

FEG INSIGHT

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A PIRATE LOOKS AT FORTY

Innovations in Biotech for a Long Life
and Long-Term Investing

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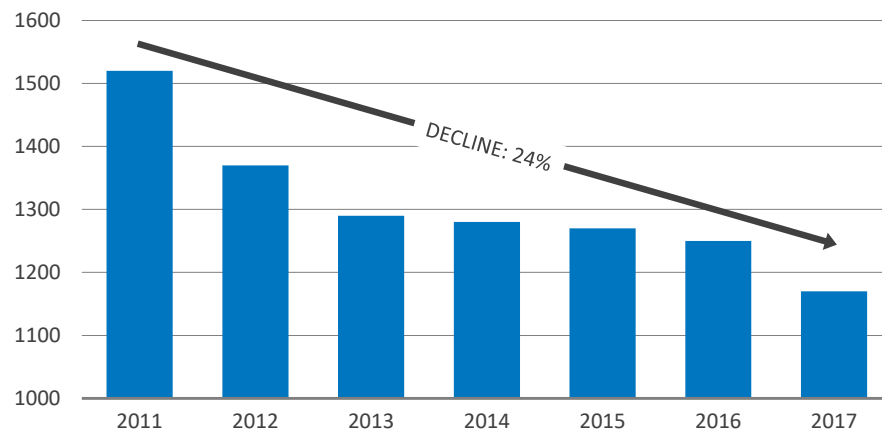
As a music buff who just turned 40, I cannot help but wonder if this milestone of being squarely middle-aged and my body starting to break down has fueled my growing interest in biotechnology as an investment opportunity. For those unfamiliar with the song, *A Pirate Looks at 40*, Jimmy Buffett reflects upon living 200 years too late and mourns missing the peak of pirating and a romanticized view of such a life on the sea. Despite my affinity for his music, I do not share his view. I much prefer entering middle age during this period of biotech innovation, and as an investor, am excited about the opportunities the innovation presents. At 73, Mr. Buffett should also care deeply about biotech innovation, and given his Key West beach-party and concert-fueled life, perhaps a cure for any liver ailments.

Thinking about investing in biotech should be done in the same manner one thinks about a long life. Investors can easily get sucked into short-term thinking and place too much emphasis on presidential tweets, central banker commentary, and daily fluctuation in the markets. For permanent pools of capital, pausing to study long-term trends—which can create multi-decade investment opportunities—is often helpful. Unlike many other sectors, biotech is uniquely suited for long-term, patient capital—as evidenced by performance over the past decade—and will likely continue to be an opportunity for many years to come.

MARKET EVOLUTION

Beginning around the early 2000s, big pharma companies realized that they were large, somewhat bureaucratic organizations that were not well-suited for innovation and entrepreneurialism. So a shift occurred in which these companies began focusing on the distribution and marketing of drugs and reduced their budgets for research and development (R&D). Increasingly, big pharma R&D spending today focuses on late-stage clinical development rather than new and innovative therapies and treatments.

NUMBER OF BIG PHARMA EARLY CLINICAL PROGRAMS



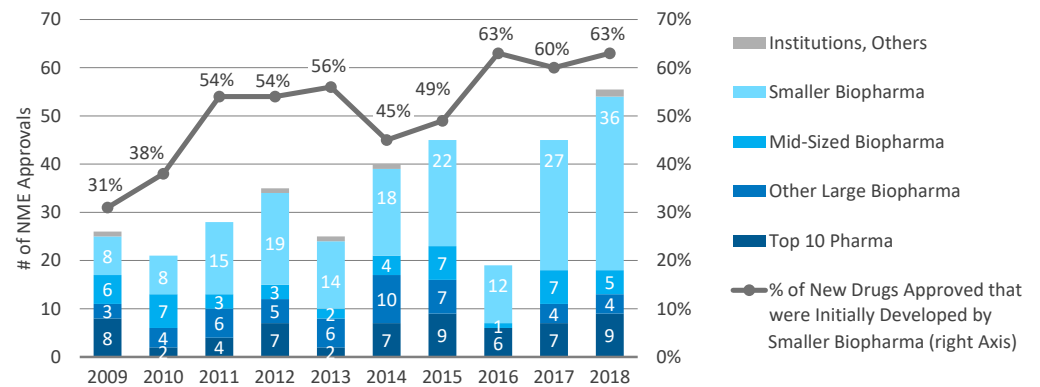
Data source: CMR Consortium, representing 80% of Top 20 Big Pharma, reflects prior two years

Given the hefty free cash flow that these companies have generated just from marketing and selling what was already in place, they largely decided that it was a better capital allocation decision to buy new drugs after some level of efficacy has been proven—versus spending the money to develop new drugs completely in-house.

To be fair, that cash flow is not insignificant. HighVista Strategies estimates that the 20 largest pharma companies could buy every publicly-traded biotech company with a market cap less than \$2.5 billion at a 25% premium using just the free cash flow those companies expect to generate over the next three years!

Thus, a symbiotic relationship has developed between big pharma, venture capitalists, and increasingly small, publicly-traded biotech companies. To illustrate the result of this shift from developing to acquiring, consider the originators of drugs approved over the past 10 years as shown in the chart. Notably, smaller biopharma/biotech companies have doubled from 31% of originations in 2009 to 63% in 2018.

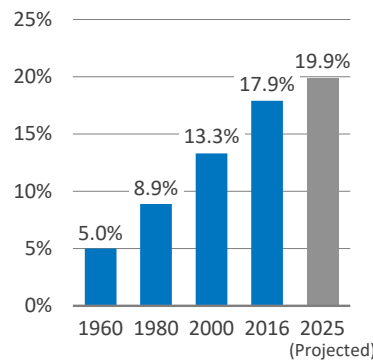
SMALLER BIOPHARMA HAS BECOME THE DOMINANT SOURCE OF NEW DRUGS



Data source: FDA, HBM Analysis
NME = New Molecular Entity

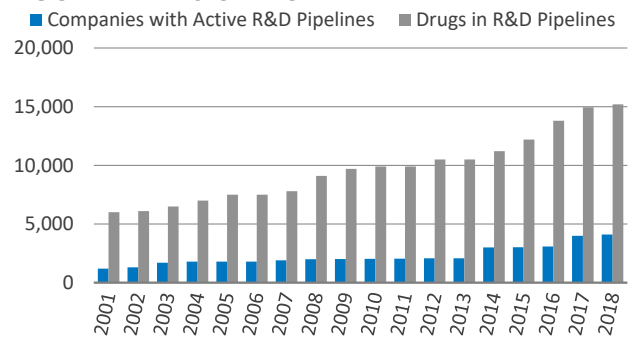
These trends, combined with an aging population and growth in spending on healthcare, have formed a confluence of events creating opportunities for investment in biotech.

HEALTHCARE IS APPROACHING 20% OF U.S. GDP



Data source: Centers for Medicare and Medicaid Services

BOTH THE NUMBER OF COMPANIES AND DRUGS IN PIPELINE HAVE MORE THAN DOUBLED THIS CENTURY



Data source: Pharmaprojects, Pharma Intelligence, Wasatch

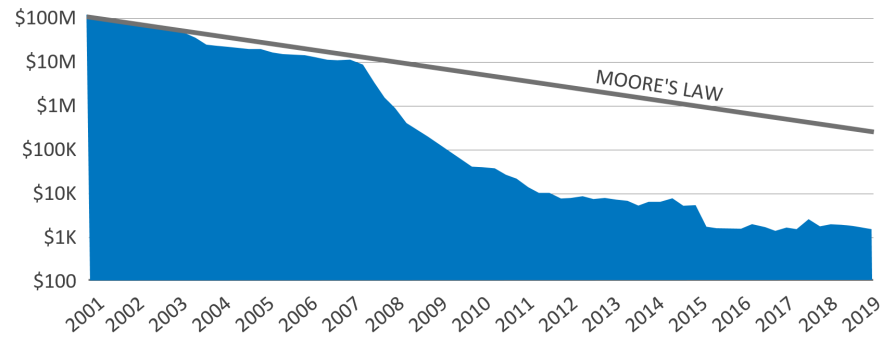
SCIENCE

Prior to joining FEG, I had the good fortune of being selected for the Kauffman Entrepreneur Internship Program while I was getting my master’s degree.¹ This allowed me to spend time within an early-stage life sciences venture capital firm. I can assure you that was a lonely place in the early 2000s and is where IRRs went to die. Times, however, have changed.

The understanding of disease and molecular biology has grown in leaps and bounds over the past decade—somewhat akin to Moore’s Law on the growth rates of computing power, which states that the number of transistors in a circuit doubles approximately every two years.

One often-cited scientific example of innovation in this field is the cost of DNA sequencing, which has profoundly outpaced Moore’s Law since January 2008, ending at just over \$1,000 per genome in 2019.

COST PER HUMAN GENOME



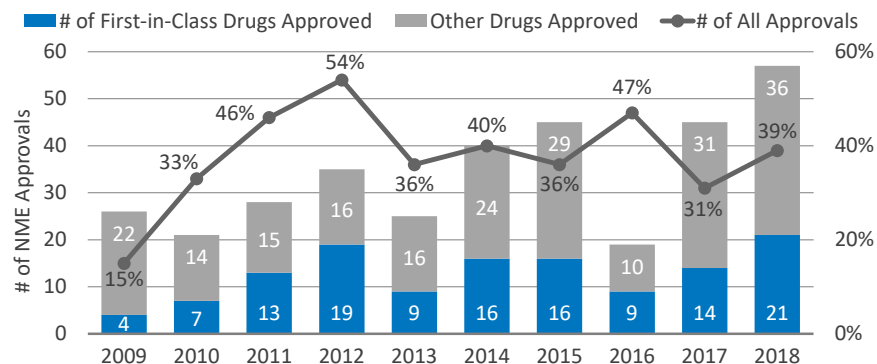
Data source: <https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data>

In addition to DNA sequencing, other innovations include gene editing (CRISPR) and CAR-T cell therapy, which has been called a game-changer in providing new opportunities for patient treatment. Improvements in biological understanding have led to an increased probability of success in early-stage trials and a reduction in the time and cost of proving efficacy.

The improvements in time and cost are not only good for scientists, but investors benefit as well. The result of scientific improvement for venture capitalists is a shortened J-curve and better rates of return (IRRs). This has also created more publicly traded companies in the space, as the number of diseases with cost effective treatment has grown.

To highlight the impact of this innovation, the number of “First-In-Class” drugs has increased from just 15% of new drugs approved in 2009 to nearly 40% in 2018. This title has a specific FDA definition—“drugs which use a new and unique mechanism of action for treating a medical condition”—and should be regarded as a proxy for innovation in biotech.

INNOVATION IN BIOTECH IS GROWING

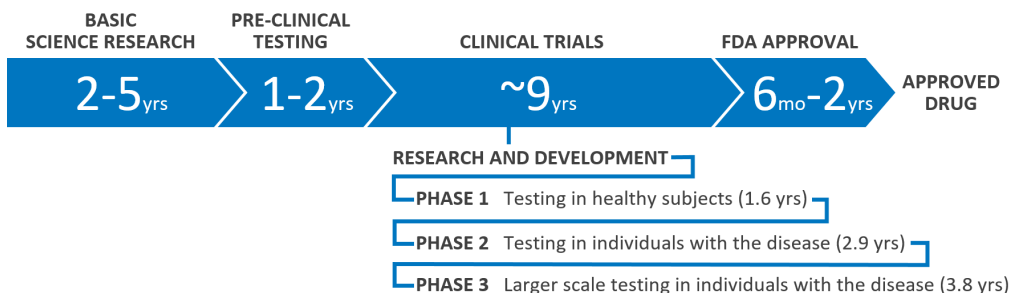


Data source: FDA, HBM Analysis
NME = New Molecular Entity

REGULATION

The approval process for a new drug is understandably long and robust to protect patients, spanning over a decade or more. While there are exceptions to any rule, different types of investors get involved at different points in the process. Generally, the earlier the investment, the greater the potential reward, as well as the greater the risk.

FDA DRUG-APPROVAL PROCESS

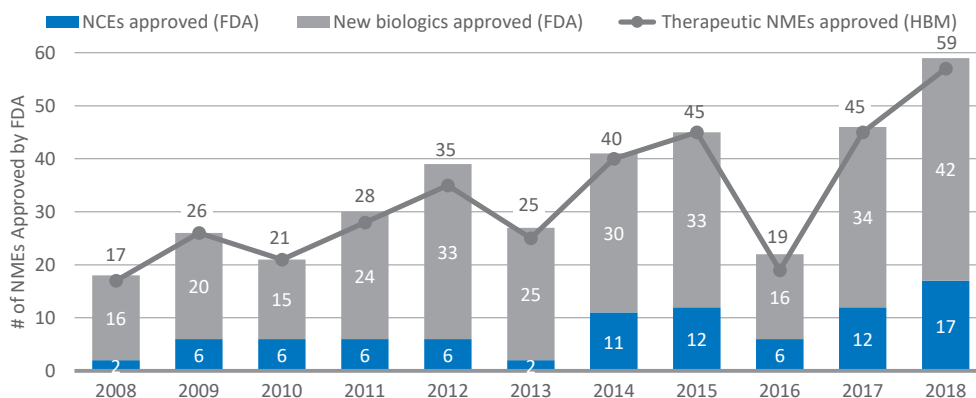


Data source: <https://www.optum.com/resources/library/drug-approval-process.html>

Early-stage venture capital (VC) funds tend to invest at the pre-clinic and Phase I stage of the process, while mid-stage VCs typically get involved in Phase I-III of clinical trials. Specialist biotech investors—most likely hedge funds—invest out of a smaller fund size and invest in smaller market cap businesses. The portfolio size of drugs/therapies can vary but tend to be more concentrated in number and tend to be within the clinical trial phase. Lastly, generalists and mutual funds dominate the investor base for larger cap (\$10 billion+) companies, which often have a more diversified mix of assets and less early-stage risk, but commensurately lower returns.

In recent years, the coupling of scientific advancement and a friendlier environment within the FDA has led to an increase in the number of new drugs approved. In fact, 2018 was a record year with 59 new drugs approved, compared to only 18 a decade earlier.

FDA DRUG APPROVALS REACH RECORD HIGH



Data source: FDA, HBM Analysis

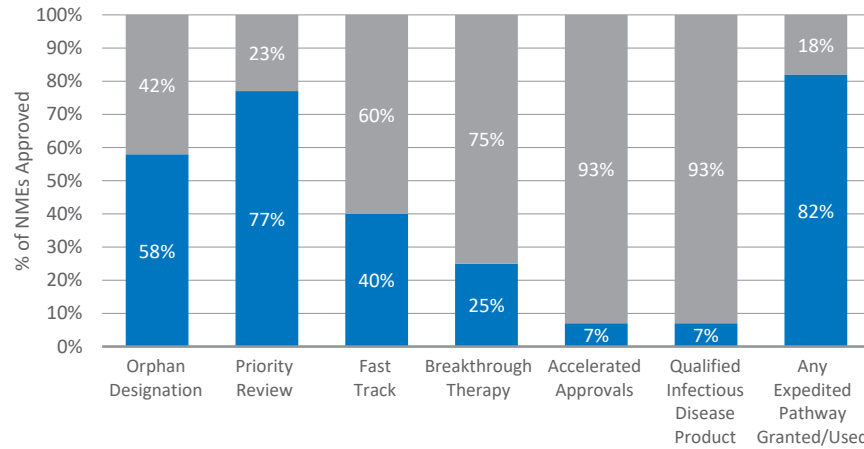
NME = New Molecular Entity

NCE = New Chemical Entity, i.e., small molecule

Additionally, in an effort to overcome the approval bureaucracy, over 80% of the drugs approved in 2018 used expedited pathways to truncate the time required, and consequently the costs, to go to market.

FASTER TIME TO MARKET

Drugs Approved in 2018 Using Expedited Pathways

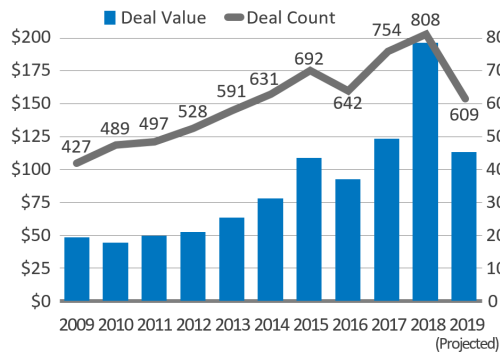


Data source: HBM New Drug Approval Report – Analysis of FDA New Drug Approvals in 2018 (and multi-year trends)

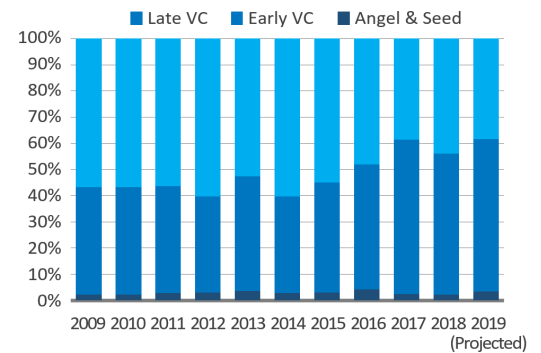
CAPITAL MARKETS

Pharma and biotech investment activity in capital markets is robust and continues to increase. Within private markets, 2018 was a record year in terms of both deal count and value, with over half of the activity concentrated in early-stage rounds.

PHARMA VC DEAL COUNT ON PACE TO MATCH 2018 RECORD



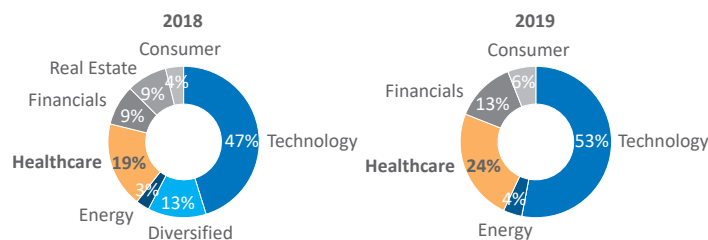
DEALMAKING CONTINUES TO CONCENTRATE IN THE EARLY STAGE



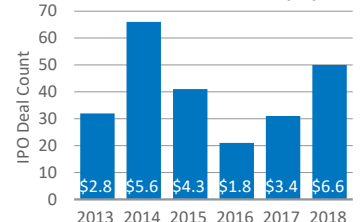
Data source: PitchBook-NVCA Venture Monitor; data as of September 30, 2019

The initial public offering (IPO) window has largely been open as well. More broadly, healthcare continues to be the second largest sector for IPOs—after technology—and has accounted for nearly a quarter of all IPOs thus far in 2019.

BIOTECH IPOs INCREASING



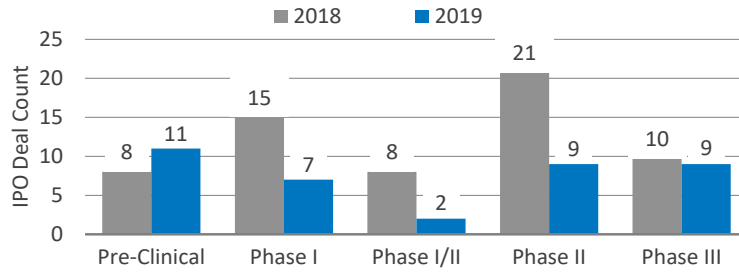
Biotech IPO Issuance Over Time (\$B)



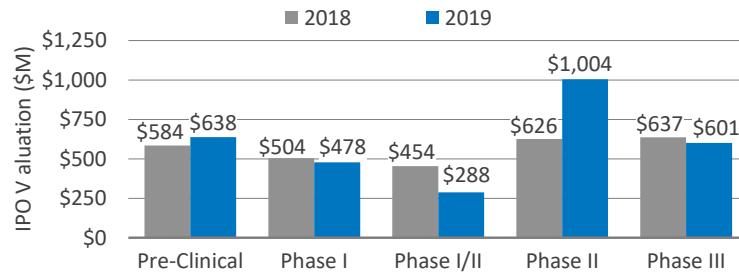
Data sources: J.P. Morgan Equity Capital Markets Update April 2019; Dealogic, Bloomberg and FactSet as of April 18, 2019, Sofinnova Investments

Unlike tech, where the trend has been for VC-backed companies to stay private longer, biotech companies are going public much earlier in the company’s life, comparatively, improving the exit environment for private investors and creating more opportunities in the public markets. In fact, 2019 has already seen 11 IPOs at the pre-clinical stage!

EARLY-STAGE COMPANIES HAVE BEEN ENTERING PUBLIC MARKETS ...



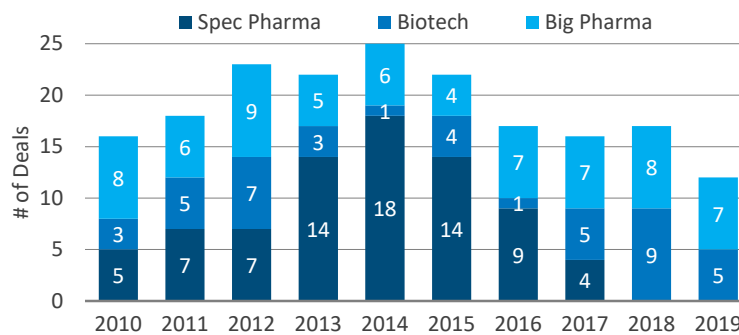
... AND ARE BEING SUPPORTED BY HEALTHY VALUATIONS



Data sources: Jefferies, 5AM Ventures

This has led to an increase in the number of publicly traded biotech stocks. There are more than 1,200 publicly-listed small cap biotechnology companies (sub \$2.5 billion market cap) with an aggregate market value of \$458 billion. In addition to the growth in new companies via IPOs, merger and acquisition (M&A) activity also remains robust.

YEARLY SNAPSHOT OF BIOPHARMA M&A (\$B)



Data sources: J.P. Morgan, 5AM Ventures

Returns across biotech have been volatile over time, but investors have been rewarded for their risk. The annualized risk-return chart shows the historical returns of the S&P Biotech Select Index (XBI) and Nasdaq Biotechnology Index (NBI). The XBI was launched in 2006 and is more representative of smaller cap biotech stocks. The NBI has a larger cap tilt and, while well-known, is slightly less representative of the types of businesses where we typically see the biotech specialist managers invest as contrasted to the smaller cap XBI.

GREATER RISK AND REWARD WITH BIOTECH

Annualized Risk-Return from March 2006–September 2019

	ROR	STANDARD DEVIATION	SHARPE	MAX DRAWDOWN	BETA	CORRELATION
S&P 500 Index	8.6%	15.7%	0.48	-50.9%	—	—
S&P Biotech Select Index	12.3%	31.3%	0.36	-43.6%	0.31	0.57
Nasdaq Biotech Index	10.5%	23.4%	0.40	-33.4%	0.46	0.65

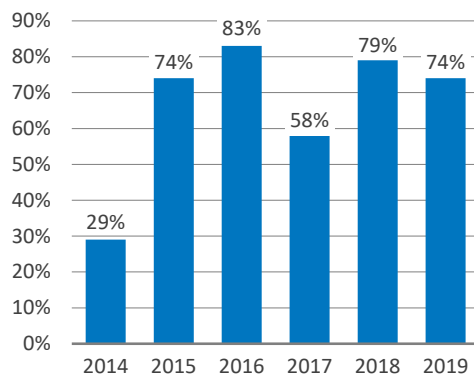
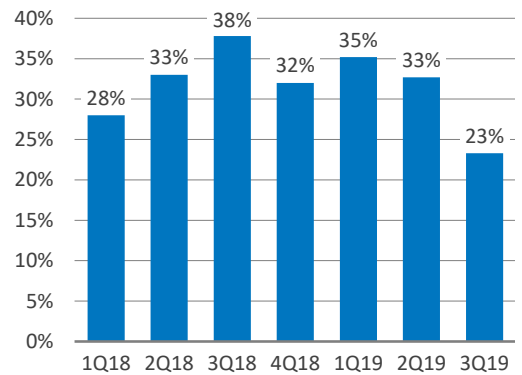
Data source: Lipper

The key highlights of biotech performance are higher long-term returns, higher volatility, and lower correlation to the overall stock market, as represented by the S&P 500 Index.

CROSSOVER INVESTORS

One trend to be aware of within the asset management community is the increasing prevalence of “crossover” investors. Many biotech-focused hedge funds, which initially focused on publicly traded stocks, are becoming increasingly active with private companies. While this increases the opportunity set and return potential for these funds, investors need to monitor the liquidity of their investments and ensure the hedge funds themselves have appropriate liquidity terms that match their underlying investments.

Crossover investing has generally been beneficial to those with ability. In the recent paper “Exploration or Exploitation? Hedge Funds in Venture Capital” Aragon, Li, and Lindsey found that crossover hedge funds generate alpha of 1.7% per annum from this VC knowledge and activity.²

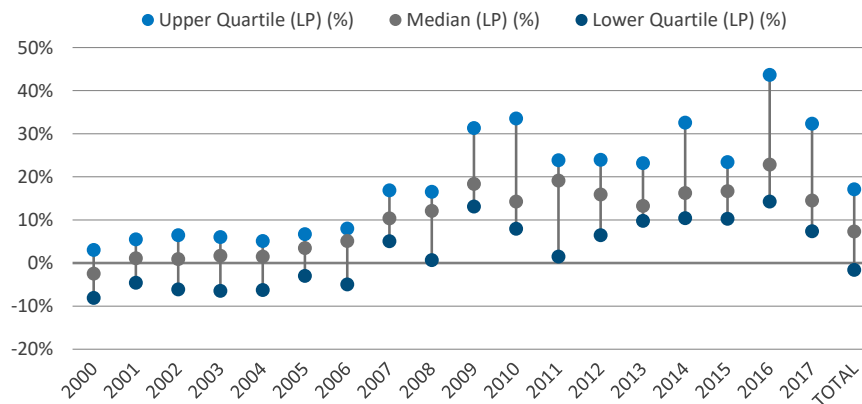
PERCENT OF IPOs WITH CROSSOVER INVESTMENTS**AVERAGE PERCENT INSIDER PARTICIPATION AT PRICING***Data sources: Evercore, Dealogic, Renaissance Capital, Bloomberg, Company Filings, 5AM Ventures*

At IPO, the number of biotech companies with crossover investors has more than doubled since 2014, a trend which does not appear to be reversing any time soon. The average insider participation at IPO is also significant, as owners are motivated to cash-in. Crossover should help ensure alignment of interest between management and investors, as they are incented to hold their shares beyond the first post-IPO cash-in opportunity.

PRIVATE MARKETS

While the universe is relatively modest in number, the chart detailing returns for healthcare VC funds broken down by vintage year shows a meaningful increase in returns starting around 2007, corresponding to when scientific breakthroughs began to significantly increase.

HEALTHCARE VC RETURNS BY VINTAGE YEAR



Data source: Cambridge Associates - US Venture Capital Index and Selected Benchmark Statistics 2017

Historically, successful early-stage biotech VC funds have delivered high returns, but they also present great risk in terms of scientific validity, illiquidity, etc. Additionally, many funds are relatively modestly-sized and can be difficult to access.

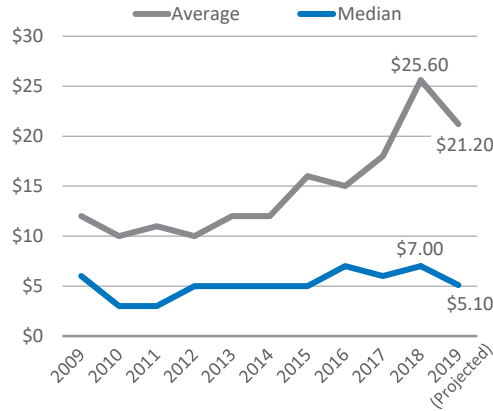
One potential benefit of VC funds is that they provide quarterly valuations, which somewhat alter an investors experience of risk. Investors are not forced to see—and therefore avoid—the distraction of the large daily and monthly swings in returns which are expected with public market-oriented funds.

Hedge funds and other public market biotech funds have historically delivered slightly lower returns, on average, than VC funds. The primary benefit, however, is more liquidity and the ability to rebalance exposure more quickly when the inevitable large upward and downward moves occur. Ultimately, FEG believes there is room for both public and private biotech investments in a diversified portfolio.

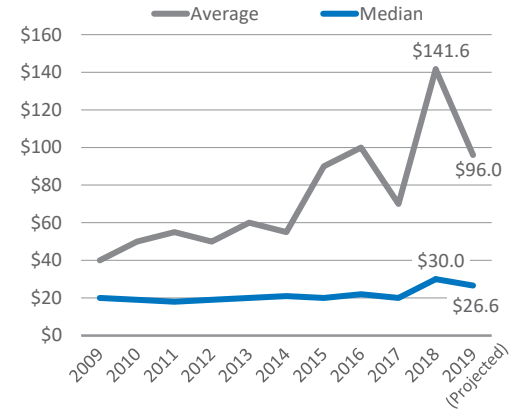
CURRENT ENVIRONMENT

2019 witnessed a modest sell-off across both public and private valuations for the data currently available—private data is available on a lag. The median valuation dropped from a pre-money round of \$30 million in 2018 to \$26 million in 2019 on the private side.

PHARMA DEAL SIZES FALL FROM 2018 PEAK



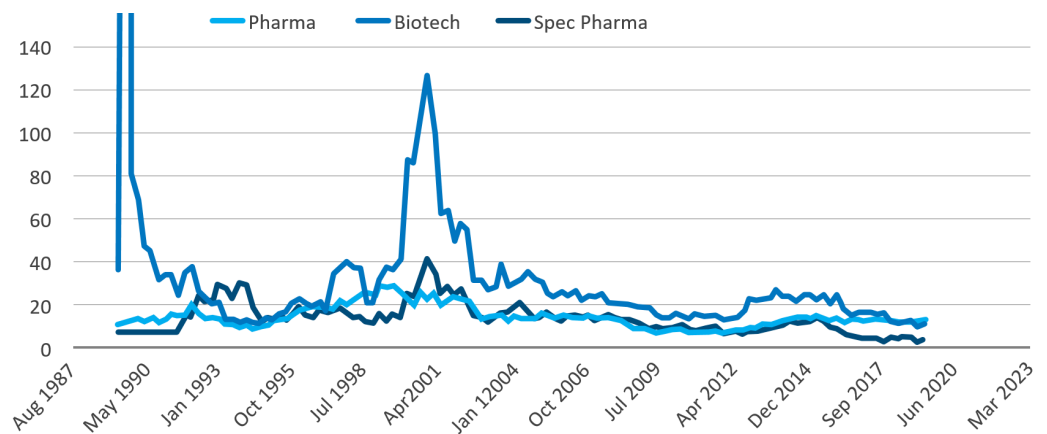
VALUATIONS DROP IN TANDEM WITH DEAL SIZES



Data source: PitchBook-NVCA Venture Monitor; data as of September 30, 2019

Within public markets, the Nasdaq Biotechnology Index was weak for most of 2019. The index had only returned about 3% through the first nine months of the year before rallying from historically cheap valuations to return 25% for the year, illustrating the volatile nature of public biotech equities. Valuations, which have most likely changed again as this is read, increased toward more equilibrium—yet still attractive—levels at year-end.

VALUATION OF BIOTECH vs. PHARMA (1FY P/E)



Data source: RTW Investments

RISKS

While much of this is exciting news, there are several hazards as well. First and foremost, this is a risky sector. Invest with eyes wide open and size positions accordingly. Within venture capital, it is common for many of the underlying companies to fizzle and be complete zeros. Within publicly-traded biotech companies, many fail to make any profit and need to reach additional scientific milestones for their investment to work, have often led to binary win/loss outcomes with nothing in between.

To put some numbers to this, consider five-year returns following IPOs going back roughly 40 years. The dispersion is massive for all sectors, but health care in general has historically exhibited even greater amounts of dispersion than average. So, the buyer must always beware.

IPO FIVE-YEAR BUY-AND-HOLD PRICE RETURN BY SECTOR

SECTOR	N	PERCENTILE				
		10%	25%	50%	75%	90%
Communication Services	294	-100%	-97%	-68%	-10%	87%
Information Technology	922	-98%	-88%	-55%	30%	169%
Health Care	832	-97%	-83%	-44%	47%	191%
Industrials	328	-97%	-79%	-41%	47%	135%
Consumer Staples	92	-94%	-82%	-41%	44%	145%
Consumer Discretionary	425	-99%	-83%	-38%	51%	187%
Materials	75	-99%	-88%	-34%	48%	146%
Energy	233	-96%	-73%	-22%	52%	135%
Financials	378	-86%	-51%	-12%	49%	140%
Real Estate	75	-82%	-53%	-3%	43%	87%
Utilities	20	-87%	-60%	-1%	41%	111%
ALL	3674	-98%	-83%	-41%	39%	160%

Data sources: Capital IQ, Verdad Capital

One hedge fund manager recently shared with FEG that he found traditional valuation models, such as discounted cash flows, are irrelevant since most biotech companies do not earn profits in the early years. Rather, the most useful financial framework to think about these companies is akin to buying a long-dated out-of-the-money option. To avoid overpaying for such an option, investors need to consider that a reasonable valuation for a drug or therapy business is potentially 4-5x revenue, understand the size of the total addressable market, and determine the probability that a given drug or therapy will make it through clinic trials and receive FDA approval. This might sound simple, but factoring in these different variables is not easy.

An additional risk is drug pricing. While lower costs for treatment is generally a good thing for society, low prices effectively reduce profitability for healthcare companies—both big pharma and smaller biotech—and makes these companies less valuable. More broadly related to these risks are political pressures, which may become more pronounced in 2020, given the presidential election.

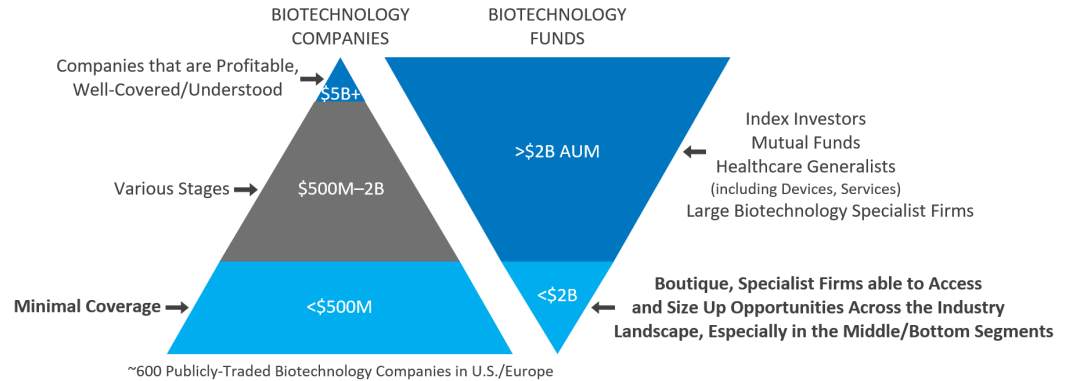
Given the risks and specialized knowledge needed to successfully navigate potential landmines in this area, FEG believes manager due diligence is paramount to ensure investors have the requisite knowledge to invest in this sector. Investment “tourists” often flock to areas that have generated outsized returns, leading to increased investment activity in the space. The prime example of this is Theranos, a failed health technology company that had several well-known individuals and venture capitalists as investors/board members, yet none of these people were experts in the biotech and healthcare fields. Had there been industry expertise on the board, perhaps the validity of the Theranos’ scientific claims, later proved to be false, would have been questioned earlier.

ACTIVE MANAGEMENT

FEG views biotech as a strong area for active management. While manager selection is always important, VC does not offer passive options, so the spread in returns between top- and bottom-quartile managers for this sector is significant.

Public markets have also begun to show characteristics that suggest a good backdrop for active management. The domain expertise needed to underwrite the science, as well as the investment merits, deter many traditional active managers from investing. This also creates inefficiencies in a market with significant volatility and dispersion of returns.

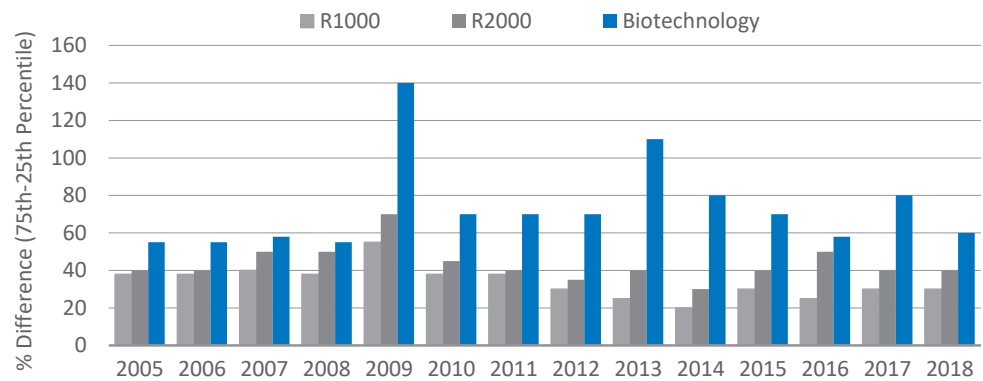
THE BIOTECHNOLOGY SECTOR OFFERS FERTILE GROUND FOR CAPABLE MANAGERS WITH APPROPRIATE FUND SIZES



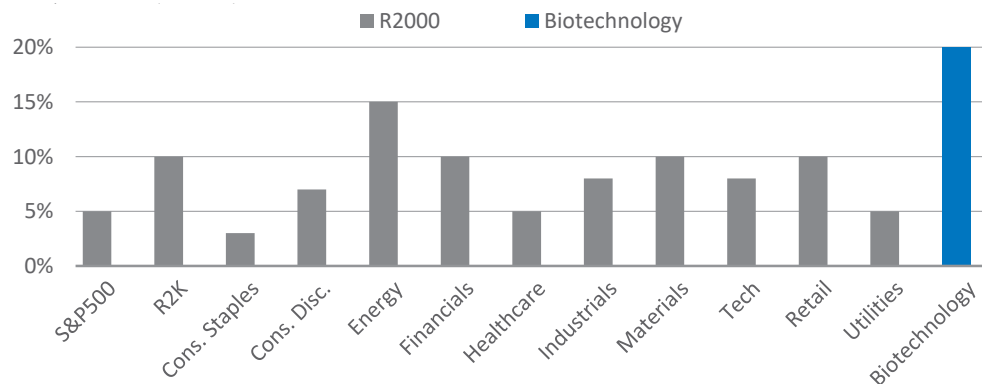
Data sources: Ecor1 Capital, HighVista

PUBLIC BIOTECHNOLOGY FIRMS EXPERIENCE EXTREMELY HIGH DISPERSION AND VOLATILITY, OFFERING AMPLE OPPORTUNITIES FOR SECURITY SELECTION TO DRIVE RETURNS

Annual Dispersion – 75th Less 25th Percentile



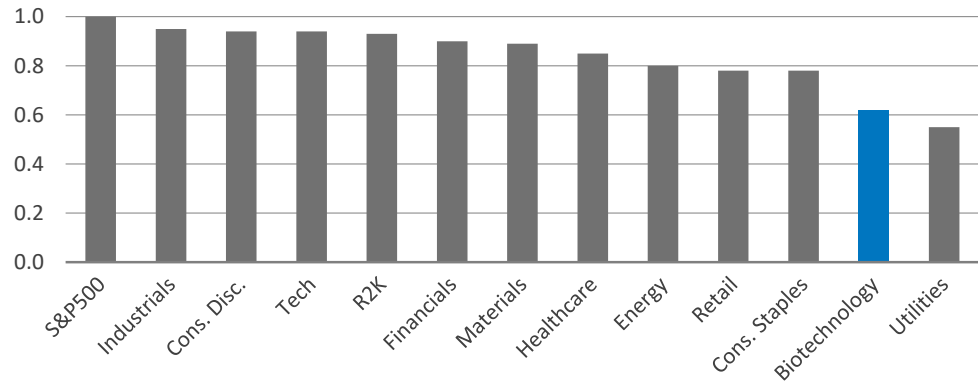
Percentage of Days With >2% Move (2010–2019)



Data source: HighVista Strategies Biotechnology Opportunities Program as of January 31, 2019

MAJOR CLINICAL AND REGULATORY EVENTS LEAD TO BIG MOVES IN BIOTECHNOLOGY STOCKS WHICH CREATES LOW CORRELATION TO THE BROADER MARKET

Correlation to S&P 500



Data source: HighVista Strategies Biotechnology Opportunities Program as of January 31, 2019

CONCLUSION

For long-term pools of capital, biotech is a unique market that appears to have many structural tailwinds, such as evolving market participation from big pharma, small cap biotech companies, and VCs, dramatically growing scientific innovation, and vibrant capital market activity—all of which drive opportunity.

Biotech is, however, an ever-changing, deeply-regulated, high risk-return sector. Sized appropriately and done with managers that have the domain expertise, FEG believes both public and private markets can play a role in helping investors gaining exposure to the innovative biotech market.

“Yes, I am a pirate, two hundred years too late, the cannons don’t thunder, there’s nothing to plunder, I’m an over-forty victim of fate.”

While nostalgic parrot heads may think they were born 200 years too late, as it pertains to our own health—and potential to benefit from investing in biotech—we think now is a great time to be alive. I look forward to seeing you in Margaritaville. Cheers.



¹ <https://www.kauffman.org/what-we-do/entrepreneurship>.

³ Aragon, Li, Lindsay, 2018, Exploration or Exploitation? Hedge Funds in Venture Capital.

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The Bloomberg Barclays Capital Aggregate Bond Index is a benchmark index made up of the Bloomberg Barclays Capital Government/Corporate Bond Index, Mortgage-Backed Securities Index, and Asset-Backed Securities Index, including securities that are of investment-grade quality or better, have at least one year to maturity, and have an outstanding par value of at least \$100 million.

The MSCI ACWI (All Country World Index) Index is a free float-adjusted market capitalization weighted index that is designed to measure the equity market performance of developed and emerging markets. The MSCI ACWI consists of 45 country indices comprising 24 developed and 21 emerging market country indices. The developed market country indices included are: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Hong Kong, Ireland, Israel, Italy, Japan, Netherlands, New Zealand, Norway, Portugal, Singapore, Spain, Sweden, Switzerland, the United Kingdom and the United States. The emerging market country indices included are: Brazil, Chile, China, Colombia, Czech Republic, Egypt, Hungary, India, Indonesia, Korea, Malaysia, Mexico, Morocco, Peru, Philippines, Poland, Russia, South Africa, Taiwan, Thailand, and Turkey. See www.msci.com for more information.

The Bank of America/Merrill Lynch (BoFA/ML) indices are compiled monthly by Bank of America/Merrill Lynch under various criteria and characteristics. See www.bofam.com for more information.

The Credit Suisse High Yield Index is designed to mirror the investible universe of the US dollar denominated high yield debt market. Please see www.creditsuisse.com for more information.