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Understanding the U.S. Biopharmaceutical Innovation Ecosystem

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Introduction

The biopharmaceutical innovation system—which brings novel, life-improving, and life-saving therapies from the researcher's bench to a patient's bedside—is a major engine powering health improvements, economic output, and wealth creation in the United States. But while the commercial and national security competition with China has brought policy attention to securing the semiconductor industry, the importance of sustaining a world-leading U.S. biopharmaceutical industry remains underappreciated.

In the United States, the pace of biopharmaceutical innovation has enjoyed remarkable growth over the last decade. New drug approvals by the Food and Drug Administration **increased** from **209** between 2000-2008 to **302** between 2009-2017—a 44.5 percent surge. Furthermore, U.S. firms filed nearly **38 percent** of global biotechnology patents from 2015-2020, bolstering the U.S. biotech industry's position over those of competitors such as China, the European Union, Japan, and the United Kingdom.

Yet, despite its growth and notable recent successes—such as the development of Covid-19 mRNA vaccines; new treatments for cancer, Alzheimer's disease, and sickle cell anemia; and medications for weight loss—the U.S. biopharmaceutical ecosystem is under pressure from a number of directions.

Notably, U.S. policymakers, responding to concerns by some consumer advocates over the high prices of particular drugs, have sought to lower prices by weakening the patent system. A well-functioning patent system **secures property rights** in inventions so that innovators can share and collaborate safely with others to bring new ideas to the marketplace. Patents also incentivize this effort by allowing patent holders to gain financially from their innovation for a limited period. It is this second feature of patents that is at issue with advocates seeking to lower drug prices. But a broad assault on patents may

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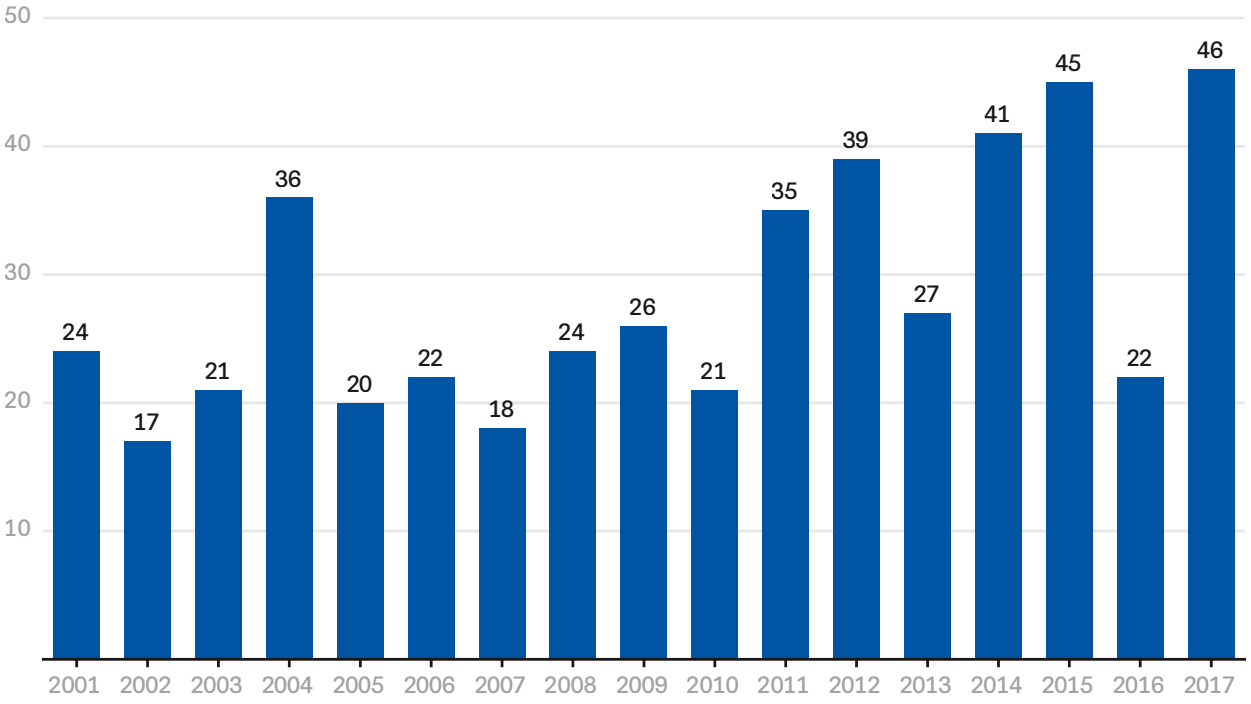
well damage the very features of the innovation system that make possible the collaboration needed to produce innovative drugs, medical devices, and other therapies that improve well-being.

This endangerment of to the patent system places the U.S. biopharmaceutical industry at a competitive disadvantage globally, at the same time that sweeping **regulatory reforms** and injections of **capital** are propelling China's biopharmaceutical industry forward at an unprecedented pace. This presents a long-term challenge to U.S. dominance in the industry.

It is therefore important to understand the nature of the innovation ecosystem on which this leading U.S. industry is based. The first section of this paper gives a brief overview of the drug development and approval process in the United States. The second section explores the core components that comprise and drive the U.S. biopharmaceutical innovation system. Later sections address the threats to this ecosystem, including the growth of the Chinese biopharmaceutical industry and new concerns around march-in rights.

Figure 1: Drug Development by Year and Type, 2001–2017



Source: Angelika Batta, Bhupinder Singh Kalra, and Raj Khirasaria, "Trends in FDA drug approvals over last 2 decades: An observational study," *Journal of Family Medicine and Primary Care* 9, no. 1 (January 2020), https://doi.org/10.4103/jfmpc.jfmpc_578_19.

The Drug Development Process: From Bench to Bedside

Pharmaceutical innovation is a complex process involving multiple actors across different stages that work together to bring new drugs and therapies to market.

Basic Research: Basic research explores the underlying biological pathways and the pathophysiology **behind** a disease. This process often identifies potential targets for treatments and includes the search for new molecular entities that can modulate such targets.

- *Key Actors:* Universities and other not-for-profit research institutions, various federal agencies, and certain large, research-intensive pharmaceutical companies perform the overwhelming majority of basic research in the United States. The Department of Defense and the Department of Health and Human Services (DHHS) are the leading agencies conducting basic research in biomedicine. Within the DHHS, the National Institutes of Health (NIH) is the world's largest biomedical research institution, with a 2023 budget of some **$49 billion**. In addition to its intramural research, the NIH's extramural program provides 83 percent of its funding to universities, allowing them to carry out the bulk of U.S. basic biomedical research. It makes available some **50,000 competitive grants** to more than 300,000 researchers annually.

Pre-Clinical Research: The pre-clinical phase uses ***in vitro* laboratory** and animal testing to hone the discoveries in basic research and identify molecular entities that favorably modulate the target. Preclinical research can also identify negative safety signals of potential therapies—an important prerequisite for **initiating** clinical trials in humans.

- *Key Actors:* Private sector companies—startups, small-to-medium biopharmaceutical companies, specialized clinical or contract research organizations (CROs), and, on occasion, large pharmaceutical companies—drive the process of preclinical research. They often work closely with universities and medical institutions in carrying out this next phase of the process.

Clinical Research: Successful preclinical research is followed by three phases of human clinical trials. Phase I applies the drug to a small sample of healthy **participants** to test the safety and tolerability of the drug at various doses. Phase II enlists a larger number of volunteers affected with the condition of interest to check the **efficacy** of the drug at the dose found to be tolerable during phase I. Phase III of testing uses a large set of affected volunteers to comprehensively test the safety and efficacy of the drug compared to a **placebo**, while phase IV trials **study** effects over time after the drug has reached the market. Successful completion of phase III allows pharmaceutical companies to apply for regulatory approval. The expertise and infrastructure requirements for clinical research are quite high, with the bulk of the estimated **$2.6 billion** necessary to bring a new drug to market going toward clinical research. Cumulatively, the clinical research takes around six to seven years, with only **13.8 percent** of new drugs making it through the **process**.

- *Key Actors:* Clinical trials are predominantly conducted by private sector companies. In many cases, smaller firms partner with CROs, or larger firms that have the **expertise** and the resources (e.g., site locations, recruitment network, and reporting capabilities) to conduct clinical trials. The process operates on a continuum. Phases I and II are typically carried out by small-to-medium enterprises (including startups) with the help of CROs. Phase III and IV, on the other hand, are almost always carried out by the larger, more established companies (often under sublicense from the original licensee).

Manufacturing: The ability to manufacture a consistently high-quality product in sufficient quantities to meet global demand is no less important than other steps in the process. This capability is often taken for granted, as biopharmaceutical manufacturing tends to be lumped in with other less sophisticated manufacturing. The Covid-19 vaccines and emerging personalized cell-based therapies, however, illustrate the **high-degree of complexity** and know-how required for some of today's therapies.

- *Key Actors:* Larger pharmaceutical companies with existing manufacturing expertise and facilities, including established supply chains, predominate. Depending on the size and business model of the firm, however, manufacturing may be outsourced to specialized companies known as **contract manufacturing organizations**. They typically work with smaller firms or startups that lack the capital and know-how for manufacturing at scale.

Sales, Marketing, and Distribution: Once the new drug is approved for sale and capable of being manufactured and distributed in sufficient quantities, it is ready to be **marketed** to physicians for prescribing to their patients.

- *Key Actors:* **Well-established pharmaceutical companies** with existing sales forces do the bulk of the sales and marketing of today's new products. A sophisticated and highly trained sales force is necessary to engage with the complex therapies being developed in the twenty-first century and to navigate the contemporary healthcare marketplace. Smaller companies are unlikely to have the **resources necessary** to deploy such a sales force. For distribution, **retail pharmacy chains** and mail-order pharmacies dispense most of the medication in the United States. Additionally, specialty pharmacies are playing an increasing role, as more and more of the newest treatments are not in pill form (e.g., injections or infusions).

Health Insurance Coverage: After the new drug becomes available for prescription, health insurance coverage is essential for patient access and widespread uptake. Pharmaceutical companies work closely with payors to **negotiate** formulary status and actual prices paid (via rebates and discounts) based on a variety of pharmacoeconomic and market factors.

- *Key Actors:* Payors include government insurance programs for select groups (e.g., Medicare, Medicaid, and TRICARE), along with private insurance plans and their associated pharmacy benefit managers (e.g., Cigna/Express Scripts, CVS Health/Caremark, and United Healthcare/Optum).

Drivers of U.S. Biopharmaceutical Innovation

There are four pivotal drivers behind the United States' position as the world's leader in biopharmaceutical innovation:

1. Strong enforceable intellectual property rights to enable small and large firms to partner with each other and with research institutions and government at all levels. These rights are also essential to attract the investment needed to develop and bring new products to the market.
2. Steady and significant public investments for basic medical research at the NIH and other relevant agencies, as well as at U.S. universities and research centers.
3. A robust U.S. startup environment, including a vibrant venture capital sector that can provide the early-stage funding small companies need to further develop novel medical technologies and a support system of specialized vendors and service providers.
4. Large biopharmaceutical companies, with the expertise and resources to support clinical trials, obtain regulatory approval, and manufacture and market the products that result from these innovations.

Intellectual Property Rights: As noted earlier, strong intellectual property (IP) protections are a key component driving U.S. biopharmaceutical innovation. As President Abraham Lincoln once famously **remarked**, intellectual property rights add "the fuel of interest to the fire of genius." In this context, by securing the inventor's exclusive right to their invention, strong patent rights incentivize the creation of new molecular entities ("compositions of matter," in patent parlance) and their clinical development that may result in the next breakthrough treatment. It is important to note that many initially promising products fail in trials, whether on efficacy or safety grounds, and that they can also fail late in the process—thereby incurring significant losses. Given that only a few novel compositions become approved treatments and given that the cost of those that do is high, drug companies rely on the exclusive right to sell their product to recover the development costs and, ideally, to fund the creation of the next breakthrough treatment.

Public Investment in Universities and Basic Research: The Bayh-Dole Act, passed in 1980, transformed the role of universities in biopharmaceutical innovation. It allowed universities to retain ownership of and patent inventions derived from government-funded research, while providing them the ability to enter exclusive licensing **arrangements** with private firms. Before Bayh-Dole, the results of publicly funded research were considered to be government property and licensing was complex and cumbersome, resulting in limited commercialization of the results of federally funded research. The Bayh-Dole Act incentivized universities and professors to move innovation to the marketplace, providing a pathway for biomedical research to be translated into new therapies. While exact estimates are difficult to find, the Association of University Technology Managers reports that, from 1996 until 2020, over **200 new drugs and vaccines** were developed through university-industry partnerships made possible by the Bayh-Dole Act.

> *The Bayh-Dole Act incentivized universities and professors to move innovation to the marketplace, providing a pathway for biomedical research to be translated into new therapies.*

The changing role of universities in the biopharmaceutical ecosystem occurred at a time when public investment in medical research was increasing. As noted, between 1998 to 2003, the NIH budget increased from $13.6 billion to $27.1 billion. At the same time, the number of research grants awarded increased from an average of **7,000 grants** each year from 1990–1999 to 9,500 grants each year from 2000–2010. In addition to the Bayh-Dole improvements, this increase in funding and the number of grants have been major drivers of the surge in pharmaceutical innovation since the 1990s.

Startups and Venture Capital: Startups are another vital component of biopharmaceutical innovation. Recent estimates find that startups and small pharmaceutical companies were responsible for the introduction of **64 percent** of new molecular entities in 2018. In terms of research and development (R&D) expenditure, according to one report, small biopharmaceutical firms spent $637,735 per employee in 2021, compared with **$82,515** per employee in large biopharmaceutical firms during the same year. Notably, among the 260 small biopharmaceutical companies listed as the largest global R&D investors, **193** were based in the United States. With access to outstanding universities as well as a skilled workforce and extensive capital—especially in the nation's biotech hubs such as Boston

and San Francisco—these firms work at the cutting edge of biopharmaceutical research, often taking a chance on novel products that are too risky for the larger, more established players in the market. This may include pursuing abandoned projects or investing in areas of pharmaceutical research known for higher-than-normal **failure rates**. Usually, such firms concentrate their energy on a single drug or a very small set of drugs before expanding their portfolio.

Startups in the biopharmaceutical industry rely on venture capital (VC) firms and other early-stage funders (e.g., angel investors or those through the Small Business Innovation Research or Small Business Technology Transfer programs) as critical sources of capital. VCs play a particularly important role in the early stages of drug development, providing the resources to demonstrate proof of concept (preclinical and early clinical trials) before a drug reaches phase III of clinical trials. Venture financing opportunities in the U.S. biopharmaceutical space outmatch every other country by a significant margin. One study of new venture investments in the industry between 2010–2015 found that the number of investments in the United States was **2.7 times** Europe's total. Similarly, according to McKinsey's China Drug Innovation Index (2020), industry experts in the life sciences scored China's access to venture capital in the biopharmaceutical sector a **6 out of 10**, while the United States came in higher with a score of **8 out of 10**.

Given the lengthy and exorbitantly expensive clinical research and regulatory approval process coupled with the complexities of manufacturing at scale, the short investment horizons faced by investors make it so that VCs typically do not deliver a new biopharmaceutical product to the market themselves. The average length of a VC-funded deal, from early-stage funding to acquisition, is 6.3 years. Yet, most biopharmaceutical firms are unable to **secure drug approval** within this timeframe. VCs therefore tend to seek early exit opportunities through mergers, acquisitions, and initial public offerings (IPOs) and forego longer-term **value creation**. However, the short time horizon does allow them to focus on seeking the next potential breakthrough to shepherd through that critical early phase of development.

Upon VC exit, startups often look to partner with larger companies via sublicensing or through mergers and acquisitions to obtain the resources needed to scale their activities. Building out these operational capabilities poses risks in terms of delay in time to market and high capital costs. Compared to large pharmaceutical companies, startups have relatively limited institutional knowledge and experience with navigating regulatory approvals, supply chain logistics, and late-stage **commercialization**.

Large Pharmaceutical Companies: Large pharmaceutical companies can help startups address the challenges associated with scaling up operations and bringing products to market by offering a wide array of resources and expertise. These range from conducting quality clinical research, navigating the regulatory approval process, manufacturing at scale, and marketing (including product **distribution**). Here, large pharmaceutical companies can leverage their clinical research infrastructure and decades-long experience with medical supply chains and access to capital—along with their manufacturing, sales, and marketing expertise—to perform tasks startups cannot do with their limited resources and networks.

Notably, during the Covid-19 pandemic, BioNTech used this model, partnering with **Pfizer** to release its mRNA vaccine. In recent years, large pharmaceutical companies have also been playing a bigger role in funding the later stages of a startup's development. In a bit of symbiosis, the rapid pace of

technological change leading to more complex therapeutics and personalized medicine has prompted these large firms to increasingly **turn to startups**, as opposed to in-house R&D, as the source of new drug development. This shift has contributed to larger players increasingly **acquiring** smaller ones.

Addressing Biopharmaceutical Competition from China

U.S. leadership in biopharmaceuticals, built on this complex system, is being challenged today by reforms and industrial policies undertaken by China.

Easing Regulations: Since 2015, China has introduced several sweeping reforms aimed at overhauling its pharmaceutical regulations to bring it **in line** with international standards. Beijing streamlined the Center for Drug Evaluation, reducing the time required to approve clinical trials while enabling **faster approval** of new drug applications. Alongside this change, Chinese regulators included innovative drugs in the **National Drug Reimbursement List** (NDRL)—the system that decides which drugs are covered by government's Basic Medical Insurance schemes. As more than **95 percent** of China relies on government-provided health insurance, this change makes Chinese biopharmaceutical companies producing innovative drugs eligible for lucrative government contracts.

Reforming Patents: Reforms in biopharmaceutical regulations have been accompanied by similar changes to China's **patent system** and increased access to capital. In 2021, Beijing instituted stricter intellectual property laws, making it easier to enforce patents, including an increased ability for patent owners to recover enhanced damages. In terms of funding, **private equity and venture capital** are important resources enabling biopharmaceutical innovation. China is the second-largest destination in terms of VC investments, amounting to **$50 billion** in 2023. In addition, it adds to the liquidity of China's capital markets by channeling government funds into its private equity firms.

Rapid Industrial Growth: Taken together, these expansive reforms and favorable market conditions have positioned China as a major source of research and product development in the biopharmaceutical industry. China's share of the global biopharmaceutical innovation pipeline increased from 4.1 percent in 2015 to 13.9 percent in 2020. In addition, according to the 2024 ***Global Startup Innovation Report***, Chinese cities such as Beijing and Shanghai dominated the world in the number of patents produced in the life sciences, outpacing U.S. biopharmaceutical clusters. In 2023, the Chinese biopharmaceutical industry crossed an **important milestone** when outbound pharmaceutical deals surpassed inbound deals. According to news site Caixin, these deals were collectively valued at **$45 billion**. These positive developments point to a larger trend where the Chinese biopharmaceutical industry is transitioning to developing innovative first-in-class drugs as opposed to building on breakthroughs from other countries. This transition has encouraged **continued Western investment** in China's biopharmaceutical industry, despite U.S.-China geopolitical tensions and restrictive domestic laws preventing the use of medical data gathered in China outside of its borders.

Avoiding "Own Goals" and Reinforcing Strengths: U.S. policy measures, such as the new **guidelines** on march-in rights, could cause self-inflicted harm to the U.S. biopharmaceutical industry, thus growing China's presence in this space. Specifically, the federal government has recently proposed the invocation of march-in rights to take away patent ownership in order to lower the price of drugs developed in part with federal funding. Expropriating private property—based on an arbitrary claim

that the price is "too high"—weakens the U.S. innovation system, inhibiting long-term investment in drug development based on early-stage university research.

Securing the Future of the U.S. Biopharmaceutical Sector

Underpinning the U.S. biopharmaceutical industry is a diverse and interconnected innovation system that is brought together with sustained funding for basic research at universities and national laboratories as well as through partnerships among innovative startups and large pharmaceutical companies. The system also encompasses public and private research centers, philanthropic foundations, a variety of small and medium enterprises, contract research organizations, contract manufacturing organizations, and pharmacies.

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This distributed and interconnected structure—a hallmark of the U.S. biopharmaceutical innovation system—is unprecedented in its capacity to bring life-saving and health-enhancing drugs and medical devices to market. Renewing this system, and in turn sustaining the U.S. global competitive lead in biopharmaceuticals, requires policies supporting and streamlining the incentives to cooperate across its different components. Equally, it is vital to avoid measures that would weaken patent protections, as that would damage the foundations of this remarkable innovation system. With China **rapidly increasing** its competitive presence in the space, the U.S. biopharmaceutical industry needs a strategy that invests in and renews its ecosystem while defending against counterproductive policy ideas at home. ■

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