PitchBook

Betting on Biotech

Cultivating an understanding of the VC investment landscape of US-based biotech & pharma startups

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Key takeaways

- **Over the last few decades, the biotechnology & pharmaceuticals (biotech & pharma) industry has seen a shift from drug development through internal R&D efforts at large-cap public incumbents to an M&A-based model.** Legislation passed in 1984 disrupted the incumbents' business models by encouraging the manufacturing of generics, spurring drug innovation in the biologics space. The complicated manufacturing process of biologics compared to traditional pharmaceuticals and innate pre-clinical R&D risks have led many biotech & pharma incumbents to adopt an M&A approach to R&D.

- **The drug development lifecycle, characterized by clear intermittent milestones and long-payback periods with high upside, makes biotech startups uniquely positioned to receive illiquid VC investment.** VC funding for biotech & pharma startups has more than tripled in the last decade, soaring from $5.0 billion in 2009 to $17.0 billion in 2019.

- **As VC biotech investing has evolved, three distinct models have emerged for commercializing new technologies.** Examples include the classic model of research commercialization through a university's technology transfer office, residing in a corporate-backed incubator or accelerator, and the venture creation model where VCs launch and run startups themselves through internal discovery engines and a network of advisors and entrepreneurs in residence (EIRs).

- **Biotech startups take a different funding trajectory than most VC-backed startups, raising larger sums more quickly.** Our data indicates that biotech startups command a significant premium in funding rounds over non-biotech startups, namely, a 122% and 50% premium for early-stage and late-stage VC deals in 2019, respectively.

Published on July 8, 2020

Introduction

The US healthcare system is consistently touted as "ripe for disruption," with the potential to improve patient outcomes and lower costs by streamlining research efforts and aggregating disparate services across the fractured healthcare system. Given the opportunity to fund nascent technologies that have the potential to upend an industry worth nearly $4 trillion,[1] VC investors have been eagerly backing startups that have innovative products aimed at revolutionizing healthcare and providing better treatment to patients.

Healthcare investments consistently represent around 25% of all VC deal activity in the US on an annual basis. Our data indicates that VC deal value for healthcare startups has tripled in the last decade, rising from nearly $9 billion in 2009 to nearly $30 billion in 2019. 2019 also represented an all-time high of 2,544 VC deals in the healthcare industry. At a period when healthcare and medicine are at the forefront of many conversations surrounding politics and the economy, we believe the impetus to effect change has never been greater.

Many investors and entrepreneurs view healthcare investing today as a new frontier to target with a total addressable market that includes every human. The increasing penetration of digital technology within healthcare, and significant advances within the biomedical sciences, have also been major catalysts for this increase. This not only indicates investors' deep interest in game-changing healthcare companies but is also buoyed by the strength and capital-rich nature of the VC asset class.

The healthcare industry encompasses a wide array of sectors, ranging from medical devices to diagnostic tools to therapeutics. Our emerging technology analysts at PitchBook currently cover technology-enabled health & wellness, whereas this note features coverage of the biotech & pharma sector within the private markets—a class of startups that are focused on producing the next generation of drugs aimed at tackling unmet medical needs.[2] In addition to medical advancements, investments in ground-breaking and innovative healthcare startups have generated massive exits for VC investors over the last several years, with the median exit size (including IPOs) of biotech & pharma companies reaching an all-time high of $270.2 million in 2019.

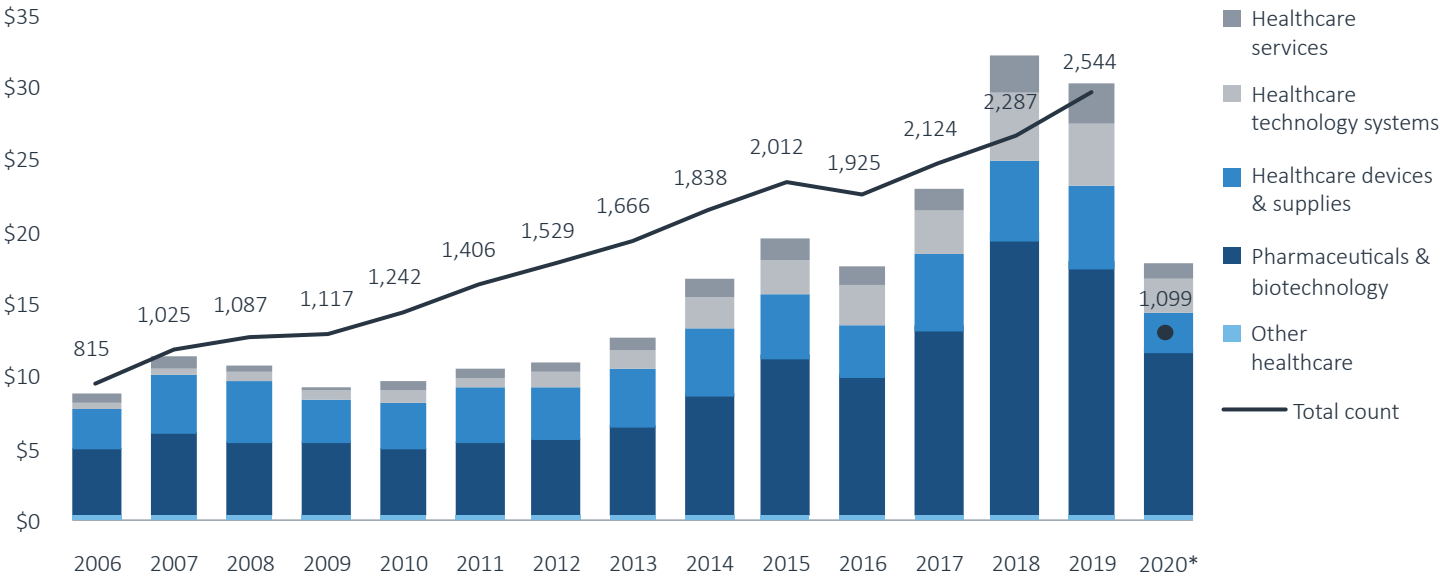
In this research note, we provide a primer on how VC-backed companies within the biotech & pharma sector have performed, as well as discuss how VC investing has evolved from government grants to newer sources of capital. Biotech investing is distinct from virtually all other sectors due to its unique company lifecycle, long product timelines, highly regulated environment, and uncoupling between end users and payers. Given that venture funding is overwhelmingly the first stop biotech startups make when seeking capital, we believe a thorough analysis of this sector will allow investors to better understand the importance that VC plays in funding and accelerating revolutionary therapies into the clinic.

"Biotech investing is distinct from virtually all other sectors due to its unique company lifecycle, long product timelines, highly regulated environment, and uncoupling between end users and payers."

1:"National Health Expenditure Data," United States Center for Medicare & Medicaid Services, December 17, 2019

2: Biotech companies use living organisms and molecular biology techniques to manufacture therapeutics. Pharmaceutical companies synthesize drugs through advanced chemistry techniques.

Healthcare VC deal activity ($B) by sector



Source: PitchBook | **Geography:** US
*As of June 22, 2020

The history of drug development

Traditionally, large pharmaceutical companies developed their drug pipelines internally through comprehensive research and development (R&D) divisions. By using earnings generated from successful drugs, companies would reinvest in their R&D program as scientists searched for the next scientific breakthrough and, subsequently, profitable drug. In fact, many of the drugs that revolutionized human medicine over the last 100 years were developed this way.

At the beginning of the 20th century, scientists at Bayer discovered a new way to formulate acetylsalicylic acid and began selling Aspirin as a commercial product, turning it into one of the most successful nonsteroidal anti-inflammatory drugs (NSAIDs). In the 1920s, scientists at Eli Lilly invented isoelectric precipitation, and through a collaboration with the University of Toronto, they were able to produce large quantities of highly refined insulin and began selling the world's first commercially available insulin product.

After a period of drug development stagnation due to WWII, scientists at Hoffmann-La Roche invented the anti-anxiety drug diazepam, marketed as Valium®, in the 1960s, which quickly became one of the most frequently prescribed medications in the world and helped Roche become the pharmaceutical industry giant that it is today. In the 1970s, scientists at Smith, Kline & French invented ulcer medication cimetidine, marketed as Tagamet®, which became the industry's first "blockbuster" drug generating over $1 billion in annual sales. In the 1980s, scientists at Eli Lilly invented the antidepressant drug fluoxetine (Prozac®) and scientists at Merck developed the first statin, lovastatin (Mevacor®), to be approved by the Food & Drug Administration (FDA).

This short and by no means exhaustive list of successful drugs that were developed in-house indicates that drug invention by large pharmaceutical companies during the latter half of the 20th century was beginning to pick up. It was not until the 1980s, however, that the industry reached a true inflection point. Up until this point, most drugs were invented and synthesized using medicinal chemistry techniques. New molecular biology techniques began to emerge during the late 1970s and early 1980s, and companies began to recognize the potential of this rapidly expanding repertoire of therapeutic modalities. As they discovered new ways to produce biological molecules such as recombinant proteins and monoclonal antibodies, they also figured out how to turn them into commercial drugs.

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Legislation alters the biopharmaceutical landscape

In addition to scientific breakthroughs, the Drug Price Competition and Patent Term Restoration Act, passed in the US in 1984, upended the biopharmaceutical industry. Informally known as the Hatch-Waxman Act, this law encouraged the manufacturing of generics for drugs with expired patents. Prior to this, only one-third of top-selling pharmaceutical drugs had generic competitors after their patents expired. Hatch-Waxman effectively disrupted companies' business models, as generics began to flood the market and eat into revenues from legacy drug products. This spurred drug innovation, with global patent filing data showing that the number of granted pharmaceutical patents began to soar less than a decade after Hatch-Waxman was passed.[3]

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Hatch-Waxman also helped shift the industry's focus from small molecule drugs to the burgeoning class of biological drugs, also known as biologics. Manufacturing generic formulations of small molecule drugs such as aspirin was relatively straightforward because many of the sourcing and quality control aspects involved were well within the technical scope of many generic drug manufacturers. As such, generics tended to enter the market almost immediately upon patent expiration, with many capturing as much as 90% of the market within months.

The process of producing generic versions of biologics is vastly more complicated. The FDA has been hesitant to adopt biosimilar approval regulations for biologics given the complexity of processes involved in manufacturing. As a result, biologics were immunized from competition from generics. The industry embraced this regulatory advantage and, along with a toolkit of innovative biology techniques, began focusing their efforts on biologics to ensure a wider revenue moat for when their drugs go off patent.

As the turn of the 21st century approached, increasing numbers of blockbuster drugs were being developed, and revenue generation began to grow. And with it, R&D costs at large biopharmaceutical companies also continued to skyrocket due to the increased costs associated with the supply chain of biologics manufacturing. Data from the trade group Pharmaceutical Researchers and Manufacturers of America (PhRMA) shows that biopharmaceutical R&D expenditure has ballooned from $2.0 billion in 1980 to a record-setting $79.6 billion in 2018.[4] Yet this has not augmented internal drug development efforts. In fact, the amount dedicated to pre-clinical work—the basic and translational science involved in drug discovery—

3: "Change of Data-Driven Drug Design Trends Through Patent Analysis," MDPI, Jong-Hyun Kim and Yong-Gil Lee, August 1, 2019
4: "2019 PhRMA Annual Membership Survey," PhRMA, 2019

accounted for only 16.4% of total R&D spending in 2018, down from the 33.8% recorded in 2002.[5] The bulk of R&D spending nowadays is focused on the late-stage clinical trials of drug assets that have shown efficacy in pre-clinical models and safety in early-stage Phase 1 trials.

The complexity and inherent risks involved in the pre-clinical discovery of next-generation biologics has made it significantly more difficult for large companies to justify the expenses. Consequently, M&A activity within the biotech sector has become extremely common.

The complexity and inherent risks involved in the pre-clinical discovery of next-generation biologics has made it significantly more difficult for large companies to justify the expenses. Consequently, M&A activity within the biotech sector has become extremely common as large incumbents use acquisitions as a strategy for building out their drug pipeline while minimizing downside associated with failed products. Analysis by STAT News shows that out of Pfizer's 44 drug products and J&J's 18 drug products, only 23% and 11%, respectively, were developed in-house.[6] The overwhelming majority of other products were initially developed by third parties and later acquired into the companies' drug portfolio, which opened the path for another industry player to step in.

Creation of the VC opportunity within the biopharmaceutical industry

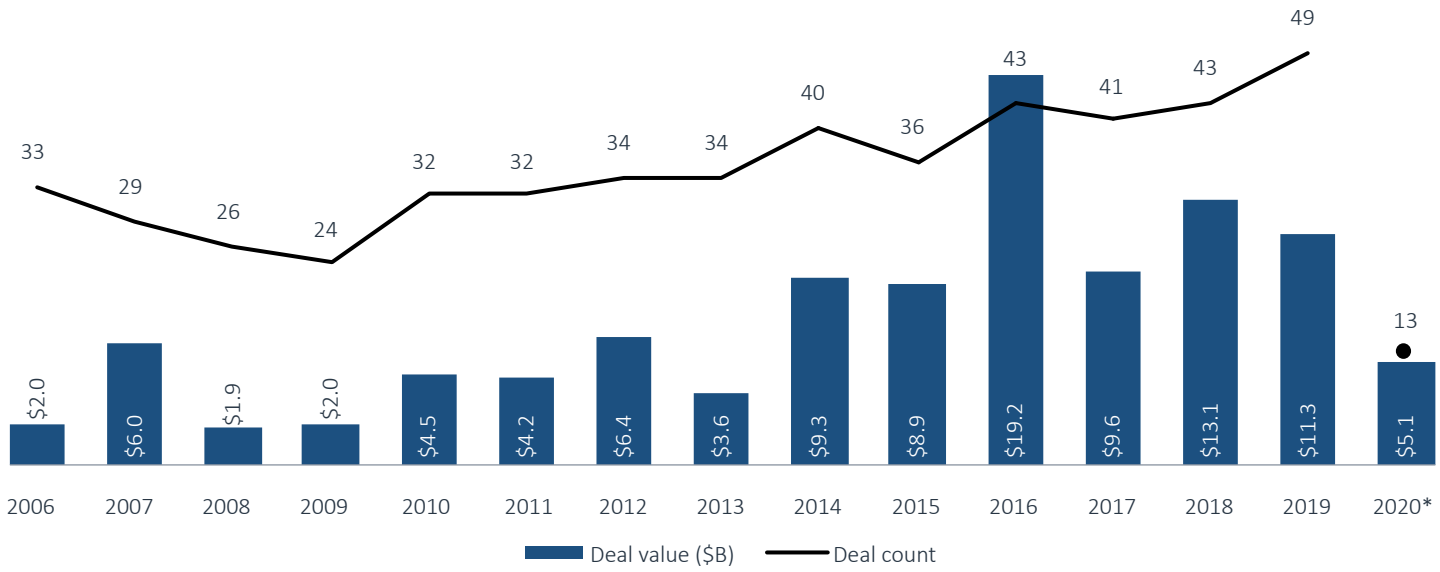
While scientific advances have allowed companies to screen for drug targets more efficiently, pre-clinical validation and platform development are risky endeavors and, as such, have high capital costs with long payback periods that exceed the threshold of most large biotech & pharma companies. Considering the relatively low pre-clinical R&D success rates and long drug development timelines, it is easy to see why drug makers in the biopharmaceutical industry have decidedly "offloaded" that risk onto VC-backed startups.

As a result, large-cap biotech & pharma companies acquire VC-backed biotech companies (and sometimes even publicly-traded biotech companies) at the forefront of immunotherapy and genetic engineering to build out their R&D drug pipeline instead of reinvesting in internal R&D efforts. By letting private-backed companies take on the risks and costs associated with early-stage drug discovery, incumbents mitigate downside by acquiring only strategic companies they feel are at an acceptable level of development. Our dataset shows that strategic M&A activity of VC-backed startups in the biotech & pharma sector has doubled in the last decade, with 40+ deals occurring annually in five out of the last six years.

This seismic shift has created an opportunity for VC-backed startups to play a crucial role in drug development pipelines. This clearly defined exit pathway has attracted many VC firms to the biotech industry given that the incumbents are essentially "forced buyers" that are constantly infusing the industry with liquidity. Business development executives at large-cap biotech & pharma companies are constantly planning the next strategic acquisitions for their three- to five-year roadmap to ensure the company meets long-term financial goals.

5: "2004 PhRMA Annual Membership Survey," PhRMA, 2004
6: "Do Large Pharma Companies Provide Drug Development Innovation? Our Analysis Says No," STAT, Emily H. Jung, Alfred Engelberg, and Aaron S. Kesselheim, December 10, 2019

VC-backed strategic M&A activity in biotech & pharma



Source: PitchBook | **Geography:** US
*As of June 22, 2020
Note: Strategic M&A only. Financial M&A (buyouts) not included.

VC-backed biotechs: An essential source of drug development

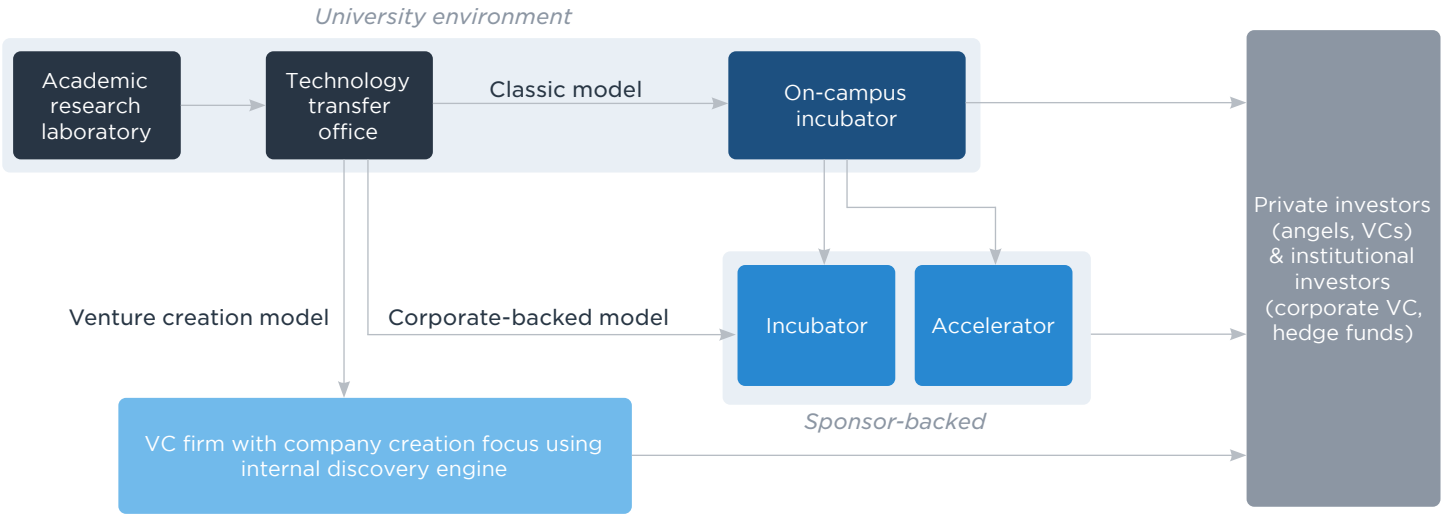
The origin of venture-backed biotech companies dates back more than 40 years to the founding of Genentech in 1976 when a Kleiner Perkins junior partner named Robert Swanson teamed up with UCSF biochemist Dr. Herbert Boyer. By leveraging their vision to commercialize recombinant DNA technology and developing a business model that initially focused on targeting insulin as a product, Genentech's founders were able to quickly raise capital from VCs, and in a few short years, Genentech produced a human version of insulin using recombinant *E. coli*. This gave Genentech a unique competitive advantage over its competitors, who were still harvesting insulin from bovine and porcine pancreases. A year later, Genentech raised $35.0 million in its IPO to become the first publicly traded biotech-focused company when it listed in 1980, valuing the company at $300.0 million. This model became one that many investors desired to mimic, and it laid the foundation for VCs to entrench themselves in the biotech sector.

Just as Genentech's key technology came from a scientific discovery at Dr. Boyer's lab, most innovative scientific discoveries today still come from academia and non-profit research organizations. The National Institutes of Health (NIH) maintains an annual budget of $41.7 billion for the 2020 fiscal year, and data from the NIH shows that over 80% is awarded through grants to support medical research at more than 2,500 universities, medical schools, and research institutions.[7] While this is three times more than what the entire US biopharmaceutical industry spent on pre-clinical R&D work in 2018, the primary focus for academics is not company formation and, as such, commercialization of scientific breakthroughs is generally not pursued

7: "Budget," National Institutes of Health, May 20, 2020

by the grant holder. If it is pursued at all, it tends to be a graduate student, postdoctoral researcher or staff scientist—whomever performed the research. How scientific discoveries ultimately turn into companies is something the industry has played around with over the last several decades and tends to follow one of the paths outlined in the accompanying graphic.

Research commercialization pathways



Source: PitchBook

The classic model of scientific research commercialization

The classic model exemplified by Genentech's commercialization journey remains the model with which most VCs and entrepreneurs are familiar. Generally, after the decision to commercialize a scientific discovery has been made, instead of publishing the results in a peer-reviewed journal, the researchers will begin the patent process with their university's technology transfer office (TTO). Ownership of the intellectual property (IP) can vary across institutions and even countries, as academic research governance depends on a multitude of factors, such as financial sponsorship, project structure, and resource allocation.

One of the primary functions of the TTO is to assist in the commercialization of research that arises from within the university. First, the researchers will begin with an invention disclosure form (IDF) stating their finding is novel. Due diligence is then performed by the university's patent attorneys to establish whether there is freedom to operate (FTO). Once FTO is established, a patent application is filed with the US Patent and Trademark Office, along with other jurisdictions of interest, and the researchers begin to determine next steps toward commercialization. Meanwhile, many universities have internal laboratory space for these early-stage ventures to work on the feasibility of their projects, and once the path to commercialization becomes more apparent, companies are spun out of the academic institution.

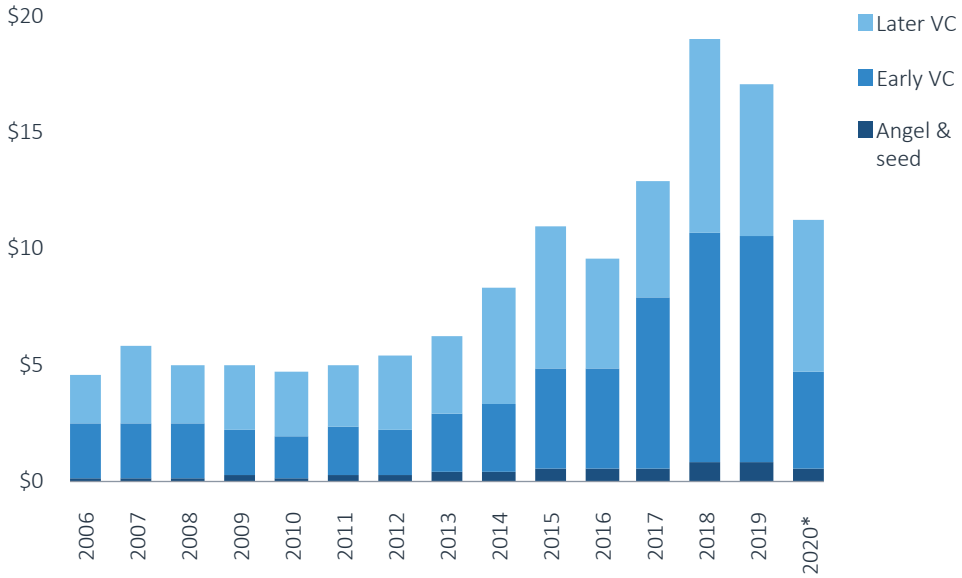
In this model, the entrepreneur is the founder (or part of a founding team) and tends to be a postdoctoral fellow or staff scientist within a professor's lab group.

In this model, the entrepreneur is the founder (or part of a founding team) and tends to be a postdoctoral fellow or staff scientist within a professor's lab group. The startup can either remain within the university's incubation space or begin looking for lab space externally. The founder(s) will begin fundraising through non-dilutive sources of capital such as NIH commercialization grants, Small Business Innovation Research (SBIR) grants, friends and family, etc., and/or will begin soliciting angel investors and VC firms for angel- and seed-stage funding.

Capital infusions at the angel & seed-stage are used by biotech startups to test their lead drug candidate or platform technology in robust pre-clinical animal models that aim to recapitulate the target clinical indication. This serves as a checkpoint for startups before progressing toward the highly regulated and extensive process of human clinical trials. According to our dataset, aggregate angel & seed stage VC deal activity in biotech & pharma startups has increased five-fold over the last decade, growing from $156.2 million across 71 deals in 2009 to $840.4 million across 304 deals in 2019.

Universities are increasingly prioritizing scientific commercialization as a metric for many researchers within academic institutions. Many academics, particularly those who have not yet reached tenure, recognize the importance that commercialization and startup creation bear on their careers. Similarly, tenured academics also view the creation of VC-backed biotech startups favorably, as this allows them to translate their laboratory's research into the clinic.

Biotech & pharma VC deals ($B) by stage



Source: PitchBook | **Geography:** US
*As of June 22, 2020

Biotech startups that follow this classic model of research commercialization can be quite formulaic in their financing rounds. Because of the precedent set by a plethora of biotech startups, investors generally have a clear idea of the costs associated with drug development, pre-clinical validation, and clinical trial testing. This makes private-backed biotech & pharma companies an attractive opportunity for investors who are familiar with the amount of capital needed to meet project milestones.

Corporate-backed incubators and accelerators

This model of biotech company formation builds upon the classic model discussed above but typically includes involvement from a large corporate player (more so than just as a passive investor). These players tend to be large-cap biotech & pharma companies or designated corporate entities set up to act as facilitators of research commercialization. Due to the geographic spread of universities and the democratization of laboratory research, world-class research breakthroughs can come out of locations that do not have a critical mass of entrepreneurship support. As such, founders will oftentimes face an uphill battle trying to attract sufficient capital to gain traction in their respective locales. This is where the innovation infrastructure of corporate-backed incubators and accelerators can be a lifeline for these startups, offering varying degrees of entrepreneurial support, working capital, equity stake, and deal terms.

Corporate incubators

Largely speaking, biotech incubators do not take equity stakes in resident startups. Rather, they provide a co-working laboratory space and entrepreneurial support for a rent-based fee. A key advantage of taking a startup through one of these corporate-backed biotech incubators is a centralized lab space with shared equipment, as this massively decreases the need for steep capital expenditures such as biosafety cabinets and other testing equipment. Furthermore, startups that are residents of these biotech incubators have access to a community of entrepreneurial-minded founders and will frequently engage with an existing investor base associated with that incubator. Many biotech startups at this stage are already in a financially fragile state, and partnering with a biotech incubator can make an impactful difference on their burn rates and cash runway.

The most prolific corporate incubator is Johnson & Johnson (J&J), with 239 US-based investments made across their network of JLABS incubators. With eight locations around the world and three affiliate sites, JLABS is a no-strings-attached model that provides the infrastructure, network, and support needed to help entrepreneurs develop their science while retaining their IP ownership. Similarly, Bayer's CoLaborator incubators have five locations worldwide and help founders build first-in-class companies in areas ranging from biotech to agricultural and crop sciences. Ultimately, companies such as J&J and Bayer view their respective incubators not as a source of short-term revenue generation, but as a potential source of innovation for their R&D drug pipelines.

Although corporate-backed biotech incubators such as JLABS and CoLaborator do not benefit financially via an equity stake, incubating biotech startups is still a net positive for incumbents as this provides them with exposure to the cutting-edge landscape of the biotech sector.

Although biotech incubators such as JLABS and CoLaborator do not benefit financially via an equity stake, incubating biotech startups is still a net positive for incumbents as this provides them with exposure to the cutting-edge landscape of the biotech sector. This also allows them to determine which drugs and technologies can enhance or threaten their internal R&D pipelines, becoming a point of deal sourcing that incumbents otherwise would not receive. Often, these incubators provide founders with mentors from the corporate backer who help with large-scale, downstream considerations. This mutualistic relationship can be very beneficial to both parties—giving incumbents an opportunity to spot new discoveries and find M&A targets while giving founders access to top scientists at these large biopharma companies.

Accelerators

Accelerators, on the other hand, tend to take an equity stake in fledgling biotech startups. Startups that participate in biotech accelerators tend to have some form of minimum viable drug product, have validated their product to some degree in pre-clinical models and are looking for the capital and support to "accelerate" them into clinical trials and scaled manufacturing. The Illumina Accelerator provides up to $100,000 in convertible notes and takes 8% of common stock equity in young biotech startups that use next-generation sequencing (NGS) techniques for drug discovery and development. The purpose of this six-month intensive program is to help startups with strategy mapping, technology advancement, and pitch development. Another biotech accelerator was Merck's California Institute for Biomedical Research (Calibr), a non-profit organization that focused on early-stage translational research. While this partnership is now defunct, it was a creative and unique structure that gave Merck the option to obtain an exclusive commercial license for any proteins or small molecule therapeutic candidates derived from work conducted by Calibr.

Biotech-focused incubators and accelerators with corporate backers

Name	Backer	Equity stake	Areas of interest
JLABS	Johnson & Johnson	--	Pharmaceuticals, medical devices, consumer and digital health
CoLaborator	Bayer	--	Pharmaceuticals, life sciences, agricultural and crop sciences
Illumina Accelerator	Illumina	8%	Genomics, next-generation sequencing technologies, bioinformatics, diagnostics
IndieBio	SOS Ventures	8%	Therapeutics, biomaterials, food science, diagnostics, synthetic biology, genomics, biological tools
Alexandria LaunchLabs™	Alexandra Real Estate Equities	--	Life sciences, agriculture technology, drug discovery platforms, diagnostics, medical technologies, bioinformatics
Boston BioHub	AstraZeneca	--	Drug discovery, oncology, cardiovascular, metabolic, respiratory, inflammation, autoimmune diseases, neuroscience
Petri Accelerator	Pillar Venture Capital	8.5%	Computation biology, biological engineering, healthtech
Xontogeny	Perceptive Advisors	n.d.	Therapeutics, life sciences, biopharmaceuticals, medical technology
Cydan	NEA, Pfizer Venture Investments, Lundbeckfond Ventures, Alexandria Venture Investments, Longitude Capital	n.d.	Orphan drugs, rare genetic diseases

Source: Company websites, PitchBook | **Geography:** US

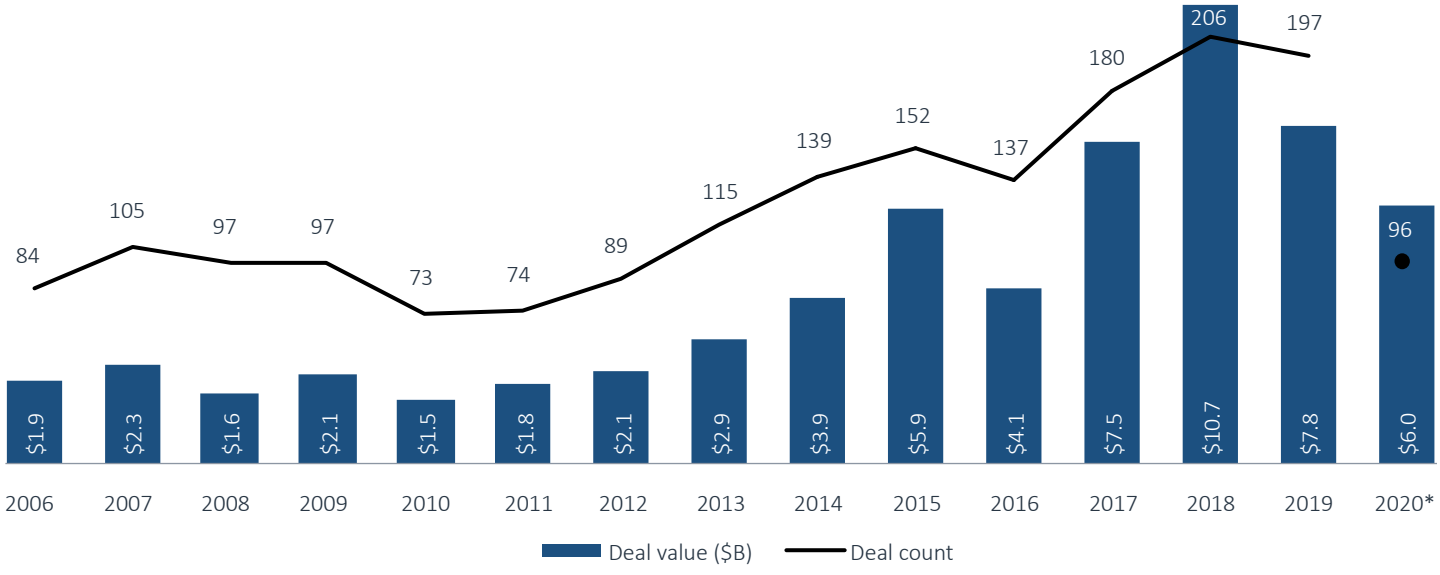
Some biotech accelerators are backed and operated by VC firms themselves. IndieBio is a four-month intensive program run by SOS Ventures that helps early-stage biology companies by providing co-working lab space and mentorship. Startups that go through IndieBio receive $250,000 in seed-stage funding for an 8% equity stake. Alexandria LaunchLabs™ is another full-service biotech accelerator run by REIT Alexandra Real Estate Equities that provides an innovative funding model by catalyzing biotech startups through their seed capital platform. VC firms recognize that by setting up these programs, they have given themselves another way to source deal flow while also being able to play a more active role in building disruptive companies.

Corporate venture capital participation

Biotech startups represent a class of companies that has the potential to generate outsized returns yet requires a specific skillset, agile operating model, and risk tolerance that many incumbents do not possess. Thus, another way for large-cap biotech & pharma companies to invest in early-stage biotech startups is through their corporate venture arm.

Previous analysis by PitchBook has shown that corporate VC (CVC) is a steady source of alternate financing for VC-backed startups. CVC arms of incumbents—such as J&J Development Corp., Pfizer Ventures, and GSK's SR One—have contributed to the success of many biotech startups, and it has been a creative way for publicly traded biotech & pharma companies to gain exposure to private-backed startups in their field. Our data shows that US VC deal activity with CVC participation has grown from $2.1 billion across 97 deals in 2009 to $7.8 billion across 197 deals in 2019. This increase reflects the interest of large-cap incumbents and other nontraditional investors in the biotech space and how they act as an extension in supporting VC-backed startups.

Biotech & pharma VC deal activity with CVC participation



Source: PitchBook | **Geography:** US
*As of June 22, 2020

The emergence of the venture creation model

The "venture creation" model of biotech startups is a relatively new one that has been embraced by some and shunned by others. Biotech-focused VCs such as Third Rock Ventures, Atlas Venture, Flagship Pioneering, and Versant Ventures have applied this model for the last decade or so in hopes of developing a framework for research commercialization and biotech company formation. VC firms begin by developing scientific hypotheses surrounding a drug platform or technology and then search for underlying IP or conceptual patents from academic research institutions. VCs utilize a network of academic partners during these early stages to both test out technologies and ensure the IP is sound.

This relationship can be advantageous as VCs pursuing this model possess the capital, human resources, and network to commercialize academics' research. Professors with strong ties to VC firms oftentimes prefer this method as it allows them to continue in their current academic capacity as well as become a scientific founder and board advisor. This model has proved fruitful in recent years, generating significant financial windfall for career academics when these startups are acquired or become publicly listed. Dr. Robert Langer, an MIT bioengineering professor, was a scientific co-founder of venture-created Moderna Therapeutics (NAS: MRNA) and held a pre-IPO stake of 3.9% worth $269 million at listing. Likewise, Dr. David Scadden, a Harvard stem cell professor, was a scientific co-founder of venture-created Magenta Therapeutics (NAS: MGTA) and held a pre-IPO stake of 2.9% worth $31 million at listing.

The venture creation model is common in biotech but rarely seen in other sectors due to the specialized scientific knowledge required, heavy reliance on patentable IP, and the necessity for lab equipment and other capital-intensive materials.

The venture creation model is common in biotech but is rarely seen in other sectors due to the specialized scientific knowledge required, heavy reliance on patentable IP, and the necessity for lab equipment and other capital-intensive materials. The venture creation model has only been made feasible recently thanks to cost-saving innovation in prototyping and initial drug experimentation, which in turn has lowered the barriers to entry for testing out multiple hypotheses in tandem. The rise of co-working lab space and the availability of low-cost contract research organizations (CROs) in the last decade have also reduced the time it takes to test hypotheses. In fact, many VCs who build internal biotech startups using the venture creation model have established their own internal incubators and discovery engines to cope with the high churn rate of scientific ideas.

Once the central hypothesis is validated and the semblance of a commercial opportunity begins to form, VCs will tap into their EIR network to begin building out the foundation of a new company. VCs will then "launch" these companies and fund them with early-stage capital to begin rapidly scaling. VCs will also assemble a team of C-level executives by recruiting seasoned industry veterans to run the company, allowing them to mitigate the risks that many startups incur by installing a first-time executive. While the criteria on which a startup's potential success is judged does not change in this venture creation model, there are some key differences.

In the classic model, the founder—or founding team—owns a majority stake in the biotech startup and slowly gets diluted by VCs and other institutional investors as the company raises more and more rounds of funding. In the venture creation model, the founding VC firm begins with majority ownership, oftentimes holding it for the bulk of early-stage funding, and is diluted to a lesser degree by follow-on investors as the startup raises larger amounts of late-stage capital. This is because VCs tend to

fund 100% of seed-stage and Series A financings, and also continue to participate in follow-on financings, allowing them to maintain their position as largest shareholder. This is beneficial when it comes to liquidity events and also allows them to have more sway when controlling the trajectory of new financings and crucial decisions surrounding drug pipelines, manufacturing processes, and licensing deals.

Advantages and disadvantages of the venture creation model

Advocates of the venture creation model argue that entrepreneurship can, in fact, be institutionalized. By employing teams of scientists who comb through literature and patent filings, they argue it is possible to create the "next big thing" in biotech. Firms such as Atlas, Flagship, Third Rock, and Versant are the "aircraft carriers" of VC firms, with in-house teams covering all facets of drug discovery and development—ranging from regulatory to scientific to legal affairs. They can deploy large sums of capital, perform scientific due diligence internally, nimbly pivot existing portfolio companies, and scale clinical and manufacturing operations rapidly.

Opponents of the venture creation model argue that it is anti-competitive and squeezes entrepreneurs who are not affiliated with these networks out of business. Being a founder is already an uphill battle. Being a founder of a biotech startup that will not generate revenue for nearly a decade is a Sisyphean task. Only with the strong network support of investors and operators do companies succeed. Entrepreneurs who are unable to tap into a venture creation firm can find themselves struggling for cash. With most of the newly raised funds allocated toward internal efforts at these VC firms' discovery engines, the amount of dry powder at these firms available to external investments is dwindling. This may have downstream effects on corporate acquirers, as a potential bottleneck for early-stage funding forces fewer startups to be prime candidates for incumbents' future drug portfolios.

Liquidity events for venture-created biotechs

Liquidity events illustrate the difference between this model from the others quite clearly. One example that is often touted by proponents of "venture-created" biotech startups is Moderna Therapeutics (NAS: MRNA)—a company focused on developing a new class of therapeutics using messenger ribonucleic acid (mRNA) technology. Moderna was founded and launched by VC firm Flagship Pioneering. After raising nearly $2 billion in capital, Moderna went public and raised $604.4 million at a $7.0 billion pre-money valuation in December 2018, notching the record for the largest biotech IPO in history. While raising large sums of capital through the public markets is common, this deal was notable because Moderna's "founders" were still the largest principal shareholder with a 19.5% pre-IPO ownership stake, which is a founder stake rarely seen in the classic and incubator or accelerator models.

Portfolio companies at venture-creation-focused VC firms tend to follow the same equity stake model, where the founding VC maintains its largest shareholder position from inception to exit. The momentum generated by Moderna's IPO has continued to build over the last two years, with many VC-backed biotechs filing for IPOs. Because of the platform breadth of venture-created biotech startups, public listings are often a strategic way to raise large amounts of capital. Since these startups generally have not progressed far enough into the clinical trial timeline to be considered by an incumbent for acquisition, biotech investors view IPOs as less of a traditional exit and more of a quick-fire way to accelerate the company's drug pipeline.

Biotech & pharma IPOs in H1 2020

Company name	Date	Capital raised ($M)	Venture creation model?	Largest shareholder	Largest shareholder's pre-IPO stake
ADiTx Therapeutics (NAS: ADTX)	June 30	$11.0	No	Shahrokh Shabahang	23.1%
Akouos (NAS: AKUS)	June 26	$213.0	No	5AM Ventures	21.6%
Fusion Pharmaceuticals (NAS: FUSN)	June 26	$212.5	No	HealthCap	12.6%
PloyPid (NAS: PYPD)	June 26	$60.0	No	Aurum Ventures	18.3%
Forma Therapeutics (NAS: FMTX)	June 19	$277.6	No	RA Capital Management	21.2%
Repare Therapeutics (NAS: RPTX)	June 19	$220.0	Yes	Versant Ventures	30.1%
Generation Bio (NAS: GBIO)	June 12	$199.5	Yes	Atlas Venture	37.0%
Avidity Biosciences (NAS: RNA)	June 12	$259.2	No	RTW Investments	14.5%
VaxCyte (NAS: PCVX)	June 12	$250.0	No	TPG Growth	12.9%
Lanturn Pharma (NAS: LTRN)	June 11	$26.3	No	Bios Partners	42.1%
Legend Biotech (NAS: LEGN)	June 5	$424.0	No	GenScript Biotech Corp.	76.9%
Calliditas Therapeutics (NAS: CALT)	June 5	$90.0	No	Stiftelsen Industrifonden	14.9%
Applied Molecular Transport (NAS: AMTI)	June 4	$154.0	No	EPIQ Capital Group	25.9%
Pliant Therapeutics (NAS: PLRX)	June 3	$144.0	Yes	Third Rock Ventures	32.3%
ADC Therapeutics (NYS: ADCT)	May 15	$232.7	Yes	Auven Therapeutics	42.7%
Ayala Pharmaceuticals (NAS: AYLA)	May 8	$55.5	No	Israel Biotech Fund	35.5%
Lyra Therapeutics (NAS: LYRA)	May 1	$56.0	No	Perceptive Advisors	32.4%
ORIC Pharmaceuticals (NAS: ORIC)	April 24	$120.0	Yes	The Column Group	22.4%
Keros Therapeutics (NAS: KROS)	April 8	$96.0	No	Pontifax Venture Capital	32.6%
Zentalis Pharmaceuticals (NAS: ZNTL)	April 3	$165.2	No	Kevin Bunker, PhD	18.2%
Imara (NAS: IMRA)	March 12	$75.2	No	NEA	31.8%
Passage Bio (NAS: PASG)	February 28	$216.0	No	OrbiMed	19.6%
Revolution Medicines (NAS: RVMD)	February 13	$238.0	Yes	Third Rock Ventures	28.8%
Schrodinger (NAS: SDGR)	February 6	$202.0	No	David E. Shaw	45.3%
Beam Therapeutics (NAS: BEAM)	February 5	$180.0	No	ARCH Venture Partners	23.0%
Arcutis Biotherapeutics (NAS: ARQT)	January 31	$159.4	No	Frazier Healthcare Partners	36.9%
Annovis Bio (ASE: ANVS)	January 29	$12.0	No	Michael Hoffman	29.6%
Black Diamond Therapeutics (NAS: BDTX)	January 29	$231.3	Yes	Versant Ventures	42.1%
I-Mab Biopharma (NAS: IMAB)	January 16	$114.5	No	C-Bridge Capital	38.9%

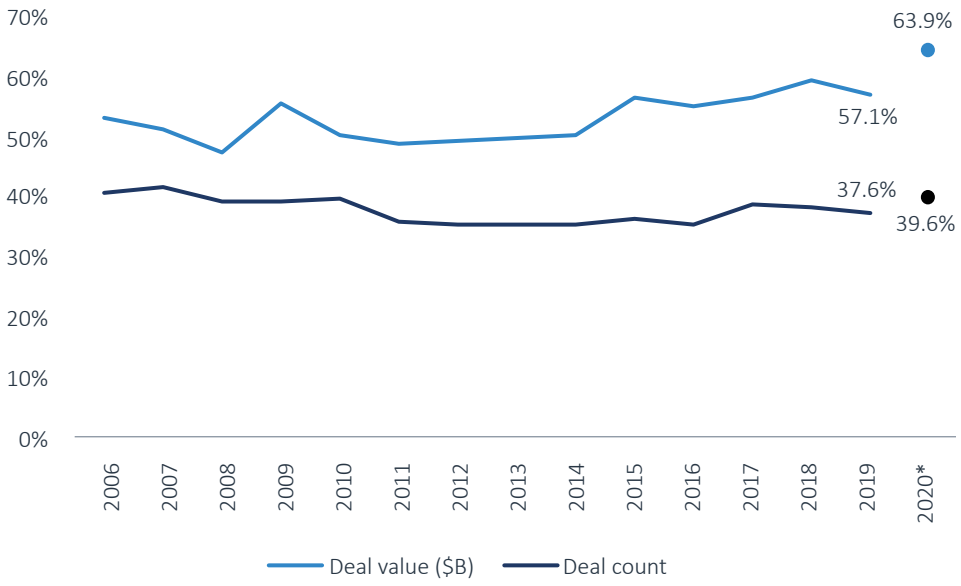
Source: PitchBook, SEC EDGAR Database | **Geography:** US

Investing in biotech & pharma startups today

Investments in biotech & pharma companies account for over 50% of all healthcare VC deal value, reaching over $17 billion a year in each of the last two calendar years. VC-backed biotech companies represent a strong source of drug development and innovation for the broader industry and tend to have the most potential to generate outsized returns for investors when compared to other sectors within healthcare.

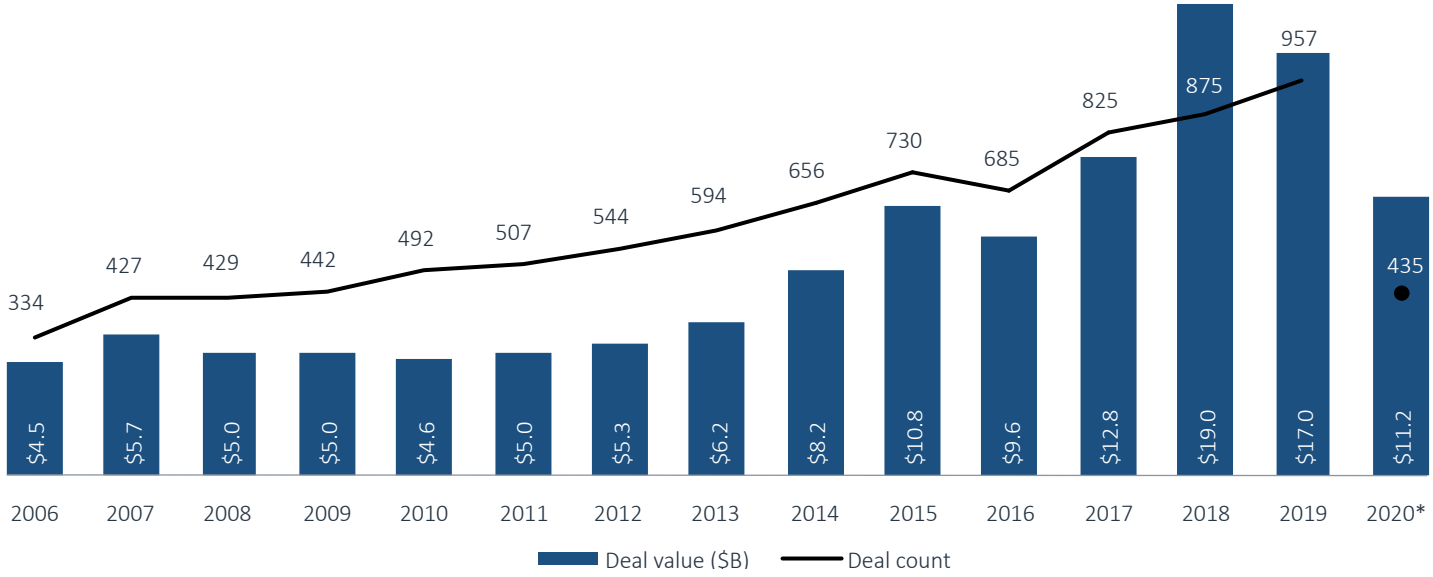
Funding for biotech & pharma companies has more than tripled in the last decade, soaring from $5.0 billion in 2009 to over $17 billion in 2019. This indicates that the development of new drugs and therapeutics from agile biotech startups has been a driving force of change within healthcare.

Biotech & pharma deal activity as proportion of overall healthcare VC deal activity



Source: PitchBook | **Geography:** US
*As of June 22, 2020

VC deal activity ($B) in biotech & pharma



Source: PitchBook | **Geography:** US
*As of June 22, 2020

Fundraising activity for VC-backed biotech startups

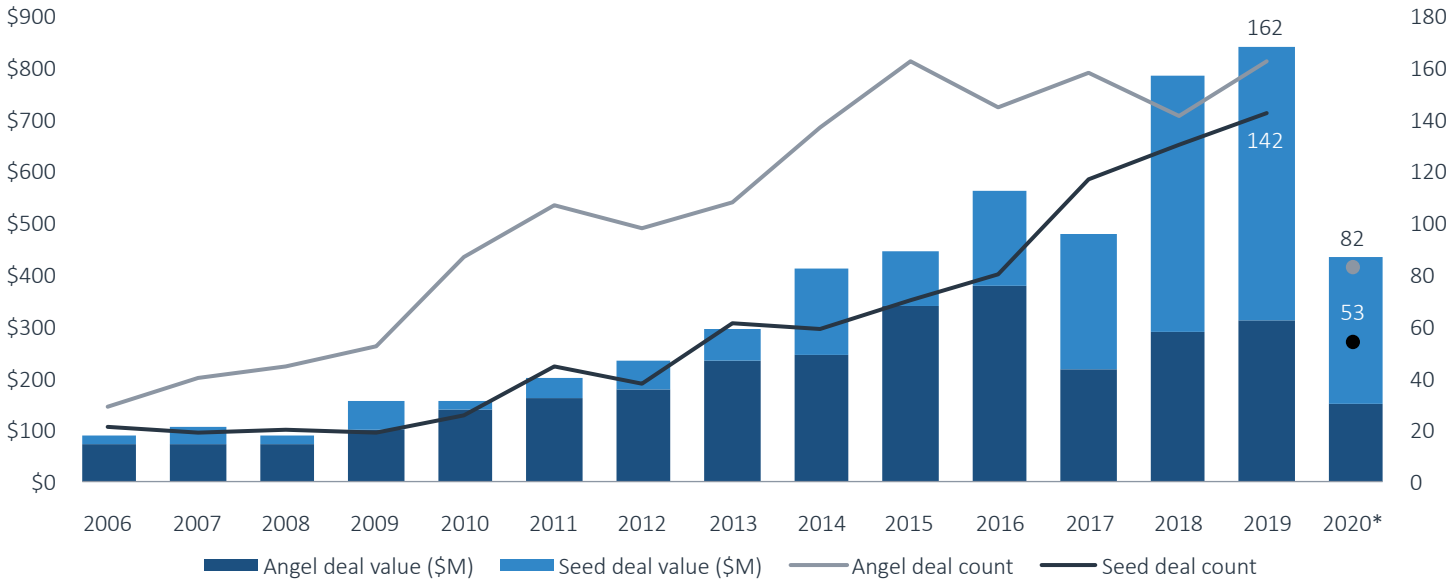
Operating a VC-backed biotech startup requires significant amounts of capital from investors as entrepreneurs aim to tackle society's most challenging unmet medical needs. The median angel- and seed-stage deal sizes for VC-backed biotech & pharma startups in 2019 was $791,420 and $3.0 million, respectively. These numbers are markedly higher when compared to median deal sizes across all the other sectors that year, which posted $500,000 and $2.1 million, respectively. This indicates that VC investments in biotech & pharma companies tend to draw angel rounds that are 58% larger and seed rounds that are 43% larger than non-biotech and non-pharma companies.

This is reflective of the capital-intensive business models surrounding nascent early-stage biotech startups. Whereas founders of software and digital technology startups can make significant headway using decentralized cloud-based computing services such as AWS, GCP, and Azure, biotech entrepreneurs are faced with high burn rates due to soaring R&D costs, increasing capital expenditures, and the need for highly specialized talent. Pre-clinical validation of a drug product/technology that could potentially be the focus of the company for the better part of a decade—as well as potentially generate outsized returns and significant financial upside if the drug is safe, clinically effective, and superior to the standard-of-care—needs to be extensively thorough. These factors play a key role in why VC-backed biotechs typically need to either raise larger financing rounds or at a more frequent pace than non-biotech startups that traditionally have lower burn rates.

Once sufficient pre-clinical data is shown using angel and seed funding, founders proceed along the fundraising timeline and raise early-stage VC rounds. The purpose of these early-stage funding rounds—namely, Series A and B rounds—is to help startups progress into first-in-human trials. The biggest

hurdle for any startup with a therapeutic product is collecting sufficient clinical trial data to convince regulators, such as the FDA or the European Medicines Agency, to grant them market authorization. Only then do drug companies begin generating revenue.

Biotech & pharma angel & seed deal activity



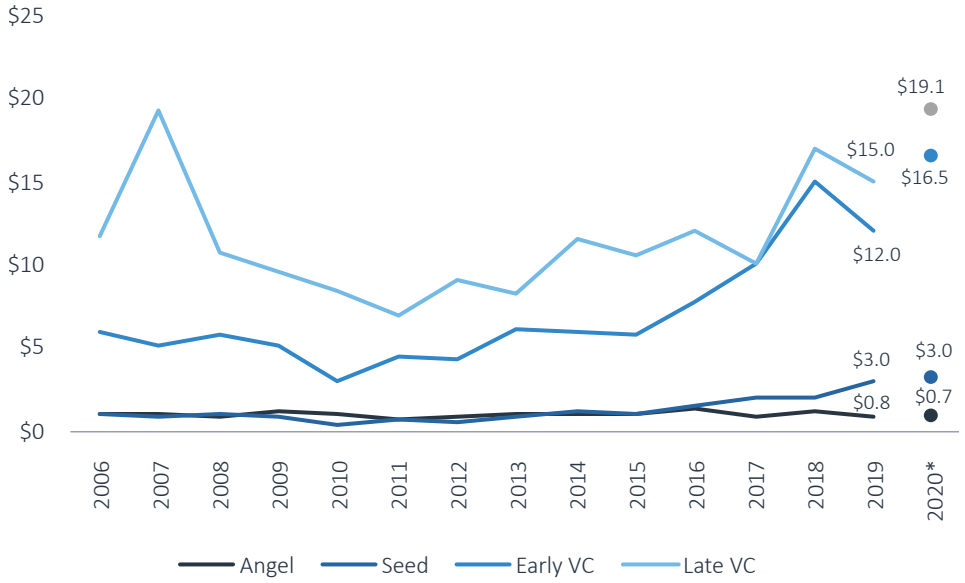
Source: PitchBook | **Geography:** US
*As of June 22, 2020

Our dataset indicates that the median early-stage VC deal size for biotech & pharma startups in 2019 was $12.0 million, which is a 122% premium compared to the $5.4 million median from non-biotech early-stage VC deals. Capital raised from early-stage VC rounds tends to be allocated for the application and operation of Phase 1 clinical trials, which are typically conducted in a small group of patients to determine the safety, tolerability, and pharmacokinetics and pharmacodynamics (PK/PD) of investigational new drugs (INDs). Efficacy, while sometimes observable, is highly speculative as it is not the primary outcome of these early-phase trials. Data from the Department of Health and Human Services shows that the average Phase 1 clinical trial cost across all therapeutic areas is $4.0 million.[8] These pivotal trials, while expensive, are key catalysts that can bolster a startup's valuation if trial results are positive, giving entrepreneurs more leverage and potentially more favorable deal terms in subsequent funding rounds.

The median late-stage VC deal size for biotech & pharma startups in 2019 was $15.0 million, which is a 50% premium when compared to the $10.0 million median from non-biotech late-stage VC deals. Late-stage VC rounds—Series C and beyond—provide startups with the capital needed to scale up production and manufacturing to meet the demands of clinical trials with larger patient enrollment numbers.

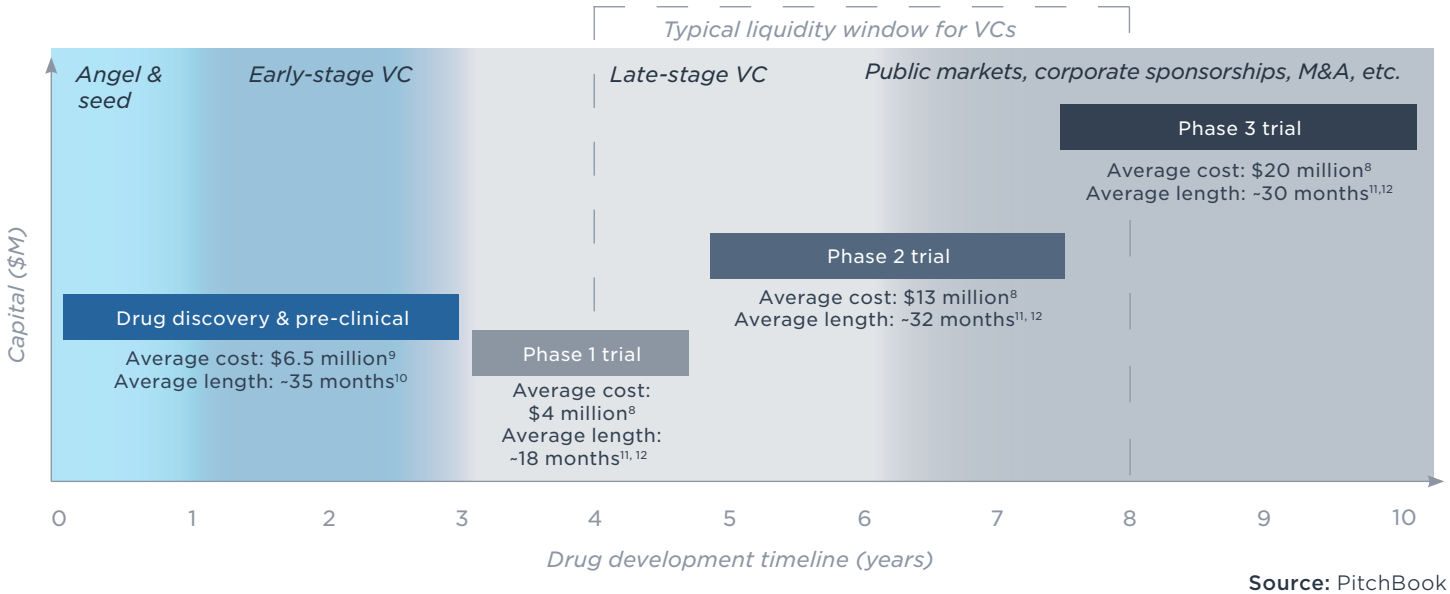
8: "Examination of Clinical Trial Costs and Barriers for Drug Development," US Department of Health and Human Services, Aylin Sertkaya, et al., July 25, 2014

Median biotech & pharma VC deal size ($M)



Source: PitchBook | **Geography:** US
*As of June 22, 2020

Typical drug development timeline and fundraising strategy



Source: PitchBook

8: "Examination of Clinical Trial Costs and Barriers for Drug Development," US Department of Health and Human Services, Aylin Sertkaya, et al., July 25, 2014
9: "The R&D Cost of a New Medicine," Office of Health Economics, Jorge Mestre-Ferrandiz, Jon Sussex, and Adrian Towse, December 2012
10: "Mapping and Characterizing the Development Pathway from Non-Clinical Through Early Clinical Drug Development," Pharmaceutical Medicine, Stella Stergiopoulos and Kenneth A. Getz, December 23, 2012
11: "Estimating the Cost of New Drug Development: Is It Really $802 Million?" Health Affairs, Christopher P. Adams and Van V. Brantner, March-April 2006
12: "The Pharmagellan Guide to Biotech Forecasting & Valuations," Frank S. David, Seth Robey, and Andrew Matthews, January 4, 2017.

This capital is also used by startups to test out the applicability of their drug(s) in other clinical indications, both as a strategy to maximize the drug's versatility and to hedge their position in the primary disease target. Once a company's drug is determined to be safe and well-tolerated, companies will typically return to their private backers and raise subsequent larger rounds of capital to progress with Phase 2 trials. These trials assess both the efficacy and dose response of the investigational drug in development, and the HHS data shows that the average cost of a Phase 2 clinical trial is $13.0 million. Often, VC-backed biotechs lack the outsized capital and multi-site coordination needed to run these larger trials and will enlist the use of contract research organizations (CROs) or partner with large-cap incumbents through a joint venture agreement. In fact, many VC-backed companies who find themselves testing multiple drug candidates in multiple clinical trials will frequently file for an IPO to raise the immense amount of capital needed to execute Phase 2 and Phase 3 trials.

The adage of "high risk, high reward" could not represent biotech investing any more clearly. Investors have little to no recourse when clinical trials yield negative results, and for the vast majority of small biotech startups in this situation, it is usually the end of the road. Investors might be able to recuperate a fraction of their initial investments by selling the underlying IP to another entity. Founders must make an extremely compelling case to investors as to why follow-on financing for a subsequent clinical trial or new drug would yield a more positive result. Given the headwinds involved in securing regulatory approval for a new drug/study and obtaining the necessary pre-clinical data for that submission, investors are largely hesitant to continue providing capital when severe adverse events or negative results come out of clinical trial endpoints.

Given the headwinds involved in securing regulatory approval for a new drug/study and obtaining the necessary pre-clinical data for that submission, investors are largely hesitant to continue providing capital when severe adverse events or negative results come out of clinical trial endpoints.

The fundraising timeline for VC-backed biotechs has been accelerated by the rapid development of the biotech industry, and capital intensity has grown sharply due to the advanced techniques involved in next-generation therapies such as immunotherapies and personalized medicines. Furthermore, investors' expectations for early-stage biotechs have also risen as the industry races to solve some of the most pressing medical challenges with the most powerful toolkit that biology has ever seen.

Ultimately, because biotech startups are plagued with long drug development timelines that often exceed 10 years, investors must perform rigorous due diligence to ensure that their capital is being put to good use and that the risk of long-term illiquidity is optimized to generate maximum return. Private backers rarely stick around until a drug is approved and, when coupled with the fact that biotech startups need significant amounts of capital to conduct clinical trials, VC-backed biotech companies will oftentimes exit via IPO without an approved product to gain access to the public markets to raise capital and provide liquidity back to investors. The capital intensity and difficulties/costs surrounding due diligence do not necessarily fit with the standard fund structures of many GPs. Yet, the ability for biotech companies to generate substantial returns for investors has encouraged many investors to pursue this sector.

The current environment and future of biotech investing

Scientific knowledge and new biomedical discoveries are advancing at an unprecedented pace, and the industry is rapidly adopting these technologies to improve the treatment of patients and disease. Investor sentiment toward the biotech sector has been quite positive as more and more generalist VCs are investing in biotech startups in recent years. Many investors have raised dedicated funds and hired new partners within the firm to focus on their efforts within this space.

When it comes to investing in VC-backed biotech companies, there is no "one size fits all." All three models discussed in this note bear potential upside for investors to realize financial gains, as well as non-financial metrics such as patient impact and treating disease. It all comes down to investment preference and capacity. Investors are likely to stick with what is most comfortable for them, rather than shift between the models, given the high barriers to entry.

Investors must recognize that biotech companies are long-term oriented with short-term financing structures. This seemingly paradoxical statement indicates that there are multiple points of entry for VCs into biotech and that drug development cycles align with the long-term illiquid timeline of venture investments.

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Research commercializing and company formation following the classic model have become increasingly more difficult. While fundraising within the VC asset class has seen record levels in recent years, we anticipate headwinds for entrepreneurs who want to build biotech startups through the classic model. Biotech investors are heavily network-dependent, and access to capital for new entrepreneurs will become more challenging if they are not acquainted with a top-tier investor or part of a venture creation network.

Certainly, the rise of commercial laboratory real estate investment firms such as Alexandria Real Estate Equities and Longfellow Real Estate Partners has helped dampen many of the difficulties encountered by these entrepreneurs by providing startups with capital, dedicated lab space, and a network of investors. This democratization of biotech has also allowed secondary and tertiary biotech ecosystems such as Raleigh-Durham, Philadelphia, and San Diego to gain momentum and attract biotech venture investments. Yet the financial moat that large VC firms ($1.0 billion+ AUM) enjoy in biotech epicenters such as Boston/Cambridge and the San Francisco Bay Area can make for a competitive landscape. First-time funds and smaller biotech investors must rely on their agility and other competitive edges to compete with industry stalwarts. Perhaps we may see a fourth model of biotech startups emerge.

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We believe the venture creation model has shown to be capable of generating outsized returns for VC firms. LPs that have a relationship with GPs at these firms are likely to increase contributions to these funds over the next several years. The number of venture-created biotech startups has been increasing in prevalence. In the last year alone, there has been substantial capital raised to fund this venture creation model, with Third Rock Ventures raising a $770.0 million fund, Flagship Pioneering raising a $1.1 billion fund, and Atlas Venture raising a $400.0 million fund.

As VCs raise larger and larger funds, we are seeing firms double down on their respective strategies to biotech startup formation. The biotech sector is largely insulated from many of the macroeconomic headwinds currently being experienced by other sectors, and given investors' demand for these companies as seen recently in the public markets, we anticipate a continued stream of VC deal activity in the sector.

We are also seeing a concentration of biotech investors who are doing a huge volume of deals. Our data shows that the top 50 investors (out of over 2,400 unique investors) have completed almost one-quarter of the deals within biotech & pharma in the last three years. Given the specialized knowledge involved with research commercialization, firms that have a track record of doing these deals are well positioned to see more successful deal flow.

Outlook

As innovations in computer hardware and software begin to plateau, investors are turning to healthcare—specifically biotech—startups as the next wave of high-impact, high-return opportunities. While biotech investing contains a different set of risk profiles compared to tech startups, this has not deterred investors from increasing their positions in this sector.

VC-backed biotechs have been a flight to quality for many investors outside of the VC asset class. More and more institutional investors have climbed aboard as interest in biotech investing has continued to grow.

In fact, VC-backed biotechs have been a flight to quality for many investors outside of the VC asset class. More and more institutional investors have climbed aboard as interest in biotech investing has continued to grow. Biotech company valuations have, in large part, been buoyed by publicly traded large-cap biotech & pharma companies acting as forced buyers. Incumbents need to protect their future drug revenue streams and have become a sure source of liquidity for investors who previously had their money tied up in a VC-backed biotech. This mitigates the risk involved for many investors and provides them with a clear and formulaic path to profitability.

While the biotech sector is less swayed by public market volatility, macroeconomic factors can still have an impact on both private-backed and publicly held biopharma companies. On the one hand, trade tensions between the US and China have put a strain on the drug manufacturing supply chain of many biotech companies. On the other hand, the diminishing possibility of a "Medicare-for-all" system in the US and a diversion away from drug pricing discussions have resulted in significant upside for VC-backed biotechs. Furthermore, record-breaking drug approval rates by the FDA in the last few years, as well as very few antitrust issues surrounding M&A activity, ensure that revenue generation and exit opportunities for VC-backed biotechs remain lucrative.

The biopharma sector is one of resilience and is operated and backed by equally resilient entrepreneurs and investors. We believe the industry has benefited from the opportunity that was carved out by incumbents for VC to fund game-changing, revolutionary science. Future notes will take a data-driven deep-dive into the nuances of the biotech company lifecycle, licensing and royalty deals, forecasting and valuations, and things to look out for when investing in biotech companies.