Will Reducing Drug Prices Slow Innovation?

Strategic resource allocation can mitigate any negative impact of price controls

Gregory Vaughan, Ph.D.
Fred D. Ledley, M.D.
Center for Integration of Science and Industry
Departments of Mathematical Sciences; Natural & Applied Sciences; Management
Bentley University

The Center for Integration of Science and Industry at Bentley University focuses on advancing the translation of scientific discoveries to create public value. The Center is a nexus for broadly interdisciplinary scholarship designed to integrate biomedical science, data analytics, economics, business, and public policy. Visit www.bentley.edu/sciindustry and follow us on Twitter @sciindustry.

Bentley University is one of the nation's top business schools. It is a lifelong-learning community that trains leaders to make business a force for positive change. With a combination of business and the arts and sciences as well as a flexible, personalized approach to education, Bentley provides students with critical thinking and practical skills that prepare them for successful, rewarding careers. Founded in 1917, the university enrolls 4,200 undergraduate and 1,000 graduate and PhD students and is set on 163 acres in Waltham, Massachusetts, 10 miles west of Boston. For more information, visit www.bentley.edu. Follow us on Twitter @BentleyU #BentleyUResearch.

The West Health Policy Center is focused on research and education to identify innovations and policy solutions that can slow the trajectory of rising healthcare costs while improving access to—and the quality of—care, particularly for our nation's growing population of seniors. Specific areas of focus include reducing growth in U.S. spending on prescription drugs, promoting value-based care models, increasing price transparency, and limiting consumer exposure to high out-of-pocket costs. Solely funded by philanthropists Gary and Mary West, the Policy Center is based in Washington, D.C., and is part of West Health, a family of nonpartisan, nonprofit organizations dedicated to lowering the cost of healthcare to enable successful aging. For more information visit https://www.westhealth.org/ or follow us on Twitter @WestHealth.

CIDSA, the Council for Informed Drug Spending Analysis, is a nonpartisan expert group funded by West Health and focused on bringing a non-pharma perspective to drug spending policy dialogue. Learn more at www.cidsa.org and on Twitter at @CIDSAexperts.

Study Authors

Gregory Vaughan, PhD is assistant professor, Department of Mathematical Sciences at Bentley University. His research focuses on statistical learning and computing, longitudinal data analysis biostatistics, and applications to public health. He can be reached at gvaughan@bentley.edu.

Fred D. Ledley, MD is professor, Natural & Applied Sciences and Management, and director, Center for Integration of Science and Industry at Bentley University. His work focuses on advancing the translation of scientific discoveries for public value. He has served previously on the faculties of the Howard Hughes Medical Institute and the Baylor College of Medicine and has also founded several public biotechnology companies, serving in the roles of CSO, President, and CEO. He can be reached at fledley@bentley.edu and on Twitter @SciIndustry.

Project Lead for West Health Policy Center and CIDSA

Sean Dickson, JD, MPH is director, health policy, at West Health Policy Center. He is a nationally recognized technical expert on the American drug system, including the full market lifecycle of pharmaceuticals. He can be reached at sdickson@westhealth.org and on Twitter @sean_r_dickson

Table of Contents

Introduction

The pharmaceutical industry has long argued that high drug prices reflect the high cost of innovation and that reducing drug prices would necessarily slow the pipeline of new drugs. These arguments have been bolstered by studies of large pharmaceutical companies showing statistical associations between the projected market size or revenue for pharmaceutical products and research & development (R&D) activity. Our analysis recognizes the increasingly important role of small biopharmaceuticals in drug development, companies that typically have little revenue and negative earnings, but are now responsible for more than 40% of new drug approvals.

Any negative impact of drug price reductions on the pipeline of pharmaceutical innovation may be mitigated through strategic allocation of cost reductions by large pharmaceutical companies.

We examine the relationship between changes in revenue and R&D for companies of different size from 2000-2018. While changes in R&D expense correlate with changes in revenue for the largest biopharmaceutical companies (>$7B market cap), no such relationship is found for smaller companies. Modeling the impact of differential cost reductions on the pipeline of new products, we find that any negative impact of drug price reductions may be mitigated through strategic allocation of cost reductions by large companies to different stages of clinical development.

Background

A flurry of legislative activity in the 117th Congress is aimed at reducing drug prices to ensure that essential medicines for preventing and treating disease are affordable to all Americans.[1] One of the major concerns about such legislation is that reducing drug prices would necessarily lead to reduced investment in industry spending on research and development (R&D) and slow the pipeline of innovative, new treatments for currently intractable diseases.

This concern was bolstered by an April 2021 report from the Congressional Budget Office (CBO) titled Research and Development in the Pharmaceutical Industry, which considered the impact of legislation introduced in the 116th Congress that would have authorized the Secretary of Health and Human Services to negotiate drug prices paid by Medicare or Medicaid.[2] The CBO concluded that "The prospect of such lower revenues would make investments in R&D less attractive to pharmaceutical companies…" and that "…approximately 8 fewer drugs would be introduced to the U.S. market over the 2020–2029 period and about 30 fewer drugs over the subsequent 10 years."

The CBO's findings are not unprecedented. A series of papers by Vernon and colleagues examined the finances of the pharmaceutical industry from 1993-1994, years that the Clinton Health Plan was being debated in Congress. These studies showed that pharmaceutical R&D spending decreased during the years that the Clinton plan was being debated, then experienced a (slow) rebound after the Clinton proposals were rejected.[3] A complementary dynamic has been observed in response to exogenous factors that increase the market for pharmaceutical products such as demographic changes in the US population[4] and passage of Medicare Part D.[5] Both factors have been shown to be associated with increased R&D spending and clinical trial activity specifically in therapeutic areas most impacted by anticipated changes in market size.

These observations are consistent with a financialized view of the biopharmaceutical industry, which posits that the allocation of resources to R&D is driven by the projected revenue from product sales and return on investment.[6] In this context, product pricing and the size of the available market are considered to be the primary determinants of R&D spending. A corollary to this view of the industry is that, faced with declining revenue or lower projections of future revenue, companies would choose to reduce investments in R&D and prioritize their profitability, rather than develop new products with lower profit margins or returns on investment.

Is reducing R&D an inevitable response to lowering drug prices?

Other analyses, however, have questioned the assumption that pharmaceutical companies would choose to reduce R&D spending to ensure profitability. A 2019 white paper from the West Health Policy Center and Johns Hopkins Bloomberg School of Public Health examined the profitability of a set of 23 large pharmaceutical companies, measured by return on invested capital (ROIC), from 2011-2019 compared to companies in other industrial sectors. The analysis concluded that large pharmaceutical companies had significantly higher ROIC than companies and other sectors, and that "...large pharmaceutical manufacturers could endure significant revenue reductions, including the reductions considered in recent legislative proposals, while maintaining current research investments and still achieve the highest returns of any market sector."[7] They concluded that capital investments by large pharmaceutical companies would remain more attractive than alternative investments despite substantial reductions in drug prices and the associated revenue. They concluded that "While we recognize that any reduction in revenues will change a company's operational strategy, we find that large pharmaceutical companies would still maintain industry-leading returns on capital."

Analogous results were described in a 2020 study from the Center for Integration of Science and Industry at Bentley University. This study demonstrated that the profits of 35 large pharmaceutical companies, measured by net income (earnings), were significantly larger than those of other companies in the S&P500 from 2000-2018,[8] though the difference was partly accounted for by controlling for company size, year, and involvement in R&D. This study also highlighted the scale of pharmaceutical revenue, profit, and spending, showing that from 2010-2018, these companies reported cumulative revenue of $11.5 trillion and net income of $1.9 trillion, while expensing $1.8 trillion for R&D and distributing $1.8 trillion to shareholders in the form of dividends or stock buybacks. This study showed that large pharmaceutical companies have the capacity to absorb substantial reductions in revenue without compromising the resources necessary to sustain R&D and earnings comparable to other leading industrial sectors.

The growing impact of small biopharmaceutical companies

The present analysis recognizes the increasingly important role of small biopharmaceuticals in drug development. A 2020 report from IQVIA noted that, while large pharmaceutical companies traditionally played the dominant role in late-stage development and marketing of pharmaceutical products, this dynamic has changed over the past decade.[9] The report showed that from 2016-2020, approximately 40% of new products were both originated and launched by emerging biopharmaceutical companies, defined by IQVIA as revenue <$500 million and R&D spending <$200 million. Another 20% of new products arose from development programs initiated by emerging companies, but were launched after licensing or acquisition by established firms. This is notably different than the situation from 2011-2015, when less than 20% of new products were launched by emerging biopharmaceutical companies.

Previous studies have erred by considering only the impact of price reductions on the largest pharmaceutical companies.

The finances of small biotechnology companies are dramatically different from those of established firms. A recent study examined the financial performance and late-stage product development pipelines of the 319 biotechnology companies that had Initial Public Offerings (IPOs) on NASDAQ from 1997-2016.[10] This cohort of emerging, public biotechnology companies reported sustained R&D spending throughout the study period and contributed to the late-stage development of 144 new products, including 78 New Molecular Entities (NMEs) and 34 first-in-class drugs, despite also reporting little revenue and consistently negative earnings. Nevertheless, these companies achieved growth of market capitalization and shareholder value similar to that of a matched set of non-biotechnology companies with concurrent IPO dates.

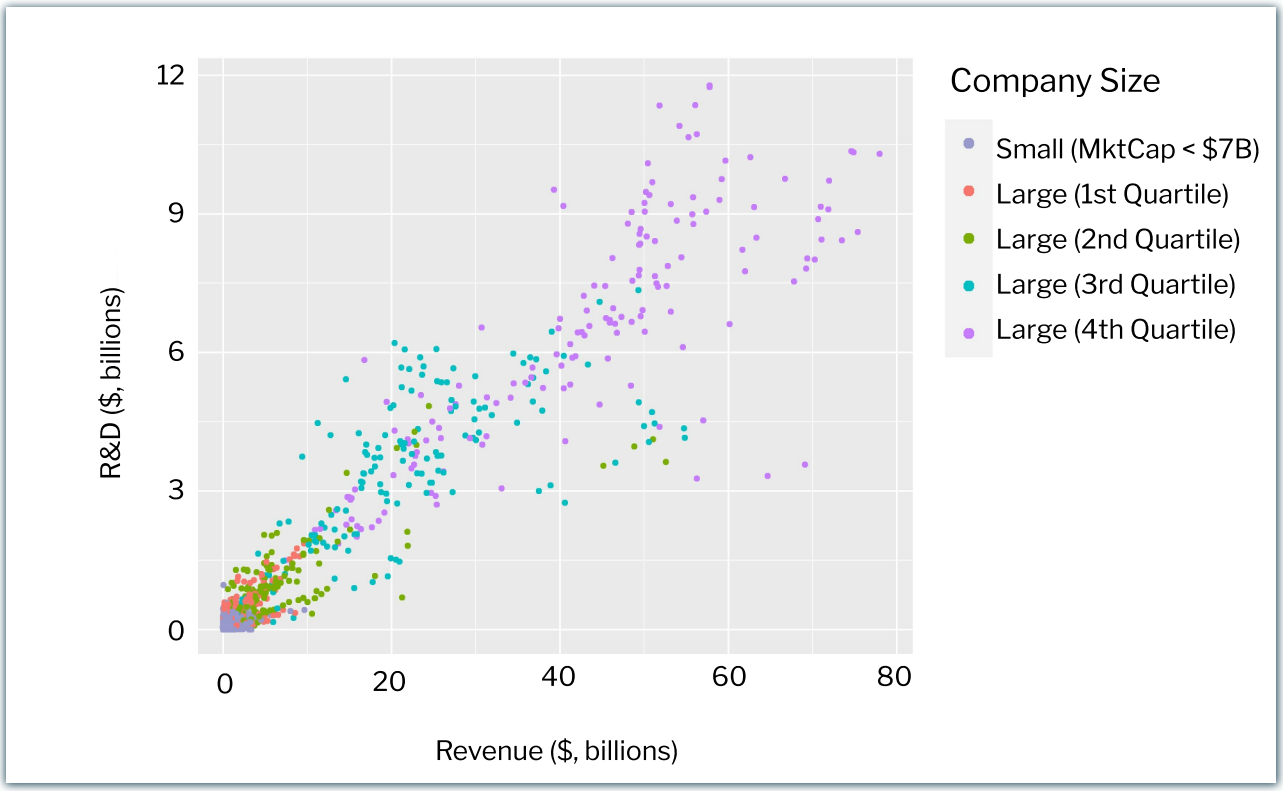
The strategic role of R&D spending in small biotechnology companies is often different than in larger companies. Many early and emerging biopharmaceutical companies have a science-based business model, where the return on investment is predicated on increasing the value of its intellectual property and a variety of potential applications, rather than the projected returns from a specific product with a delimited market.[11] Moreover, many companies are founded explicitly to advance a specific technology or cure for a particular disease entity, and allocate their R&D spending to maximize these opportunities. Thus, the relationship between revenue and R&D spending may not be the same in emerging, small public biotechnology companies as in large, established pharmaceutical companies.

Relationship between revenue and R&D for companies of different size

This analysis considered the relationship between revenue and R&D expense for all publicly traded biopharmaceutical companies for the years 2000-2018.[12] The dataset comprises 1379 companies and 10,035 fiscal years of reported financial data (see Attachments). When considering the entire dataset, there was a strong association between annual revenue and R&D expense (Figure 1).

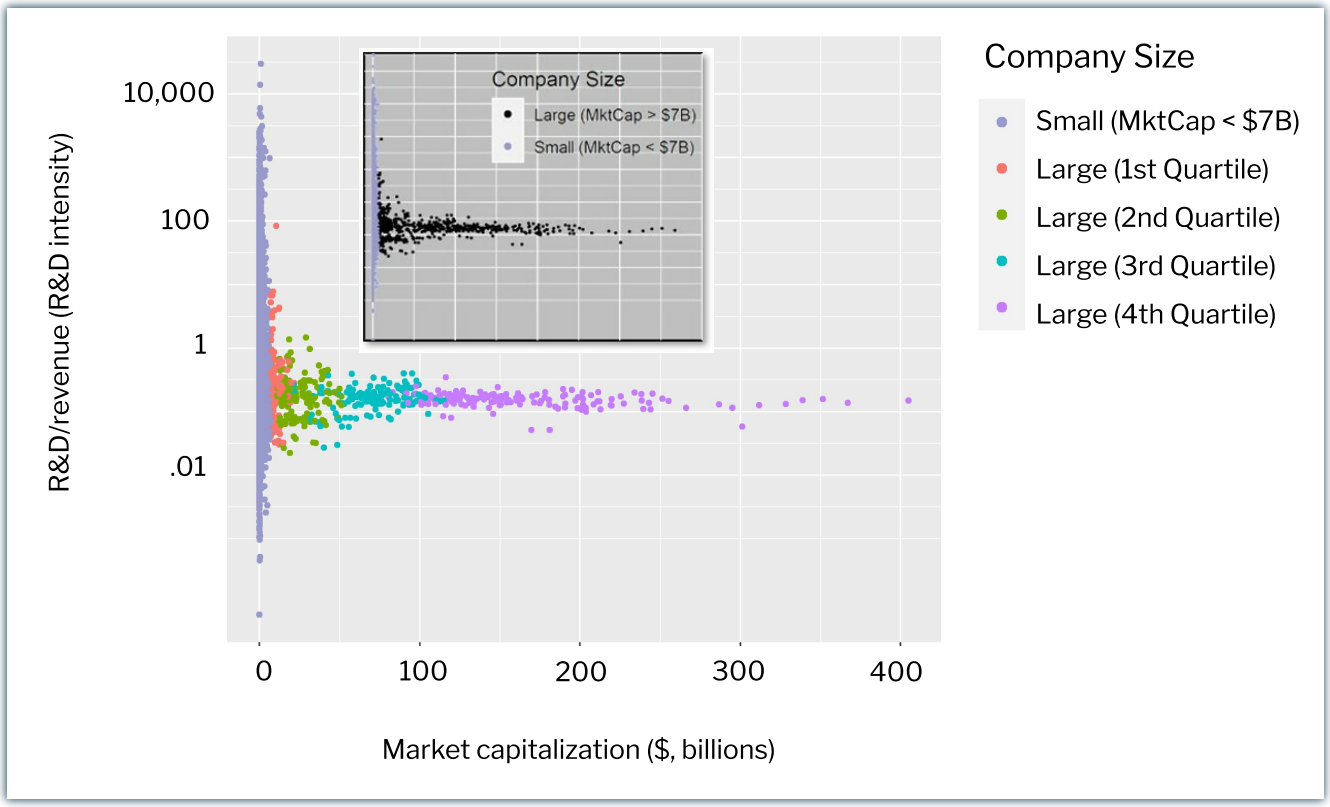
Examining the relationship between revenue and R&D in more detail, we considered the relationship between revenue and R&D separately for large pharmaceutical companies, defined as having a market capitalization >$7 billion, and small biopharmaceutical companies, defined as having a market capitalization <$7 billion. For large companies, the fraction of revenue expensed as R&D, often referred to as "R&D intensity," was found to be relatively constant (Figure 2), with a median value of 16.6% (IQR 12.9%-21.6%).[13] Further segmenting large companies into quartiles by their market capitalization, the fraction of revenue expensed as R&D is most consistent for the largest companies (2nd, 3rd, 4th quartiles) (Figure 2). In contrast, the fraction of revenue expensed as R&D varies widely for smaller companies with a market capitalization <$7 billion.

Figure 1:



Relationship between annual revenue and R&D expense for 1,379 public biopharmaceutical companies 2010-2018. Company size is indicated for companies with market capitalization <$7 billion ("small companies") and companies with market capitalization >$7 billion ("large companies") separated by quartile from larger (4th quartile) to smaller (1st quartile.) Each point represents one fiscal year of data for one company.

Figure 2:



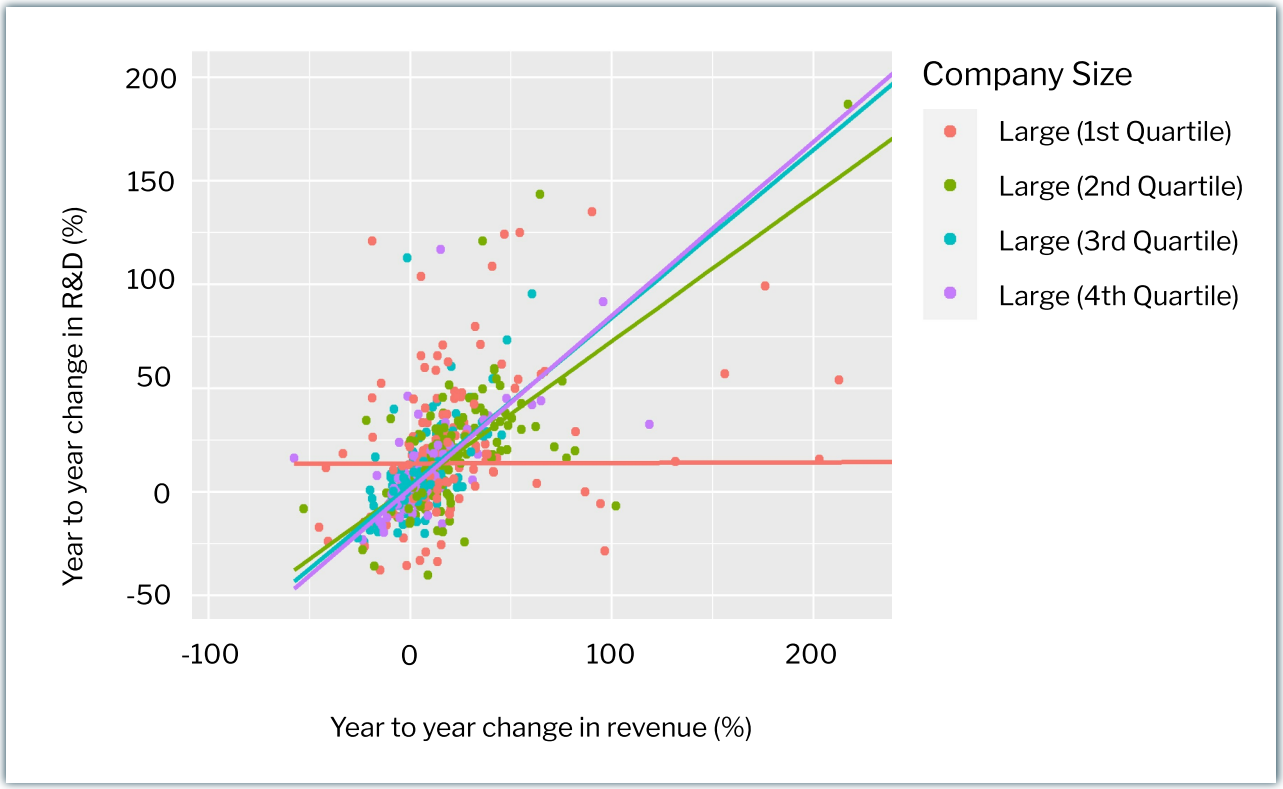
Relationship between market capitalization and the fraction of revenue expensed as R&D (R&D intensity) for 1,379 public biopharmaceutical companies 2010-2018. Each point represents one fiscal year of data for one company. INSERT shows the distinctly different pattern for large companies (market capitalization >$7 billion) and small companies (market capitalization <$7 billion). The larger figure separates large companies by quartile with the largest companies represented in quartile 4.

The relationship between year-to-year changes in revenue and changes in R&D for large pharmaceutical companies is shown in Figure 3. There was significant positive association between changes in revenue and changes in R&D for large companies (Figure 2, INSERT). This association was significant for companies in the three largest quartiles (2nd, 3rd, 4th quartiles), but not for companies in the lowest quartile (1st quartile) (Figure 2). The slope of the trendlines reflects the change in R&D expense associated with change in revenue for large companies in the 2nd, 3rd, or 4th quartiles. Specifically, for these companies, reductions of revenue up to 10% were associated with reduction in R&D spending up to 8%.

There was also no significant association between changes in revenue and changes in R&D for smaller companies with market capitalization <$7 billion (not shown). No change in R&D would be expected for reductions in revenue of up to 10% in small companies with market capitalization <$7 billion.

This analysis is consistent with previous studies that described an association between revenue and R&D spending in large pharmaceutical companies. Extending this analysis to all publicly traded biopharmaceutical companies however, further demonstrated that there is no evidence for an association between revenue and R&D spending for companies with market capitalization <$7 billion.

Figure 3:



Relationship between year-to-year changes in revenue and year to year changes in R&D for companies with market capitalization >$7 billion 2010-2018. Each point represents one fiscal year of data for one company.

Unlike large pharmaceutical companies, which are responsible for marketing the large majority of pharmaceutical products and therefore generate the majority of pharmaceutical revenue, smaller biopharmaceutical companies are largely dependent on equity investments by public and private investors[14], as well as partnerships with large pharmaceutical companies, for operating capital.

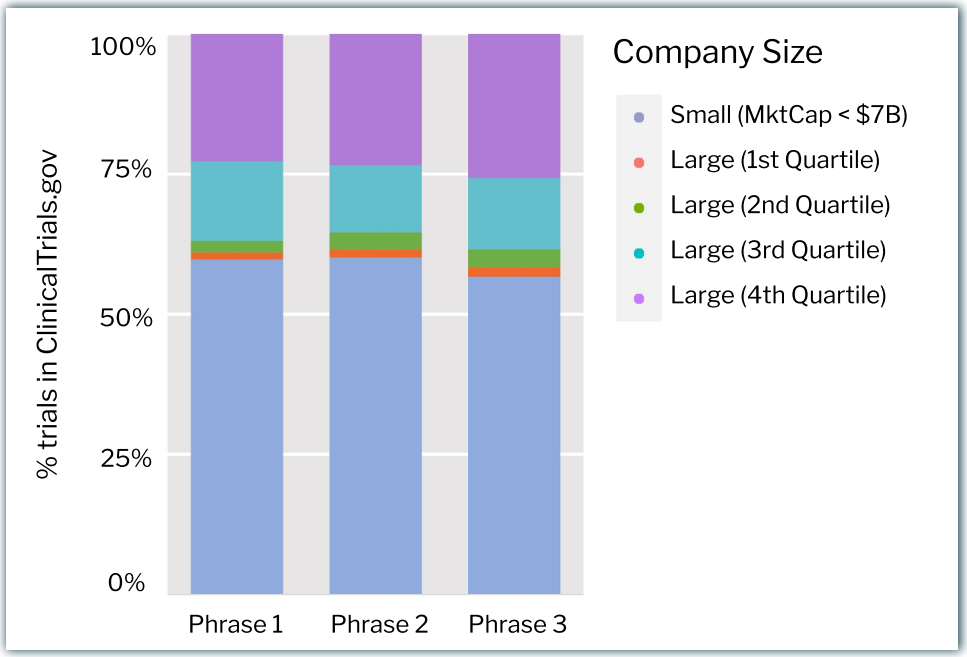
There is no evidence for an association between revenue and R&D expense for biopharmaceutical companies with market capitalization <$7 billion (2010-2018).

To assess the relationship between R&D spending and the capital available to small companies in a given fiscal year, we examined the relationship between R&D expense and the sum of cash and short-term investments at the beginning of the fiscal year, revenue, and sale of common and preferred stock.[15] When considering only companies with market capitalization <$7 billion, we observed no significant association between R&D expense and this estimate of available capital. While additional studies of the relationship between the availability of capital and R&D spending in smaller companies is warranted, this analysis does not support the assumption that R&D spending in these companies would be decreased in response to a reduction in drug prices.

Contributions of large and small companies to development

To assess the differential contribution of large and small biopharmaceutical companies to the drug development pipeline, we examined clinical trials listed in ClinicalTrials.gov.[16] We identified phase 1, phase 2, and phase 3 clinical trials initiated from 2010-2019 with at least one corporate sponsor. Clinical trials sponsored by companies with market capitalization >$7 billion at any time during the study period were considered to have been sponsored by "large companies" and were categorized by the highest quartile achieved by that company.

Figure 4:



Fraction of clinical trials sponsored by companies with market capitalization <$7 billion (small companies) or companies with market capitalization >$7 billion (large companies) separated by quartile. Data from ClinicalTrial.gov.

Other corporate clinical trials were categorized as small companies. Small companies include public companies with market capitalization <$7 billion throughout the study period as well as companies not identified by GICS codes or included in Compustat. For clinical trials with multiple sponsors, trials were categorized by the category of the largest sponsor. The results are illustrated in Figure 4.

Companies with market capitalization <$7 billion sponsor the majority (~60%) of phase 1, phase 2, and phase 3 clinical trials of new pharmaceuticals.

This analysis suggests that approximately 60% of phase 1, phase 2, and phase 3 clinical trials from 2010-2019 were sponsored by small biopharmaceutical companies with market capitalizations <$7 billion. These data are consistent with the observation by IQVIA that small companies, defined as having revenue <$500M, account for 70% of products in phase 3 trials.[17]

Modeling the impact of revenue reductions on new drug approvals

Assuming revenue-related reduction in R&D spending will impact investment in phased clinical trials, the progression of candidate therapeutics is modeled through the development pipeline. The model assumes that companies of different size will reduce R&D spending by different amounts and that cost reduction are achieved by selective allocation of resources to the three phases of clinical development. The model incorporates published data regarding the per drug costs of each clinical phase as well as the phase transition success rate.[18] The model incorporates changes in R&D spending proportional to reduction in revenue for companies of different size and the fraction of clinical trials performed by small companies as shown:

Company size	Change in R&D [a,19]	Percentage of trials by small companies		
		Phase 1	Phase 2	Phase 3
Small[b]	n/a[d]	59.8%	60.1	56.7
Large[c]				
Q1	0.3%	1.2%	1.5%	1.7%
Q2	0.86%	2.1%	3.0%	3.2%
Q3	1.06%	14.2%	12.0%	12.7%
Q4	0.95%	22.7%	23.4%	25.7%

[a] % change in R&D for each 1% reduction in revenue; [b] Small companies have market capitalization <$7 billion; [c] Large companies have market capitalization >$7 billion and are separated by quartile; [d] No change in R&D expense is anticipated for companies with market capitalization <$7 billion.

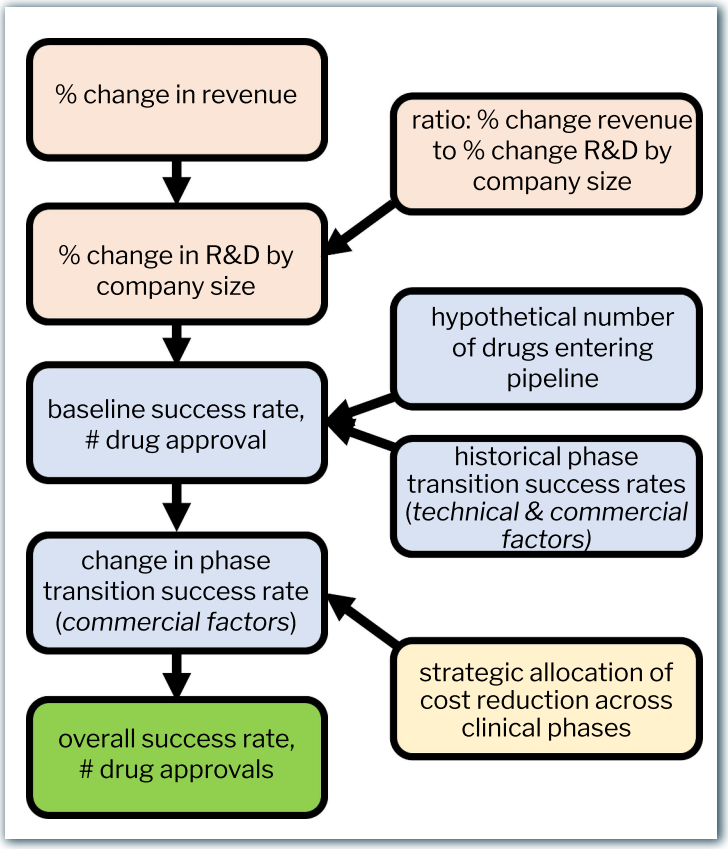
A schematic of the model is shown in Figure 5. The model estimates the steady state level of drug approvals for a hypothetical number of candidate products entering clinical development. The model enables consideration of scenarios that embody different levels of revenue reduction and differential allocation of cost savings between phase 1, phase 2, and phase 3 clinical trials.

Several aspects of this model should be emphasized. First, the model assumes that all companies are subject to a 10% decrease in revenue, regardless of size. Second, the model assumes no change in the number of new products proceeding through clinical trials sponsored by small companies. Third, reported transitional success rates between phases commonly conflatetechnical failures related to safety or efficacy, with “commercial failures” that result in discontinuation of a candidate product due to economic considerations, corporate strategy, product prioritization, or inadequate funding. The commercial failure rate for products in development is estimated to be as high as 20-30%.[20] The model assumes that the cost savings required to reduce R&D spending will be realized by reducing the number of drugs transitioning to the next phase of clinical development, effectively increasing the commercial failure rate from that phase. Cost reductions may also decrease the commercial failure rate (and increase the success rate in a specific phase) by reducing the number of products available to

enter that phase relative to the decrease in spending.

Figure 6 shows the drug approvals for a baseline case and three scenarios where pharmaceutical revenue is decreased by 10%. The baseline case assumes that 400 candidate compounds enter phase 1 trials in a typical year. Based on reported success rates, 47 of the 400 candidate compounds would be approved.[21] The 10% reduction in global pharmaceutical revenue modeled in this scenario represents approximately a 21% reduction in prices for branded pharmaceuticals in the US market. This estimate is based on branded pharmaceuticals representing 88% of US drug spending and US drug sales representing 48% of global sales.[22]

Figure 5:



Schematic of pharmaceutical pipeline model.

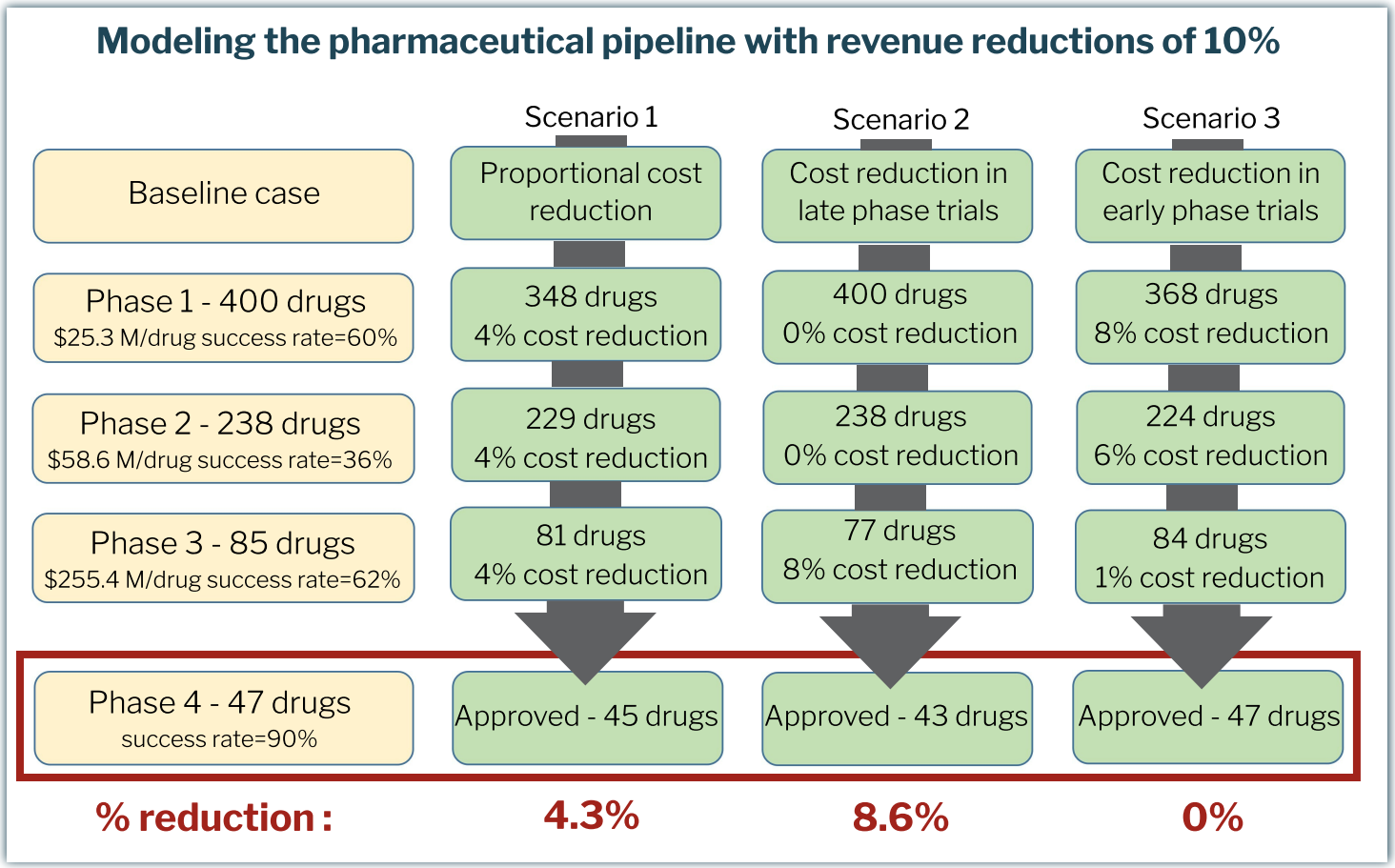
Three scenarios are shown, each of which are predicated on a 10% decrease in revenue from the baseline.

- Proportional Cut: This scenario assumes the number of products entering phase 1, phase 2, and phase 3 are each reduced in proportion to the reduction in R&D expense for companies of different size. This results in a reduction in approvals from 47 to 45 (4.3% reduction).

- Cost reduction in late phase trials: This scenario assumes that the number of products entering phase 1 or phase 2 is unchanged, but the number entering phase 3 was reduced to achieve the full reduction of R&D expense for companies of different size. This results in a worst-case scenario with 43 drug approvals (8.6% reduction).

- Cost reduction in early phase trials: This scenario assumes that 90% of the cost reduction is achieved through a proportional reduction in phase 1 or phase 2 trials. While the number of products entering phase 3 decreases, the retained spending for phase 3 is sufficient to reduce the commercial failure rate, and the number of approved products is unchanged from the baseline case (no reduction).

Figure 6:



Three scenarios for reducing R&D expense in response to a 10% decrease in pharmaceutical revenue. The model assumes different levels of cost reduction by companies of different size and that cost reductions will be achieved by reduction of spending on phased clinical trials. The three scenarios posit differential allocation of cost reductions between phase 1, phase 2, or phase 3 trials.

These three scenarios demonstrate the ability of large pharmaceutical companies to mitigate any impact of drug price reductions on their product development pipelines through strategic allocation of cost reductions to different phases of clinical development. The three scenarios shown achieve equivalent reductions in R&D spending, but result in reductions in the number of new drug approvals by 4.3%, 8.6%, and 0% respectively. It should be emphasized that this model does not posit any changes in the process of pharmaceutical development or regulatory review, but simply agile resource and asset management.

Our model shows that large companies may mitigate any negative impact of drug price reductions on pharmaceutical innovation through agile management and strategic allocation of cost reductions.

Conclusions

This analysis suggests that any negative impact of drug price reductions on the pipeline of pharmaceutical innovation may be mitigated through strategic allocation of spending reductions in large pharmaceutical companies. Policy makers do not need to make a false choice between reducing prices to ensure the affordability of pharmaceutical products currently on the market and the innovation required to bring new products to market in the future.

Policy makers do not need to make a false choice between reducing prices to ensure the availability of pharmaceutical products currently on the market and the innovation required to bring new products to market in the future.

This analysis differs substantively from previous analyses of the potential effects of reducing drug prices on the pipeline of pharmaceutical innovation.

- First, this analysis considers all public biotechnology and pharmaceutical companies identified by GICS codes listed in Compustat. Previous studies have focused primarily on limited sets of large pharmaceutical companies and have often failed to address the contributions of the much larger number of small, early-stage or emerging biopharmaceutical companies.

- Second, while a small number of large, fully integrated pharmaceutical companies are responsible for the manufacture and marketing of the great majority of products on the market, small companies conduct the majority of all clinical trials and are increasingly responsible for launching new products. This analysis shows that approximately 60% of all corporate-sponsored clinical trials are sponsored by "small" companies with a market capitalization <$7 billion. This observation is consistent with the data from IQVIA showing that that up to 70% of phase 3 trials and 40% of all product launches over the past five years involved small biopharmaceutical companies (<$500M revenue and <$200 R&D).[23]

- Third, this analysis recognizes that the finances of large pharmaceutical companies with robust revenue and earnings are very different than those of smaller biopharmaceutical companies, which consistently report limited revenue and negative earnings. This analysis suggests these two sets of companies are likely to have different strategic responses to decreasing revenue. While there is a consistent historical association between revenue and R&D for the largest pharmaceutical companies, no such association was evident for smaller companies.

These observations are not unexpected. The valuation of large, financialized pharmaceutical companies is critically dependent on metrics such as earnings per share (EPS). Decreasing R&D expense in response to reductions in revenue is an efficient strategy for sustaining the level of earnings and limiting negative impacts on corporate valuations. Moreover, large companies are increasingly focused on the manufacture and marketing of products acquired through licensing, merger, or acquisition, rather than those developed through internal R&D.[24] McKinsey has estimated that from 2001 to 2016, the fraction of large pharma revenue coming from acquisitions, rather than internal R&D, grew from 25 to 50 percent, and a recent analysis of 14 large pharmaceutical companies showed that only 40% of their new drug launches originated from internal R&D. Given this increasing focus on product acquisition, analysts expectations for future revenue may not be significantly impacted by decreasing R&D in response to reductions in drug prices and revenue.

In contrast, smaller pharmaceutical companies often have science-based business models that focus on advancing and validating platform technologies or innovative therapeutics, which are later acquired by larger companies through licensing agreements or corporate acquisition. Since these companies typically have little revenue and negative earnings, current earnings are largely irrelevant to company valuations, which are based largely on analysts' expectations for future revenue and earnings. Thus, small companies are likely to prioritize R&D spending in response to decreases in revenue. While small companies are often dependent on the availability of capital investments, we are not aware of empirical evidence that reductions in drug prices would adversely impact investments in early-stage or emerging biotechnology companies.[14] In fact, the increasing reliance of large pharmaceutical companies on early and emerging biotechnology companies for innovation is already a major driver of innovation and valuation in the biotechnology sector. These forces may become even more pronounced if large pharmaceutical companies reduce their R&D spending and turn increasingly to merger and acquisition.[25]

• Finally, previous analyses have failed to consider the ability of the pharmaceutical industry to strategically respond to reduction in R&D spending to preserve the pipeline of pharmaceutical innovation. Decades of management reform in the pharmaceutical industry has focused on implementing "agile" management systems that provide companies with substantial flexibility to respond to changing circumstances and opportunities, mitigating risks, and optimizing asset utilization.[26] Agile management practices are evident in the longstanding trend towards outsourcing clinical development and the progressive elimination of operational constraints embodied in traditional facilities, governance, communications, supply chains, and employment practices. The strategic reallocation of resources to different phases of clinical development would be a classic application of agile management practice.

This analysis shows that price reductions anticipated from the proposed legislation, if properly managed, could have minimal impact on pharmaceutical innovation and the emergence of new products for prevention, treatment, and regeneration. We would emphasize that this conclusion is based squarely on current best practices in the biopharmaceutical industry, the observed relationship between revenue and R&D spending over the past two decades, and the contributions currently being made to pharmaceutical innovation by companies of different size.

Best practices of biopharmaceutical finance and management are sufficiently robust to provide patients with relief from drug prices that make essential medicines unaffordable without inhibiting development of innovative new products for prevention, treatment, and regeneration.

This model is not aspirational; it does not presume changes in the process, financing, or regulation of pharmaceutical innovation, it does not postulate that advances in information technology or research practices will improve R&D efficiency, and it does not require changes to the business models of pharmaceutical companies or a reprioritization of patients and social responsibility over shareholders and profit. Rather, this analysis suggests that best practices of biopharmaceutical finance and management are sufficiently robust to provide patients with relief from drug prices that make essential medicines unaffordable without inhibiting development of innovative new products for prevention, treatment, and regeneration.

Acknowledgments

This work was funded by the West Health Policy Center and performed at the Center for Integration of Science and Industry at Bentley University. The Center for Integration of Science and Industry also receives research support from the National Biomedical Research Foundation, Institute for New Economic Thinking, and the National Pharmaceutical Council.

The authors thank Sean Dickson, West Health Policy Center, for his ongoing consultation and contributions to this project as well as the contributions made by Roger Du, Dr. Franklin Bright, Dr. Sarah McCoy, Kevin Zhang, and Juliana Harrison. The authors also thank Dr. Michael Boss and Dr. Nancy Hsiung for their critical perspectives.

Attachments

Attachment 1. Financial totals for large and small pharmaceutical companies 2000-2018

	ALL	Large Companies[a]	Small Companies[b]
# fiscal years (N)	10,035	618[c]	9,417[d]
# companies (N)	1,379	78[c]	1,301
		($, billions 2000 - 2018)	
Revenue	$12,066	$11,385	$681
Sale of Common and Preferred Stock	$503	$212	$290
Costs of Goods Sold	$3,140	$2,703	$436
R&D	$2,019	$1,737	$281
Gross Profit	$8,926	$8,681	$244
EBITDA (Loss)	$3,577	$3,672	-$94
Net Income (Loss)	$1,596	$1,858	-$262
Income Taxes	$549	$540	$8.87
Dividends	$979	$964	$14.5
Purchase of Common and Preferred Stock	$793	$773	$19.3

[a] Large companies are defined as having a market capitalization >$7 billion in a fiscal year; [b] Small companies are defined as having a market capitalization <$7 billion in a fiscal year; [c] Number of fiscal years with market capitalization >$ 7 billion; [d] Number of fiscal years with market capitalization <$7 billion; [e] Number of companies with at least one fiscal year with market capitalization >$7 billion. Totals are shown for the years 2000-2018. All data are from Compustat and are inflation adjusted to 2018.

Attachment 2. Median and Interquartile range of financial metrics for large and small biopharmaceutical companies.

	Small Companies[a] Median (IQR) ($ millions)	Large Companies[a] Median (IQR) ($ millions)
market capitalization[c]	111.2 (27.7 to 390.7)	40,399 (13,669 to 101,033)
revenue	3.1 (0.0 to 27.5)	9,550 (2,913 to 28,578)
sale of common and preferred stock	5.4 (0.3 to 29.8)	106.2 (25.2 to 347.5)
R&D[d]	12.5 (2.5 to 34.7)	1,513.4 (447.6 to 4,521.8)
gross profit	0 (-16.6 to 4.3)	7,233.6 (1,888 to 22,454)
EDITDA	-12.1 (-32.5 to 2.1)	3,023 (796.5 to 9,117)
net income	-14.4 (-37.8 to -2.8)	1,150 (258.2 to 4,713)
research intensity[e]	2.8 (0.4 to 121.3)	0.17 (0.13 to 0.22)
net income margin[f]	-5.1 (-562.2 to -0.5)	0.15 (0.06 to 0.21)

[a] Small companies are defined as having a market capitalization <$7 billion in a fiscal year; [b] Large companies are defined as having a market capitalization >$7 billion in a fiscal year; [c] Calculated from stock price and common shares outstanding; [d] Calculated without in-process R&D; [e] Calculated as R&D/revenue; [f] Calculated as net income/revenue. All data are from Compustat and are inflation adjusted to 2018.

Endnotes

[1] Rep. Pallone, F., 2021. Elijah E. Cummings Lower Drug Costs Now Act (H.R.3); Sen. Grassley, C., 2019. Prescription Drug Pricing Reduction Act (S.2543); Sen. Sanders, B. & Rep. Khanna, R., 2021. Prescription Drug Price Relief Act (S.909/H.R.2148); Sen. Sanders, B. & Rep. Doggett, L., 2021. Medicare Drug Price Negotiation Act (S.908/H.R.2139); Sen. Sanders, B., 2021. Affordable and Safe Prescription Drug Importation Act (S.920).

[2] These data were first described in: Congressional Budget Office. Letter to Honorable Frank Pallone Jr. Chairman Committee on Energy and Commerce U.S. House of Representatives Re: Effects of Drug Price Negotiation Stemming From Title 1 of H.R. 3, the Lower Drug Costs Now Act of 2019, on Spending and Revenues Related to Part D of Medicare, October 11, 2019. https://www.cbo.gov/system/files/2019-10/hr3ltr.pdf. That letter states that the CBO's "...preliminary estimate is that a reduction in revenues of $0.5 trillion to $1 trillion would lead to a reduction of approximately 8 to 15 new drugs coming to market over the next 10 years."; The Congressional Budget Office model has been described in: Adams, C. & Herrnstadt, E., 2021. CBO's Model of Drug Price Negotiations Under the Elijah E. Cummings Lower Drug Costs Now Act: Working Paper 2021-01 (No. 56905). *CBO*. https://www.cbo.gov/system/files/2021-02/56905-Drug-Price-Negotiations.pdf; These data were quoted in: Austin, D. & Hayford, T., 2021. Research and Development in the Pharmaceutical Industry. *CBO*. https://www.cbo.gov/system/files/2021-04/57025-Rx-RnD.pdf.

[3] Abbott, T.A. & Vernon, J.A., 2007. The cost of US pharmaceutical price regulation: a financial simulation model of R&D decisions. *Managerial and Decision Economics*, 28(4-5), pp.293-306. https://www.nber.org/papers/w11114; Giaccotto, C., Santerre, R.E. & Vernon, J.A., 2005. Drug prices and research and development investment behavior in the pharmaceutical industry. *The Journal of Law and Economics*, 48(1), pp.195-214. https://www.journals.uchicago.edu/doi/abs/10.1086/426882; Golec, J., Hegde, S. & Vernon, J. A., 2010. Pharmaceutical R&D spending and threats of price regulation. *Journal of Financial and Quantitative Analysis*, 45(1), pp.239-264. https://www.cambridge.org/core/journals/journal-of-financial-and-quantitative-analysis/article/pharmaceutical-rd-spending-and-threats-of-price-regulation/1ADD6875F2AA693D267052C2AE0AA6AF; Vernon, J.A., 2005. Examining the link between price regulation and pharmaceutical R&D investment. *Health economics*, 14(1), pp.1-16. https://onlinelibrary.wiley.com/doi/abs/10.1002/hec.897.

[4] Acemoglu, D. and Linn, J., 2004. Market size in innovation: theory and evidence from the pharmaceutical industry. *The Quarterly journal of economics*, 119(3), pp.1049-1090. https://academic.oup.com/qje/article-abstract/119/3/1049/1938820

[5] Blume-Kohout, M.E. & Sood, N., 2013. Market size and innovation: Effects of Medicare Part D on pharmaceutical research and development. *Journal of public economics*, 97, pp.327-336. https://www.sciencedirect.com/science/article/abs/pii/S0047272712001119; Dranove, D., Garthwaite, C. & Hermosilla, M., 2014. Pharmaceutical profits and the social value of innovation (No. w20212). *National Bureau of Economic Research*. https://www.nber.org/papers/w20212.

[6] Adams & Herrnstadt, 2021 op. *cit*.; For analysis of the financialization of the biopharmaceutical industry see Lazonick, W., Tulum, Ö., Hopkins, M., Sakinç, M.E. & Jacobson, K., 2019. Financialization of the US Pharmaceutical Industry. *Institute for New Economic Thinking*. https://www.ineteconomics.org/uploads/papers/Lazonick-financialization-of-the-US-pharmaceutical-industry-20191202_1-final.pdf.

[7] Dickson, S. & Ballreich, J., 2019. How Much Can Pharma Lose? A Comparison of Returns Between Pharmaceutical and Other Industries. *West Health Policy Center.* https://www.westhealth.org/wp-content/uploads/2019/11/WHPC_White-Paper_How-Much-Can-Pharma-Lose_FINAL-November-2019.pdf.

[8] Ledley, F.D., McCoy, S.S., Vaughan, G. & Cleary, E.G., 2020. Profitability of large pharmaceutical companies compared with other large public companies. *Jama*, 323(9), pp.834-843. https://jamanetwork.com/journals/jama/article-abstract/2762308.

[9] Aitken, M. & Kleinrock, M., 2021. Global trends in R&D: overview through 2020. *IQVIA Institute*. https://www.iqvia.com/insights/the-iqvia-institute/reports/global-trends-in-r-and-d.

[10] Cleary, E.G., McNamee, L.M., de Boer, S., Holden, J., Fitzgerald, L. & Ledley, F.D., 2021. Comparing long-term value creation after biotech and non-biotech IPOs, 1997–2016. Plos one, 16(1), p.e0243813. https://journals.plos.org/plosone/article/peerReview?id=10.1371/journal.pone.0243813; McNamee, L.M., Cleary, E.G., Zhang, S., Salim, U. & Ledley, F.D., 2021. Late-stage Product Development and Approvals by Biotechnology Companies After Initial Public Offering, 1997–2016. *Clinical Therapeutics*, 43(1), pp.156-171. https://www.sciencedirect.com/science/article/pii/S0149291820305221.

[11] Pisano, G., 2006. Profiting from innovation and the intellectual property revolution. Research policy, 35(8), pp.1122-1130. https://www.sciencedirect.com/science/article/abs/pii/S0048733306001442; Pisano, G.P., 2006. Science business: The promise, the reality, and the future of biotech. Boston: *Harvard Business Press*. https://www.hbs.edu/faculty/Pages/item.aspx?num=21487; Pisano, G.P., 2006. Can science be a business? Lessons from biotech. *Harvard business review*, (84)10, pp.1-12. https://pubmed.ncbi.nlm.nih.gov/17040044/; Lazonick, W. & Tulum, Ö., 2011. US biopharmaceutical finance and the sustainability of the biotech business model. Research Policy, 40(9), pp.1170-1187. https://www.sciencedirect.com/science/article/pii/S0048733311001028.

[12] Audited financial data were obtained from the Compustat database accessed through Wharton Research Data Services (https://wrds-www.wharton.upenn.edu/). Financial data was adjusted for inflation to 2016. The dataset included data for 1,282 companies identified by GICS codes 35202010 (pharmaceuticals) or 35201010 (biotechnology) from 2010-2018. This included 9453 fiscal years for companies with market capitalization <$7 billion and 618 fiscal years for companies with market capitalization >$7 billion. Over this period, 79 companies reported a market capitalization >$7 billion in at least one fiscal year and are represented in quartiles 1-4. Compustat data included: CSHO, Common Shares Outstanding; PRCC_F, Price Close - Annual - Fiscal; REVT, Revenue - Total; XRD, Research and Development Expense; RDIP, In Process R&D Expense; GP, Gross Profit (Loss); EBITDA, Earnings Before Interest Taxes Depreciation Amortization; NI, Net Income (Loss); CHE, Cash and Short-Term Investments; SSTK, Sale of Common and Preferred Stock. Market capitalization was calculated as CSHO x PRCC_F. R&D was calculated as XRD+RDIP. (Note: In-process R&D is included with reported research and development expense in Compustat and reported as a negative number.) Accounting terms and calculations are defined in Ledley et al. JAMA *op. cit*.

[13] Due to the non-normal character of the dataset, this analysis focuses on median values. Calculation of average (mean) values give spurious results and is biased by a non-normal distribution of the dataset and small number of extremely large values. IQR is the “inter-quartile range” representing half of the companies in the dataset (2nd and 3rd quartiles).

[14] Industry analysts have expressed concern that reducing drug prices would decrease private and public investments in early stage and emerging biopharmaceutical companies, who are often dependent on such investments for operating capital. See, for example, Booth, B. 2019. Venturing A Perspective On The Drug Pricing Debate. *Forbes*. https://www.forbes.com/sites/brucebooth/2019/12/10/venturing-a-perspective-on-the-drug-pricing-debate/. Analysts argue the reducing revenue expectations would reduce the estimated ROI for investments in early stage and emerging biotechnology companies and make investments in the biotechnology sector less attractive to investors. We are not, however, aware of any empirical evidence for such an association. In fact, periods when pharmaceutical prices have been subject to the greatest pressure have been some of the best years for investment in biotechnology. The years 1993-1994, when the Clinton Health Plan was under consideration by Congress and large pharmaceutical companies reduced R&D spending (see works by Vernon3) has been described as "*one of the best IPO windows in history*" (Booth, B., 2012. Biotech Past, Biotech Present: Reflections on the IPO Window of 1991-1994. *Forbes*. https://www.forbes.com/sites/brucebooth/2012/05/02/biotech-past-biotech-present-reflections-on-the-ipo-window-of-1991-1994/). Similarly, despite the slowing growth of pharmaceutical sales over the past decade (prior to COVID-19) (Aitken, M., Kleinrock, M., Simorellis, A. & Nass, D., 2019. The Global Use of Medicine in 2019 and Outlook to 2023: Forecasts and Areas to Watch. *IQVIA Institute*. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023.pdf) and numerous policy initiatives aimed at lowering drug prices, the last seven years have seen record investment activity and valuations for both early-stage, private biotechnology companies and emerging public companies.

[15] This calculation is complicated by the fact that capital investments may fund R&D over multiple years and that partnerships with large pharmaceutical companies may include up-front payments or license fees or milestone payments that are not necessarily recognized in the year received. Further analysis of the relationship between available capital and R&D spending would require more detailed analysis of cash flows.

[16] ClinicalTrials.gov. National Library of Medicine. https://clinicaltrials.gov/ct2/home. Accessed March 2021. Registration of both federally and privately funded clinical trials with clinicaltrials.gov is mandated by the Food and Drug Administration Modernization Act of 1997 (FDAMA) and by section 801 of the FDA Amendments Act of 2007 (FDAAA). Most data in clinicaltrials.gov is from 2008-present.

[17] Aitken, M., Kleinrock, M., Nass, D. & Simorellis, A., 2019. The Changing Landscape of Research and Development: Innovation, Drivers of Change, and Evolution of Clinical Trial Productivity. *IQVIA Institute*. https://www.iqvia.com/insights/the-iqvia-institute/reports/the-changing-landscape-of-research-and-development; *Quoted* in Austin & Hayford, 2021 *op. cit*.

[18] DiMasi, J.A., Grabowski, H.G. & Hansen, R.W., 2016. Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, 47, pp.20-33. https://www.sciencedirect.com/science/article/abs/pii/S0167629616000291; Wouters, O.J., McKee, M. & Luyten, J., 2020. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *Jama*, 323(9), pp.844-853. https://jamanetwork.com/journals/jama/article-abstract/2762311.

[19] The estimated % change in R&D expense is associated with 10% change in revenue based on upper bound estimates of a two-sided 95% bootstrap confidence interval with 10,000 bootstrap samples for coefficients of median regression model. Expected change for small companies is set to 0% based on lack of evidence of an association between revenue and R&D expense.

[20] DiMasi, J.A., 2001. Risks in new drug development: approval success rates for investigational drugs. *Clinical Pharmacology & Therapeutics*, 69(5), pp.297-307. https://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.625.4061&rep=rep1&type=pdf; Harrison, R.K., 2016. Phase II and phase III failures: 2013–2015. Nat Rev Drug Discov, 15(12), pp.817-818. https://www.nature.com/articles/nrd.2016.184.

[21] We note that the model embodies highly conservative assumptions that would tend to be biased towards greater reductions in the number of drug approvals. Specifically, (i) the model uses upper bound values for the likely reduction in R&D expense for each quartile of large companies; (ii) clinical trials involving multiple companies are assigned to the largest company, which exhibit the greatest reduction in R&D expense; (iii) this model assumes that reductions in R&D will be achieved exclusively by decreasing the number of compounds in clinical trials and does not contemplate innovations that might increase the efficiency of pharmaceutical R&D; (iv) the result shown reflects the steady stage level of productivity that would not be achieved for 6-10 years after implementation of price reductions. Any reduction in the number of annual drug approvals would occur gradually, and the real deficit in new drugs over this interval would be less pronounced than estimated at steady state.

[22] Mulcahy, A.W., 2021. Prescription Drug Prices in the United States Are 2.56 Times Those in Other Countries. *RAND Corporation*. https://www.rand.org/news/press/2021/01/28.html; Mikulic, M., 2021. Global pharmaceutical sales from 2017 to 2020, by region. *Statista*. https://www-statista-com.ezp.bentley.edu/statistics/272181/world-pharmaceutical-sales-by-region/.

[23] Aitken & Kleinrock, 2021 *op .cit.*

[24] Bansal, R., De Backer, R. & Ranade, V., 2018. What's Behind the Pharmaceutical Sector's M&A Push? *McKinsey & Company*, https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/whats-behind-the-pharmaceutical-sectors-m-and-a-push; Schuhmacher, A., Wilisch, L., Kuss, M., Kandelbauer, A., Hinder, M. & Gassmann, O., 2021. R&D efficiency of leading pharmaceutical companies—a 20-year analysis. *Drug discovery today*. https://www.sciencedirect.com/science/article/abs/pii/S1359644621002361.

[25] The availability of capital investments is highly dependent on changing conditions in capital markets and is historically cyclic. A recent analysis by McKinsey & Company pointed out that "With the top dozen pharma companies having more than $170 billion in excess reserves that could be available for spending on M&A, the prospects for further financing and deal making look promising." McKinsey & Company 2021. What's ahead for biotech: Another wave or low tide? https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/whats-ahead-for-biotech-another-wave-or-low-tide

[26] Apple, A., Harriet, K., Moss, R. & Sartori, V., 2019. Designing an agile transformation in pharma R&D. McKinsey & Company. https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/designing-an-agile-transformation-in-pharma-r-and-d. The report describes: "*In broad terms, an agile organization is one that combines a stable backbone of core processes and capabilities with a high degree of flexibility for rapid response to change.*"

Limitations: There are important limitations to this work. First, this analysis focuses explicitly on corporate financial data reported in accordance with U.S. GAAP standards and reported to the SEC. Financial accounting metrics do not necessarily reflect cash flows in any given fiscal year and have technical definitions that are not synonymous with their colloquial meanings. Specifically, R&D "expense" in a fiscal year is not synonymous with R&D spending in that year, and may not include the costs of facilities, equipment, other assets (including approved products), or the upfront costs of research partnerships that may be capitalized and depreciated over time. Similarly, "revenue" does not include the proceeds from capital investments (e.g., stock sales). These metrics, nevertheless, represent critical benchmarks for corporate strategy and performance, and are designed to enable greater transparency, consistency, and comparability across companies. Second, this analysis focuses explicitly on revenue accrued by biopharmaceutical companies, which is only indirectly related to the list price or the sale price of pharmaceutical products due to the layered nature of the pharmaceutical distribution system. (Sood N., Shih, T., Van Nuys, K. & Goldman, D., 2017. The Flow of Money Through the Pharmaceutical Distribution System. *USC Leonard D. Schaeffer Center for Health Policy & Economics*.

https://healthpolicy.usc.edu/research/flow-of-money-through-the-pharmaceutical-distribution-system/; Yu, N.L., Atteberry, P. & Bach, P.B., 2018. Spending on prescription drugs in the US: where does all the money go? *Health Affairs Blog*. https://www.healthaffairs.org/do/10.1377/hblog20180726.670593/full/; Dusetzina, S.B. & Bach, P.B., 2019. Prescription drugs—list price, net price, and the rebate caught in the middle. *JAMA*, 321(16) pp.1563-1564. doi:10.1001/jama.2019.2445. https://pubmed.ncbi.nlm.nih.gov/30840047/.) *Third*, further research is required on the flow of capital from drug sales by large pharmaceutical companies, which manufacture and market the large majority of pharmaceutical products, to small biopharmaceutical companies or their investors, which are responsible for an increasing share of clinical trials and drug launches. It is likely that much of this value is embodied in the premiums paid for licenses or acquisitions, and little empirical evidence as to how such premiums would be impacted by reducing drug prices . *Fourth*, a more nuanced model of the pharmaceutical pipeline is required that accounts for both the timelines of product development and the dynamic flux of products between large and small pharmaceutical companies. It is likely that such models will reveal even greater opportunities for agile management to compensate for reductions in revenue without limiting the output of new products. *Finally*, this analysis was limited to the impact of revenue reductions up to 10%, reflecting the boundary of the data used to generate the model. There is no empirical data on which to base estimates of the relationship between R&D expense and reductions of revenue >10%.