How do biotechs stay the course in uncharted waters?

Beyond borders: EY biotechnology report 2022

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CONTENTS

TO OUR CLIENTS AND FRIENDS

This 32nd edition of our *Beyond borders* report offers a chance to take stock of the biotechnology (biotech) industry's impressive performance during a period of intense global disruption. When, five years ago, we last published our *Beyond borders* overview of the sector, we noted the growing geopolitical complexities set to impact biotech. Titling our 2017 report "Staying the course," we observed that the industry would have to navigate a business environment in which, increasingly, "uncertainty is the only certainty." From the perspective of 2022, we can affirm that biotech has indeed successfully stayed the course, despite the upheavals that have affected global business since the last edition of this report.

In 2017, looming challenges included the impact of the UK's Brexit vote and the intensifying US debate over the future of health care at the outset of the Trump administration. Five years on, there is no question that biotech has not only survived but thrived throughout these and subsequent disruptions — most notably the worldwide turbulence caused by the COVID-19 pandemic since early 2020. We can quantify the industry's success in staying on track throughout this period: In 2021, the last full calendar year, the industry's revenues were 55% higher than 2016 (as we noted in our previous report); biotech market capitalization had risen 84%; financing levels had surged 116%, with huge increases in the industry's levels of venture capital (VC) investment and the biotech IPO market; and annual drug approvals were up 80% compared with 2016.

Yet in 2022, biotech must contend with an operating environment arguably even more uncertain than in 2017. The unforeseeable geopolitical situation in Eastern Europe will play out in a global business landscape still adjusting to the impact of the pandemic. In the wake of the past two years, biotech (as with other industries) is facing new tests, including supply chain disruption; intensifying competition for talent; challenges to established commercial models; and rising pressure to demonstrate commitment to addressing environmental, social and governance (ESG) issues, from access and affordability to clinical trial diversity (all explored in detail in this report). Amid global macroeconomic changes, including resurgent worldwide inflation and the ever-present risk of an economic recession, the financial environment for biotech has significantly shifted in the opening months of 2022, with valuations plunging and the IPO window closing.

Taken together, these developments leave biotech navigating uncharted waters in 2022. Yet the fundamentals for the industry remain strong. Biotech's growing R&D investments support a rich late-stage clinical pipeline that promises to remain a key driver for the US$1.4 trillion global biopharmaceutical (biopharma) industry.[1] While some biotechs may struggle with reduced access to the public markets, the sector as a whole will continue to flourish. Above all, the past five years have delivered an irrefutable lesson in the resilience of biotech: Despite these challenges, we can be confident that the industry will continue to stay the course.

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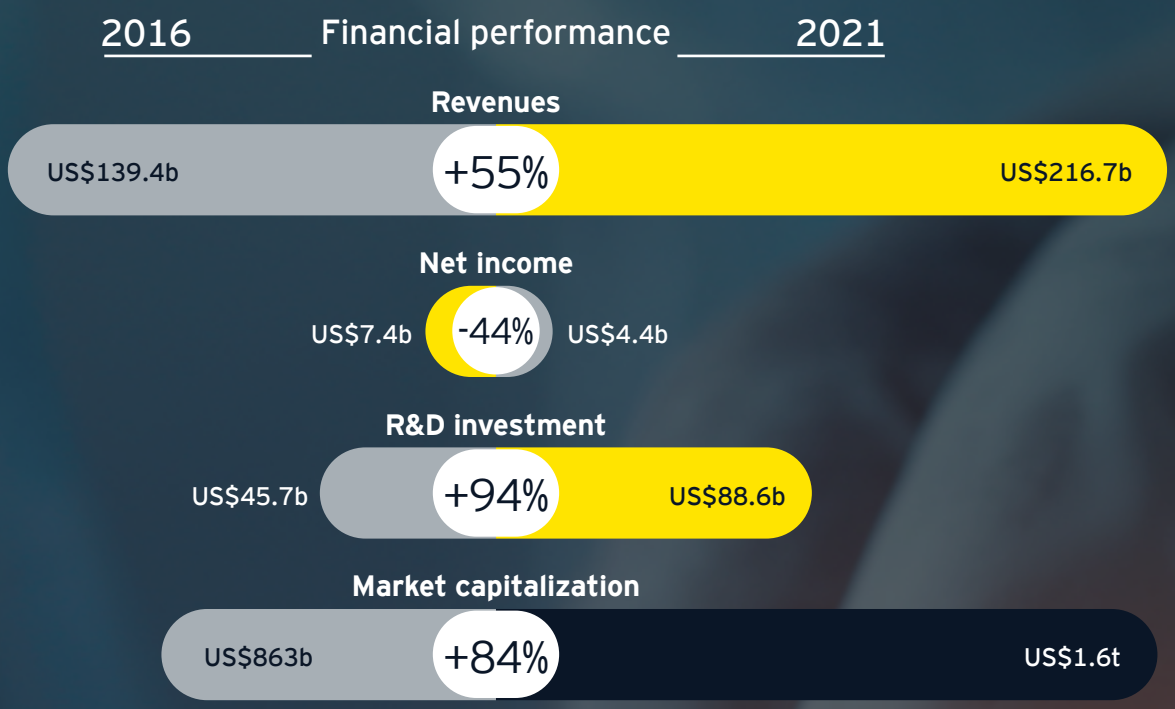
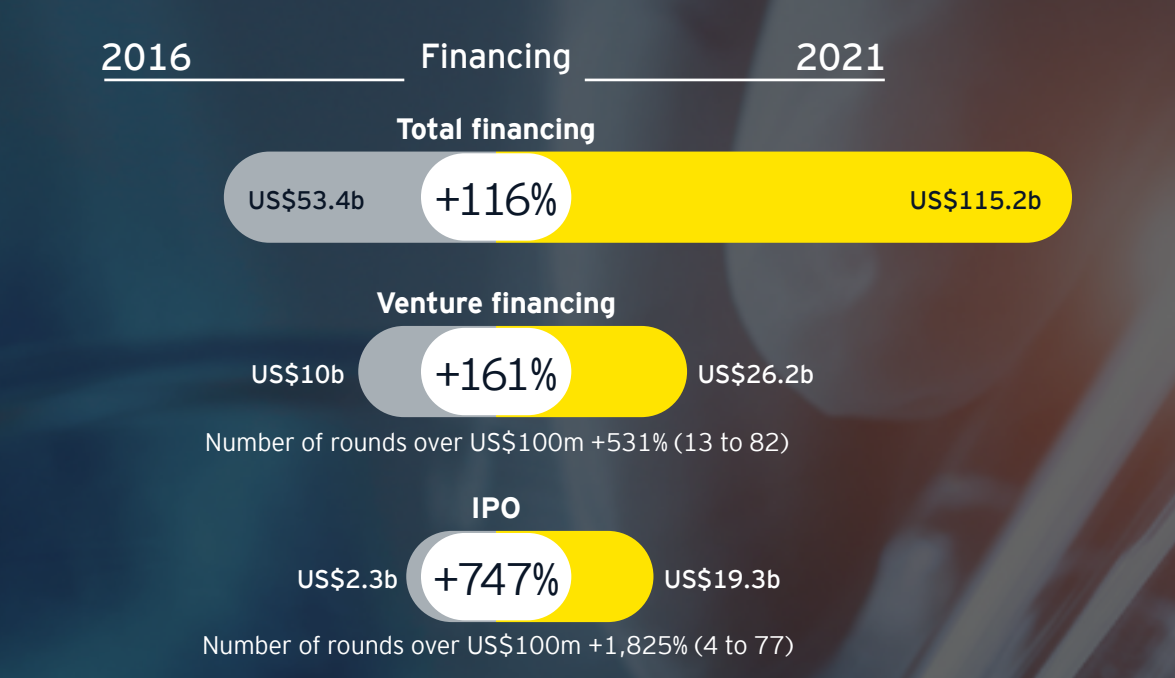
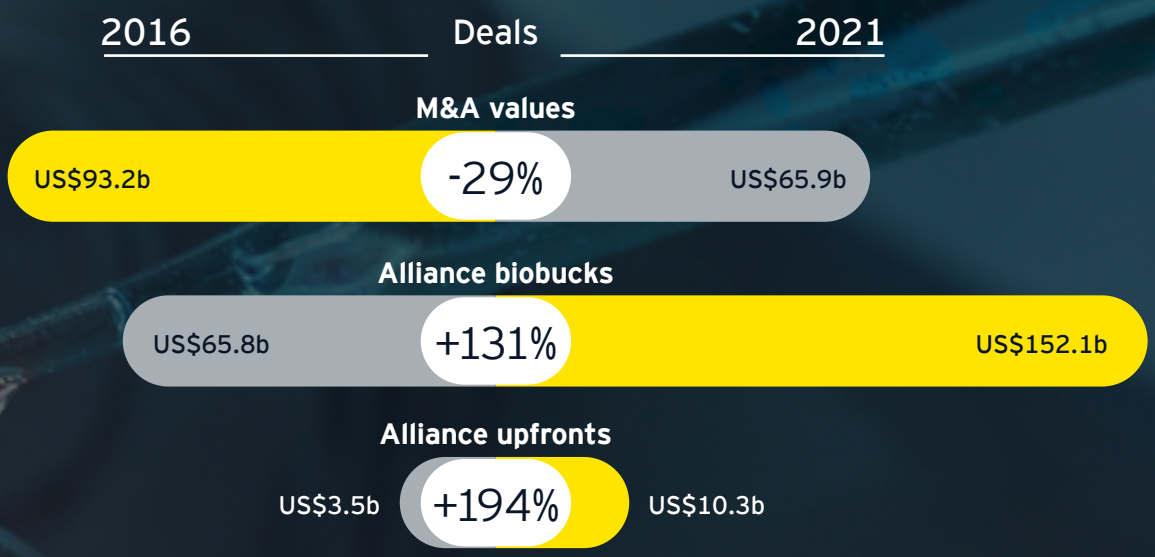
1. *The Global Use of Medicines 2022*, IQVIA, January 2022.

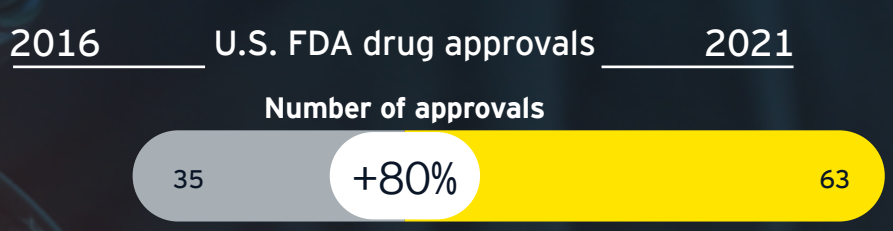
BEYOND BORDERS
5-YEAR DIFFERENCE (2016 vs. 2021)

The state of the biotech industry has significantly evolved over the past five years









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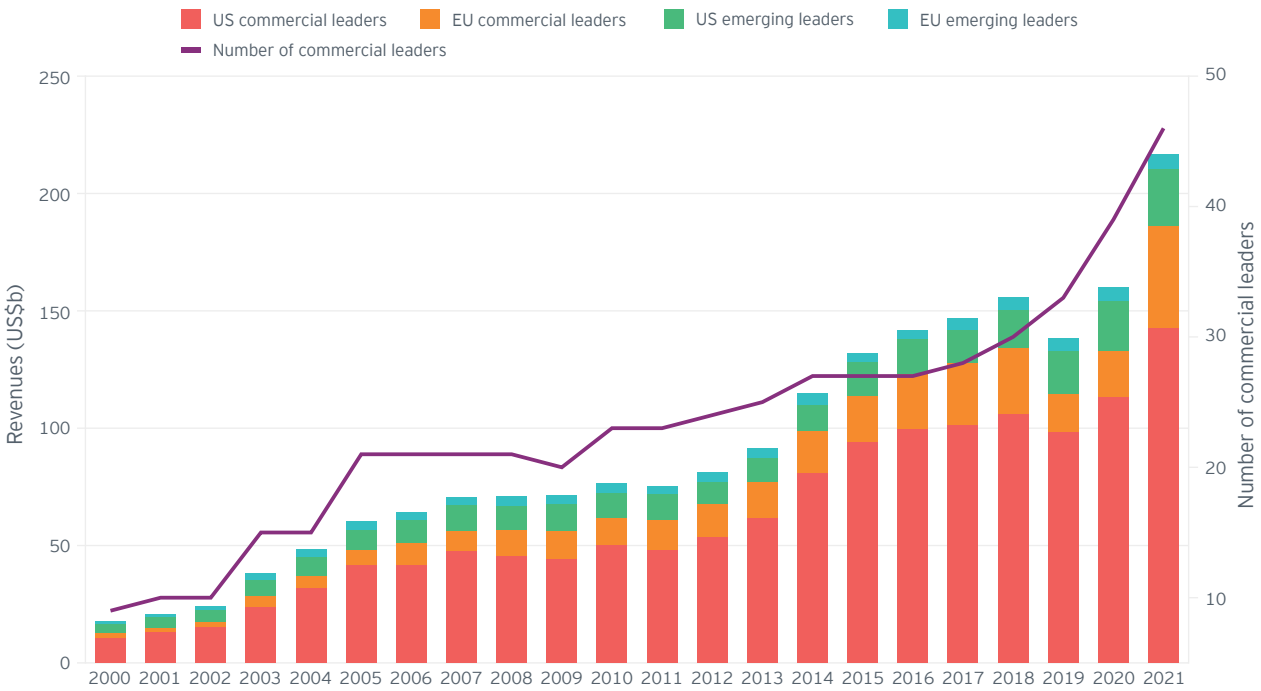
THE YEAR IN REVIEW

Biotech performed exceptionally well in 2021, not in spite of but because of the COVID-19 crisis. The pandemic continues to disrupt health care delivery and is projected to result in a cumulative reduction in global medicine spending of US$175 billion over the next seven years compared with the pre-pandemic outlook.[2] Yet the vaccines and antivirals biotech has innovated to address COVID-19 have delivered a significant top-line surge, with biotech revenues hitting US$216.7 billion in 2021 – a dramatic 35% annual increase on 2020 (see Figure 1).

Figure 1. US and EU public company revenues, 2000–21



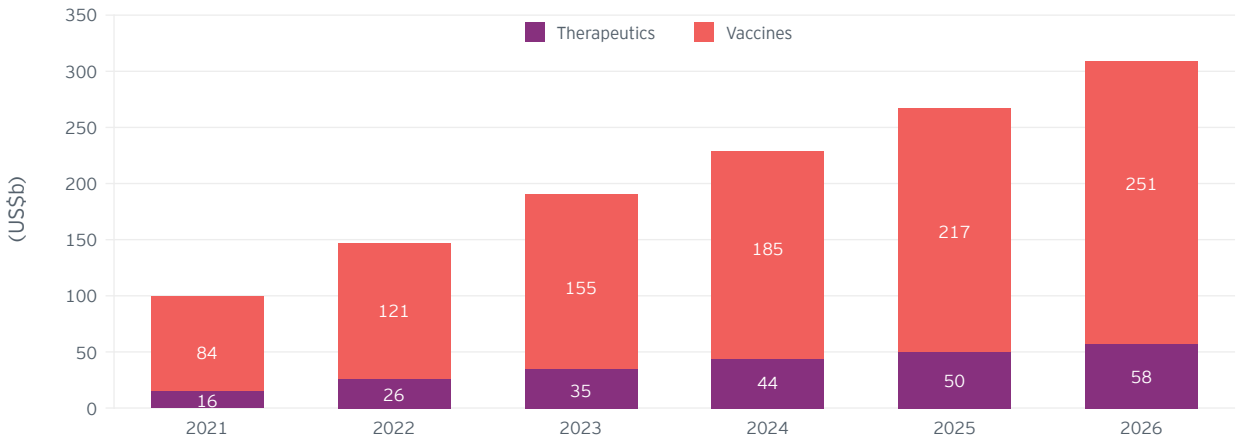
Source: EY analysis, company reports
Commercial leaders are companies with revenues >=US$500m

Traditionally, the vast majority of biotech revenues are generated by the industry's commercial leaders (defined here as the companies that generate more than US$500 million in annual revenue). Indeed, in 2021, the 46 commercial leaders generated 86% of the industry's total revenues. However, within this leading group, an astonishing 22% of all revenues were generated solely by the two companies that pioneered mRNA-based vaccines against COVID-19: BioNTech and Moderna, which collectively generated over US$40 billion in 2021 revenues.

2. Ibid.

BioNTech and Moderna only joined the ranks of the commercial leaders in 2020, yet they are generating revenues greater than any other biotech in the world, barring long-standing industry leaders Amgen and Gilead. This dramatic rise underscores the extent to which the COVID-19 market dominated the biotech story in 2021. Moreover, this explosive growth is not going to disappear overnight — on the contrary, projections indicate that cumulative spending on vaccines and therapeutics targeting the coronavirus will more than double by 2026 (see Figure 2).

Figure 2. Projected cumulative spending on COVID-19 vaccines and therapeutics (2021–26)

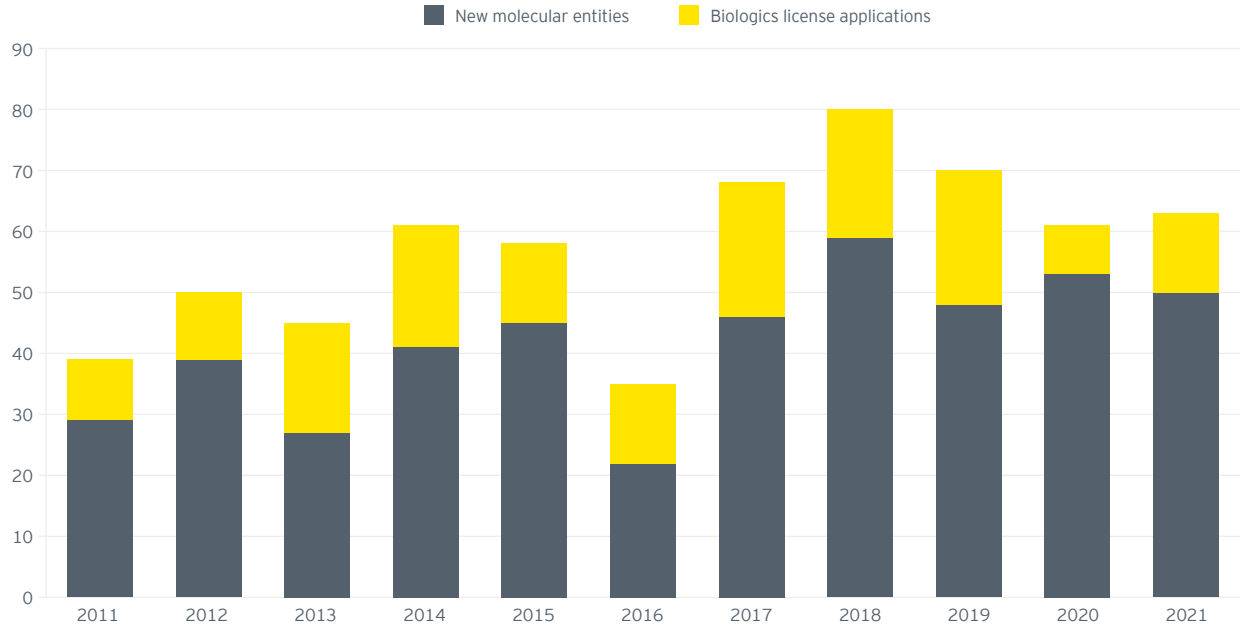


The Global Use of Medicines 2022: Outlook to 2026, IQVIA, December 2021

Though vaccines will continue to dominate this space, drugs will take a growing share of the market. Multiple biotechs are already addressing this opportunity, including leading industry players Regeneron and Gilead. Regeneron's REGEN-COV treatment brought the company 89% revenue growth in 2021, while Gilead recorded 11% growth on the strength of its Veklury (remdesivir) product. Both featured among the top biotech revenue growth stories of 2021, as did Vir Biotechnology, a new entrant in the commercial leader group in 2021. Vir's Xevudy (sotrovimab) monoclonal antibody (mAb) treatment for COVID-19 reached US$1.1 billion in revenues on the strength of its profit-sharing arrangement with its partner, GlaxoSmithKline.

Of course, despite the commercial significance of COVID-19 in 2021, biotech innovation extends far beyond this market. Indeed, despite regulatory delays caused by the ongoing challenges at the Food and Drug Administration (FDA) with inspection delays caused by the pandemic, 2021 saw 63 new products approved (50 new molecular entities and 13 biologics license applications; see Figure 3). This exceeded 2020's total, even excluding the emergency use authorizations that brought certain COVID-19 products to market.

Figure 3. U.S. FDA product approvals, 2011–21



*Data for biologics license applications from 2000-2021; new molecular entities from 2011-2021.
Source: FDA website

These approvals should be only the start of a wave of new innovations reaching the market. Biotech pipelines are full: Over 6,000 drugs are in active development, with emerging biotechs accounting for a record 65% of them. This total includes around 800 next-generation biotherapeutics, with notable R&D activity in CAR-T and NK cell therapies, gene editing and RNA therapeutics.

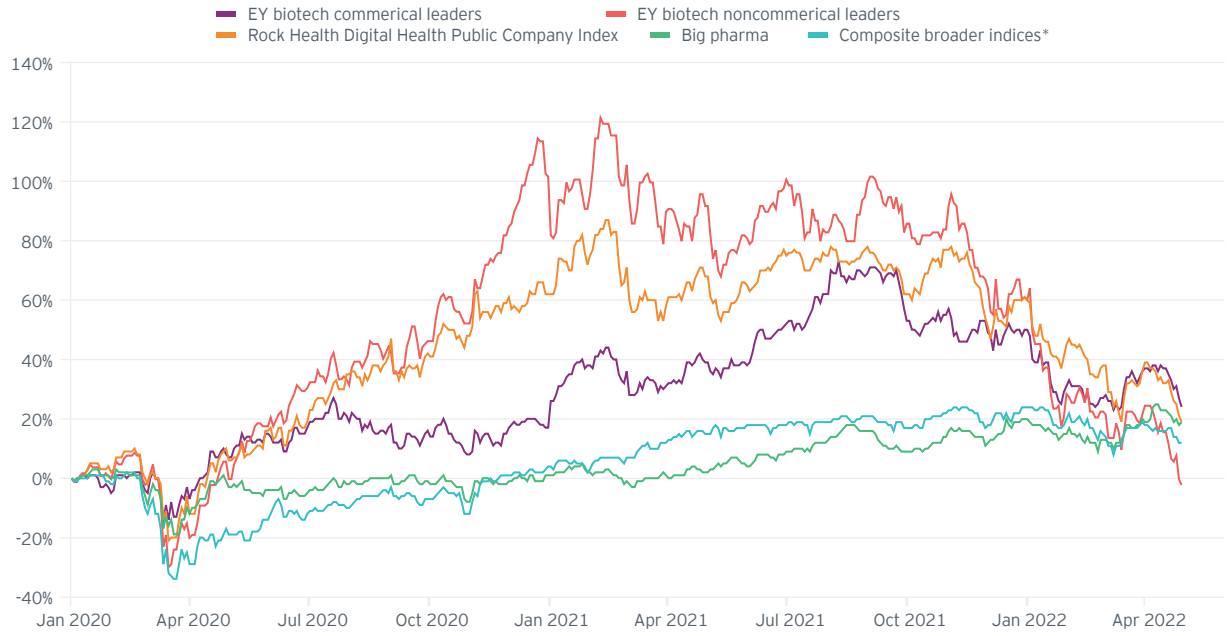
Moreover, the big pharma leaders need access to these biotech innovations, with loss of exclusivity threatening to erode an estimated US$252 billion from industry revenues by 2026. Replacing these revenues will depend heavily on biotech pipelines, particularly on the development of new modalities (analysis of the leading pharmas' exposure to patent expirations, and the importance of new modalities for closing the resulting "growth gaps," can be found in the 2022 EY *M&A Firepower* report). These new modalities include the mRNA platforms that achieved significant commercial success in 2021, as well as next-generation antibodies and cell and gene therapies. Further into the future, these innovations will synergize with other novel technologies, including next-generation neural nets with OMICs sequencing tools, bioinformatics and AI-powered analytics (for more discussion of the potential of bioconvergence, see our guest perspective, *Bioconvergence: A multidisciplinary approach to advance human health*, by Belén Garijo of Merck Group).

> “... from a stock market perspective, we are living through the deepest and longest correction that we’ve seen in the biotech indexes since their inception.
>
> Barbara Ryan
> Ernst & Young LLP senior advisor

The health of the biotech R&D engine is cause for optimism, as is the normalization of health care delivery as COVID-19 recedes. After more than two years of pandemic disruption, this normalization should bring a rebound in product demand. However, there are signs that the aftermath of the pandemic will also leave biotech with significant challenges.

Among these challenges is a decisive shift in investor sentiment, which began in the last quarter of 2021. Over the past decade and particularly during the pandemic, biotech has enjoyed soaring valuations. By early 2022, these valuations had plunged dramatically (see Figure 4). As Barbara Ryan, an Ernst & Young LLP senior advisor, described it, “We are clearly living through an innovation renaissance, and the fundamentals of the industry are quite strong. But from a stock market perspective, we are living through the deepest and longest correction that we’ve seen in the biotech indexes since their inception.”

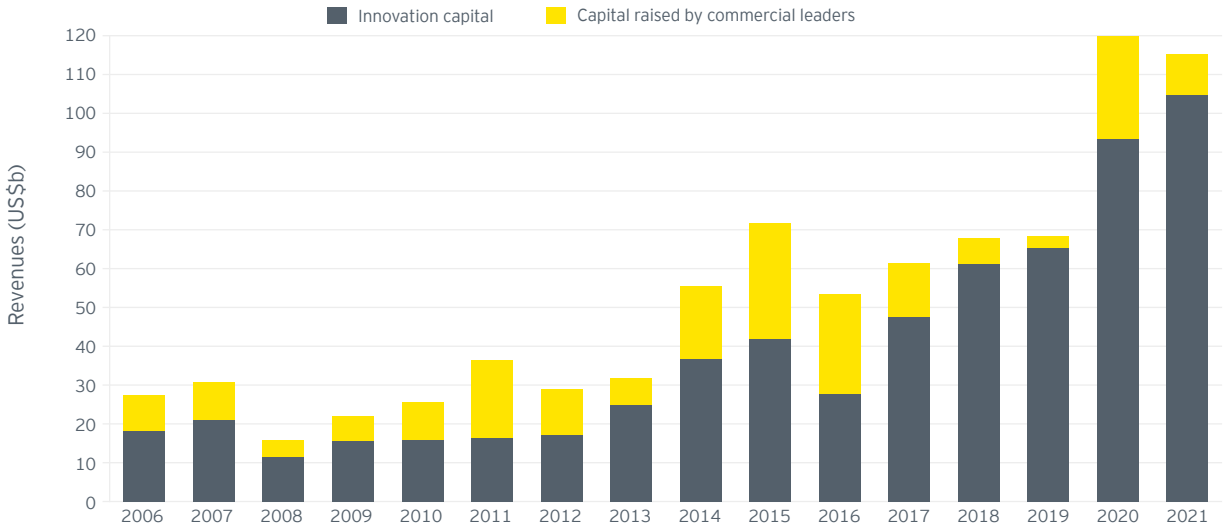
Figure 4. US and European biotech market capitalization relative to leading indices, Jan 2020–Apr 2022



Source: EY analysis and Capital IQ
Charts includes companies that were active on 30 March 2022. *Composite broader indices refers to the daily average of leading US and European indices: Russell 3000, Dow Jones Industrial Average, NYSE, S&P 500, CAC-40, DAX and FTSE 100.

Among the casualties of this return to pre-pandemic valuations is the biotech IPO market, which saw unprecedented levels of activity in 2020 and 2021 but slowed significantly in the first quarter of 2022. Biotech financing is notoriously cyclical, and after growing from US$53.4 billion in 2016 to well over double this total in the record financing years of 2020 and 2021, the industry can now expect a significant reset. In 2021, innovation capital (defined as the amount of capital raised by companies with revenues of less than US$500 million) reached an all-time high of US$104.7 billion. By comparison, the average over the previous 15 years was US$34.3 billion (see Figure 5). These smaller companies now face a more arduous path to the capital markets.

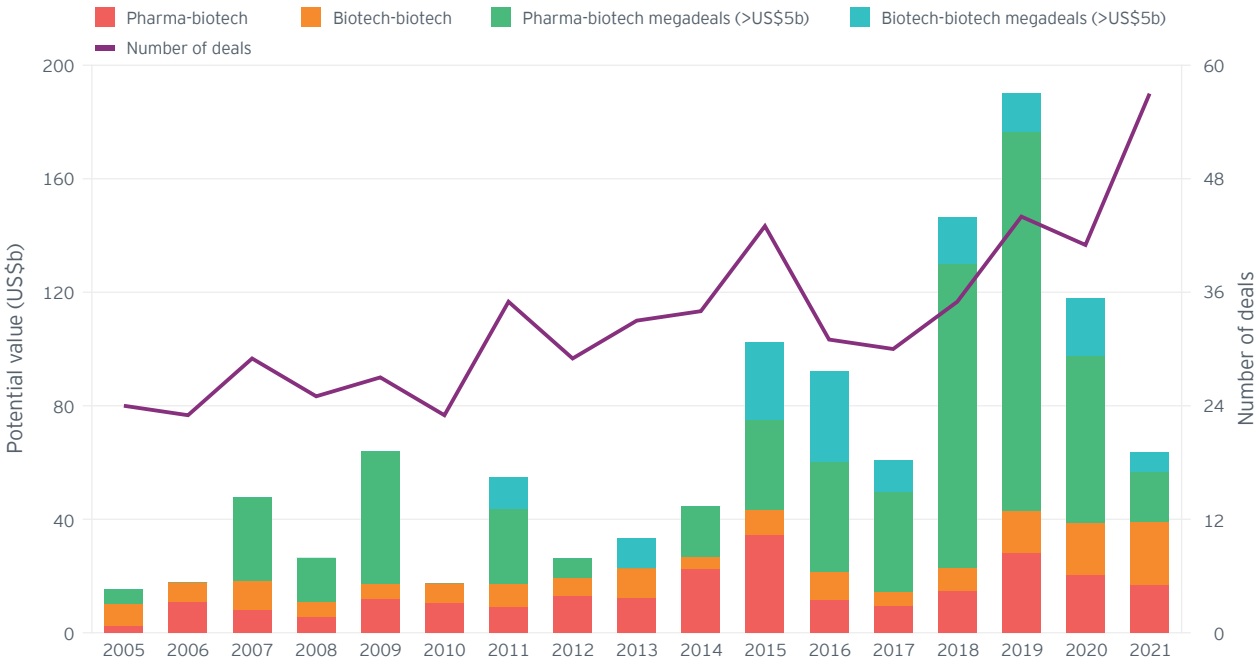
Figure 5. Capital in the US and Europe, 2006–21



Source: EY analysis, Capital IQ and VentureSource.
2019 data is until 30 June 2019. Innovation capital is the amount of capital raised by companies with revenues of less than US$500 million.

For some biotechs, reduced access to capital will mean they have to navigate existential challenges. For many others, this shift will increase the desirability of exiting via acquisition, and it may galvanize M&A activity in the sector. Though a high number of deals were signed in 2021, most were minor plays, and overall dealmaking value declined by 46% (see Figure 6). High valuations and the array of possible funding options available to companies in the sector have slowed M&A activity.

Figure 6. US and European M&As, 2005–2021



Source: EY analysis, Capital IQ, MedTRACK and company news
Chart excludes transactions where deal terms were not publicly disclosed. Chart excludes Thermo-Fischer/Life Technologies transaction (US$13.6 billion) because the acquirer is neither a pharma nor a biotech.

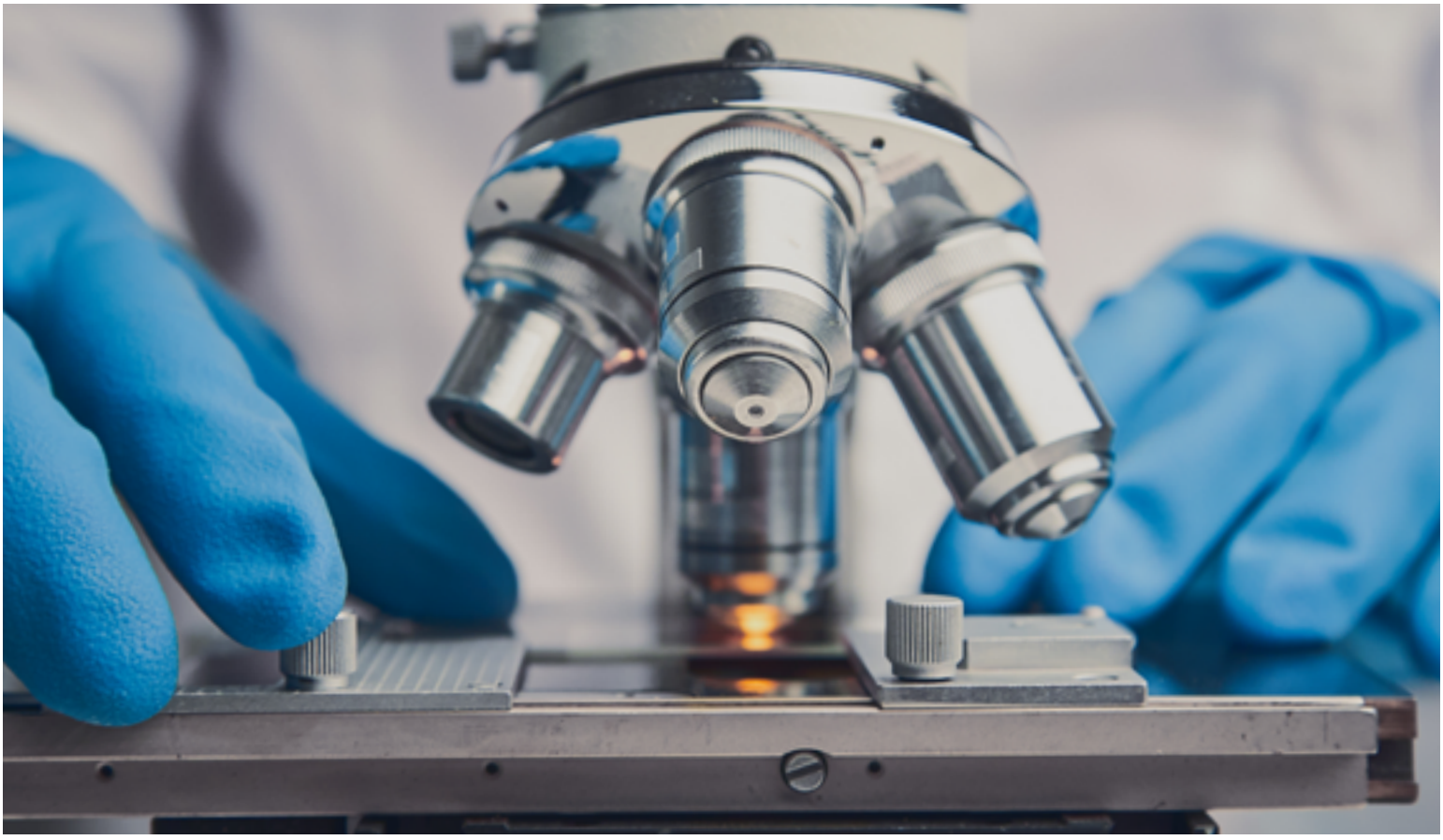
As valuations sink and financing becomes more challenging, a buyer's market may emerge, with big pharma CEOs potentially reconsidering targets that proved too expensive to justify acquiring in the past. De-risked, late-stage biotech assets that fit naturally into a company's strategic pipeline will be an M&A priority for these companies. Alternatively, leading companies may seek to pursue strategic alliances rather than outright acquisitions, continuing a notable trend in recent years (see Databook). Our guest perspective from Terry Rosen of Arcus Biosciences, *Novel combination therapies — the path to differentiation in oncology*, provides more discussion of how partnership models may work effectively in the sector. While an M&A rebound seems probable, there is little evidence of it so far in 2022.

Negotiating the uncertainties around both dealmaking and the broader shifts in the business landscape will not be the only challenge biotechs face in 2022. The pandemic has undoubtedly reshaped the industry in multiple ways, as emphasized in our discussions with industry stakeholders. Thomas Wozniewski, Global Manufacturing & Supply Officer of Takeda, writes that "COVID-19 has required diverse ways of working for all of us" and "the industry has learned from it substantially" (see his guest perspective, *Staying curious to make our supply chains better*). Among the lessons learned is the need for more effective use of digital technologies and data

across the industry; as Chris Picariello, President of Johnson & Johnson Innovation, notes, "One positive impact from the past few years has been the accelerated convergence of health, technology and data" (see his guest perspective, *Partnering for an innovative and sustainable future*). Below we discuss the shifts the industry is now experiencing in the wake of the pandemic and the ways that digital transformation can help address existing challenges and open new opportunities. We explore several aspects of this ongoing evolution:

- The impact of the pandemic on the industry's commercial models, which have accelerated firms' adoption of digital and omnichannel approaches while face-to-face access to clinicians has been challenging (see *How biotech can improve its commercial launch capabilities*)
- The rethinking of supply chain strategies in the wake of ongoing disruption to global networks and the expected response of global policymakers to this perceived threat, which may include localization requirements and other significant reforms (see *How will biotech and its stakeholders secure future supply chain resilience?*)
- The escalating challenges around attracting and retaining the necessary talent in an increasingly hypercompetitive labor market (see *How should biotechs close the emerging talent gaps?*)
- The heightened awareness of ESG issues among investors and the wider public — and the growing imperative for biotechs to address issues such as access to medicine (see *How biotechs can add societal value by expanding access*) and lack of diversity in clinical trials (see *How can biotech benefit from improving clinical trial diversity?*)

The business of biotech will not return to its pre-pandemic "old normal." Companies will need to adapt to many new challenges in the rapidly evolving business environment. Yet, as 2021 demonstrated, there are also huge potential opportunities for biotech as it faces the future.



Belén Garijo

Chair of the Executive Board and Chief Executive Officer

Merck Group

Bioconvergence: A multidisciplinary approach to advance human health

Isaac Newton's theory of gravity, developed after he observed an apple falling from a tree, is one of the earliest examples of how nature has inspired modern science. The materials, structures and processes that provide organisms with their functionality and behaviors have contributed to countless discoveries. Nature and science are now being further aligned through bioconvergence, a multidisciplinary approach harnessing synergies across biology, software and engineering to create novel market solutions.

Until recently, scientific disciplines such as biotech or medicine operated mainly in isolation. While the achievements of this siloed approach are undeniable, there is risk of future technological stagnation. For example, today's generation of computers ultimately may reach capacity in processing power and energy consumption. Traditional health care models also have struggled to meet industry demand to better value the long-term outcomes of patient care.

Bioconvergence represents a multidisciplinary approach (see Figure 1) to improve the speed and impact of scientific discovery. Operating at the intersection between the natural and formal sciences, it unifies the latest theories, processes and products in life science, health care and electronics to enhance human health and well-being.

Success depends on fusing a broad mix of competencies across several disciplines to generate novel functionality or application outcomes. Below are three examples where bioconvergence has already begun to transform health care.

Figure 1. Bioconvergence hive of competencies required for market success (examples for illustration purposes only)

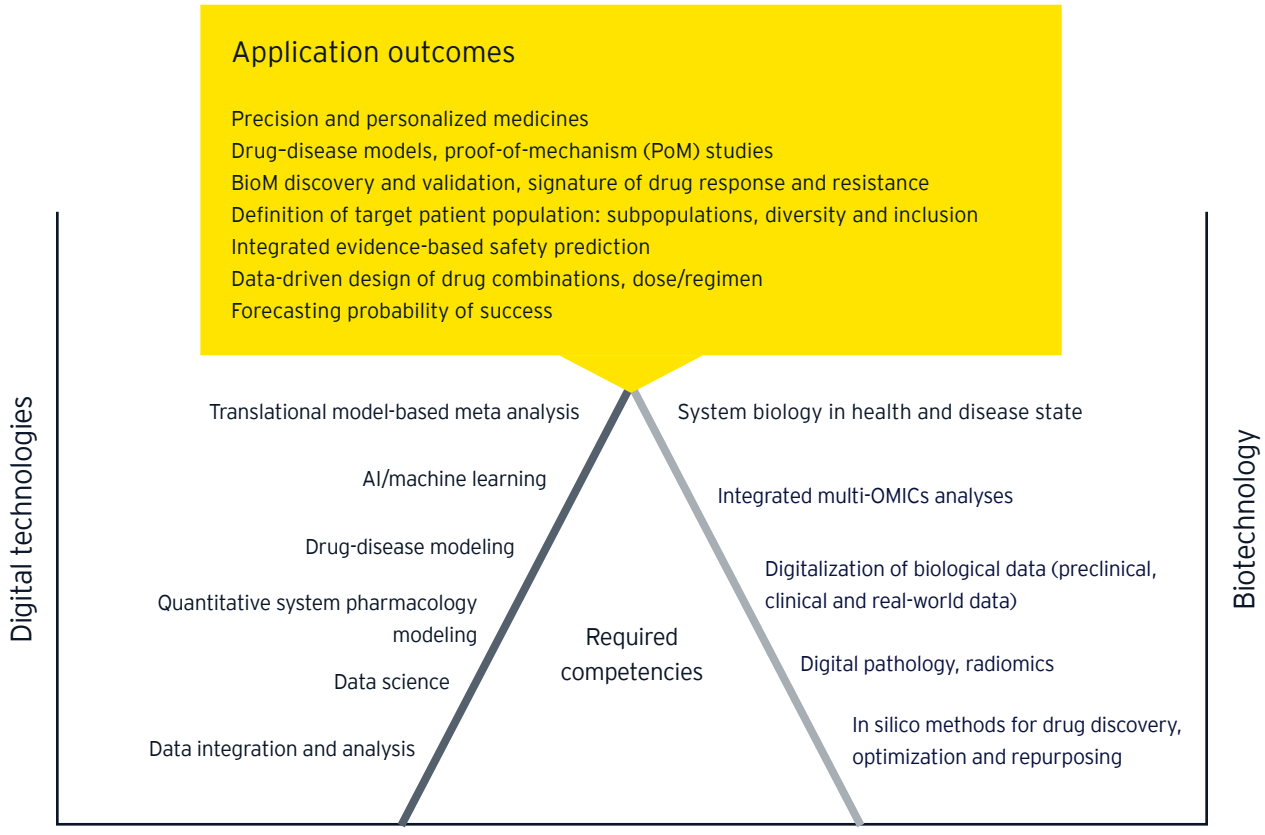
GUEST PERSPECTIVE

1. Translational medicine

Our ability to leverage multiple biological and clinical data points for medicines between initial discovery and patient use has increased exponentially in recent years. Forward and reverse translation techniques using analytics and artificial intelligence (AI), including machine learning (ML), are enabling the extraction of hidden insights from massive data sets. In addition, potential compound properties are now being predicted earlier, while the development of novel targeted medicines or combination therapies can occur faster and with reduced risk.

Thanks to the alignment of modern biomarker, sequencing and other technologies, bioconvergence for translational medicine (see Figure 2) now promises to make medicines far more personal, precise and inclusive. One immediate opportunity is a universal molecular signature of human diversity where multiple intrinsic and extrinsic factors linked to disease are characterized in unison. Advances in our ability to analyze OMICs (refers to a field of study in biological sciences that ends with -omic) data sourced from multiple genome, microbiome, proteome, metabolome and other patient-specific databases have been one primary catalyst for innovation. When these databases are further integrated with quantitative translation tools such as organs-on-chips, bioelectronics and bioinformatics, we can decrease access lag and individualize therapeutics with the right drug, target and dose.

Figure 2: Bioconvergence of competencies for translational medicine



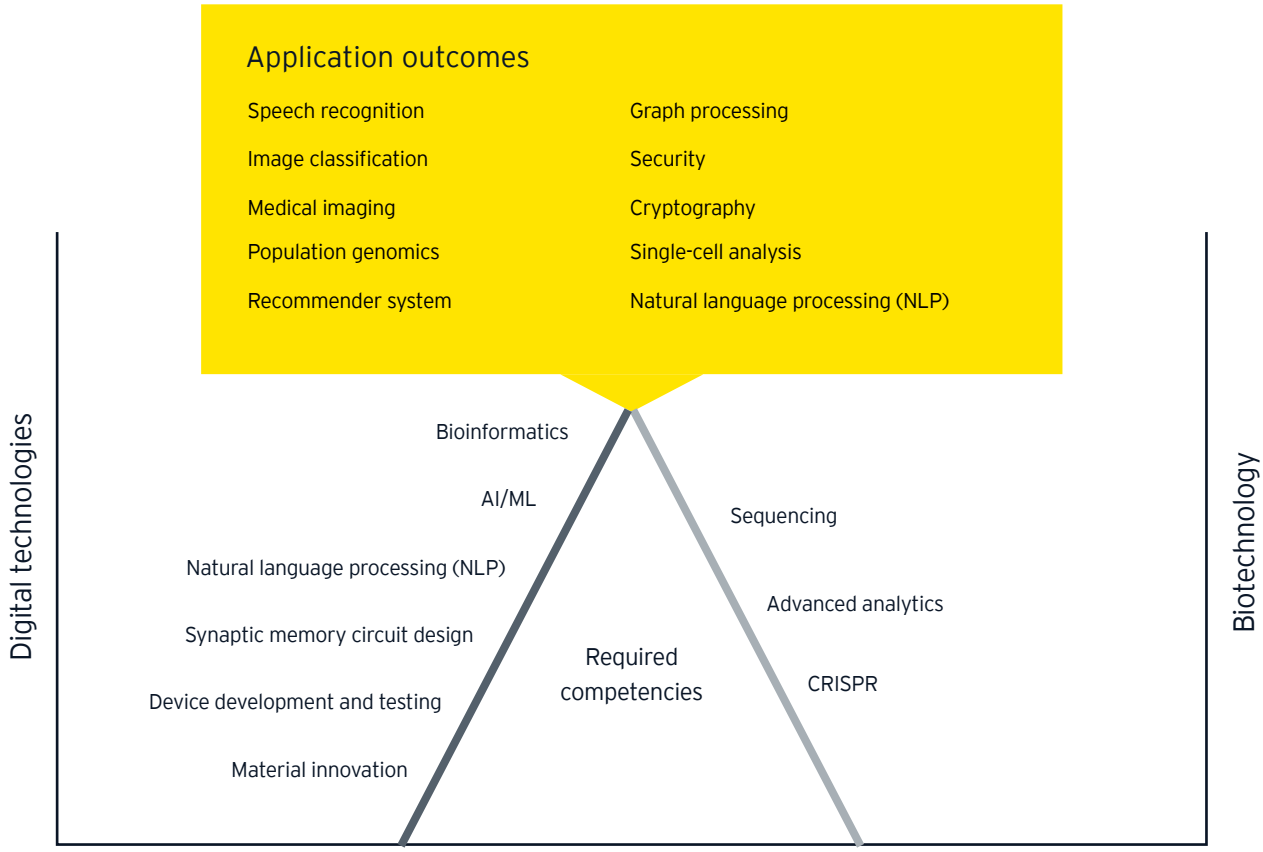
2. Neuromorphic computing

Ten of the world's fastest supercomputers consume the same energy as 1.5 million lightbulbs. A human brain can achieve the same processing capacity with less power than a single lightbulb. Neuromorphic computing seeks to emulate the biological neural structure of the brain to achieve unparalleled levels of processing performance and energy efficiency. First-generation neural nets have already made significant progress in areas such as speech recognition, medical imaging and accelerated COVID-19 prediction.

By combining next-generation neural nets with OMICs sequencing tools, bioinformatics and AI-powered analytics, we can more accurately identify and model new solutions in areas such as tissue engineering or cancer development. When these disciplines are further combined with clustered regularly interspaced short palindromic repeats (CRISPR) for gene editing, a new wave of safe, personalized medicines become possible (see Figure 3).

To meet demand in the related field of genomics, sequencing times per human must be reduced from the current record of five hours to mere minutes. The bioconvergence of neuromorphic computing with advanced semiconductors, novel algorithms and other tools should help genomics achieve this goal while simultaneously decreasing cost.

Figure 3: Bioconvergence of competencies for neuromorphic computing



3. Digital twins for clinical trials

Through bioconvergence, technologies such as AI, sequencing, bioinformatics, imaging and biosensors can be used to create a comprehensive digital profile of each clinical trial participant. Access to this vast trove of "clinico-omics" patient data, coupled with AI-enabled disease modeling techniques, enables in silico simulations of trial outcomes calibrated to specific patient characteristics for virtual synthetic control arms. Digital twins can thus facilitate model-informed, proof-of-concept clinical trial designs to reduce cost, increase speed and improve the probability of success. By narrowing the gap with patients in real-world medical practice, digital twins will also enhance clinical diversity and inclusion.

Ethical approaches

Participants in this emerging era of bioconvergence may encounter ethical questions regarding how their technologies should best be combined and applied for the good of humanity. Merck has leveraged its deep experience in areas such as bioethics to take the lead. First, we have developed our Code of Digital Ethics, which lists the core principles that must guide all activities involving digital products and processes. When biotechnologies and digital tools are able converge to create opportunities in unexplored areas, joint panels comprising independent experts with different perspectives will be established to determine the right path forward.

A new frontier for scientific collaboration

Bioconvergence is a new frontier of scientific collaboration, enabling us to live longer, healthier and more sustainably. Healthcare companies can increasingly focus more on prevention, early detection and responsive remote treatment with personalized, precise therapies. As bioconvergence continues to evolve, we can also look forward to an acceleration of innovation across other emerging markets such as bioelectronics, nanorobotics and regenerative medicine.

Terry Rosen, PhD

Chief Executive Officer
Arcus Biosciences

Novel combination therapies: the path to differentiation in oncology

As the immunologist Daniel M. Davis has said, "We are at the cusp of a revolutionary time in virtually every aspect of human biology."[3] In particular, expanding knowledge of immune biology has opened up new possibilities for understanding and treating pathologies from inflammation to oncology. Though attempts to use the immune system to treat cancer can be traced back to William Coley's 1891 experiments with introducing Streptococcus pyogenes into sarcoma patients,[4] the field has finally reached clinical and commercial maturity in the past decade. ***In 2020, the clinical pipeline already contained over 4,700 immune-oncology products addressing over 500 distinct targets[5],*** while approved products such as anti-PD-1 antibodies and CAR T-cell therapies are already redefining the standard of care in for several types of tumors.

New therapeutic modalities are projected to grow their revenues in the oncology market by a CAGR of 45% between 2020 and 2026, indicating the advanced level of innovation around cancer treatment. These new oncology treatments are set to play a key part in securing overall industry growth, as large biopharmas seek to weather the next wave of patent expirations, projected to put US$226 billion in global prescription sales at risk through 2026. As discussed in the above and in the Databook, these major pharma companies are increasingly embracing external innovation through strategic partnerships, as a complement or alternative to traditional M&A, to access external innovation capabilities and close emerging growth gaps.

The deal between Arcus Biosciences and Gilead Sciences is one such example, creating a long-term strategic collaborative framework. This 10-year partnership announced in 2020 gave Gilead access to Arcus' immuno-oncology portfolio, including rights to its anti-PD-1 inhibitor and an opt-in right to all other pipeline programs for the duration of this agreement. In November 2021, Gilead exercised its options to three additional Arcus programs (anti-TIGIT antibody; small molecule CD73 inhibitor; A2a/A2b adenosine receptor antagonist) that increased its investment to $1.4 billion. This collaboration is notable since it allows the smaller biotech to continue to grow as a fully independent company and enables the larger partner to build a parallel R&D engine to further expand its portfolio.

EY: What were you looking to accomplish when you started Arcus?

Terry: Arcus was founded in 2015 with the ambition to become a disciplined, R&D-driven long-term biotech organization. From day one, our goal has been to identify and develop targets for combination therapies against cancer. Arcus's pipeline includes first- and/or best-in-class medicines against well-characterized biological targets and pathways that have the potential to change the treatment landscape for patients battling various types of cancer. Our drug candidates leverage complementary mechanisms of small molecule and antibody combinations to maximize clinical benefits for patients. While many people are focused on anti-TIGIT as our "hottest" asset, I view our anti-TIGIT and anti-PD-1 as our backbone and our adenosine axis molecules as true potential differentiators in the competitive immuno-oncology landscape.

3. Davis, Daniel M., *The Secret Body: How the New Science of the Human Body is Changing the Way We Live* (Princeton University Press, 2021).
4. Zhang, Yuanyuan and Zhang, Zemin, "The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications," *Springer Nature website*, https://www.nature.com/articles/s41423-020-0488-6, May 2022.
5. "Immuno-Oncology Landscape," *Cancer Research Institute website*, https://www.cancerresearch.org/scientists/immuno-oncology-landscape, accessed 24 May 2022.

EY: Liquidity and financial independence appear to be strong reasons for the Gilead deal. What were some of the other motivating factors?

Terry: The central component of our approach is focusing on combination therapies and working on targets where the opportunity for intra-portfolio combinations would be high. We are the only company with a portfolio that comprises molecules targeting TIGIT, PD-1, CD73 and A2b/A2b. It was imperative to have a single, long-term partner in Gilead Sciences in an all-in partnership to maximize the clinical and commercial potential of our pipeline. In essence, Gilead not only provided us with the capital to act on and fully leverage the scientific opportunity, but also helped us to maintain the integrity of our portfolio. With the recent opt-ins announced in November 2021, Gilead and Arcus are executing a broad joint development plan to maximize the potential of our combined clinical portfolio.

The collaboration with Gilead has provided Arcus with significant clinical, manufacturing and commercial expertise. Moreover, having a single, integrated partner allows Arcus to avoid the logistical and operational challenges and distractions around collaborating and managing multiple development partnerships.

EY: After the Gilead deal, Arcus is very well capitalized. How does this change your business development strategy?

Terry: Arcus maintains a very active business development effort, which works to enhance our clinical opportunities and leverage clinical value for patients and economic value for our investors. We're actively exploring clinical collaborations to combine our proprietary molecules with current or emerging standard-of-care therapies. The collaboration with AstraZeneca is an example of this, where we are evaluating the combination of their anti-PD-L1, which is the standard of care for stage 3 lung cancer, with our anti-TIGIT candidates.

EY: Do you think the Gilead–Arcus partnership is a model that others will use going forward?

Terry: A few very strategic components came together to result in the 10-year collaboration with Gilead. It's not common for a well-capitalized and profitable company such as Gilead to make a foray into a new therapeutic area in a big way. Gilead is investing to position itself strongly in the oncology market, and Arcus has enabled the company to achieve critical mass in immuno-oncology without going through a full-blown M&A deal. The Gilead–Arcus partnership is a rare example that offers significant long-term strategic benefits for both companies. This arrangement enables both partners to capitalize on the opportunities of the emerging wave of data and technology that promise to transform the biotech industry and, most importantly, the lives of patients.

Chris Picariello

President, Johnson & Johnson Innovation JJDC, Inc.

Partnering for an innovative and sustainable future

> We recognize that we can't solve the world's biggest health care problems alone and that we need to partner beyond our walls to accelerate the best science.

What is your view of the current market landscape and JJDC's role within it?

JJDC, the strategic venture capital arm of Johnson & Johnson, is the oldest health care corporate venture firm and about to celebrate its 50-year anniversary. That legacy and perspective shape our thinking; we are always investing for the long term. We've seen investment cycles, bubbles and other market changes come and go, and while there has been a lot of transformation over the past six months, this does not alter our long-term investment strategy. We're still looking for the best opportunities to harness innovation for the health of everyone, everywhere.

We focus on investing in transformative science and extraordinarily talented management teams because these are characteristics of the best companies — those that will succeed in translating science and innovation into solutions for patients and consumers. For these companies, we aim to be the partner of choice, and we accomplish this by providing much more than just venture capital. We blend a strategic outlook with a collaborative mindset, bringing years of expertise to our partners, whether clinical, development or regulatory, and guiding them even through growing pains and challenging markets. We stick with our companies for the long term, and that is very much valued by our partners.

At Johnson & Johnson, we have the capabilities to assist companies at any stage of the lifecycle. These days, with companies seeking earlier IPOs, there is a definite trend for corporate investors to come in earlier. We invest in new companies across the pharmaceutical, medical technology (medtech) and consumer sectors and bring them into our global JLABS incubator network to help nurture and accelerate their science, enabling them to conserve their precious capital. We also carry out very early dealmaking and collaboration via our Innovation Centers based in Shanghai, London, California and Boston. Meanwhile, via JJDC, we have invested an average of $325 million over the last five years in new and follow-on investments to accelerate innovation.

Our ultimate goal is to onboard the most strategically aligned innovations into our portfolio. We recognize that we can't solve the world's biggest health care problems alone and that we need to partner beyond our walls to accelerate the best science. We're trying to use all of Johnson and Johnson's capabilities — our breadth of health care expertise, our clinical development and commercial capabilities, our understanding of regulation, financial mechanisms and business structures — to bring leading science to patients and consumers around the world.

How will we improve care outcomes after the pandemic?

The global COVID-19 pandemic has changed our society in ways both large and small, but despite these ongoing challenges, science and innovation have continued to advance. One positive impact from the past few years has been the accelerated convergence of health, technology and data. To take one example, artificial intelligence (AI) is gaining prominence. Within health care, AI can play a major role in improving productivity, accelerating drug discovery and development, streamlining access to patient records, and enabling more precise patient stratification and better clinical diagnostics. With the impact of the pandemic, we see consumers embracing self-care and telemedicine, and these concepts and technologies will continue to shape the future of medicine.

What opportunities do you see in this environment for improving health equity?

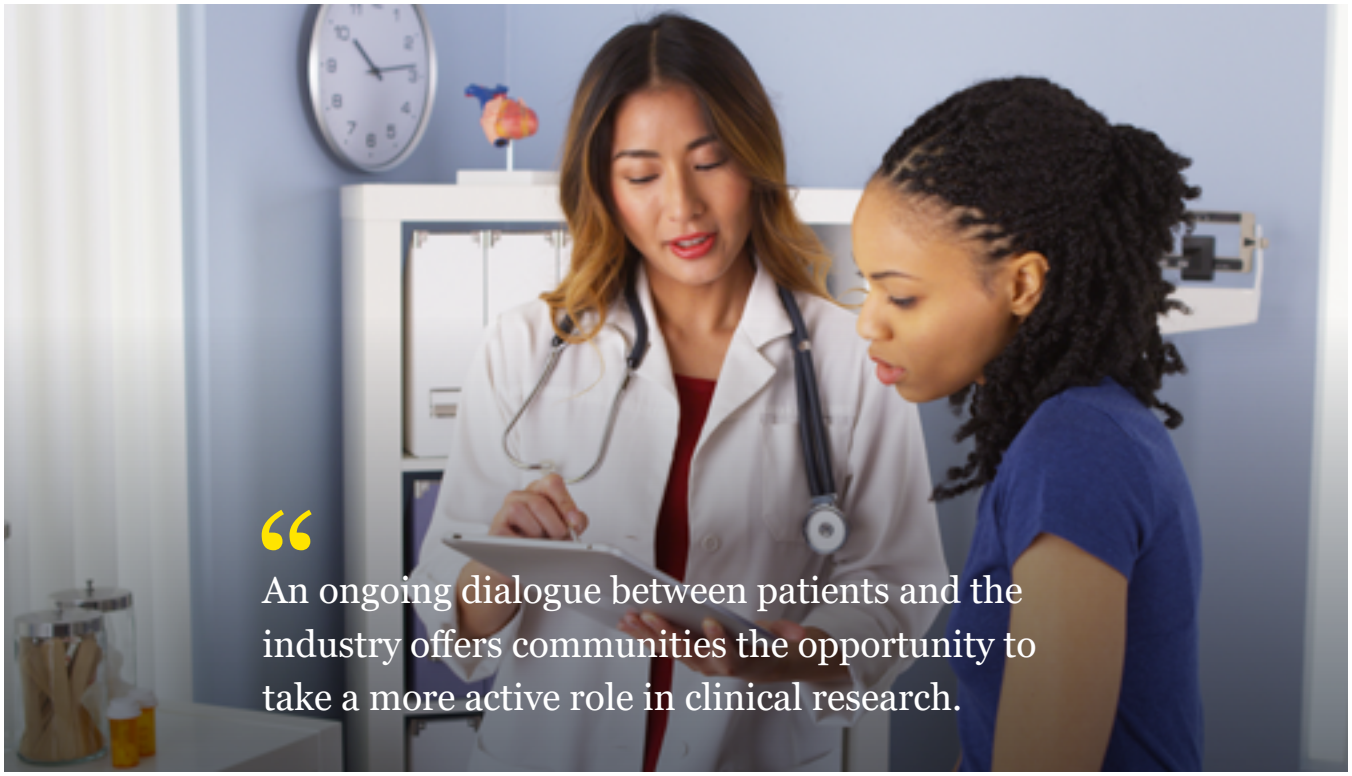
One key opportunity for digital technology is to enable better access to care, helping to address challenges around health equity and begin to close the gap in health outcomes linked to disparities across the world. In each of our JJDC investments, we are also looking at prospective partners from a diversity perspective; if we do not feel that companies are aligned to Johnson & Johnson's mission in this respect, then we decline to invest. It is ultimately a two-way street: we can help bring diversity and equitable solutions to some of the companies that we partner with, and they can do the same for us. For example, we can help provide companies with tools that enable them to design a clinical trial that more fully contemplates diversity and inclusion in its recruitment criteria. In many instances, we participate on the boards of companies with which we partner, to help foster leading principles to drive the mission and vision of that company.

Ultimately, at JJDC, our goal is not to invest for profit, but rather to advance the most promising science into real-world solutions for patients and consumers. That philosophy has served us extremely well for 50 years and will continue to guide our efforts moving forward.

HOW BIOTECH CAN BENEFIT FROM IMPROVING CLINICAL TRIAL DIVERSITY

Race and ethnicity are among the most important and pervasive determinants of health inequities today. According to a January 2022 study on health care in the US, "Black, Hispanic, and AIAN [American Indian and Alaska Native] people fare worse than White people across the majority of examined measures."[6] Since these inequities extend across "health coverage, access, and use; health status, outcomes, and behaviors; and social determinants of health," socioeconomic factors are heavily implicated in these differences in outcomes. However, the effectiveness of certain medications may vary significantly for different ethnic groups.

Addressing this latter problem means addressing the long-standing issue of the lack of diversity in clinical trials. A 2020 report from the U.S. Food and Drug Administration's Center for Drug Evaluation and Research indicated that white patients are overrepresented in innovative drug trial recruitment, making up 75% of enrollees in these trials, with recruitment disproportionately low among non-white ethnic groups.[7] Another report has confirmed this: After analyzing disease-specific epidemiology in 22 US-based trials for novel active substances between 2019 and 2021, one organization concluded that Black patients were underrepresented in 78% of trials, with Hispanic and Latino patients and Asian patients underrepresented by 45% and 41%, respectively.[8]



6. Hill, Latoya, Artiga, Samantha and Haldar, Sweta, "Key Facts on Health and Health Care by Race and Ethnicity," *Kaiser Family Foundation website*, https://www.kff.org/report-section/key-facts-on-health-and-health-care-by-race-and-ethnicity-health-coverage-and-access-to-and-use-of-care, May 2022 .
7. "2020 Drug Trials Snapshot Summary Report," *U.S. Food and Drug Administration (FDA) website*, www.fda.gov/media/145718/ download, accessed 29 March 2022.
8. "Global Trends in R&D 2022: Overview through 2021," *IQVIA website*, www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d-2022, accessed 29 March 2022.

Fortunately, there is growing momentum, both within the biopharmaceutical and health care industries as well as among lawmakers and regulators, to try to improve trial recruitment diversity. The biopharmaceutical and health care industries must collectively prioritize diversity, equity and inclusion (DEI) and center their strategies and initiatives around communities. A community-based approach should focus on increasing patients' general knowledge and awareness of the clinical trial process, improving access to trials and providing ongoing engagement. This approach has the potential to impact every stage of the trial process as follows:

- Before a clinical trial. Companies must make greater efforts to educate and expand awareness of clinical trials within underserved communities. Given the well-founded and decades-long mistrust of medical research and its sponsors within certain communities, sponsors and stakeholders must actively understand, listen to and engage with the patients they are seeking to enroll.
- During a clinical trial. Companies should seek to enhance the ease and convenience of participation in clinical trials. This may require going beyond community outreach and also investing in the accessibility of clinical trial sites for the underserved communities they are trying to reach. Biopharmaceutical industry stakeholders and sponsors may consider:
  - Developing relationships with, and providing the needed support for, trial sites in underserved communities since staff members at these sites often have trusted relationships with their patients, but may need support in getting adequate training and infrastructure to conduct trials themselves
  - Partnering with trusted institutions, such as pharmacies and urgent care clinics, to develop nontraditional clinical trial sites that may be easier for patients to access
  - Continuing to develop and invest in easing the burden of travel, for example, by developing decentralized clinical trials and mobile nursing and lab units
- After a clinical trial. Companies should seek to maintain community relationships through ongoing engagement and investment. For these outreach strategies to achieve a lasting impact and support sustained diverse trial recruitment, sponsors and other stakeholders must maintain their engagement after trials are concluded. This continued engagement may take the form of collecting formalized post-trial feedback, conducting community awareness and health literacy events, and providing continuing education and training programs for investigators and site staff. The goal should be establishing an ongoing dialogue between the industry and the communities it seeks to serve.

The biopharmaceutical and health care industries must collectively prioritize diversity, equity and inclusion (DEI) and center their strategies and initiatives around communities.

While there are limited precedents for biopharma to invest in broadening clinical trial recruitment in this way, adopting this strategy could benefit the industry and its partners within the health ecosystem, such as:

- Underserved patients and communities will gain more equitable access to lifesaving therapeutics.
- Biopharma companies (or the clinical research organizations to which they may outsource trials) will be able to gather data that more accurately reflects the efficacy of novel therapeutics on real-world patient populations. This data could support companies' pricing and reimbursement policies. Moreover, proactively working to increase diversity at this stage would allow companies to be prepared for attempts by regulators or policymakers to enforce greater inclusivity in the future.
- The overall health ecosystem will benefit if underserved communities develop meaningful, ongoing and mutually valuable relationships with both biopharma companies and health care providers.

An ongoing dialogue between patients and the industry offers communities the opportunity to take a more active role in clinical research. Ultimately, this can lead to greater patient access, sustained community engagement and improved health care outcomes.

HOW BIOTECH AND ITS STAKEHOLDERS WILL SECURE FUTURE SUPPLY CHAIN RESILIENCE

Biotech supply chains face an uncertain future in 2022. The positive news is that the industry has largely met the challenges of the COVID-19 pandemic, which continues to cause significant disruptions to supply chains in other industries. While there were reported shortages of certain raw materials and consumables among biotechs (such as the sterile filters used in biological drug manufacturing), very few products have been unavailable during the crisis. In fact, within the US, issues have been reported for less than 1.5% of the more than 20,000 FDA-registered prescription drugs in 2020 and 2021.

However, the pandemic has created a perception that biopharma supply chains need more attention from policymakers. In June 2021, Janet Woodcock, then-acting U.S. FDA Commissioner, stated: "The COVID-19 pandemic revealed just how vulnerable the supply chain is in this country."[9] A yearlong review of US public health supply chains, published in February 2022,[10] reaffirms the Biden administration's ongoing efforts to encourage domestic production and innovation, develop redundancies and ensure that diversification within drug supply chains continues.

The EU has made similar moves, with its Pharmaceutical Strategy for Europe adopted at the end of 2020 aiming to "develop the EU open strategic autonomy and ensure robust supply chains."[11] In an effort to effectively monitor its supply chains, the EU has imposed temporary vaccine export restrictions to secure supplies of vital medicines, assessed stockpiles and built regional capacity via its Health Emergency Preparedness and Response Authority (HERA).

These moves toward greater governmental involvement in supply chains are likely to continue. In recent decades, we have seen the increased globalization of biopharmaceutical supply chains. Now, amid anxieties over the security of national drug supplies, we may be witnessing the beginning of a countertrend toward increased localization of supply chains and a greater emphasis on regional or national self-reliance.

9. Quoted in U.S. Department of Health & Human Services press release, "Biden Administration Recommends Policy Changes to Secure U.S. Pharmaceutical Supply Chain," 8 June 2021.
10. Ibid.
11. European Commission, "Pharmaceutical Strategy for Europe." November 2020.

Other macro factors fueling this shift include the changing globalization model wherein global trade agreements are declining in relevance in favor of increased regionalized trade and bilateral agreements. The pandemic may have accelerated this trend, but as the armed attack in Eastern Europe in 2022 emphasizes, COVID-19 will not be the last major crisis of the 21st century. Future global shocks are likely to heighten geopolitical tensions further; whether they come in the form of future pandemic outbreaks or cyber attacks (or even cyber war), the impacts of climate change or yet unforeseen crises will impact global stability.

In response, we are likely to see greater concern from policymakers about enabling supply chain resilience within their regions. Companies are already taking certain measures to build resilience: implementing multi-sourcing, leveraged local contract development and manufacturing companies (CDMOs) and establishing cross-registered manufacturing sites. Companies may begin collaborating more closely with nation-states to build strategic inventories or initiate public-private partnerships.

Policymakers also may actively seek to force greater localization of supply chains. This could be through measures designed to encourage the local development and manufacturing of biopharma products, such as R&D credits and incentives. Alternatively, they may impose measures constraining companies to implement some degree of localization, such as imposing export quotas, procurement mandates or limitations on market access for companies without a local footprint.

More radically, governments may seek to impose localization of some or all stages of the biopharma supply chain. The degree of logistical challenges and investment needed to make this concept a reality would depend on the scope of the effort. It would be relatively simple for a biopharma to localize secondary product packaging. By contrast, localizing active pharmaceutical ingredient (API) manufacturing would be a major challenge, both in terms of the scale of capital investment and the levels of technical and quality competency required.

What would governments gain from localization? A localized supply chain would have a significant capability to respond to local conditions. However, it would entail building and maintaining infrastructure,

services and talent at local sites. Separating operations from established centers of excellence in quality, process engineering, regulatory and IT operations might negatively affect supply chain reliability. There may be political benefits from localization — for example, in the creation of jobs for a local workforce — but it is unclear if these incentives would justify the effort and expenditure.

Policymakers and biotech companies also may consider hybrid models in the future. Many approaches to building resiliency have been suggested, from hub-and-spoke manufacturing models to joint manufacturing or joint warehousing operations between companies, establishment of a joint procurement clearinghouse or the use of digital technology to build greater end-to-end transparency across the supply chain. Success in combining these approaches will depend on the costs and opportunities they generate for governments and companies. The biotech industry, policymakers and other stakeholder partners will therefore need to establish a dialogue for mutual education. In collaboration, they can adapt supply chain models to deliver the results prioritized by each partner in the future.

Thomas Wozniewski
Global Manufacturing & Supply Officer
Takeda Pharmaceutical Company Ltd.

Staying curious to make our supply chains better

Insights gained from the COVID-19 crisis

The pandemic definitely challenged our processes and, in most cases, confirmed that we have a resilient and robust supply chain with good safety stock policies, redundant distribution lanes and viable business continuity plans. We were able maintain our operations and supply without major disruptions. But, of course, the pandemic also exposed some gaps. Single-use bags, specific excipients and other raw materials supplies became very tight, and we have since started to look at how we can strengthen this as part of our enterprise risk management. We have seen that the risks associated with reliance on a single outsourcing partner, manufacturing site or supplier have become unsustainable, which is why dual sourcing has become more important to help mitigate supply chain risks, reduce lead times and improve supply chain agility.

COVID-19 has required diverse ways of working for all of us and has accelerated conventional timelines by years. Many of the lead times and fast-tracked approvals were due to the pandemic, and all the individuals and organizations involved in this effort across the industry have learned from it substantially.

The experience has also highlighted the importance of strong collaboration with our partners. Internally, we have strengthened the continuous dialogue and collaboration with commercial organizations, operating units and regulatory affairs to ensure early alignment and involvement of all necessary parties. Additionally, a transparent and trustworthy collaboration with our external suppliers has been critical, which is why it is important for us that our suppliers reflect our values of diversity, teamwork, commitment, transparency, passion and innovation. Using the power of digital and transforming how we manage information have clear benefits for us and our partners. Increasing the availability and improving the accuracy of real-time data have been important achievements to enable better collaboration with all stakeholders.

The role of data and digital in supply chain

Data and digital are key priorities for Takeda overall and stand at the core of our corporate philosophy. Together, as a company, we strive to transform Takeda into the most trusted, data-driven, outcomes-based biopharmaceutical company. That is why we are continuously maximizing the opportunities presented by artificial intelligence (AI), machine learning (ML) and other innovative technologies to transform the way we work. We have implemented some interesting improvements with robotic process automation and have started leveraging technologies such as blockchain in our supply chain.

> “… we are continuously maximizing the opportunities presented by AI, ML and other innovative technologies to transform the way we work.

GUEST PERSPECTIVE

Novel application of principles, systems and management tools in supply chain

This is a dynamic space with many exciting developments and achievements. Let me just name two that are quite different from each other to show the broad range of how data and digital improve our supply chain management and eventually the supply to our patients.

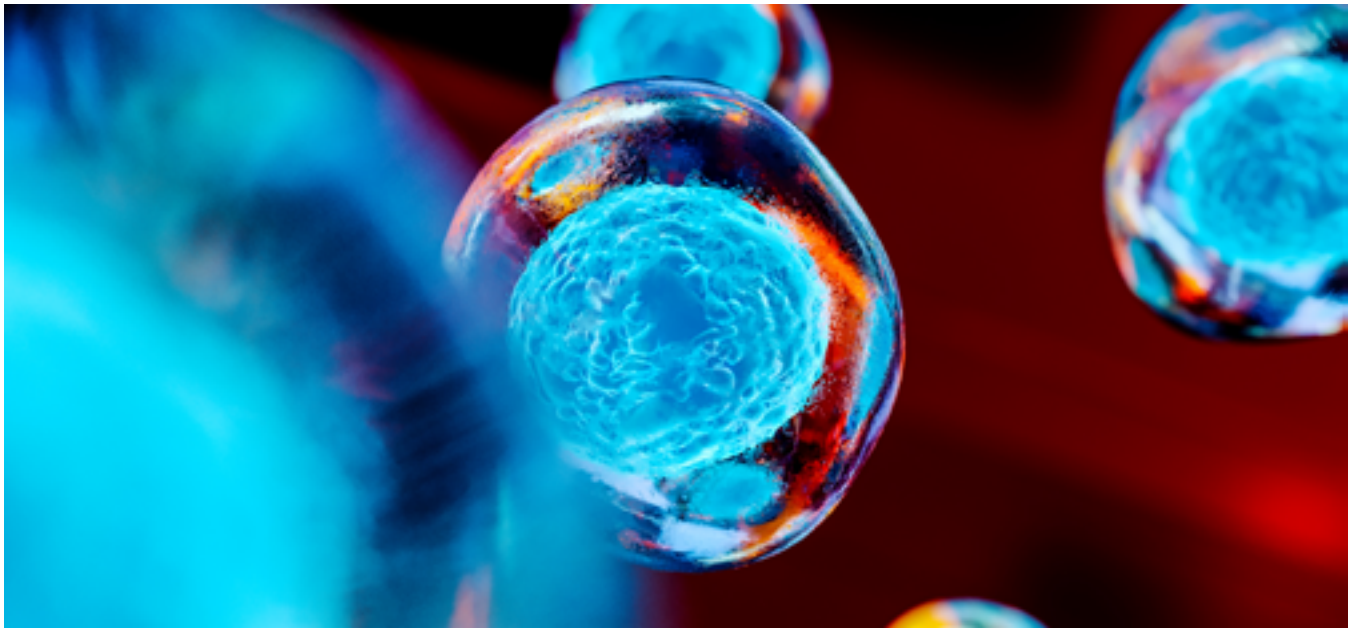
About a year and a half ago, we released a visualization dashboard to bring visibility and transparency to end-to-end product flow data – not only within Takeda, but also with external partners, such as contract manufacturers. This helps boost efficiency by reducing the time and effort required to map product flows and improves reactiveness to potential supply risks. And it reduces the risk of tax, regulatory and other noncompliance. By enhancing the quality of master data, it also makes the detection and correction of potential discrepancies much easier.

Another example is the implementation of a new patient-focused supply chain for our stem cell therapy. Since the maximum time from final product manufacture to patient administration is just 72 hours, speed is essential. Therefore, we introduced a cloud-based control tower platform to connect the product ecosystem and enable a "make-to-order" process. This allows hospitals to book a manufacturing slot directly via a web portal, then track the final product delivery status through end-to-end visibility and alerts at each step of the supply chain. This is a groundbreaking achievement, and I am proud that this work was recently acknowledged by the International Society for Pharmaceutical Engineering with the 2022 Facility of the Year Awards in the Supply Chain category.

The future of supply chain

Speed to market and the fast-evolving market environment will remain a high priority. There is a high likelihood that globalized supply chains for certain products will be replaced by regionalized supply chains as companies seek an appropriate strategy across global, regional and local sites to enhance their supply resilience. At the same time, the future of the supply chain is going to be more predictive, and the importance of utilizing innovative technologies like ML and automation will continue to grow. Due to the increased adoption of digital tools, telehealth and app-based ecosystems, supply chains are also becoming more patient-centric.

Having the right culture and people will be the necessary foundation supporting robust processes. The democratization of technology will be critical, so that all of our people can be empowered to make decisions based on the best data and insights available. At Takeda, we will continue to investigate, challenge our processes and stay curious about new technologies and ways of working so that we can make our supply chains better.



HOW BIOTECH CAN IMPROVE ITS COMMERCIAL LAUNCH CAPABILITIES

Small and midsize biotechs are responsible for a growing number of FDA approvals for new drugs. In 2021, companies with less than US$1 billion in total sales represented 30% of new molecular entity (NME) market approvals and launches, up from only 10% in 2017, when we last published our *Beyond borders* sector overview. While this change underlines the success of biotech innovation, it also means that biotechs increasingly confront the problem of achieving a successful launch of their newly approved products.

Launching a new drug is challenging and complex. Our analysis suggests that fewer than one-third of biopharma products launched since January 2020 have met prelaunch analyst expectations. Biotechs have been disproportionately associated with underachievement in product launches, and smaller companies accounted for 59% of the launches that missed analyst projections. This is why the industry needs to build commercialization capabilities that match its innovation expertise.

Traditionally, biotechs have relied on the commercial experience and infrastructure of the bigger biopharmas to achieve successful launches, with smaller companies seeking either acquisitions or partnerships as they approach the commercialization phase of the product lifecycle. However, the biopharma M&A market has slowed since 2019, making exits potentially more challenging. As described in the 2022 EY *M&A Firepower* report, acquirers in 2021 paid an average 62% premium for public companies relative to their share price one month earlier.

Valuations for small and midsize biotechs dropped sharply in 2022 (see Databook), which may reignite the M&A market. At present, however, acquirers seem to be taking a more cautious approach and increasing their value expectations for therapeutics. Strategic partnerships may fill the gap, but with larger companies seeking to de-risk investments, biotechs may still need to navigate the earlier stages of commercial launch alone.

So, biotechs may need to develop their own commercialization capabilities and expand their ability to successfully self-launch the products they develop. To achieve that, they will need to focus on certain key imperatives. In particular, they must:

- Take a strategic approach to capturing, demonstrating and defining value.
- Develop with a digital go-to-market strategy that can compete with the big companies.

Communicating value

The ongoing drug pricing debate and the Biden administration's proposals to legislate drug pricing and social spending have obliged manufacturers to assess policy proposals, plan for various scenarios, assess pipeline investments and refresh business development approaches. In this changing environment, it is vital that biotechs take a strategic approach to communicating value to their potential partners, investors and other stakeholders. Understanding how the market perceives value and how diverse stakeholder groups will perceive a product will be essential to establish value and change the narrative around pricing negotiations.

To achieve this, biotechs need to follow established manufacturers in articulating the real-world value of their drugs and therapeutics. As part of this effort, it is critical for them to develop evidence-generating capabilities that extend beyond measuring clinical trial endpoints to embrace real-world results that demonstrate a measurable benefit to patients and the health care system. Biotechs also need to capture the broader value contribution they make through their ESG commitments. This may include efforts to expand access to care, which benefits underserved communities. (See also *How biotechs can add societal value by expanding access*.) Biotechs need the skills to effectively contextualize and externally communicate value and ESG commitment in a meaningful way to ultimately ensure and support commercial success.

Develop with a digital go-to-market strategy that is optimized to compete with big companies

The COVID-19 pandemic has accelerated the shift to digital go-to-market approaches, and as biotechs build up their evidence-generating and value-articulation capabilities, they must simultaneously seek to build a digital mindset across all business functions.

To compete with larger biopharma companies' substantial commercialization budgets and established infrastructure, biotechs need to move toward digital models that can help them execute an effective go-to-market plan. These newer models will require biotechs to upskill their workforces and invest in new digital capabilities to understand and fulfill the needs and preferences of all of their customers, including patients, providers, caregivers, payers and all other stakeholders across the ecosystem.

For example, with reduced opportunities for in-person engagement during the pandemic, biotechs need to plan, build and deliver an omnichannel engagement model to interact with physicians. At the same time, they will need to leverage digital technologies and data to build an improved end-to-end patient experience. Embedding digitally driven patient and physician engagement into existing processes will enable biotechs to better connect with patients and doctors alike and to understand and meet these stakeholders' needs.

Biotechs that achieve this shift in mindset and embrace the need for digital capabilities and solutions will be best positioned to overcome the challenges surrounding product launches and maximize their market penetration and returns.

> "… biotechs may need to develop their own commercialization capabilities and expand their ability to successfully self-launch the products they develop.

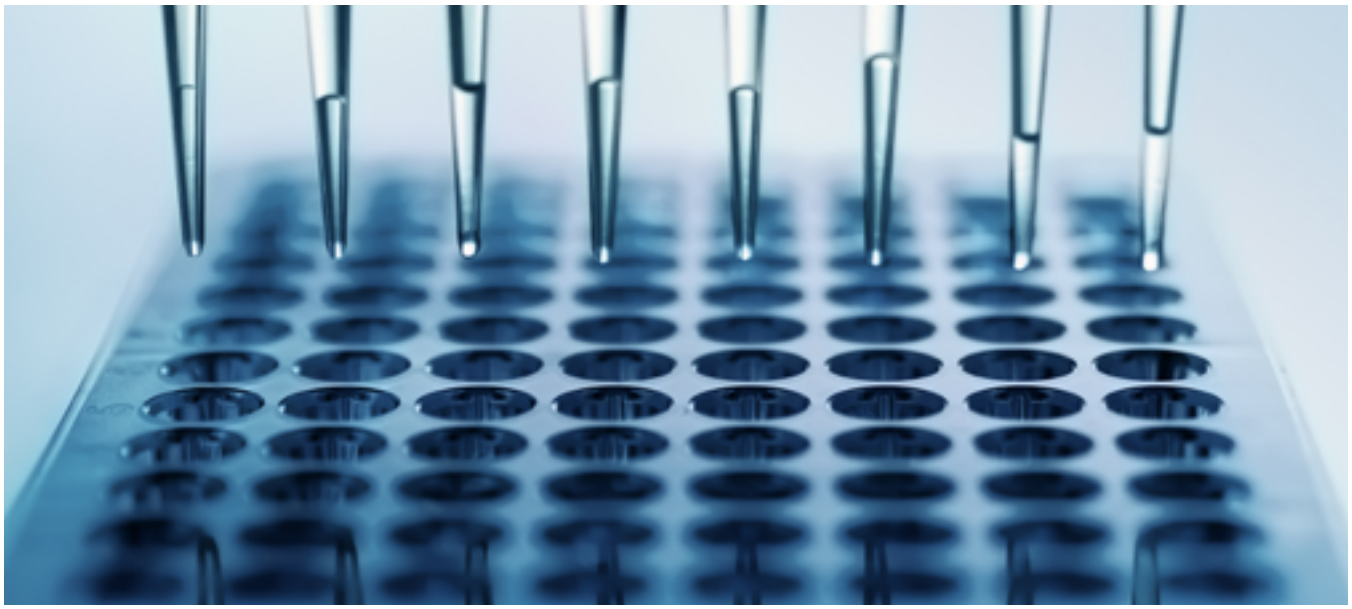
HOW BIOTECHS CAN ADD SOCIETAL VALUE BY EXPANDING ACCESS

Biopharma valuations soared during the early phases of the COVID-19 pandemic, as the industry's frontline role in the global health battle captured investors' attention. Since late 2021, however, valuations have dramatically reset to pre-pandemic levels, with investors increasingly focused on moving toward other sectors. This precipitous stock market drop underscores the need for biotechs to understand how the market perceives value and better communicate the value of their own offerings.

Biotech's traditional strengths in R&D and product innovation will remain central to the industry's market value. However, perceptions of cost and value are evolving as the dynamics within the health care ecosystem change. Notably, the *EY 2022 CEO Outlook Survey* emphasized that environmental, social and governance (ESG) factors are increasingly becoming an important lens through which to evaluate assets. Almost all CEO dealmakers stated that they factor ESG issues into their M&A decisions, seeking to acquire assets that will help them to accelerate their own sustainability strategies.

CEOs are embracing the ESG agenda because they recognize that these values increasingly shape how companies are perceived in the marketplace — by potential partners and investors, as well as the broad base of consumers. Since 2020, the COVID-19 pandemic has significantly heightened public awareness of the societal impact of companies' products and activities, in the process increasing the attention paid to companies' ESG undertakings. For biotech companies, there is a particular need to address the underappreciated "S" pillar in the ESG agenda — societal value.

In researching and manufacturing drugs that can improve health and save lives, biotechs are intrinsically committed to driving societal value. Yet, to have the widest possible impact, these companies also need to invest time and effort in ensuring that their treatments are as accessible as possible to those who need them the most. The challenge of widening access is multifaceted: for example, there is a well-recognized need to make recruitment for clinical trials more diverse and inclusive (see our article titled,



How biotech can benefit from improving clinical trial diversity) to address a significant obstacle to access equity. Companies should also work to ensure that their products are getting to those patients who need them the most, which means making products physically and financially accessible to all relevant communities and populations — not all of which will have access to a first-rate distribution infrastructure. Most critically, companies must prioritize ways to increase the affordability of their products for underserved patient groups.

Biotechs that place the highest priority on societal values often do the following:

- Design a targeted access vision and strategy that specifically addresses the creation of societal value.
- Build strategies that enable the appropriate patient populations, especially those with the highest unmet needs, to access the company's products.
- Develop and monitor metrics that objectively measure progress toward the company's patient access vision.

In underserved communities, improving access will require companies to build a multifaceted approach, including some or all of these steps: engaging with communities directly to build trust and improve communications; providing linguistically accessible and culturally competent educational materials; or offering resources such as free mobile or community screening clinics, transportation assistance, benefit portals, affordability programs and other tools to improve patient outreach.

These efforts to widen access and affordability should target not only underserved communities within the major markets, but also lower-income countries (LICs). A recent report concluded: "Companies are addressing access for the poor for less than half of key products analyzed. Low-income countries, as classified by the World Bank, are most consistently overlooked."[12]

Several biopharma companies have already initiated plans to address access inequity in this direction. Pfizer has stated its aim to halve the number of patients who cannot afford to access its medicines by 2023, while Merck & Co. has committed itself to social investments with a target of reaching 30 million people in LICs and in underserved US populations by 2025.

Yet, major global access disparities remain and have been starkly illustrated by the global response to the COVID-19 pandemic. Though nearly 12 billion doses of the coronavirus vaccine have been distributed, priority has overwhelmingly gone to the richest countries. According to *The Economist*, by August 2021, 60% of higher-income countries' populations had received one or more doses of the COVID-19 vaccine — while in LICs, the equivalent figure was 1%.[13] Moreover, the same analysis suggests that the lack of vaccine access could cost the global economy US$2.3 trillion by 2025, potentially driving significant political and social destabilization.

The COVID-19 vaccine access gap illustrates a broader truth for the industry: Access inequity has economic, as well as ethical, consequences. On both counts, there is a growing imperative for companies in the sector to address access and related issues of societal value. Upholding ESG values will be increasingly important for biotech companies over the next decade as patients and investors increasingly demand that companies demonstrate this commitment. By integrating ESG principles into their strategy, companies can gain a competitive edge. Biotechs must therefore learn how to measure and communicate the impact of their initiatives in a meaningful way. Critically, these companies need to collaborate with stakeholders to align around robust, standardized industry-specific metrics that can capture the impact of their efforts to deliver societal value.

12. "2021 Access to Medicine Index," *Access to Medicine Foundation website*, https://accesstomedicinefoundation.org/publications/2021-access-to-medicine-index#:~:text=The%207th%20Access%20to%20Medicine,%2D%20and%20middle%2Dincome%20countries, 26 January 2022.
13. *How much will vaccine inequity cost?* Economist Intelligence Unit, August 2021.

HOW BIOTECHS CAN CLOSE EMERGING TALENT GAPS

Perhaps biotech's biggest success story of the past couple of years has been the mRNA vaccines for combating COVID-19. In addition to this monumental R&D feat, the rapid deployment of complex global supply chains to manufacture and distribute billions of doses of the vaccines worldwide is in itself a major achievement. However, the companies responsible for the vaccines have reported one major constraint in their efforts to roll out the vaccines: talent recruitment. Both Moderna and Pfizer say that a shortage within the skilled workforce has posed a significant challenge to the vaccine program, with Pfizer's representatives telling the Massachusetts Legislative Manufacturing Caucus: "The biggest challenge is how do we continue bringing and creating the external talent pipeline in advance of the biotech sector growth?"[14]

Across the whole biotech sector, the talent pipeline is becoming an increasingly major issue. Biotech inherently has workforce requirements to keep its operations running. From the industry's science-driven R&D engines to the commercial and compliance expertise needed to bring products to market and the executive skill sets needed to navigate a complex and shifting business landscape – and across many other key roles – biotech requires a constant supply of niche talent. Securing this talent requires a strategic approach encompassing both recruitment and the ongoing training and upskilling of the existing workforce – potentially in alliance with universities.

Across the whole biotech sector, the talent pipeline is becoming an increasingly major issue.

14. "Vaccine makers are struggling with a labor shortage in Mass." *The Boston Globe*, July 2021

In recent years, the imperative for companies to build this type of strategic approach to talent has become more pressing than ever, as a result of three convergent trends: the impact of the biotech boom, the impact of COVID-19 and the increasing importance of what the World Economic Forum has termed "the fourth industrial revolution."

The biotech boom

The extraordinary success of biotechs.[15] [16]

Filling these roles is increasingly challenging, particularly as many biotechs pursue new modalities that require more specialized skill sets. The development, manufacturing, commercialization and scaling of cell and gene therapies, for example, needs different (and yet more specialized) skills than traditional biotech product lifecycle management.

The impact of COVID-19

Like other industries, biotech has experienced major workforce attrition during the pandemic. Burnout may have played some role in this, as biotech's position on the front line against COVID-19 has required extraordinary efforts from its workforces in 2020 and 2021. However, across all sectors, employees have demonstrated a well-recognized pattern of leaving their roles during the pandemic, a trend popularly described as the Great Resignation.[17] Given the tremendous pressure on biotech workforces, this trend is helping drive the emergence of a hypercompetitive labor market within the sector.

The fourth industrial revolution

As different industries evolve and converge, biotech roles will require an increasing level of cross-disciplinary expertise and familiarity with complex new technologies. (See *Bioconvergence: A multidisciplinary approach to advance human health*, a guest perspective by Belén Garijo of Merck Group, for more discussion about this trend.) Biotechs are increasingly leveraging advances in other tech spaces, including, among others, digital manufacturing, the internet of things, automation and AI, along with the tools they need to deliver customization and better user experiences.

These skill sets are growing in importance for biotech, yet they lie outside the industry's traditional talent base. As it seeks to build expertise in these areas, the industry is likely to find itself in competition with other sectors; for example, recruiting data scientists will be a priority for multiple industries.

How biotech can meet these challenges

Some of the pressures on biotech recruitment may ease in the near future. For example, with the boom in public biotech investment already fading in 2022, the recent proliferation of biotechs may undergo a correction, as smaller companies fold, merge, or are acquired and consolidated into larger entities. The impact of COVID-19 may also recede, although the effect of subsequent waves of the pandemic is difficult to predict.

Yet, the aftermath of the pandemic may well bring further challenges. Consider industry supply chains: if governments decide, in the wake of the pandemic, to localize elements of biopharma manufacturing and distribution, they will increase the demand for domestic talent across the industry. Moreover, the demands on talent from the rise in new technologies will only increase, and university systems are unlikely to generate the breadth of talent needed to meet these growing requirements.

Biotech will therefore need to find solutions to these workforce pressures. Companies need to identify the capabilities and skills they will need in the future and establish a build vs. buy strategy as they decide when to hire and when to develop from within. To help its existing talent thrive and grow, a company needs to promote in-role growth, skills development and internal mobility to ensure motivation and job satisfaction. Above all else, each biotech needs to define its own purpose and core values and allow those to drive the culture of the company. This is ultimately the only way the industry can engage with, recruit and retain the talent it will need in the future.

15. "MassBio: 40K new biopharma jobs predicted in next three years," *Boston Business Journal*, August 2021; "Vaccine makers are struggling with a labor shortage in Massachusetts," *The Boston Globe*, 28 July 2021.
16. Office of the Assistant Secretary for Preparedness & Response, "Public Health Supply Chain and Industrial Base One-Year Report". February 2022.
17. "The Great Resignation could last for years, says the expert who coined the term," *Fortune website*, https://fortune.com/2022/04/04/great-resignation-could-last-years-expert-says/, April 2022; "Vaccine makers are struggling with a labor shortage in Massachusetts," *The Boston Globe*, 28 July 2021.

DATABOOK

FINANCIAL PERFORMANCE

Growth in the US and European biotechnology markets

Financial at a glance (US$b)

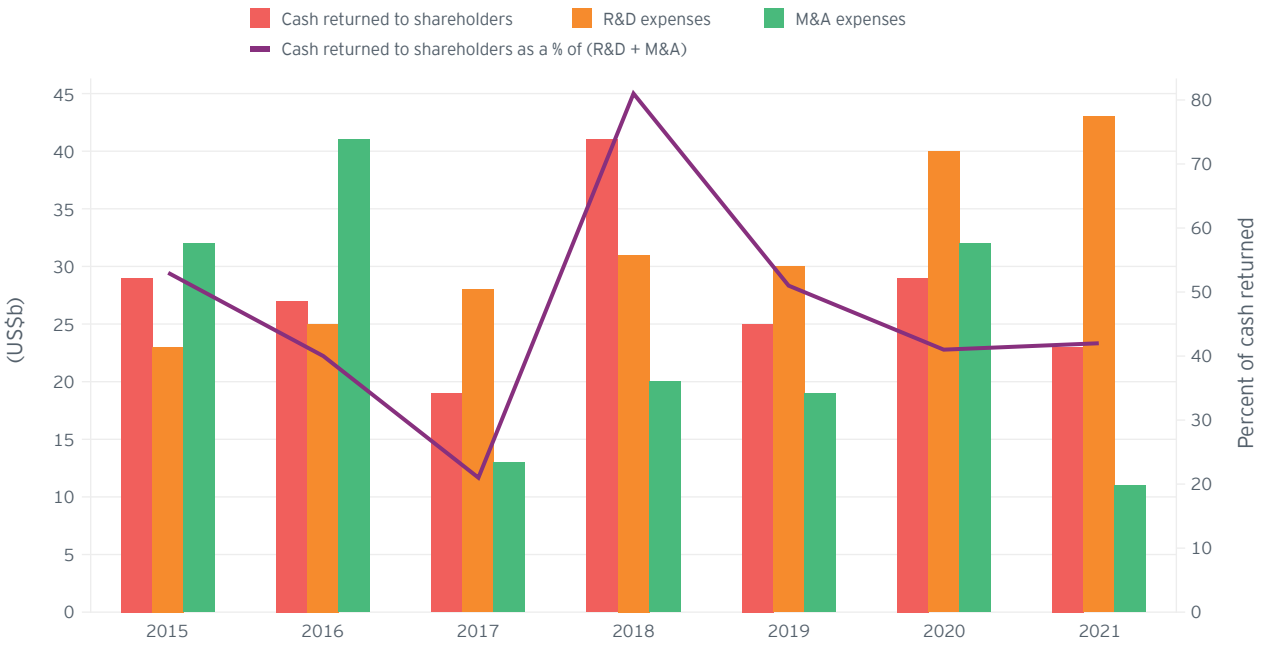
	2021	2020	Change	% change
Public data company				
Revenues	216.7	160.3	56.4	35%
R&D expense	88.6	79.8	8.8	11%
Net income	4.4	(18.8)	23.2	124%
Market capitalization	1,590.4	1,552.8	37.6	2%
Number of employees	276,500	256,400	20,100	8%
Number of companies				
Public companies	937	953	(16.0)	-2%

Source: EY analysis, Capital IQ, company financial statement data

- Public biotechs experienced a huge surge in revenues in 2021, with 63% of companies growing their top lines. Emerging leaders (companies with less than US$500 million in annual revenue) recorded a higher annual revenue growth rate (40%) than commercial leaders (35%). Collectively, the industry recorded an impressive 35% growth, compared with 16% growth in 2020, and hit nearly US$217 billion in total revenues. Net incomes had an extraordinary increase of US$23.2 billion, going from US$(18.8) billion in 2020 to US$4.4 billion in 2021.
- The surge in revenues and net income was overwhelmingly driven by products related to the COVID-19 pandemic, particularly the mRNA vaccines developed by BioNTech and Moderna. If the top- and bottom-line results for BioNTech and Moderna were excluded, total industry revenues would have been US$176.6 billion (up from 11% in 2020), with net income essentially flat at US$(19.5) billion. Nevertheless, there were other biotech growth stories, notably in the cell and gene therapy field, where CRISPR Therapeutics increased its revenues by US$914 million as a result of an up-front payment from Vertex to develop, manufacture and commercialize its CTX001 gene-editing therapy, and uniQure's license agreement with CSL Behring boosted its revenues by US$486 million.
- Biotechs also invested in talent, adding 20,000 employees to their payrolls over the course of the year (up 8% on 2020 employee numbers). Market caps rose by around 2% to just under US$1.6 trillion. However, this represented a steep decline from the 39% market cap growth in 2020, presaging the huge fall in biotech valuations that began late in 2021.

US and European biotechs prioritized R&D investments in 2021

Cash returned to shareholders

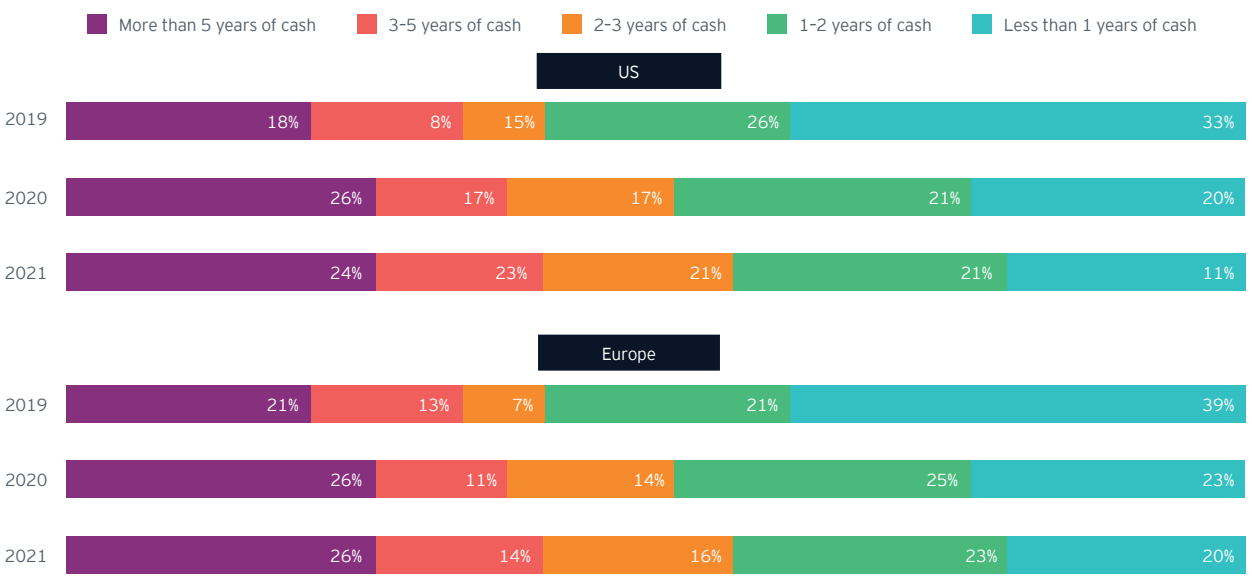


Source: EY analysis, Capital IQ, company financial statement data

- Throughout its history, biotech has very much been an R&D-driven industry, with significant amounts of capital spent to develop the next generation of therapies and diagnostics.
- With M&A activity (US$11 billion) reaching a multiyear low in 2021, biotech commercial leaders opted to heavily invest in R&D (US$43 billion), while also returning US$23 billion to shareholders (in the form of stock buybacks and dividends) — the 56% of deployable capital to R&D far surpassed the previous five-year average of 38%.
- Overall, 68% of public biotechs increased their R&D investment, led by Amgen, Novavax and Vertex, which all grew their R&D spending by over US$1 billion.

EY survival index, 2019–21 – emerging leaders

Survival index



Source: EY analysis, Capital IQ, company financial statement data

- With public valuations dropping sharply, access to capital markets becoming more difficult and M&A yet to rebound thus far in 2022, biotechs that effectively manage their cash reserves will be in a stronger position than other competitors. Cash reserves are particularly critical for pre-commercial companies with no marketed assets. Companies unable to secure funding may be forced to restructure, shed employees or scale back research projects to limit their cash burn.
- Encouragingly, however, over the 2019–21 period, public biotechs have significantly improved their cash reserves, driven by a sustained influx of capital from commercial revenues and investments. In all, 84% of commercial leaders hold more than five years' worth of cash, and 98% hold at least three years' worth.
- While emerging leaders have lower cash reserves, their overall cash positions have improved markedly between 2019 and 2021, with only 14% now holding less than a year's worth of cash reserves (compared with 35% in 2019), and 44% having at least three years' worth (from 29% in 2019). That being said, according to one recent report, 128 biotechs were trading at a market cap smaller than the cash they had on hand.[1]

1. "A record number of small biotechs are now trading below cash. Is this the bottom yet?," *Endpoints News website*, https://endpts.com/a-record-number-of-small-biotechs-are-now-trading-below-cash-is-this-the-bottom-yet/, 9 May 2022.

Top 10 changes in public company market capitalizations, 2016–21 (US$m)

Company	Market cap 31 December 2021	Market cap 31 December 2016	US$ change	CAGR (2012-16)
Moderna	102,976	5,023	97,953	174%
BioNTech	62,264	7,666	54,598	185%
IDEXX Laboratories	55,833	10,514	45,319	40%
Illumina	59,463	18,809	40,654	26%
Vertex Pharmaceuticals	55,834	18,272	37,561	25%
Regeneron Pharmaceuticals	66,029	39,394	26,635	11%
Horizon Therapeutics	24,442	2,609	21,833	56%
Seagen	28,270	7,470	20,800	30%
argenx SE	18,527	339	18,189	123%
Amgen	126,718	108,769	17,949	3%

Source: EY analysis, Capital IQ and company financial statement data

- Unsurprisingly, BioNTech and Moderna recorded the highest growth in public valuations between 2016 and 2021, driven by the runaway success of their respective mRNA vaccines against COVID-19 in the past two years. Regeneron has also benefited from COVID-19-related products via its monoclonal antibody cocktail, REGEN-COV, supplementing the revenues from its legacy products Eylea and Dupixent.
- Other notable leaps in market cap since our previous edition of *Beyond borders* include Vertex, responsible for the cystic fibrosis orphan disease franchise; Seagen, a pioneer in next-generation antibodies, one of the new modalities promising to be of major significance for sustaining biopharma growth; and argenx for its recently approved Vyvgart, the only current treatment for anti-AChR antibody positive generalized myasthenia gravis (gMG).

Top 10 US biotech regions, 2021

Region	Number of public companies	Market capitalization 12.31.2021	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term	Total assets
US-Massachusetts	152 -3%	344,979 1%	44,236 30%	20,466 10%	4,254 -214%	60,078 18%	114,553 6%
US-Northern California	107 -6%	278,598 -9%	42,428 17%	18,121 -15%	458 -111%	39,246 -7%	143,434 9%
US-Southern California	79 7%	268,827 -3%	36,511 10%	13,116 45%	2,209 -49%	27,990 -2%	102,625 14%
US-New York	45 -2%	86,496 13%	17,359 84%	4,475 4%	6,140 465%	9,395 16%	30,836 32%
US-New Jersey	38 -12%	26,152 1%	1,760 45%	2,271 11%	(2,947) 3%	5,806 7%	8,928 7%
US-Texas	24 -4%	9,120 -30%	136 -75%	773 -1%	(1,129) 31%	2,813 -10%	3,472 -17%
US-Pennsylvania	21 -13%	12,382 -18%	428 13%	1,421 21%	(1,878) 21%	3,261 14%	4,532 19%
US-Maryland	19 -21%	30,689 13%	5,348 18%	4,043 74%	(1,413) 46%	5,855 4%	13,747 2%
US-Florida	19 -10%	13,190 -7%	3,231 21%	533 31%	(519) 31%	2,486 39%	7,976 31%
US Washington	15 -6%	41,802 -17%	1,966 -18%	2,186 34%	(1,614) 222%	5,000 -7%	8,788 9%

Source: EY analysis, Capital IQ and company financial statement data
Percentage changes refer to change over December 2020. Numbers may appear inconsistent because of rounding.

- The traditional biotech clusters of Boston and Cambridge (Massachusetts), the Bay Area (Northern California), and San Diego and Los Angeles and Orange County (Southern California) account for a significant amount of the industry's financial presence in the US.
- Massachusetts is the base for long-standing biotech leaders, including Biogen and Vertex, as well as new major players, such as Moderna, and leads all US regions in terms of the number of public companies, revenue, R&D spend and market capitalization.
- The number of US commercial leaders (public companies with more than US$500 million in annual revenue) has jumped from 17 in 2016 to 31 in 2021. A record eight new companies joined the commercial leader group in 2021, led by Novavax, Fulgent Genetics and Vir Biotechnology, all of which saw their revenues grow by at least 840%.

Top 10 European biotech regions, 2021

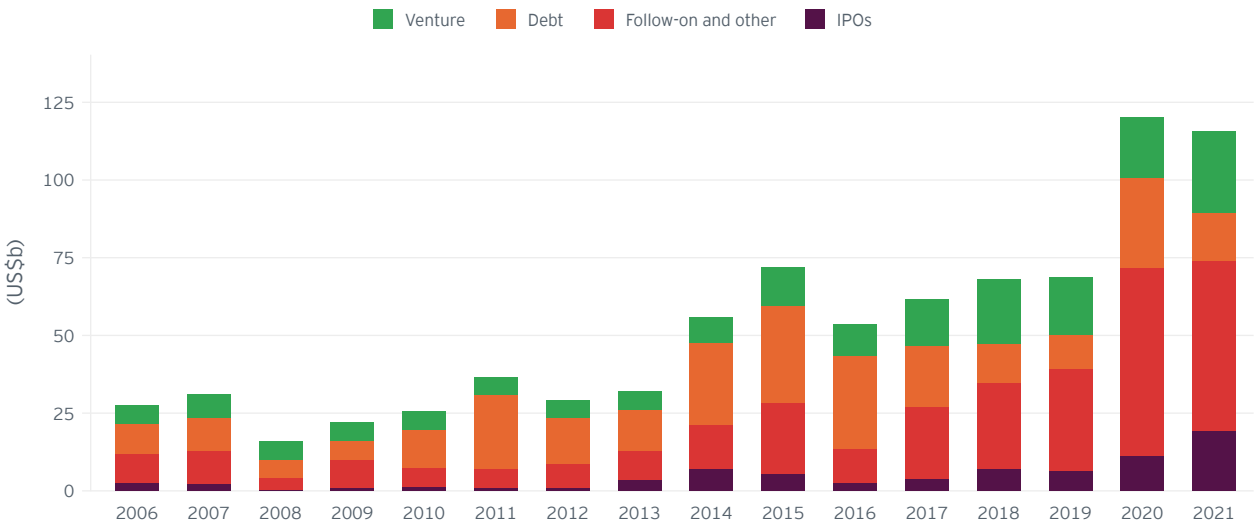
Region	Number of public companies	Market capitalization 12.31.2021	Revenue	R&D	Net income (loss)	Cash and equivalents plus short-term	Total assets
Sweden	79 8%	22,098 0%	2,704 4%	764 16%	(526) 62%	1,726 3%	10,869 7%
United Kingdom	57 -7%	25,779 37%	969 -34%	2,663 47%	(2,776) 333%	8,236 8%	11,322 20%
France	41 5%	16,510 13%	4,636 15%	1,401 7%	172 -207%	2,836 8%	9,267 5%
Israel	32 7%	2,826 -30%	299 13%	425 19%	(616) 22%	1.126 18%	2,175 38%
Germany	23 5%	83,725 76%	23,076 1012%	2172 38%	10,288 -1635%	7,052 19%	26,910 166%
Switzerland	17 0%	13,647 -37%	1,207 295%	1,497 11%	(1,047) -35%	4,803 16%	6,653 23%
Denmark	16 0%	61,529 10%	3,937 -9%	1,569 11%	(34) -107%	4,659 10%	11,536 14%
Norway	15 0%	7,400 -18%	215 -40%	125 6%	(352) -304%	973 2%	1,504 7%
Ireland	9 0%	41,461 27%	8,381 33%	2,371 45%	38 -86%	4,253 -31%	26,014 53%
Netherlands	7 -13%	34,744 18%	3,560 58%	1,168 36%	268 -145%	4,907 40%	11,038 18%

Source: EY analysis, Capital IQ and company financial statement data
Percentage changes refer to change over December 2020. Numbers may appear inconsistent because of rounding.

- In comparison with the US, Europe lacks dominant biotech clusters that play a leadership role across the region. Sweden has the largest number of public companies, and the UK has the highest levels of R&D investment; however, Germany leads in terms of total revenue, market capitalization and net income, a performance driven almost exclusively by the enormous success of BioNTech in 2021.
- The European financial metrics are dominated by a small number of commercial leaders, a group that included 15 companies in 2021 (compared with 10 in 2016). Three companies ascended to the financial leader group in 2021, with cannabinoid-focused GW Pharmaceuticals exiting via acquisition by Jazz Pharmaceuticals in May 2021.
- Joining the commercial leader group in 2021 were argenx, CRISPR Therapeutics and uniQure, which each grew their annual revenues by over 1,300% in 2021. Notably, these companies all focus on new modalities: Argenx is developing first-in-class antibody fragment technologies, while CRISPR Therapeutics and uniQure are focused on cell and gene therapy approaches.

FINANCING

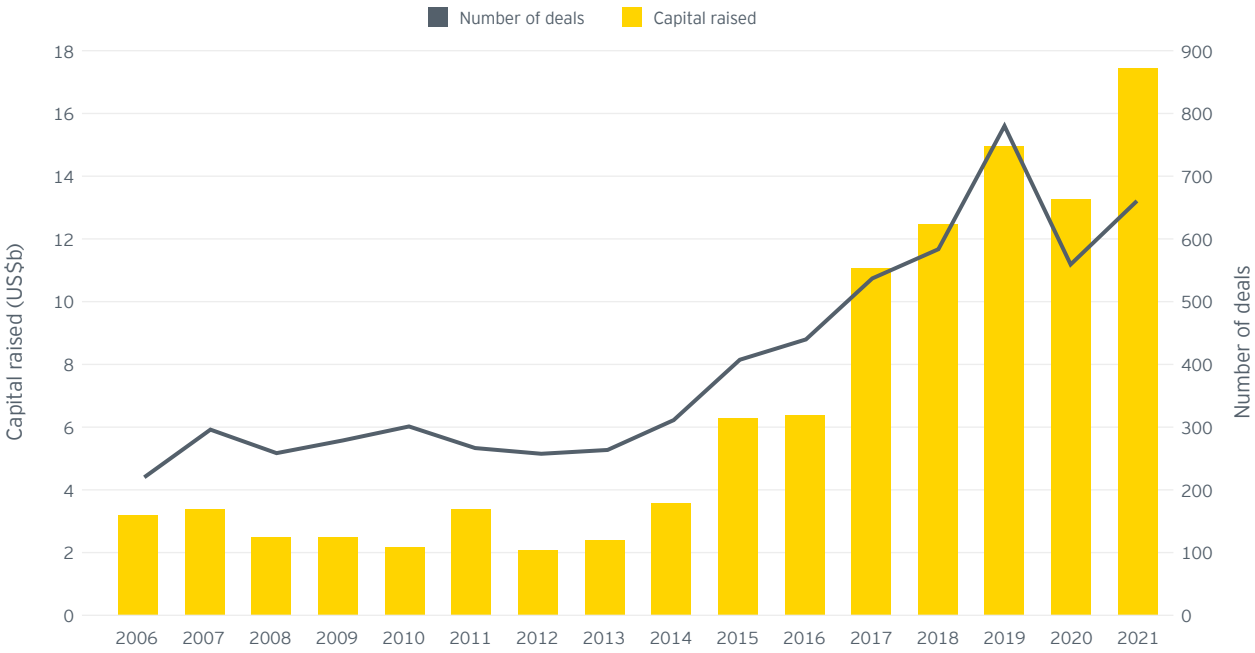
Capital raised in the US and Europe by year (US$b)



Source: EY analysis, Capital IQ and VentureSource

- Last year delivered another impressive year for biotech financing: The US$115.3 billion raised by the industry was the second-highest total ever recorded (and 69% greater than the third-biggest total in 2019). Though it fell 4% short of the record-breaking performance in 2020, these two years jointly account for 29% of all of the financing raised by biotechs in the past 15 years. US-based biotechs contributed 79% of this total, dominating in all types of fundraising.
- Debt and follow-on financing fell 48% and 10%, respectively (in each case, following an extremely active 2020), but venture financing and IPOs broke all previous records in 2021. Venture financing reached US$26.2 billion, a 25% increase over the previous record of US$20.8 billion in 2018. Meanwhile, a record 143 biotech IPOs occurred in the US and Europe (compared with a previous high of 96 in 2014), generating US$19.3 billion, 72% higher than the existing record set only the previous year. Of these IPOs, 30 were funded via special-purpose acquisition companies (SPACs) — another record.
- The dramatic scale of financing in 2021 in part reflects the prominent public role biotech has played during the pandemic, particularly the validation of technology concepts, such as the mRNA platform used to create the BioNTech and Moderna COVID-19 vaccines. With few other competing fields for investment during the pandemic, large-scale institutional investors poured capital into the biotech sector in 2020 and 2021. With these institutional investors seemingly now rotating to other industries, the financing boom for biotech looks to be ending in 2022. Just US$16.3 billion was raised in the first quarter — less than half of what the industry had been raising quarterly over the previous two years, though the debt market is sustaining the pace seen in 2021.

US and European early stage venture investment, 2006-21



Source: EY analysis, Capital IQ and VentureSource
2019 data is until 30 June 2019

- Early stage biotech venture funding has changed dramatically since we last published *Beyond borders*. In 2016, total early stage capital amounted to US$6.4 billion across 432 deals; in 2021, we saw a record US$17.5 billion across 650 deals. Around 66% of the total US$26 billion VC investment in biotech in 2021 went to early stage deals, compared with a 15-year average of around 59%.
- Over the past five years, early stage VC investment has totaled US$69.3 billion — nearly doubling the US$34.9 billion the industry raised over the previous 10 years. This in part reflects that late-stage companies have enjoyed high valuations and easy access to capital markets in recent years, with many consequently opting to go public rather than pursue late-stage VC investment.
- Amid a generally darkening financing picture in 2022, note that VC investment continued to flow into biotechs in the first quarter. In all, the industry raised US$8.3 billion in the first quarter. Of that, US$3 billion was generated by Altos Labs, based in the Bay Area, San Diego and Cambridge, UK, focused on cellular rejuvenation programming, with Amazon's Jeff Bezos among its investors. A key consideration for biotech VC funding will be whether the investor appetite will remain high if companies are struggling to exit, with the IPO market sinking and M&A still sluggish in early 2022.

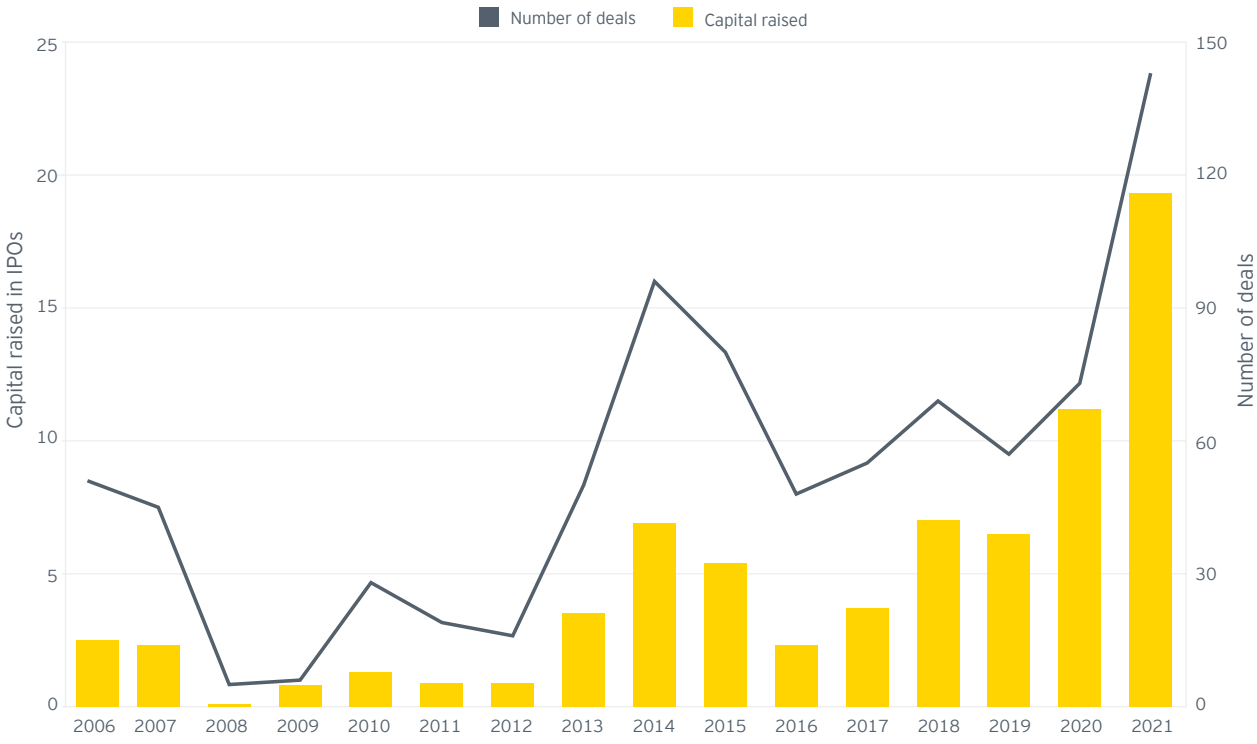
Early stage biotechs focused on cancer and multiple indications attracted significant venture capital in 2021

Name	Region	Therapeutic focus of lead candidate	Clinical stage of lead candidate	Gross raised (US$m)	Quarter	Round type
Caris Life Sciences	US-Texas	Research & other equipment	N/A	$830	Q2	Late
EQRx	US-Massachusetts	Cancer	Pre-clinical	$500	QI	Early
Neumora Therapeutics	US-Massachusetts	Neurology	Phase II	$500	Q4	Early
Adagio Therapeutics	US-Massachusetts	Infectious Disease	Phase III	$336	Q2	Late
SOTIO	Czech Republic	Cancer	Phase II	$316	Q4	Early
Prime Medicine, Inc.	US-Massachusetts	Multiple	Pre-clinical	$315	Q3	Early
Vyripharm	US-Texas	Multiple	Phase 0	$300	Q4	Early
Cardurion Pharmaceuticals	US-Massachusetts	Cardiovascular	Phase II	$300	Q4	Late
Sonoma Biotherapeutics	US-Northern California	Autoimmune	Phase I	$265	Q3	Early
Avencell	US-Massachusetts	Cancer	Phase I	$250	Q2	Early
Affinivax	US-Massachusetts	Infectious Disease	Phase II	$226	QI	Late
Odyssey Therapeutics	US-Massachusetts	Multiple	Pre-clinical	$218	Q4	Early
Immunai	US-New York	Diagnostics	N/A	$215	Q4	Early
Umoja BioPharma	US-Washington	Cancer	Phase III	$210	Q2	Early
Venn Biosciences	US-Northern California	Diagnostic	N/A	$201	Q3	Late
G2 Bio	US-Pennsylvania	Multiple	Pre-clinical	$200	Q2	Early
NewAmsterdam Pharma	Netherlands	Cardiovascular	Phase III	$196	QI	Early
Wugen	US-Missouri	Cancer	Phase 1/11	$172	Q3	Early
GentiBio	US-Massachusetts	Autoimmune	Pre-clinical	$157	Q3	Early
Quell Therapeutics	UK	Hematology/Renal	Pre-clinical	$156	Q4	Early

Source: EY analysis, Capital IQ and VentureSource

- In all, four of the top six (and 12 of the top 20) largest VC rounds ever recorded by biotechs took place in 2021. Of the overall US$26 billion invested, more than half came from just 82 funding rounds — 36 of which were investments targeting the oncology space. Again, the US dominated fundraising, accounting for 66 of these 82 rounds.
- The largest of these rounds went to Texas-based precision medicine company Caris Life Sciences, which raised US$830 million — the third-largest round in biotech history, behind only Grail Bio and Roivant Sciences in 2017. Caris has raised approximately US$1.3 billion in external financing over the past three years for its first-in-class liquid biopsy platform in oncology.
- Some of the other largest early stage rounds of 2021 included:
  - Massachusetts-based EQRx, which received US$500 million in second-round investments as it pursues its goal of creating more affordable cancer drugs
  - Neumora, also of Massachusetts, which attracted the third-largest seed round in industry history (US$500 million) for its neurology drug candidates and discovery platform
  - Massachusetts-based biotech Adagio Therapeutics, which raised US$336 million to advance its COVID-19 antibody treatment
  - SOTIO Biotech, based in the Czech Republic, which attracted the largest VC investment of any European biotech, drawing US$316 million for its oncology candidate
  - Prime Medicine, which secured US$315 million in Series A and Series B investment to develop its Prime Editing gene-editing platform, a spin-off from The Broad Institute

US and European biotechnology IPOs, 2006-21



Source: EY analysis, Capital IQ and VentureSource
2019 data is until 30 June 2019

- During 2020 and 2021, US and European biotechs carried out an unprecedented 216 IPOs, raising US$30.6 billion in the process (for contrast, the previous 10 years saw the biotech IPO market raise a total of only US$24.7 billion).
- The record-breaking 2021 IPO performance saw 93% of companies priced in or above their proposed ranges as they entered the public market, with an average size of US$135 million. Biotechs Sana Biotechnology, Lyell and Erasca secured investments several times larger than they initially asked for when going public in 2021; Recursion Pharmaceuticals, an AI company focused on drug discovery, raised US$502 million after initially seeking US$100 million.
- However, the pace of IPOs significantly slowed in the fourth quarter of 2021, with only 10% of the year's total coming in the final three months. With biotech stock valuations beginning to decline in the third quarter, the end of 2021 saw just 15% of the year's IPOs recording positive returns, with 31% seeing their value drop by 50% or more, and 66% losing at least 25%. In the first months of 2022, just eight biotechs executed IPOs, raising a cumulative US$342 million. This slow start in 2022 leaves biotech on track to raise its lowest total IPO capital in at least a decade.

Top US and European IPOs, 2021

Name	Region	Therapeutic focus of lead candidate	Clinical stage of lead candidate	Gross raised (US$m)	Quarter	Post-IPO performance (31 Dec 2021)
Sana Biotechnology	US-Washington	Cancer	Pre-clinical	$676	Q1	-56%
Recursion Pharmaceuticals	US-Utah	Multiple	Phase I	$502	Q2	-45%
Evotec	Germany	Neurology	Phase III	$500	Q3	6%
Lyell Immunopharma	US-Northern California	Cancer	Phase I	$425	Q2	-54%
Instil Bio	US-Texas	Cancer	Phase II/III	$368	Q1	-35%
Adagio Therapeutics	US-Massachusetts	Infectious disease	Phase II/III	$356	Q3	-65%
Exscientia	UK	Cancer	Phase I	$350	Q3	-27%
Erasca	US-Southern California	Cancer	Phase II	$345	Q3	-11%
LianBio	US-New Jersey	Multiple	Phase III	$325	Q4	-55%
Verve Therapeutics	US-Massachusetts	Cardiovascular	Pre-clinical	$307	Q2	16%
Caribou Biosciences	US-Northern California	Cancer	Phase I	$304	Q3	-8%
Immunocore	UK	Cancer	Phase III	$297	Q1	-21%
Cullinan Oncology	US-Massachusetts	Cancer	Phase II	$287	Q1	-48%
Design Therapeutics	US-Southern California	Neurology	Pre-clinical	$276	Q1	-48%
Graphite Bio	US-Northern California	Cardiovascular	Phase I	$274	Q2	-33%
Atai Life Sciences	Germany	Neurology	Phase II	$259	Q2	-61%
Singular Genomics Systems	US-Southern California	Research & other equipment	N/A	$258	Q2	-55%
Talis Biomedical	US-Northern California	Diagnostics	N/A	$254	Q1	-86%
Century Therapeutics	US-Pennsylvania	Cancer	Pre-clinical	$243	Q2	-31%
Janux Therapeutics	US-Southern California	Cancer	Pre-clinical	$223	Q2	-22%

Source: EY analysis, Biomedtracker and company news
"Total potential value" includes up-front, milestone and other payments from publicly available sources. "ND" refers to deals where up-front amounts were not publicly disclosed.

- Over the course of 2021, 56 companies executed IPOs raising over US$100 million, up from 46 in 2020. Once again, oncology was a major target, with 49 IPOs generating US$7.4 billion overall (for comparison, the next most prominent therapeutic area was neurology, with 14 IPOs raising US$1.1 billion).
- Ten of the top 20 IPOs went to companies with lead drug candidates either at a preclinical stage or in phase I of clinical development. This includes the year's largest IPO, Washington-based Sana Biotechnology, which raised US$676 million — a biotech IPO record — surpassing Moderna's US$604 million in 2018, and second only to Serono's US$1.1 billion IPO in 2000. Sana Biotechnology is focused on developing oncology treatments, including targeting T cells to address various blood cancers.
- Other notable IPOs of 2021 included:
  - Utah-based Recursion Pharmaceuticals, which raised nearly US$502 million for its AI-driven drug discovery engine. The company has four clinical-stage programs and raised around US$420 million in VC funding prior to its IPO.
  - Evotec of Germany, which recorded Europe's largest biotech IPO of 2021. Evotec has been traded on the Frankfurt Stock Exchange since 1999, but debuted on the US NASDAQ in the last quarter of 2021. It has 11 disclosed clinical-stage programs and over 100 earlier-stage candidates.
  - Rounding out the year's top five IPO deals, Lyell Immunopharma and Instil Bio are both using cell therapy platforms to develop cancer therapies.

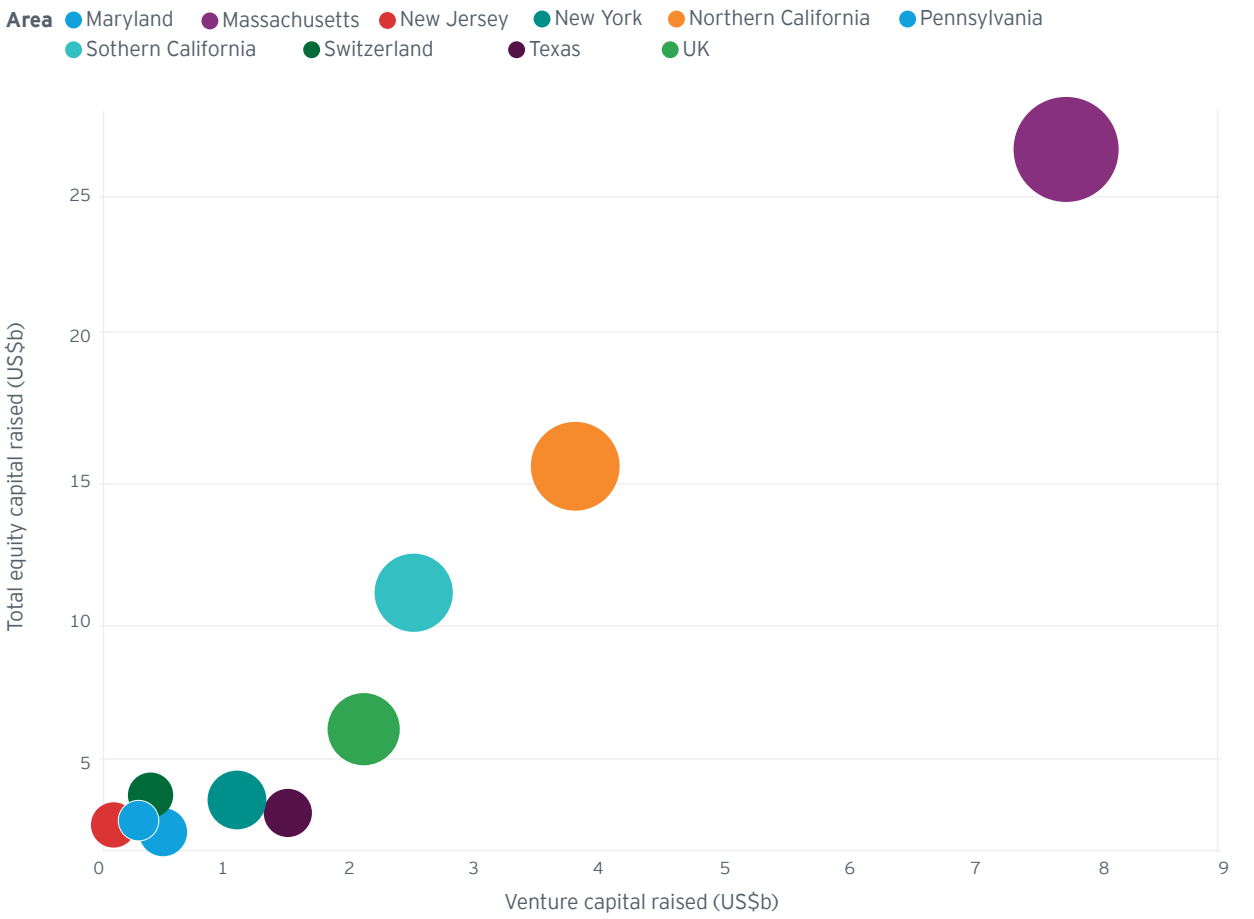
Select SPACs, 2021

Name	Region	Therapeutic focus of lead candidate	Clinical stage of lead candidate	Gross raised (US$m)	IPO (US$m)	Other investment (US$m)	Quarter
EQRx	US-Massachusetts	Cancer	Phase III	$1,800	$600	$1,200	Q4
Nuvation Bio	US-Northern California	Cancer	Phase I	$650	$150	$500	Q1
Soma Logic	US-Colorado	Diagnostics	N/A	$630	$275	$355	Q3
Roivant Sciences	UK	Dermatology	Reg1strat1on	$611	$411	$200	Q2
23andme	US-Northern California	Cancer	Phase I	$592	$342	$250	Q2
Quantum-Si	US-Connecticut	Research and other equipment	N/A	$540	$115	$425	Q4
Alvotech Holdings SA	US-Southern California	Multiple	Approval	$450	$300	$150	Q3
GreenLight Biosciences	US-Massachusetts	Multiple	Pre-clinical	$387	$282	$105	Q3
Gelesis Holdings, Inc.	US-Texas	Gastrointestinal	N/A	$376	$276	$100	Q3
Tango Therapeutics	US-Massachusetts	Cancer	Phase I	$353	$167	$186	Q3
Nautilus Biotechnology	US-Washington	Research and other equipment	N/A	$345	$145	$200	Q2
POINT Biopharma Global Inc.	US-Massachusetts	Cancer	Phase III	$287	$122	$165	Q1
Pardes Biosciences	US-Southern California	Infections disease	Phase I	$274	$199	$75	Q4
Humacyte	US-North Carolina	Cardiovascular	Phase III	$245	$70	$175	Q3
eFFECTOR Therapeutics	US-Southern California	Cancer	Phase II	$235	$175	$60	Q3
Gemini Therapeutics	US-Massachusetts	Ophthalmology	Phase II	$216	$121	$95	Q1
Surrozen	US-Northern California	Multiple	Pre-clinical	$212	$92	$120	Q3
Ensysce Biosciences	US-Southern California	Neurology	Phase I	$200	$200	–	Q2
Celularity	US-New Jersey	Multiple	Phase II	$138	$138	–	Q3
NRx Pharmaceuticals	Israel	Respiratory	Phase III	$120	$120	–	Q2
SAB Biotherapeutics, Inc.	US-Florida	Infectious disease	Phase III	$118	$116	$2	Q2
Renovacor, Inc.	US-New York	Cardiovascular	Pre-clinical	$116	$86	$30	Q1
LumiraDx	UK	Diagnostics	N/A	$115	$115	–	Q3
Better Therapeutics	US-Northern California	Hematology/Renal	Phase III	$110	$70	$40	Q3
Jasper Therapeutics	US-Northern California	Multiple	Phase I	$107	$7	$100	Q3
Revelation Biosciences	US-Southern California	Infectious disease	Phase II	$73	$73	–	Q3
4D Pharma	UK	Cancer	Phase II	$38	$38	–	Q1
Clarus Therapeutics	US-Illinois	Urology	Marketed	$25	$25	–	Q3
PsyBio Therapeutics	US-Florida	Neurology	N/A	$18	$18	–	Q1
3D Bio-Tissues Limited	UK	Research and other equipment	N/A	$3	$3	–	Q3

Source: EY analysis, Capital IQ and VentureSource

- According to EY research, 2021 saw 30 biotech SPACs, generating US$9.4 billion in investment capital; of this, more than US$4.8 billion came in the form of IPOs, while another US$4.5 billion came from private follow-on offerings — representing a significant uptick from the five SPAC deals that raised US$852 million in the previous year.
- The largest of 2021's SPAC deals was secured by Massachusetts-based EQRx, which aims to develop versions of blockbuster medicines at "radically lower" prices. As noted, the company previously raised US$800 million from VC investors and announced its first five pipeline drug candidates.
- Only three of the year's SPAC deals happened in the final quarter of 2021, with the market, like other financing streams, appearing to dry up. The market will be further constrained by the U.S. Securities and Exchange Commission's March 2022 announcement of new rules intended to place greater restrictions on the SPAC market to protect investors.

Capital raised by leading US and European regions excluding debt, 2021



Size of bubbles shows relative number of financings per region.
Source: EY analysis, BMO Capital Markets, Dow Jones VentureSource and Capital IQ

- Massachusetts, Northern California and Southern California led the way in total equity and VC funding, as well as in the total number of equity rounds. Massachusetts alone raised US$26.6 billion in total equity financing (27% of the combined total for the US and Europe), and US$7.8 billion in VC (30% of the US and Europe total).
- The US as a whole dominated the VC market, raising US$20.2 billion compared with US$6 billion for Europe. In terms of total equity, the US generated US$79.3 billion, compared with US$20.7 billion for Europe. The UK was the only European country to figure among the top five overall biotech investment regions, with Texas rounding out the list.

M&A

Select US and European biotech M&As, 2021

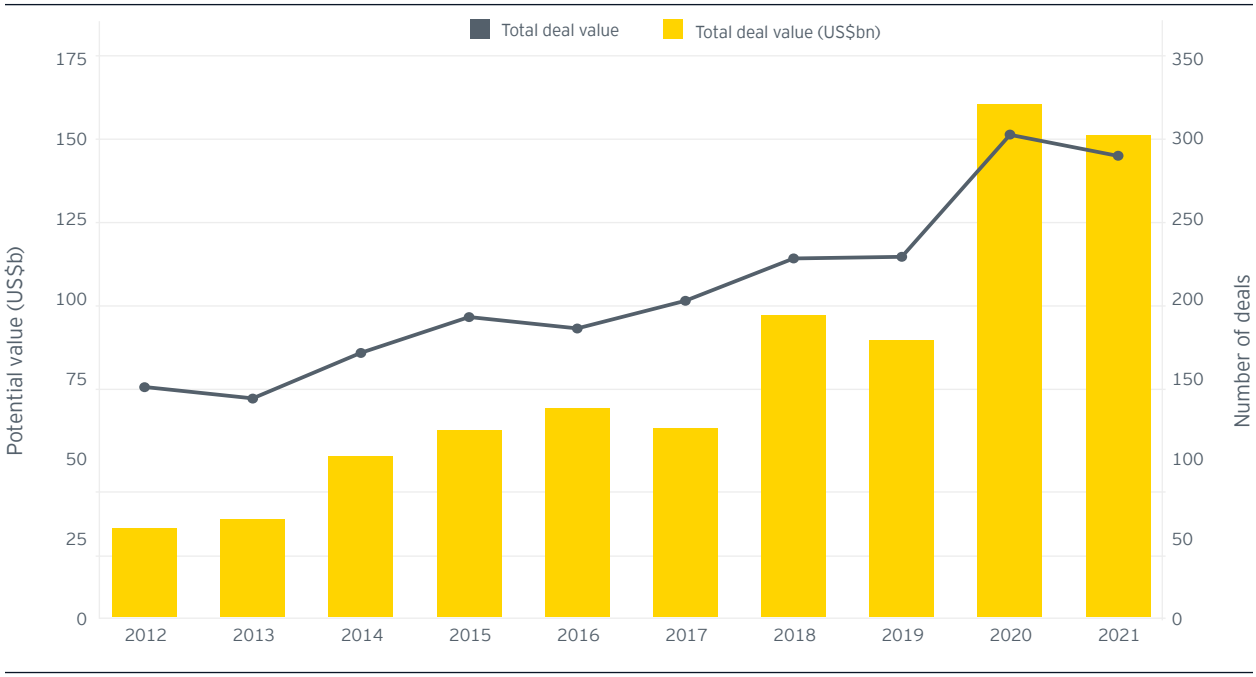
Company	Country	Acquired or merged company	Country	Total potential value (US$m)	Upfront
Merck & Co.	US-New Jersey	Acceleron	US-Massachusetts	11,500	All
Jazz Pharmaceuticals	Ireland	GW Pharmaceuticals	UK	7,200	All
Pfizer	US-New York	Arena Pharmaceuticals	US-Southern California	6,700	All
PerkinElmer	US-Massachusetts	BioLegend	US-Southern California	5,250	All
Novo Nordisk	Denmark	Dicerna Pharmaceuticals	US-Massachusetts	3,300	All
Sanofi	France	Translate Bio	US-Massachusetts	3,200	All
Horizon Therapeutics	Ireland	Viela Bio	US-Maryland	31050	All
Amgen	US-Southern California	TeneoBio	US-Northern California	2,500	900
Pfizer	US-New York	Trillium Therapeutics	Canada	2,260	All
Bayer	Germany	Vividion Therapeutics	US-Southern California	2,000	1500
Sanofi	France	Kadmon Holdings	US-New York	1,900	All
Amgen	US-Southern California	Five Prime Therapeutics	US-Northern California	1,900	All
Merck & Co..	US-New Jersey	Pandion Therapeutics	US-Massachusetts	1,850	All
MorphoSys	Germany	Constellation Pharmaceuticals	US-Massachusetts	1,700	All
Novartis	Switzerland	Gyroscope Therapeutics	UK	1,500	800

Source: EY analysis, Capital IQ and company news
"Total potential value" includes up-front, milestone and other payments from publicly available sources.

- As described in our companion EY *M&A Firepower* 2022 report, 2021 biopharma M&A was a volume story, with smaller bolt-on transactions dominating the market. While the number of M&As with announced deal values (57 in 2021) reached its highest point for at least 15 years, the total value of those deals (US$65.9 billion) dropped for the second consecutive year, and reached its lowest level since 2017, down from US$164.3 billion in 2019 and US$119.2 billion in 2020.
- The average deal size in 2021 was US$1.2 billion, lower than the average of US$1.8 billion over the previous 15 years. The largest M&A deal of 2021, Merck & Company's US$11.5 billion acquisition of Acceleron's late-stage rare disease candidate sotatercept, was dwarfed by the big transactions of recent years, such as Bristol Myers Squibb's US$74 billion purchase of Celgene, or the AstraZeneca-Alexion (US$39 billion) and Takeda-Shire (US$62 billion) deals. Other notable transactions of the year included Jazz Pharmaceuticals' move to acquire GW Pharmaceuticals and its Epidiolex product (the first marijuana-derived drug approved in the US), Horizon Therapeutics' acquisition of AstraZeneca spin-out Viela Bio, and Sanofi's purchase of Translate Bio and its mRNA technology platform. Pfizer followed up its deal with Arena Pharmaceuticals and its Phase III inflammatory bowel disease treatment etrasimod with a US$11.6 billion acquisition of Biohaven Therapeutics in Q1 2022. Biohaven's therapies focus on debilitating neurological and neuropsychiatric diseases.
- High valuations ensured that biotech remained essentially a seller's market in 2021. The drastic correction in biotech stock markets may change this dynamic substantially in 2022. However, in the first quarter, there was no sign of an M&A resurgence in the sector, with only eight deals of US$100 million or more completed, generating just US$4.9 billion. If that trend continues, 2022 would be the lowest M&A value year since 2010; however, the industry's need to secure access to innovations and the falling valuations of biotechs may converge to reinvigorate dealmaking over the remainder of 2022.

ALLIANCES

US and European strategic alliances based on biobucks, 2012–21



- In 2021, there were 283 alliances announced involving US and European biotechs — the total value reached US$152.1 billion. This included 54 alliances valued at over US$1 billion.
- While this was a slight decrease from the record 296 alliances for US$161.6 billion recorded in 2020, both years are significant outliers for alliance deals, with the industry clearly embracing the opportunities of non-M&A dealmaking. The EY analysis (see our EY *M&A Firepower* 2022 report) suggests that the historical ROI for alliances is 33% higher than for M&A, and that since the beginning of 2020, leading biopharma players have deployed 1.5 times more firepower toward alliances compared with M&A. (The EY report defines firepower as a company's capacity to fund transactions based on the strength of its balance sheet. It has multiple inputs: cash and cash equivalents, existing debt and market capitalization.) Moreover, these partnerships offer large companies a way to access new innovations without paying the high prices demanded by inflated valuations in recent years, thereby offsetting the dealmaking risk.
- Despite the sharp drop in biotech valuations, alliances continued to play a major role in the first quarter of 2022. The three-month period saw 64 announced alliance deals, valued at total US$48.9 billion; however, only US$2.4 billion (5%) of this value was paid up front, well below the 12% average recorded over the past decade.

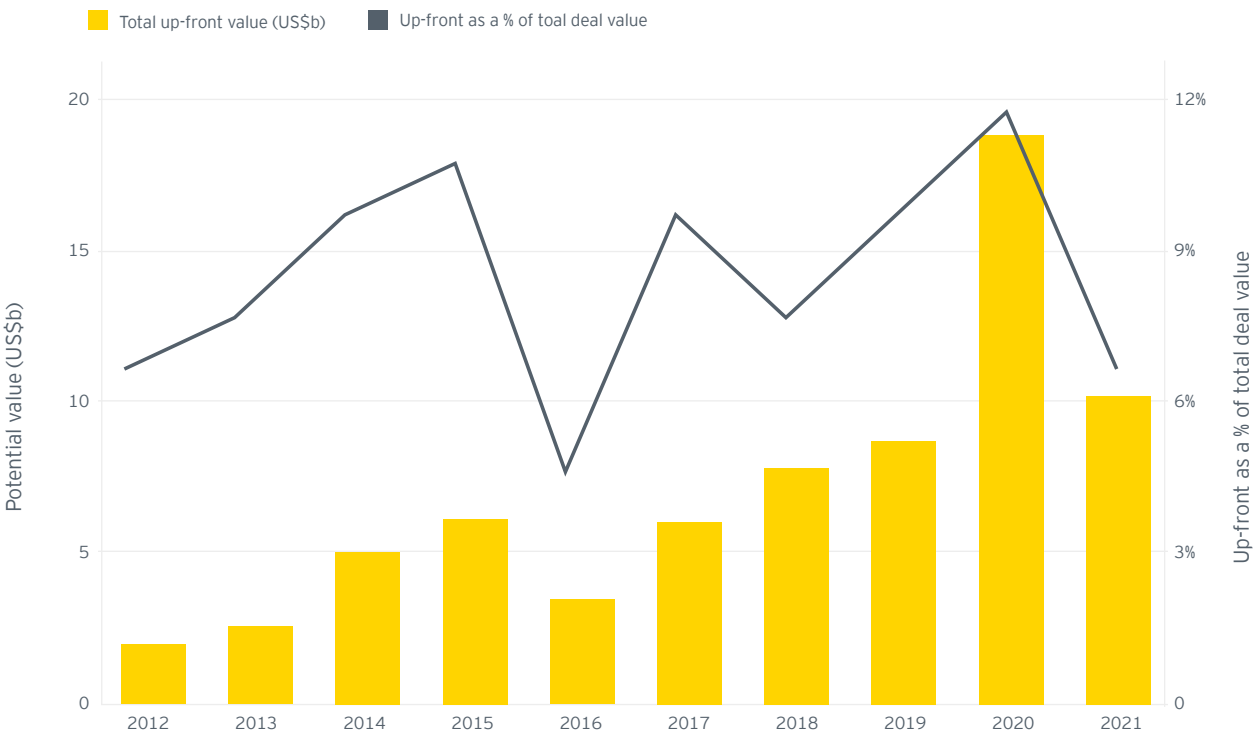
Leading biobucks alliances, 2021

Company	Country	Partner	Country	Total potential value (US$m)	Up-front payments (US$m)
Roche (Genentech)	Switzerland	Recursion Pharmaceuticals	US-Utah	12,150	150
AstraZeneca	UK	Ionis Pharmaceuticals	US-Southern California	3,585	200
Roche (Genentech)	Switzerland	Adaptimmune Therapeutics	UK	3,300	150
Roche (Genentech)	Switzerland	Shape Therapeutics	US-Washington	3,000	-
Novartis	Switzerland	BeiGene	China	2,895	300
Takeda	Japan	Poseida Therapeutics	US-Southern California	2,760	45
Neurocrine Biosciences	US-Southern California	Sosei	Japan	2,700	100
Seagen	US-Washington	RemeGen	China	2,600	200
Bridge Bio (QED Therapeutics)	US-Northern California	Helsinn Healthcare	Switzerland	2,450	100
Pfizer	US-New York	Arvinas	US-Connecticut	2,400	650
Gilead (Kite Pharma)	US-Northern California	Shoreline Biosciences	US-Southern California	2,300	-
GlaxoSmithKline	UK	Alector	US-Northern California	2,200	700
Novartis	Switzerland	BeiGene	China	2,200	650
Alnylam Pharmaceuticals	US-Massachusetts	PeptiDream	Japan	2,200	-
GlaxoSmithKline	UK	iTeos Therapeutics	US-Massachusetts	2,075	625
Eli Lilly (Loxo Oncology)	US-Indiana	Kumquat Biosciences	US-Southern California	2,070	70

Source: EY analysis, Biomedtracker and company news
"Total potential value" includes up-front, milestone and other payments from publicly available sources. "ND" refers to deals where up-front amounts were not publicly disclosed

- The 2021 Roche (Genentech)-Recursion alliance is potentially worth US$12.2 billion, making it the largest biobucks deal of all time (overtaking the 2019 US$9.4 billion alliance between Galapagos and Gilead). Of this total, Roche is investing US$150 million up front and will use the AI-driven Recursion Operating System to advance 40 therapeutic programs in both neurology and cancer indications.
- Aside from Recursion, Roche was extremely busy within the alliance space, agreeing to seven further alliances (including three of the year's top four) worth a potential US$22.2 billion, though only US$410 million was guaranteed up front. Notable alliance partners for Roche included Adaptimmune Therapeutics, focused on allogeneic cell therapies, which signed a deal with the Swiss pharma giant that is worth a potential US$3.3 billion, and Shape Therapeutics, with an AI platform focused on gene therapy, which signed a deal worth up to US$3 billion.
- Among the other Big Pharma, leading alliance makers included Eli Lilly, which agreed to 10 alliances for US$11.6 billion in biobucks, with US$440 million guaranteed up front; Novartis, with six alliances for US$10 billion and US$950 million up front; Takeda with 10 alliances for US$9 billion and US$396 million up front; and GlaxoSmithKline with five alliances for US$6.4 billion and US$1.2 billion up front. More recently, Sanofi announced in the first quarter of 2022 two deals that would rank among the largest biobucks alliances yet seen: a US$6.2 billion deal with IGM Biosciences, a developer of engineered antibodies, and a US$5.3 billion deal with AI drug discovery company Exscientia.

US and European strategic alliances based on up-front payments



- While 2020 was remarkable for up-front payments, with alliances signed that guaranteed US$19 billion up front, 2021 saw that number fall to US$9.7 billion — just 6% of the total potential value, the second-lowest in a decade and well behind the 9% annual average seen over the previous 10 years.
- In 2020, there were 38 deals with more than US$100 million paid up front, but 2021 saw only 30, with the average up-front payment dropping by US$30 million compared with the previous year.

In short, biopharma companies in 2021 prioritized smaller alliances with lower up-front payments. Early data for 2022 suggests this trend will continue: The first quarter of the year saw US$3.3 billion of up-front capital committed to alliances, in line with 2021, but well below the levels seen in 2019 and 2020.

Data exhibit index

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