R&D spending in order to produce the medicines of the future. This can be viewed through the lens of Citeline's drug development database, Pharmaprojects, which has tracked industry R&D over several decades. Annual snapshots are available going back to 1995, when European biopharmaceutical companies had a combined pipeline containing 2,500 assets under active development. This number has grown steadily year-on-year, before accelerating rapidly between 2012 and 2017 to reach almost 6,000 pipeline drugs.

However, rather than continue the ascent, European drug developers have reached a ceiling at this level, whereby current levels of investment cannot sustain any further expansion. Within this pipeline, 47% of drugs are in preclinical development, while 39% are at the various clinical stages from Phase I through to pre-registration. The remaining 14% are drugs that have already been approved and are being further developed in additional indications, patient subpopulations, or new geographies. These dynamics are shown in Figure 1 below; please note these static snapshots are taken annually each May.

2. Politico (2022) Dropping the dogma: Europe can support patients and innovation. Available from: https://www.politico.eu/sponsored-content/dropping-the-dogma-europe-can-support-patients-and-innovation/ [Accessed 27 September 2022].

Figure 1. Evolution of European biopharma R&D pipeline by highest stage of development



Source: Pharmaprojects, September 2022

In the years following 2017, the global pipeline has seen a notable shift. While Europe has remained stuck at around 5,900 assets, the global pipeline has expanded from 15,000 to exceed 20,000 drugs in 2022 with a compound annual growth rate (CAGR) of 6%. This has caused Europe's share of global R&D to plummet from 39% to 28% in just five years.

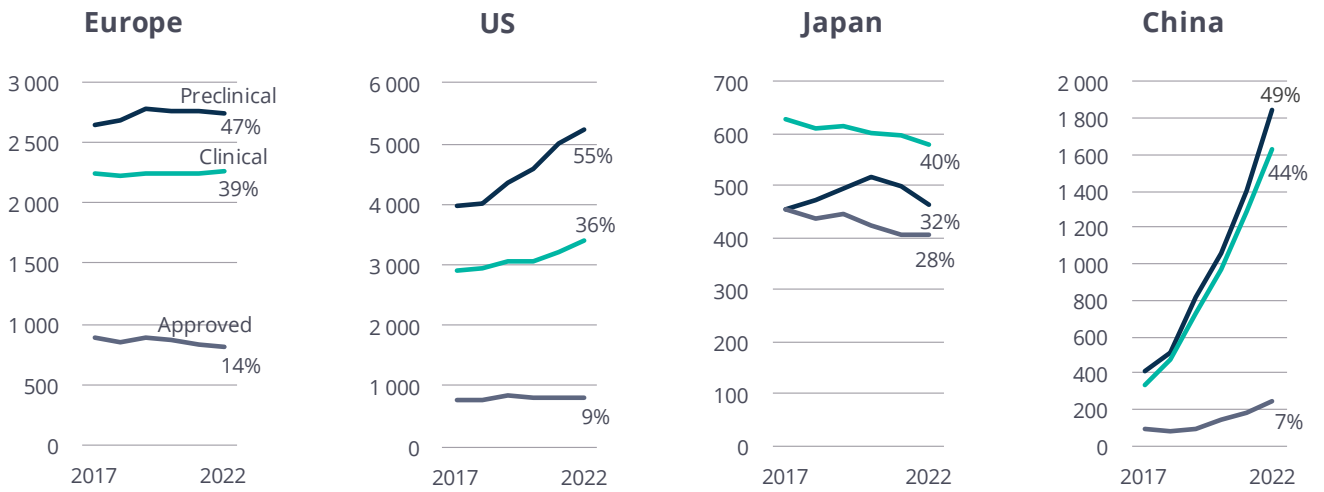
A large proportion of the global growth has come from China, which has seen a remarkable 35% CAGR over the last five years. Starting from a small base, Chinese companies have surged from 800 R&D projects to almost 3,800 during this time. The US biopharmaceutical pipeline has maintained its upward trajectory, adding further distance to Europe in second place with a 4% CAGR. Japan, which for a long time has been a major R&D hotspot, has declined in recent years and now finds itself comfortably behind China. These dynamics are shown in Table 1 and Figure 2 below. Note, drugs will be counted across more than one region if a licensee in a different geography is also pursuing development, so the totals will not sum.

Table 1. Drug pipeline growth by company headquarter location, 2017–22

	2017	2018	2019	2020	2021	2022	CAGR 2017–22
Europe	5,877	5,824	5,981	5,962	5,884	5,873	0.0%
US	7,737	7,832	8,341	8,535	9,113	9,481	4.1%
Japan	1,553	1,532	1,568	1,552	1,513	1,453	-1.3%
China	843	1,069	1,637	2,170	2,865	3,743	34.7%
Global	**14,926**	**15,264**	**16,690**	**17,717**	**19,012**	**20,384**	**6.4%**

Source: Pharmaprojects, September 2022

Figure 2. Pipeline growth sparklines by stage of development, 2017–22



Source: Pharmaprojects, September 2022

Richer pipeline quality can compensate for smaller quantity

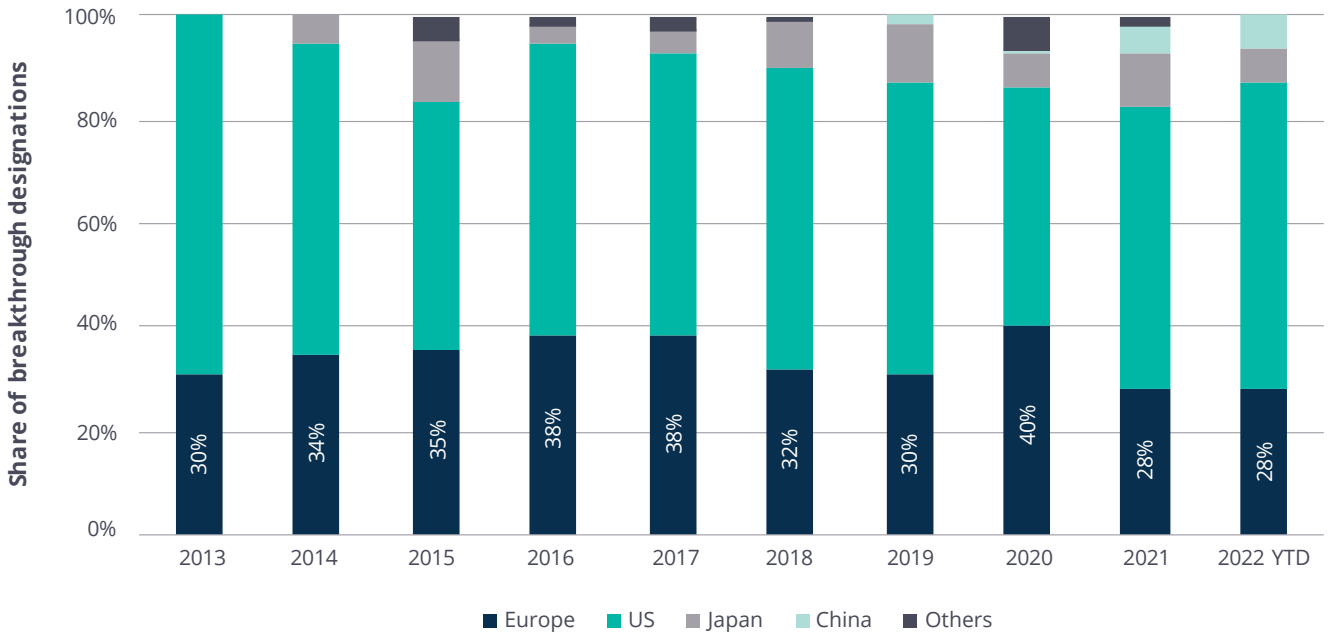
The absolute size of pipelines is at best a crude measure of innovation and health, considering that a vast majority of early stage assets will not reach the market. As shown in Figure 2, the European pipeline is less heavily weighted towards preclinical drugs (47%) than either the US (55%) or China (49%). Much of the recent growth within the US and China has come from this preclinical expansion, which is only a weak proxy for clinical innovation. Conversely, European companies have a larger proportion of assets in late-stage clinical trials, or those that are already approved and undergoing further development. It is these products that can be more confidently predicted to succeed, rather than a bloated pool of early stage drugs with little-to-no patient experience.

Even within clinical-stage assets, there is huge variability in likelihoods of approval, with factors such as therapy area, drug modality, and clinical trial design features all weighing heavily on a drug's prospects. Even securing regulatory approval is no guarantee of having a tangible effect on patient outcomes and thus truly being innovative. With all of this in mind, it is relevant to segment the European biopharmaceutical pipeline to better understand how it is competitively positioned on the global stage.

One measure of pipeline quality is to evaluate the number of drugs awarded regulatory designations suggesting that the drug represents an improvement in the standard of care. The US Food and Drug Administration (FDA) began its Breakthrough Therapy Designation (BTD) scheme in 2012, to expedite the development of drugs for serious or life-threatening diseases where preliminary clinical evidence suggests substantial

improvement over available therapies. Drug regulators in Europe and Japan subsequently created similar incentives for their markets, termed PRIME and Sakigake, respectively. Since inception, a total of 433 discrete drugs have been awarded at least one of these designations, which is a notable milestone and endorsement for the quality and potential innovation that the drug provides.

Figure 3. Breakthrough designation awards by location of lead company, 2013–22



Source: Pharmaprojects, September 2022

As noted previously, Europe's share of global R&D stands at 28%, having declined from 39% in 2017. This trend is mirrored almost perfectly in Figure 3, which plots the headquarter location of companies being awarded breakthrough status for their pipeline drug. European companies have retained an approximate 30–40% share of such designations since 2013, although this has dipped to 28% in the last two years. European pharmaceutical companies have therefore been unable to compensate for a declining share of the pipeline with a disproportionate number of therapeutic breakthroughs.

Europe is underweight in oncology, cell and gene therapy

Europe's exposure to emerging science will also have long-lasting implications for its future prospects. As the industry pivoted towards biological drugs in previous decades, European companies have been well positioned with strong capabilities in antibody drug discovery. Pioneers include Cambridge Antibody Technology and Genmab, while large European pharmaceutical companies have made strategic acquisitions to bolster their capabilities, such as Roche (Genentech) and AstraZeneca (MedImmune). This biotechnology

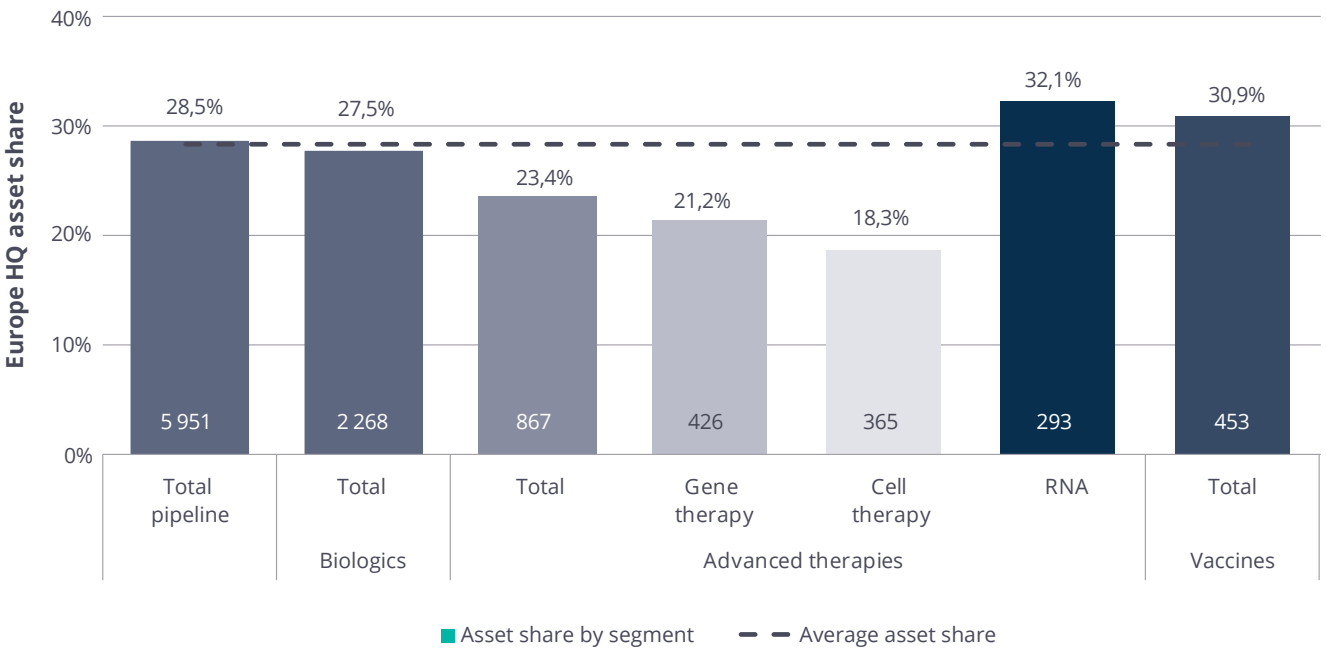
3. Sherman et al. (2013) Expediting Drug Development — The FDA's New "Breakthrough Therapy" Designation. Available from: https://www.nejm.org/doi/full/10.1056/NEJMp1311439 [Accessed 26 September 2022].

revolution has also extended beyond the design of drugs, also modernizing the way vaccines can be manufactured. Europe has a long-established leadership position in the vaccines space through companies such as Sanofi and GlaxoSmithKline.

The next wave of evolution within the pipeline is well underway, as drug developers are seeking to capitalize on new genomics technologies to create drugs and vaccines based on cell, gene and RNA scaffolds.

As shown in Figure 4, Europe is part of this transition, but with varying levels of exposure. With 5,951 drugs in active development as of September 2022, European biopharma has a 28% share of the total global pipeline. The proportion of biologics under development (2,268, 27%) is on par, while vaccines remain a strength (31%), although the subset of advanced therapies is notably below average. Europe possesses just 23% of the global pipeline for advanced therapies, with 867 gene, cell or RNA-based drugs in development as of September 2022. Within this, Europe is well positioned in RNA drug development (32%), thanks to innovators such as BioNTech and CureVac, in addition to acquisitive larger companies like Novo Nordisk and Sanofi. Counterbalancing this, Europe is trailing rivals from the US and China in gene (21%) and cell therapy (18%), with much smaller domestic pipelines. While these are not yet mainstream drug modalities, European innovators are already giving away a large head start, which will be difficult to overturn through acquisitions alone as the technologies gain further clinical validation.

Figure 4. European exposure to R&D growth segments by modality



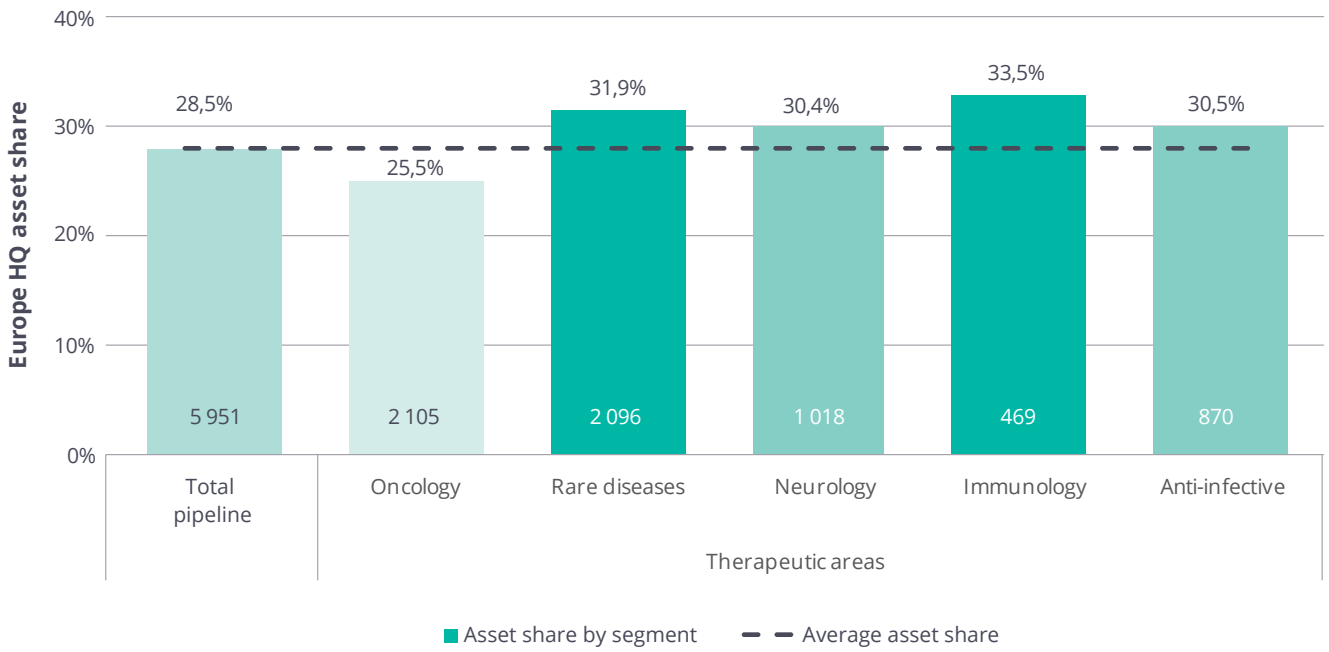
Source: Pharmaprojects, September 2022

A similar analysis by therapy area shows an analogous trend, whereby Europe as a collective is underexposed to the single largest growth driver in R&D trends — oncology — but has pockets of strength in other growth drivers. Europe's share of global oncology drug development is just 25%, which leaves it underexposed to a therapy area that accounts for approximately 40% of active pipeline assets, new clinical trial starts and partnering activities globally.

By contrast, Europe is a global leader in rare diseases R&D. 32% of global rare disease drug development is taking place within European-headquartered biopharmaceutical companies, even despite the international acquisitions of former standalone companies such as Actelion, Shire and GW Pharmaceuticals. This position is supported by the R&D legacy of such companies, plus the strategic emphasis that larger players place on rare diseases. AstraZeneca and Sanofi are two such big pharma companies that have placed large bets on Alexion ($39bn) and Genzyme ($20bn), respectively.

Besides oncology and rare diseases, the other prominent segments of the pipeline are neurology, immunology and anti-infectives. Europe carries an above-average share of the global pipeline in each area, ranging from 30% to 34%, as shown in Figure 5. It could be argued that the European pipeline has better overall balance across the major therapeutic challenges. By limiting exposure to the hyper-competitive oncology drug landscape, eventual success rates and patient access may counterbalance any slower growth rates.

Figure 5. European exposure to R&D growth segments by therapy area



Source: Pharmaprojects, September 2022

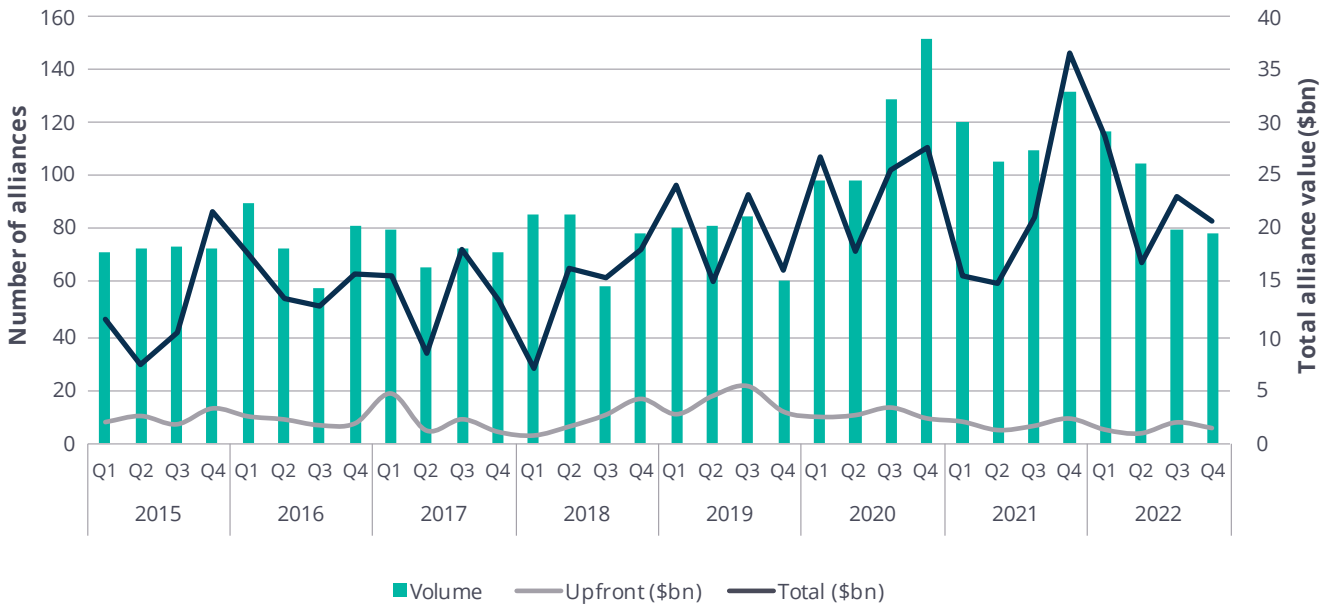
European Alliances and Financing

Healthy and growing appetite for partnering deals

European companies continue to play an active and prominent role in the global partnering landscape. Almost half (43%) of all alliances since 2015 involved at least one European company as either the licensee or licensor, which trails only the US (68%) and is a long way ahead of the nearest rival (China 13%. Japan 11%).

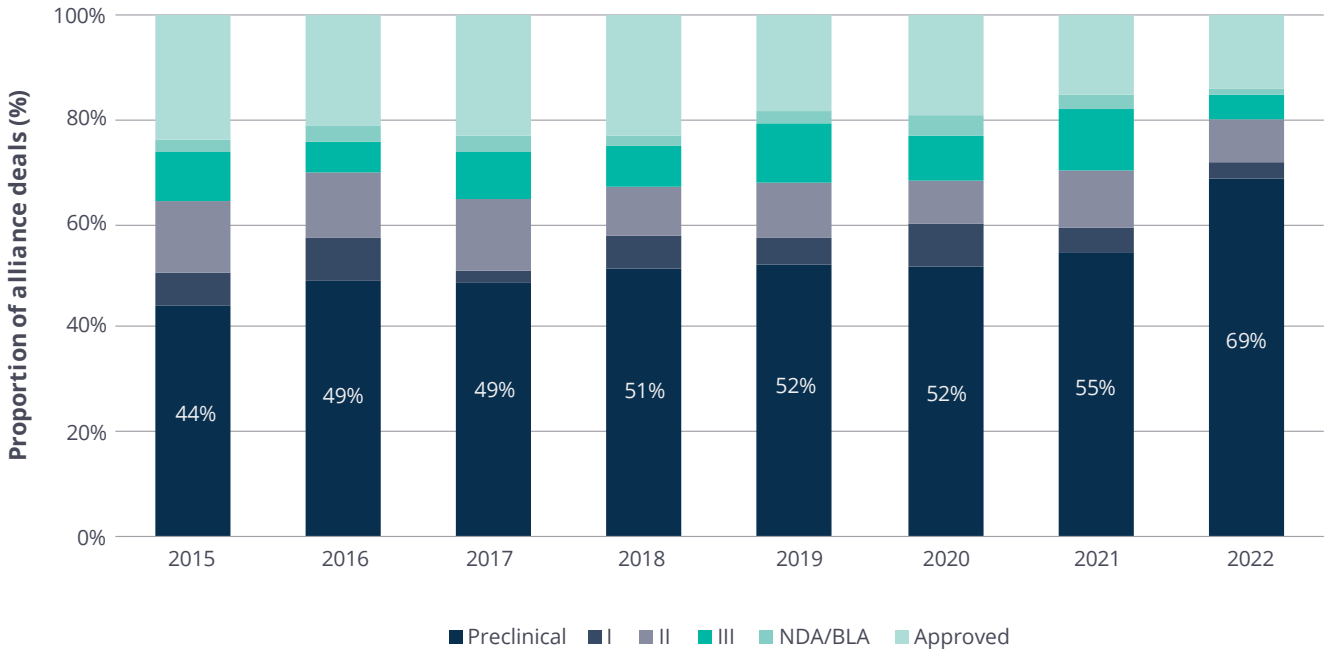
As can be seen in Figure 6, the general trend within Europe is one of increasing partnering activity, measured either as the number of deals or their value. In the most recent period, there are an average of 95 alliances involving European biopharmaceutical companies each quarter, with combined upfront payments of $1.4bn and a total potential value in excess of $20bn. The number of deals has expanded at a compound annual growth rate (CAGR) of 4% between 2015 and 2022, which the total potential deal value achieving an 8% CAGR. Few deals will realize all the milestones required to hit this limit, so it is noteworthy that total upfront payments have declined at a CAGR of -7% over the same period. Set against the increase in the number of alliances, this reflects the growing tendencies of pharmaceutical companies to license assets at earlier stages of development and adapt typical deal structures to reflect this risk. This trend is observed in Figure 7, which segments European licensing deals with single assets by clinical development phase. Over this time period, the average upfront for a preclinical deal was $8m, rising to $37m for Phase III assets and $51m for those under regulatory review.

Figure 6. Europe biopharma alliance trends, 2015–22



Source: Biomedtracker, February 2023

Figure 7. Alliance deals by developmental stage of asset

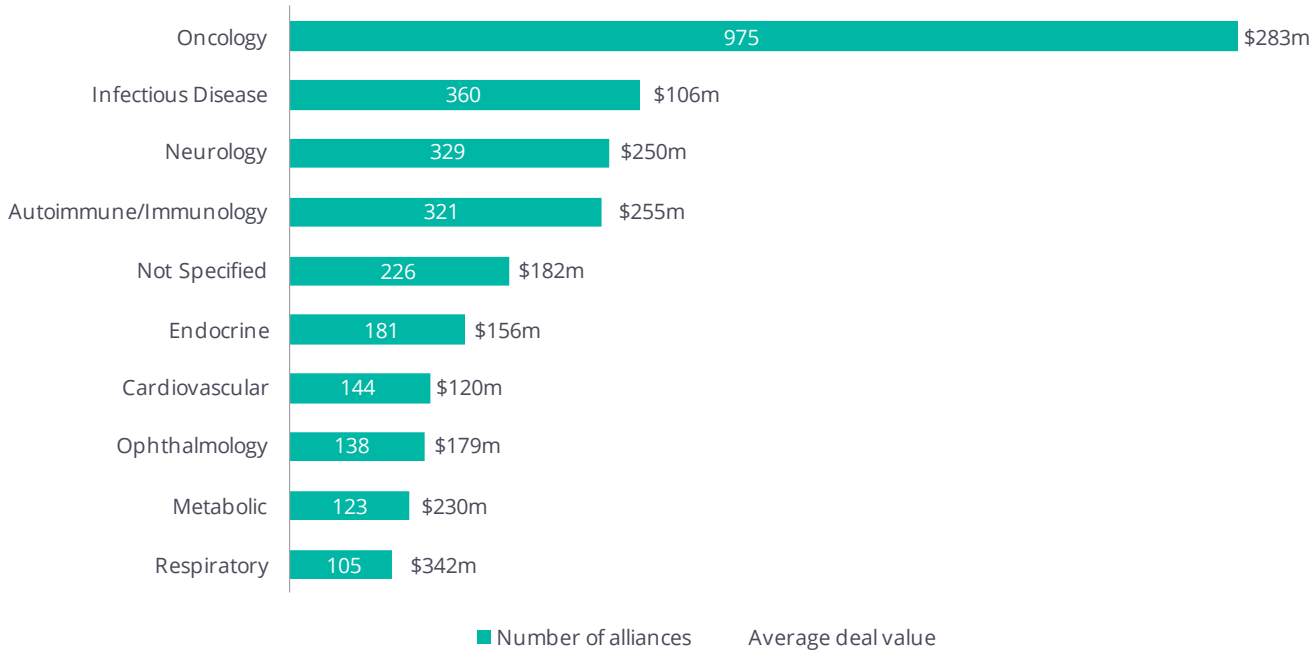


Source: Biomedtracker, February 2023

In line with the prevailing global trend of the last decade, a large proportion of alliances involving European biopharmaceutical companies are centered on oncology. In total, 37% of all partnerships disclose an oncology focus. A total of 975 oncology alliances have been signed since 2015, at an average potential deal value of $283m each, as shown in Figure 8 below. This value is considerably above the average ($200m) and almost double the typical deal value of non-oncology alliances ($152m). Partners are therefore paying a considerable premium to gain external capabilities in the development of cancer therapeutics.

Beyond oncology, more than 300 deals have been agreed concerning the development of assets for infectious diseases, neurology and immunology, although these are very distant runners up. More than half of infectious disease deals in this period were signed since the start of the COVID-19 pandemic, suggesting the change in strategic focuses of many pharmaceutical companies in response to COVID-19. Neurology and immunology are perennially in the top three or four therapeutic areas for R&D activity on account of the unmet need within chronic disorders in these categories and the size of their target populations.

Figure 8. Top ten therapy area focuses of European biopharma alliances, 2015–22

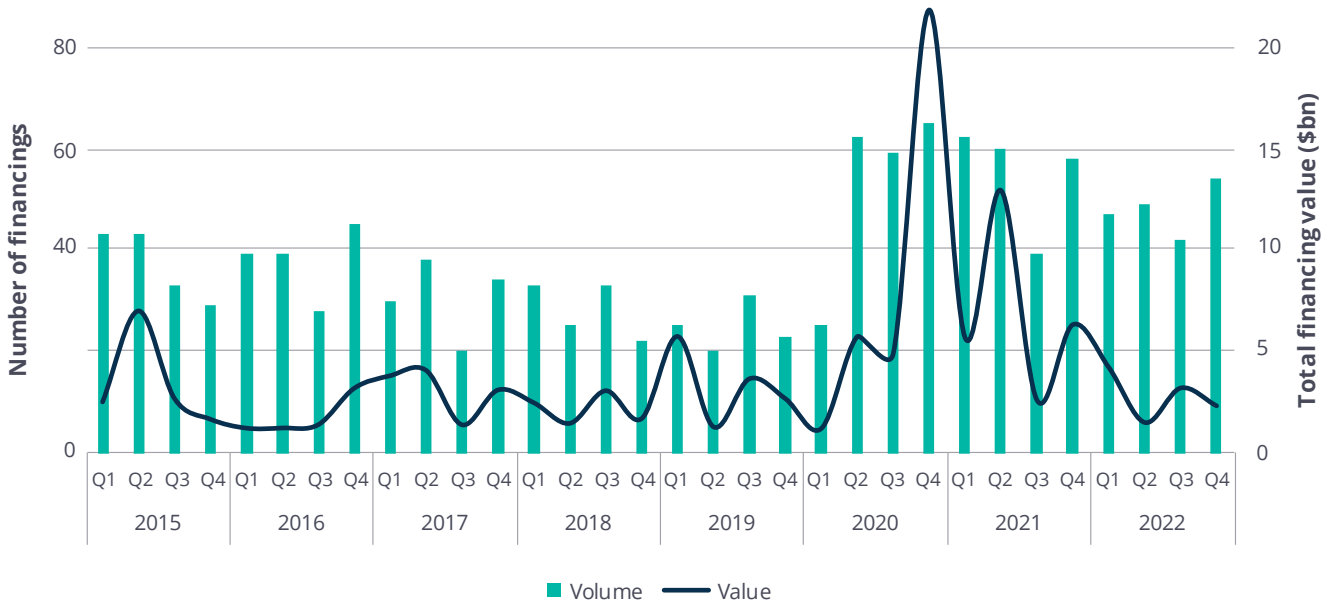


Source: Biomedtracker, February 2023

Normality restored after pandemic-related capital influx

European companies seeking to raise capital were among the beneficiaries of the pandemic, in line with broader investor interest in the biopharmaceutical sector. After several years of relatively stable levels of financing deals, 2020 saw a remarkable uptick in both the number and potential value of fundraising activities. This peaked in Q4 2020 with 65 separate financings tracked by Biomedtracker for a total value of $22bn, before gradually regressing back towards the mean. Some degree of fluctuation is inevitable, although the last full four quarters show an average run rate of approximately $3bn raised across 50 deals per quarter. It is not yet clear whether this is a new baseline level of fundraising activity, as activity is still approximately 50% higher than in the years prior to the pandemic.

Figure 9. Europe biopharma financing trends, 2015–22



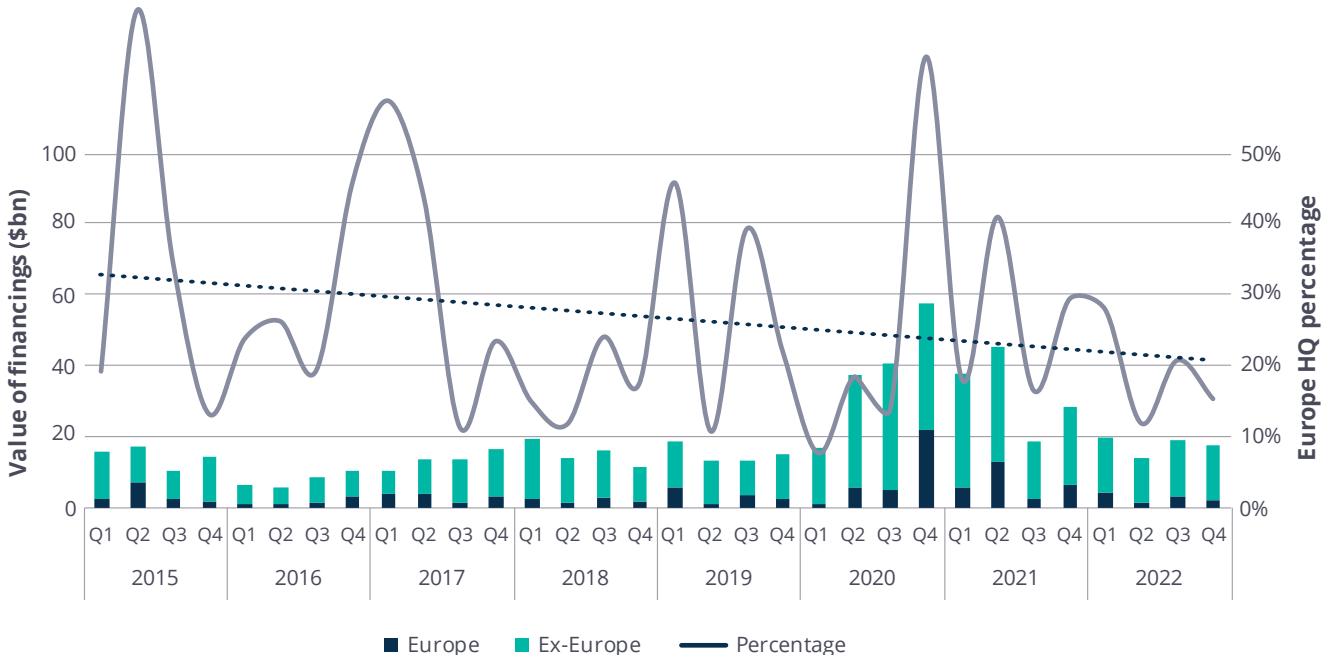
Source: Biomedtracker, February 2023

Europe is gradually losing share on the global stage

Charting the proportion of global fundraising activities conducted by European-headquartered biopharma companies shows a gradually diminishing share. In terms of deal volumes, European-headquartered companies had a one-quarter share in 2015, although this has ticked down to one in five financings on average by 2022. Assessing by the value of these financings, as shown in Figure 10, the ratio declined from one-third to one-quarter of all activity over the same time period.

The chief beneficiary –or cause – of Europe's decline on this metric has been the rising attractiveness of Asian markets. In particular, China is capturing an ever-increasing portion of investment as both the domestic drug market increases in size and volume, and China-headquartered pharma companies expand their R&D capabilities to include innovative drug discovery as well as generics and manufacturing. In the meantime, the US has retained its standing as the leader in life sciences innovation and entrepreneurship.

Figure 10. Europe vs. ex-Europe for biopharma financing, 2015–22

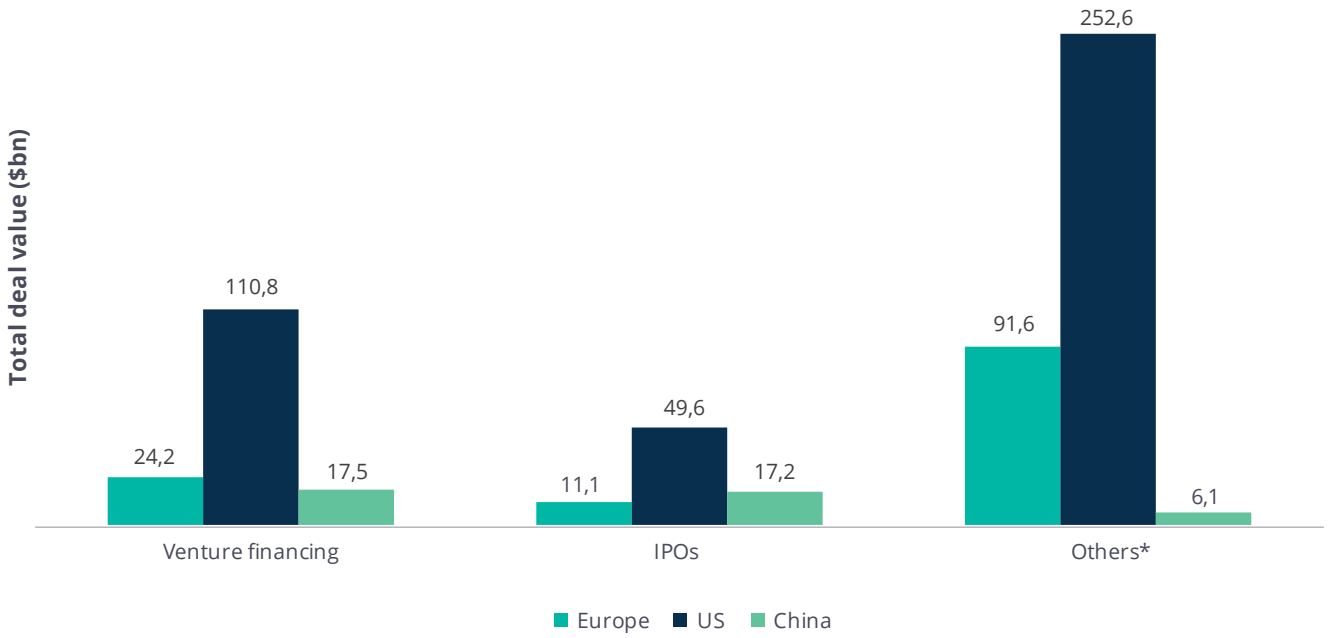


Source: Biomedtracker, February 2023

In recent years, investment into new companies in Europe has lagged international comparators. Rather, the balance of investment in Europe has largely been towards older companies that are either taking on debt or seeking follow-on public offerings (FOPOs). Assessing financing deals since 2015, companies in Europe have raised a combined $35bn via venture financing or initial public offerings (IPOs), accounting for just 15% of global activities via these two methods. This is overshadowed by the $160bn in new company financing that originates in the US, which possesses a two-thirds share of the global total. Rather than competing with the US, China is now a much more appropriate comparator, where companies have also raised $35bn via venture financing or IPOs since 2015 (see Figure 11).

With the US position entrenched, and China's capabilities and influence only growing, Europe risks slipping further adrift into third place on the global scale. For a mature region, lower levels of start-up activity threaten its incumbent position. Another concern is the tendency of European start-ups to raise funds via US investors. It is perceived that private US investors are willing to grant higher valuations to new companies on the strength of future growth potential, rather than anchoring in traditional measures of value such as data and clinical milestones. On the public side, the vast majority of recent European-headquartered IPOs are taking place on US stock exchanges. Since 2019, just two European companies – Amniotics and Hyloris – have completed IPOs in Europe, compared to the 40 companies that have new listings on the Nasdaq Global or NYSE.

Figure 11. Biopharma financing in Europe, US, and China by deal type since 2015



Source: Biomedtracker, February 2023

It remains to be seen whether the balance of life sciences investment will continue to tip in favor of the US and China ahead of Europe, or whether wider geopolitical and economic circumstances will indirectly boost Europe's standing. As the pandemic-related influx of capital winds down and some degree of normality is restored, it may be that reduced access to capital will harm regions in which companies attempted to grow more aggressively. Publicly listed US biotechs have faced a particularly torrid 18 months, while investor demand for Chinese companies has also cooled. The more measured and conservative behaviors of European innovators may mean that they are better placed to weather the biotech winter of 2021–22 and emerge as attractive investment propositions.

Key Takeaways

Collectively, European biopharmaceutical companies are actively developing around 6,000 assets. While the global pipeline has grown at a CAGR of 6% in recent years, Europe has been stubbornly flat as small increases in R&D spend have been swallowed by the complexity and cost of drug development. Moreso than in other countries, Europe's pipeline is more heavily weighted towards later-stage drugs that are expensive to sustain, although there is no discernible difference in the quality of these assets.

Beyond stage of development, the constitution of Europe's pipeline is both similar to and different from its peers. Oncology is naturally a strong focus, as are advanced therapies using genetic technologies. Despite this, European companies are underexposed to these high-growth areas, and the region runs the risk of falling behind technologically, particularly in the cell and gene therapy field. Outside of these areas, Europe is entrenching its leadership position in rare diseases, vaccines, neurology and immunology.

Europe, like the rest of the world, saw a flurry of dealmaking activity at the turn of the decade, linked to pandemic-related investment and broader R&D collaboration. The number and value of drug development alliances has grown further since, with a strong shift towards early-stage assets and access to platform technologies. In contrast, fundraising activities have pulled back from the peaks of 2020 and H1 2021 but remain at elevated levels. However, when viewed as a proportion of global activity, Europe is losing ground, dropping its share of financing deals to around one-fifth of absolute number, and one-quarter for value. European fundraising is more typically weighted towards mature companies taking on debt, rather than the amount of entrepreneurial activity witnessed in the US through venture capital and initial public offerings (IPOs).

Europe is no longer the force it once was. While humbling to admit, the axis between the US and Europe has tilted, such that Europe now occupies less than a 30% share of the global market across various measures. This includes the scale of innovation, from pipeline size to the number of therapeutic breakthroughs, as well as commercial indicators such as prescription pharmaceutical sales and financial investment. It is incumbent on the full range of stakeholders — drug developers, academia, investors, payers, regulators, policymakers — to set about a strategy to halt any further decline and protect Europe's standing in the global innovation ecosystem. On the part of industry players, this involves an impartial assessment of scientific strengths and technological shortcomings, prioritizing investment at the cutting edge of innovation and unmet patient needs.

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Daniel has over a decade of experience as an analyst in the biopharma industry, spanning roles in drug discovery, market analysis, competitive intelligence, and strategic consulting. He now develops and leads Citeline's Thought Leadership program, producing materials that help clients across a range of hot topics in the biopharma industry. As part of this, Daniel regularly participates in webinars, conferences, and other speaking arrangements, and he has provided expert insights across a wide range of leading industry and business publications. Prior to joining Citeline, Daniel worked as a medicinal chemist at the UK biotech company Summit Therapeutics and graduated with First Class Honors in Natural Sciences from the University of Bath.

About Citeline

About Citeline

Citeline (formerly Pharma Intelligence) powers a full suite of complementary business intelligence offerings to meet the evolving needs of health science professionals to accelerate the connection of treatments to patients and patients to treatments. These patient-focused solutions and services deliver and analyze data used to drive clinical, commercial, and regulatory related-decisions and create real-world opportunities for growth.

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