ASSESSING THE EFFECTS of Biopharmaceutical Price Regulation on Innovation

July 2022

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Michael Ciarametaro, MBA, Vice President of Research
Lisabeth Buelt, MPH, Consultant
National Pharmaceutical Council

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Executive Summary

As policymakers consider legislative and regulatory proposals to lower biopharmaceutical prices, it is important to consider how such policies affect future innovation. To gain a better understanding of what is known about price regulation and its impact on future drug development and innovation, we conducted a targeted literature review, exploring the qualitative and quantitative research published in peer-reviewed journals, gray literature reports, and policy white papers. Our analysis explores the evidence surrounding the relationship between biopharmaceutical revenues and market size and the level of research and development (R&D) spending or innovative output in the form of new drug approvals. This analysis has five key findings and three main policy implications

KEY FINDINGS

KEY FINDING #1
Reducing incentives to invest in biopharmaceutical R&D results in less innovation.

- Reductions in market size or expected economic return negatively impacts biopharmaceutical innovation (e.g., the number of clinical trials conducted and the number of new drugs approved).

KEY FINDING #2
Public policy interventions can either increase or decrease incentives for innovation.

- Policies reducing drug reimbursement would lower incentives for developing new drugs. Similarly promoting increased demand (e.g., pro-vaccination policies) or increased market size through more comprehensive prescription drug coverage has been associated with improvements in innovative output (e.g., new biopharmaceuticals coming to market).

KEY FINDING #3
There is significant uncertainty surrounding the extent to which price regulations will negatively impact future innovation.

- A 1% reduction in potential market size could result in a 0.2% to 6% reduction in the number of new drugs approved, reflecting differences in the specific policies, metrics, timeframes, and countries studied.
- This reduction could have a broad spectrum of potential consequences for future innovation and patient health outcomes.

KEY FINDING #4
The impact of price regulation policies is likely to vary across disease areas.

- The impact of price regulation on innovative output varies by disease type, with greater effects related to sensory organs (e.g., ADHD medications), nervous system, and antineoplastic and immunomodulating agents (e.g., cancer) compared to other disease areas.

KEY FINDING #5
Analyses of price regulation policies often do not accurately reflect the current biopharmaceutical landscape.

- The current body of evidence does not account for recent changes in market characteristics, including the growing role of venture capital firm investment in biopharmaceutical R&D and the increasing proportion of next-generation therapies and biologics in the R&D pipeline. Failure to account for changes in such market characteristics undermines the accuracy and generalizability of analyses trying to forecast how price regulation policies will impact biopharmaceutical innovation.

POLICY CONSIDERATIONS AND PREMISE

POLICY CONSIDERATION #1
Policymakers must acknowledge the trade-offs and risks associated with price regulation policies.

- Enactment of price regulations in the U.S. will result in fewer therapies coming to market. When it comes to biopharmaceutical innovation, even a small number of therapies can make a big difference to patient health outcomes. Therefore, adoption of price regulation policies comes with an inherent risk that must be recognized: We don't know which therapies we'll miss or what their clinical significance would have been.

POLICY CONSIDERATION #2
Policymakers must consider how price regulation policies will affect market incentives and how this might change the nature of biopharmaceutical innovation.

- The biopharmaceutical innovation ecosystem is extraordinarily complex, and the risks and costs associated with R&D vary substantially within and across treatment areas and therapeutic types. Impact analyses of price regulation policies should not be limited to an assessment of the reduction in the number of new therapies but rather they must also consider how incentives will change the nature and mix of new therapies coming to the market.
- Analyses of price regulation policies should be fit-for-purpose and should not rely on a singular one-size-fits-all model, as it cannot accurately account for the variation in R&D funding streams and R&D activity across treatment areas.

POLICY CONSIDERATION #3
Policymakers must consider how enactment of price regulation policy might affect patient health outcomes.

- We currently lack substantive research on how drug pricing policies will affect patient health outcomes. Even small changes in incentives, compounded over the many years drugs are in development, could result in substantial downside risks to innovative output, and subsequently patient outcomes. Therefore, policymakers must consider how policy implementation may affect patient health outcomes over time.

Background

Over the last few decades, the U.S. has observed dramatic improvement in patient health outcomes and a reduction in morbidity and mortality outcomes for several health conditions, including HIV/AIDS, cancer, cardiovascular disease, and other diseases.[1] A key driver of this improvement is the increasing availability of more effective therapies and other innovative health care technologies that led to meaningful advancement in life expectancy and improved quality of life. For example, a recent study found that U.S. life expectancy increased by 3.3 years between 1990 and 2015, with 35% of the improvement due to biopharmaceuticals.[2]

Although the U.S. has experienced substantial improvements in patient outcomes, these improvements coincided with significant annual increases in U.S. health care expenditures. As a result, policymakers and health care decision-makers face growing pressure to address perceived drivers of unsustainable spending, including hospital consolidation, out-of-network billing, and prescription drug costs. Recently, much of the policy debate has focused on prescription drugs and policymakers have introduced several efforts aimed at constraining prescription drug prices, including proposed federal regulations like the "Most Favored Nation Model" proposed by the Centers for Medicare and Medicaid Services in 2020.[3] In addition, lawmakers have introduced legislative proposals such as H.R. 3 — "The Elijah E. Cummings Lower Drug Cost Now Act" — which proposes price regulation policies such as international reference pricing and price setting that would affect both public and private health care payers.[4] The Build Back Better Act includes a proposal that would allow the federal government to negotiate the prices of select prescription drugs.[5]

As policymakers consider legislative and regulatory proposals to lower biopharmaceutical prices, it is important to examine how such policies will affect incentives for future biopharmaceutical innovation, which is a source of public and academic debate. For example, estimates of the 10-year impact of H.R. 3, which was first introduced in the House of Representatives in 2019, vary significantly, from 30 to 56 fewer drugs that would be developed if it were enacted.[6,7]

To gain a better understanding of what is known about how price regulation may affect future drug development and innovation, we conducted a targeted literature review to synthesize the existing qualitative and quantitative research published in peer-reviewed journals, gray literature reports, and policy white papers. We examined the landscape of existing research on the relationship between biopharmaceutical revenues and/or market size and resultant changes in the level of research and development (R&D) spending or innovative output in the form of new drug approvals. To seed this literature review, we began with empirical studies cited by the Congressional Budget Office (CBO) in assessing the estimated impact of H.R. 3.[8,9,10]

The CBO also used these studies to inform its 2021 working paper, *CBO's Simulation Model of New Drug Development,*[11] as well as its 2021 report, *Research and Development in the Pharmaceutical Industry*.[12]

Methods

In collaboration with research partners at the Analysis Group,[1] we reviewed the existing literature on the relationship between pharmaceutical revenues and/or market size changes and resultant changes in the level of R&D spending, number of clinical trials conducted, or innovative output (e.g., the number of new molecular entities approved). This was a targeted literature review, sometimes referred to as focused literature reviews or scoping reviews, used to explore the issues surrounding a clearly formulated question, provide a solid foundation for further analysis, and identify research areas in need of further investigation. To optimize the relevance of this analysis to current policy discussions, we began the search by reviewing a set of high-quality, high-impact empirical studies cited in numerous CBO assessments of how government policy interventions will impact biopharmaceutical innovation.

We then broadened our review to include: 1) examination of the citations (by title) contained in these studies, and those which cite them, to determine if any should be included in our abstract review; 2) a review of selected authors' publications for relevance; and 3) a keyword-driven database search. We reviewed the literature for analyses published between 2000-2020. We screened 265 unique peer-reviewed journal articles, gray literature reports, and policy white papers for relevance, screening out 182 due to irrelevance, leaving 64 classified as possibly relevant and 21 as highly relevant. We conducted a full-text review of these 21 articles, retaining 19 of them in the final sample. Additional details about our methodology can be found in Appendix A and B.

1 Genia Long, MPP and Noam Kirson, PhD of the Analysis Group assisted with research for this analysis and conducted the targeted literature review.

Key Findings

All 19 studies included in our review identify factors that precipitated positive or negative changes in innovative output, which we refer to as "determinants of innovation." Sixteen studies included an empirical estimation or theoretical analysis of the relationship between pharmaceutical revenues and/or market size changes and resultant changes in the level of R&D spending, the number of clinical trials conducted, or innovative output (e.g., the number of new molecular entities approved) (Table 1). The remaining three articles included policy analyses related to this relationship (Table 2). A detailed summary of the literature can be found in Appendix C.

TABLE 1: Summary of Empirical Estimation/Theoretical Analysis Studies Included in Targeted Literature Review, by Lead Author

Citation	Outcomes of Interest	Data - Countries	Data - Years	Determinant of Innovation	Direction of Innovation Change
Acemoglu, 2004[10]	Number of new molecular entities	United States	1970-2002	Expected market expansion due to demographic changes	Positive effect on innovation
Blume-Kohout, 2013[9]	Number of new drugs entering clinical trials	United States	1998-2010	Market expansion due to implementation of Medicare Part D	Positive effect on innovation
Cerda, 2007[13]	Number of new molecular entities	United States	1939-1997	Market expansion due to demographic changes	Positive effect on innovation
Civan, 2006[14]	Number of new drugs entering clinical trials, R&D spending	United States and Ex-U.S. (EU, North America, South/Central America, Asia/ Pacific, Africa)	2003	Expected economic opportunity/ intensity of consumer demand in specific disease areas	Positive effect on innovation; effect varies across disease areas
Danzon, 2004[15]	Number of new molecular entities	United States and Ex-U.S. (Germany, New Zealand, Netherlands)	1980s-1990s	Price regulation (reference pricing)	Negative effect on innovation
Danzon, 2005[16]	Time to market for new chemical entities	United States and Ex-U.S. (EU, Australia, Canada, Japan, Mexico, New Zealand, South Africa, Norway, Switzerland)	1994-1998	Price regulation	Negative effect on innovation (fewer launches)

Citation	Outcomes of Interest	Data - Countries	Data - Years	Determinant of Innovation	Direction of Innovation Change
Dranove, 2020[17]	Novelty of new drug candidates entering clinical trials (novel targeted-based action or TBA, and novel combinations of TBAs)	United States	1997-2018	Market expansion due to implementation of Medicare Part D	Positive effect on innovation; more nuanced results with respect to types of follow-on activity
Dubois, 2015[8]	Number of new chemical entities	United States and Ex-U.S. (EU, Australia, Brazil, Canada, China, Japan, Mexico, Korea, Turkey)	1997-2007	Expected market size/economic opportunity	Positive effect on innovation; effect varies across disease areas
Finkelstein, 2004[18]	Number of new vaccines entering clinical trials	United States	1983-1999	Pro-vaccination demand-side public policies	Positive effect on innovation for clinical trials for specific diseases, but no effect on early-stage research
Giaccotto, 2005[19]	Pharmaceutical R&D spending	United States	1952-2001	Expected economic opportunity (real drug prices); price regulations (price caps)	Higher drug prices have positive effect on innovation, but price regulations have negative effect on innovation
Golec, 2006[20]	Pharmaceutical R&D spending	United States and Ex-U.S. (EU)	1993-2004	Expected economic opportunity; price regulations (price caps)	Positive effect on innovation (expected economic opportunity) vs price regulations
Golec, 2010[21]	Pharmaceutical R&D spending	United States	1993-1995	Price regulation (price caps)	Negative effect on innovation
Grossmann, 2003[22]	N/A	N/A	N/A	Price regulation and strict utilization management strategies	Negative effect on innovation
Scherer, 2001[23]	Pharmaceutical R&D spending	United States	1962-1996	Expected economic opportunity	Positive effect on innovation

Citation	Outcomes of Interest	Data - Countries	Data - Years	Determinant of Innovation	Direction of Innovation Change
Troyer, 2002[24]	Number of new chemical entities, number of new drug applications (NDA) approved, number of new drug applications filed, number of investigational new drug applications filed	United States	1970-2000	Medicaid drug rebate program (a form of price regulation)	Negative effect on innovation
Vernon, 2005[25]	Pharmaceutical R&D spending	United States	1994-1997	Price regulations	Negative effect on innovation, but effect varies based on current marginal productivity

Notes: This table includes the authors' analysis of 16 peer-reviewed articles published between 2000 and 2020 that explore the relationship between changes in biopharmaceutical revenues/market size and changes in the level of R&D spending or the level of innovative output (e.g., the number of new molecular entities approved). These articles conduct empirical estimations or theoretical analyses of this relationship.

TABLE 2: Summary of Policy Discussion Studies Included in Targeted Literature Review, by Lead Author

Citation	Outcomes of Interest	Data - Countries	Data - Years	Determinant of Innovation	Direction of Innovation Change
Goldman, 2016[26]	N/A	N/A	N/A	Expected economic opportunity ("market forces set prices") and price regulations (price caps)	Expected economic opportunity has positive effect on innovation vs. global price caps and limits on prices of individual drugs
Lemley, 2020[27]	N/A	N/A	N/A	Demand-side public policy interventions (e.g., Medicare insurance coverage)	Positive effect on innovation
Patterson, 2020[28]	N/A	N/A	N/A	Price regulation	Negative effect on innovation

Notes: This table includes the authors' analysis of 3 peer-reviewed articles published between 2000 and 2020 that explore the relationship between changes in biopharmaceutical revenues/market size and changes in the level of R&D spending or the level of innovative output (e.g., the number of new molecular entities approved). These articles include policy discussions/analyses of this relationship.

The main objective of this analysis was to review the existing literature on the relationship between changes in pharmaceutical revenues and/or market size and resultant innovative output to inform health care policy interventions aimed at reducing health care costs through the implementation of biopharmaceutical pricing regulations. Exploring this topic is crucial, as such policies could have a range of downstream consequences for the global biopharmaceutical market. Our analysis has five key findings.

KEY FINDING #1
Reducing incentives to invest in biopharmaceutical R&D results in less innovation.

Our targeted review of the literature found robust empirical evidence of a relationship between drugmakers' expected economic returns and innovative output. Multiple studies found that reductions in market size or expected economic returns, or the potential for reduction in these returns, negatively affects innovative output including the number of clinical trials conducted and the number of new drugs approved. [15,16,21,22,24,25,28]

Conversely, numerous studies found that increases in expected returns or economic opportunity elicits a positive innovation response. [8-10,13,14,17,19,20,23,26] While the magnitude of the effect varies depending on the specific circumstances, the directional relationship between expected economic returns and innovative output is clear.

KEY FINDING #2
Public policy interventions can either increase or decrease incentives for innovation.

Many of the studies included in this analysis examine public policy as a determinant of innovation. Empirical analyses of demand-side public policies, such as government-led pro-vaccination efforts and those that expand market size (e.g., Medicare Part D), found that these policies may incentivize the development of new technologies and induce biopharmaceutical innovation. In addition, other studies found that certain forms of market entry deregulation and allowing market forces to set drug prices may lead to higher R&D spending and increased innovative output.[22,26]

Conversely, public policies that constrain biopharmaceutical prices or shrink expected economic returns for manufacturers have been found to reduce R&D spending and are associated with fewer drug approvals. Policy analyses of the potential impact of price regulations on innovative output the U.S. underscore the importance of the federal government in maintaining incentives for innovation and conclude that reducing drug reimbursement would lower incentives for developing new drugs, which could negatively impact innovation.[22,26,27]

KEY FINDING #3
There is significant uncertainty surrounding the extent to which price regulations will negatively impact future innovation.

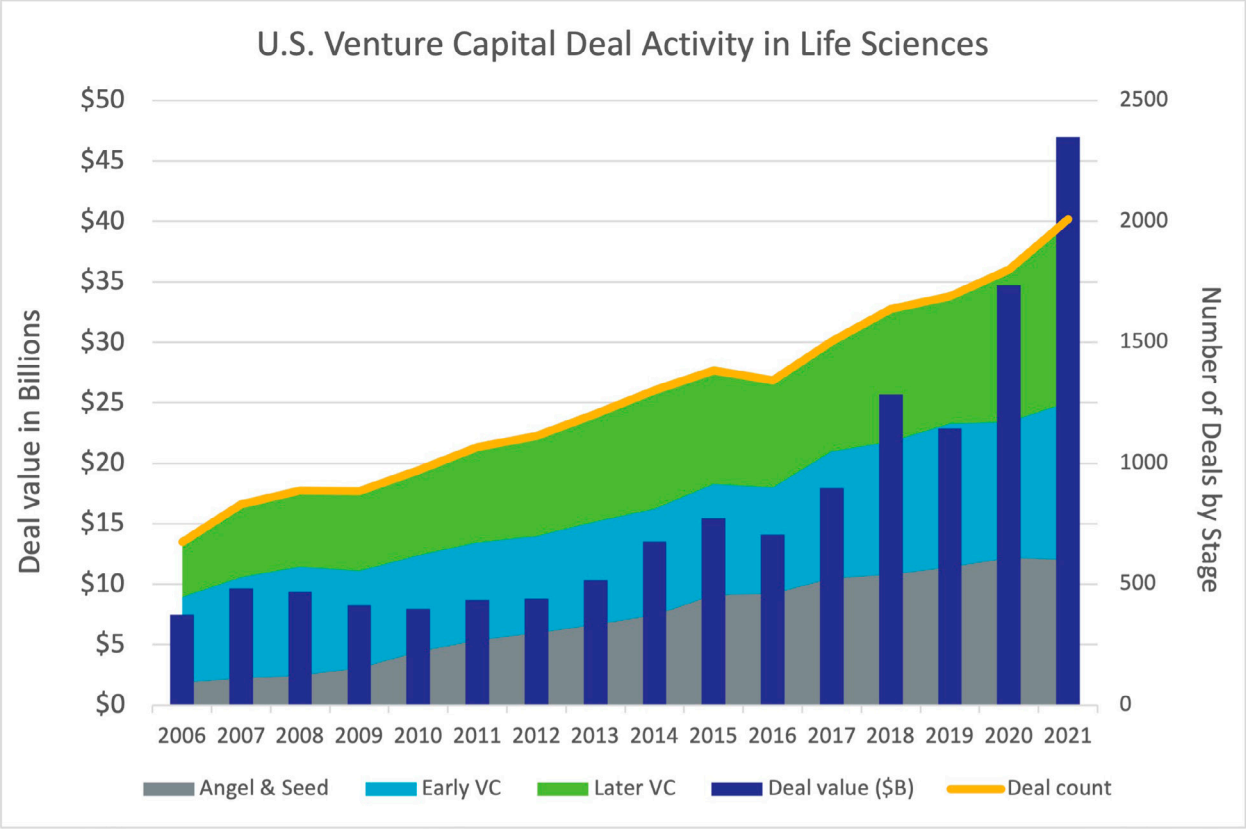
Peer-reviewed literature indicates that a 1% reduction in potential market size could result in a 0.2%[8] to 4%-6%[10] reduction in the number of new drugs approved, reflecting differences in the specific policies, metrics, timeframes, and countries studied. The wide range in estimates indicates that price regulations could have a broad spectrum of potential consequences for future innovation and patient health outcomes. If effects on innovation are modest, reducing biopharmaceutical spending today through price regulation would come at the expense of only modest reductions in new drug development tomorrow. However, if the effects are larger, patients and society risk forgoing a larger number of innovative therapies that would have yielded substantial benefits to individual and population health.

KEY FINDING #4
The impact of price regulation policies is likely to vary across disease areas.

Due to uncertainty and gaps in the literature, it is currently unclear how the impact of pricing regulation on innovative output will vary by disease area. However, one study in our review found that the impact of price regulation on innovative output had greater effects related to sensory organs, nervous system, and antineoplastic and immunomodulating agents compared with other disease areas.[8]

KEY FINDING #5
Analyses of price regulation policies often do not accurately reflect the current biopharmaceutical landscape.

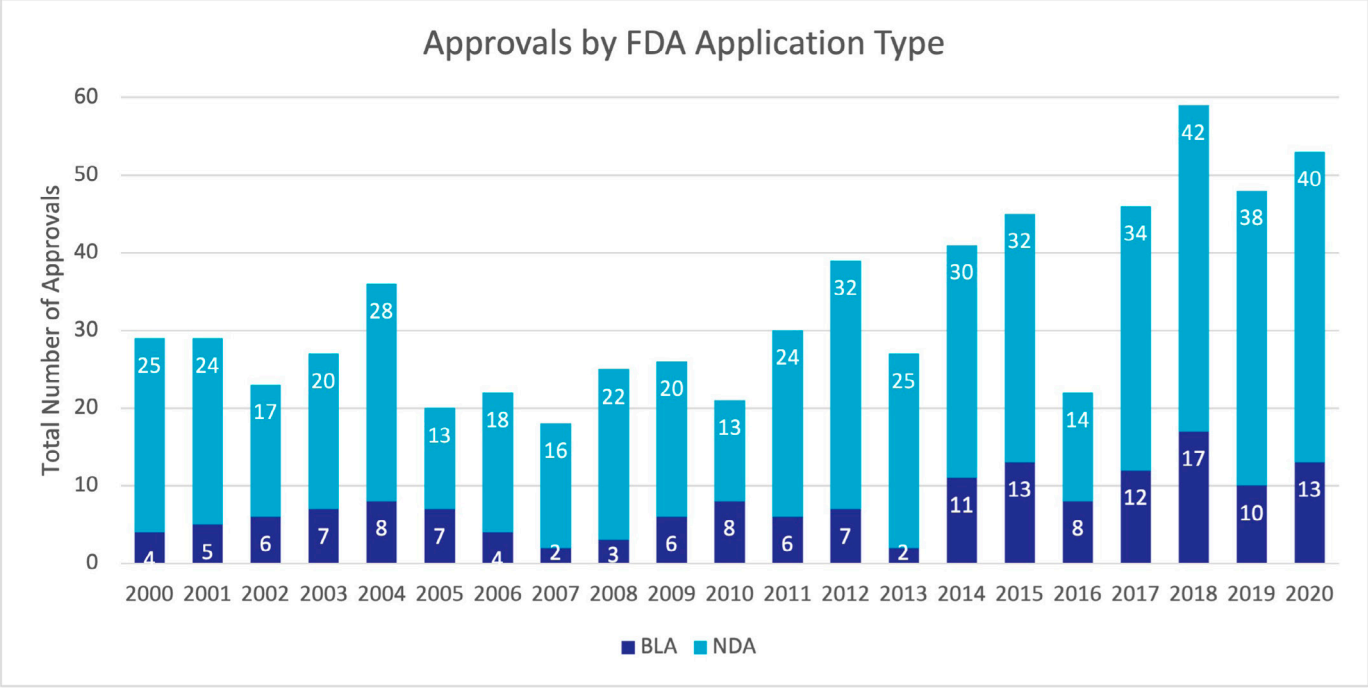
The empirical analyses examined in this targeted literature review are subject to several limitations. First, several studies rely on dated assumptions pertaining to the funding of biopharmaceutical R&D and do not reflect contemporary market dynamics. For example, few studies consider the evolving role of venture capital investment, which is now a key source of private-sector R&D funding and has increased substantially over time. In 2006, there were an estimated 670 life science venture capital deals valued at approximately $7.5 billion.[29] Since then, venture capital activity has accelerated significantly, and in 2021 there were a total of 2,009 deals valued at $47 billion.[30]



Source: PitchBook-NVCA Venture Monitor Q4 2021. Available from: https://pitchbook.com/news/reports/q4-2021-pitchbook-nvcaventure-monitor.

Venture capital firms face different risks and economic return structures than publicly traded stocks, including those of large pharmaceutical companies, and have greater flexibility than large pharmaceutical companies to shift investment to other industries to avoid reduced risk-adjusted return rates due to price regulation. Differences in risk and investment agility suggest that venture capital firms may behave differently than large pharmaceutical companies in response to changes in investment conditions, including price regulation. Given the growing role of venture capital investment as a key funding source for biopharmaceutical R&D funding, it is important that assessments of policy proposals and the elasticity of innovation reflect real-world market conditions.

Second, there has been a dramatic shift in the types of products entering the market, and the proportion of the market that these new products represent. Next generation biotherapeutics (NGBs) such as cell and gene therapies and RNA therapeutics, represent a growing portion of the R&D biotherapeutic pipeline.[30] Because these are relatively new mechanisms, the existing literature has not sufficiently explored how the implementation of price regulation policies will affect investment in R&D and new drug approvals. Several of the studies included in this literature review rely on assumptions based on more traditional products, which may underestimate the effect of price regulation, particularly if clinical trial success rates for NGBs and large-molecule biologics are lower than for more traditional small-molecule therapies or if the average cost of development for novel NGBs and biologics exceeds that of traditional products.



Source: https://www.fda.gov/media/135307/download. Acronyms: Biologic License Application (BLA), New Drug Application (NDA)

Policy Implications and Premise

POLICY IMPLICATION #1

Policymakers must acknowledge the trade-offs and risks associated with price regulation policies.

This analysis found robust empirical evidence that reductions in drugmaker revenue or profits (either expected or realized) are associated with reductions in R&D funding and fewer commercialized therapies. This finding is corroborated by analyses conducted by the CBO, including its analysis of H.R. 3 and its model for new drug development, which found that implementation of price regulation policy would reduce the number of new drugs coming to market by 10%.

However, there is significant uncertainty in the existing literature regarding the extent to which pricing regulation will negatively impact future innovative output, including investment in R&D and new drug approvals. This uncertainty also extends to how price regulation policy will affect innovative output in different disease areas. Therefore, when forecasting the estimated impact of a price regulation policy, it is essential to consider how the policy will affect the development of new treatments across disease areas and how such policies might unintentionally skew the incentives for future development. For example, policies that place caps on Medicare spending could reduce economic opportunity and incentives for R&D investment in treatment areas that primarily service elderly populations but may have less of an effect on innovation in other treatment classes that serve alternative patient populations.

Given the uncertainties and risks associated with estimating the effects of price control policies in the United States, it is incumbent upon policymakers to consider the full range of potential downstream consequences, including additional risk to commercialization.

POLICY IMPLICATION #2

Policymakers must consider how price regulation policies will affect market incentives and how this might change the nature of biopharmaceutical innovation.

The biopharmaceutical innovation ecosystem in the United States is highly complex and dynamic. This complexity is evident across several dimensions of the ecosystem, including stakeholder types, disease areas, and therapy types. Each of these dimensions is associated with varying costs and risk profiles. For example, the innovation ecosystem incorporates numerous stakeholders, including large life sciences companies, small biotechnology companies, academics, public and private funders of R&D, government regulators, patients and their caregivers, among others.

But the enactment of government price regulation will affect some stakeholders more than others. For instance, small biotechnology companies must raise capital to conduct R&D, whereas large life sciences companies can rely on revenue from existing sales. This means that greater economic risks, coupled with lower returns, may result in less available capital for drug development due to these investments becoming less attractive to potential funders. Because small biotech firms dominate the early stages of clinical development, the impact of less capital may translate into fewer new drugs over time as the impact on early clinical development translates to the later stages of clinical development.

In addition, the costs and risks associated with biopharmaceutical R&D vary substantially within and across treatment areas and therapeutic types. For example, a recent study found that the median cost of bringing a drug to market was much higher for biologic drugs than for pharmacologic drugs, and that costs differ substantially by therapeutic area with cancer being the highest.[31]

Therefore, as policymakers and other health care leaders assess the impact of price regulation policies, these assessments should not be limited to the reduction in the number of new therapies; instead, they must also consider how a policy will disrupt existing market incentives and how this might change the nature and mix of new therapies coming to the market. In addition, changes in incentives that leverage international pricing may see impacts that extend beyond the U.S. borders in the form of reduced access to new therapies in referenced countries. Thus, it is critical to consider how a shift in innovation incentives might lead to reductions in R&D and access for impacted patient populations.

POLICY IMPLICATION #3
Policymakers must consider how enactment of price regulation policy might affect patient health outcomes.

Despite the recent groundswell of interest in price regulation policy, gaps and uncertainty in the literature leave several questions unanswered regarding how policy implementation will affect the innovation ecosystem and patient health.

For example, it is difficult to approximate how price regulation policies will affect biopharmaceutical innovation and we cannot accurately predict the clinical importance of the therapies that we will miss out on due to policy implementation. Undeveloped treatments could include life-saving therapies for patient populations with high unmet need, treatments that contribute valuable, incremental progress toward future significant innovation, or treatments that provide an important source of therapeutic competition in categories with multiple clinical options. Conversely, even small changes in incentives compounded over the many years drugs are in development could result in substantial downside risks to innovative output, and subsequently patient outcomes.[32,33] Therefore, policymakers must consider how the implementation of price regulation policy may affect patient health outcomes over time.

Conclusion

Biopharmaceuticals are a key driver of improvements in patient health outcomes. As such, policymakers should consider how legislative and regulatory proposals to lower biopharmaceutical prices will affect incentives for future innovation. A targeted review of the literature found robust empirical evidence of a directional relationship between drugmakers' expected economic returns and resultant innovation. In other words, reducing expected or actual returns to investment has a negative effect on innovative output including new drug approvals and investment in R&D; conversely, increasing opportunities for returns elicits a positive innovation response.

We also identified substantial uncertainty regarding the potential impact of applying price regulation in the U.S. market. Given this uncertainty and the importance of biopharmaceuticals to patient health, policymakers should proceed with caution and consider the full range of possible consequences of policies aimed at constraining drug prices. In addition, policymakers should expand their focus beyond drug prices to evaluate opportunities for spending efficiency across the health care system.

Appendix A

METHODS

We conducted a targeted literature review on the economics of biopharmaceutical innovation. The search focused on empirical studies published in peer-reviewed journals related to the economics of innovation. Specifically, we searched for studies that explore the relationship between changes in biopharmaceutical revenues/market size and changes in the level of R&D spending or the level of innovative output (e.g., the number of new molecular entities approved).

Our literature review strategy had four steps (Figure 1). First, we generated citations. We began the search by reviewing a set of high-quality, high-impact empirical studies cited in the CBO's assessment of the estimated impact of H.R. 3 on biopharmaceutical innovation.[4] In this analysis, the CBO cites three studies (Dubois et al.; Blume-Kohout and Sood; Acemoglu and Lin) estimating the relationship between changes in revenues/market size and changes in the level of R&D spending and/or approved new drugs (i.e., the "elasticity of innovation with respect to market size"). Next, we broadened the search and reviewed the citations (by title) included in each study cited by the CBO (n=111) and reviewed selected authors' publications (n=55). To ensure that more recent publications were also included in the review, we identified the forward citations of the references cited by the CBO (n=75). Separately, we also conducted a keyword-driven database search of peer-reviewed literature, reports, and policy white papers published between 2000 – 2020 and that appeared in EconLit, PubMed, and selected publication sources, including *Health Affairs* (n=49). We used the following search terms: ("Drug" OR "Pharmaceutical") AND ("Price Regulation" OR "Cost") AND "Impact" AND "Innovation." We also included an additional query on the alternative definitions of profitability and their impact on findings relating to return on investment (ROI) of new drug development investment. We relied on a flexible manual search to identify at least one relevant source guided by the search terms: "Drug Development" AND "Cost" AND "Profitability," followed by a manual review. In total, 290 citations were generated. Of these 290 studies, we excluded 25 studies due to one or more of the following exclusion criteria: duplicates, non-English language publications, published before 2000, or lack of U.S. focus (although multi-country studies that included the U.S. were included), for a total of 265 studies. An itemized list of these studies is included in the appendix.

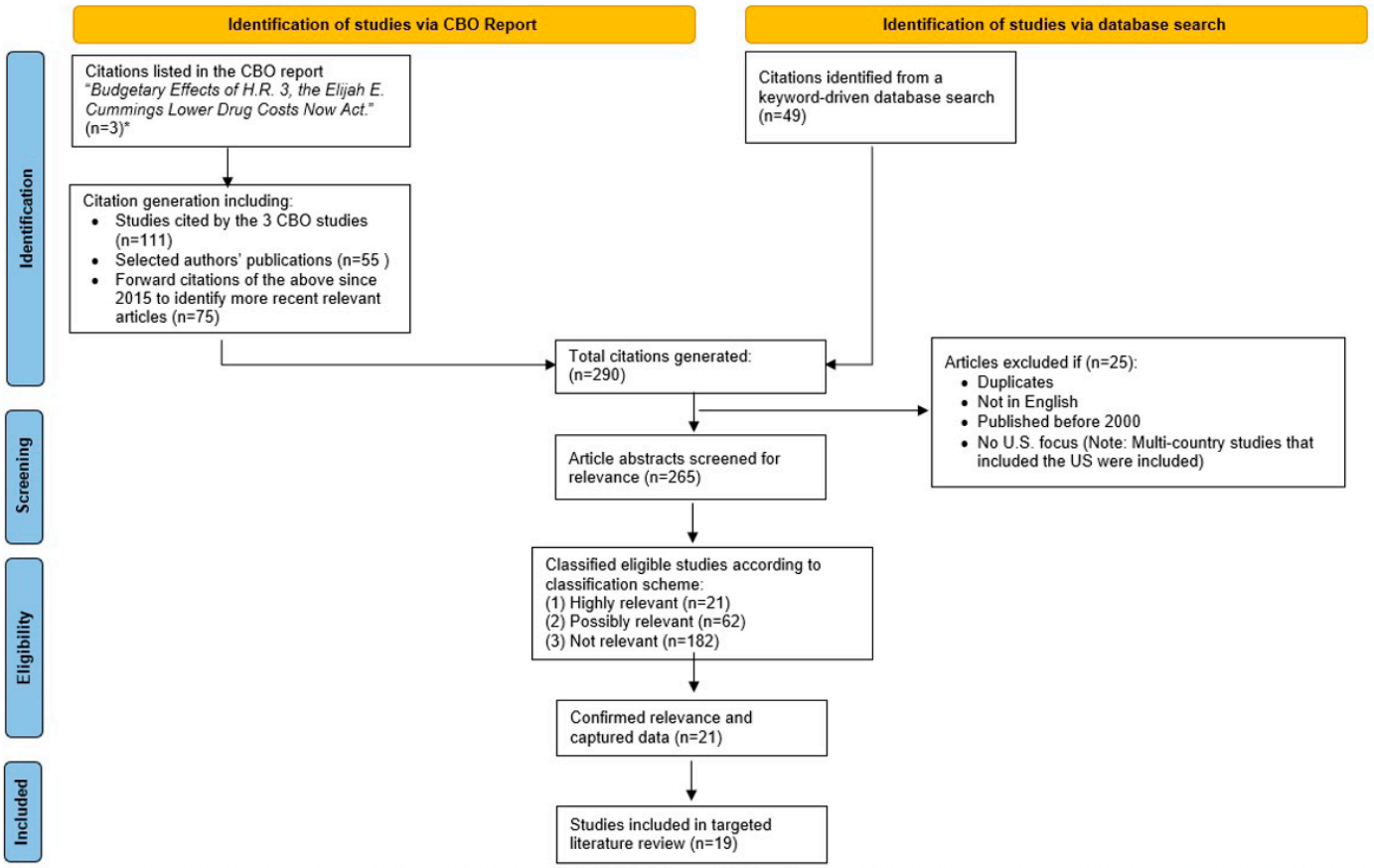
Second, we screened the abstracts collected during the citation generation step for relevance. During this step, we classified studies as highly relevant (n=21), possibly relevant (n=62), and not relevant (n=182). Third, we reviewed the full text of the 21 articles classified as highly relevant and confirmed their relevance. Fourth, we captured data and classified each eligible study according to the type of study (i.e., empirical estimation, simulation, theoretical analysis, policy discussion), key outcomes of interest, and country and period of the data used in empirical analysis. The final number of studies included in our analysis was 19.

Given that a primary goal of the CBO report was to forecast how policy provisions would impact future innovation, we also considered how well the data used to derive the elasticity estimates match current market conditions. Assessing how the market has changed since the studies were conducted, we evaluated trends in three market aspects: 1) reliance on venture capital firm investment in biopharmaceutical R&D, 2) the types of therapies in development, and 3) the manufacturer revenue gross-to-net ratio, or the percentage of sales revenues realized by manufacturers after discounts, rebates, and allowances. We conducted this evaluation using publicly available market trend data from the CBO[34] and IQVIA Institute for Human Data Science.[29,35]

This study has two main limitations. First, we conducted a targeted literature review, and consequently, our findings may be less reproducible than those from a systematic literature review. To mitigate this risk, we used the CBO's analysis of H.R. 3 to seed our literature review. Second, some studies included in this analysis were published before the implementation of domestic and international policies that subsequently altered the policy landscape and resulted in substantial changes to national health systems and biopharmaceutical marketplaces (e.g., the passage of Germany's drug pricing legislation in 2011 or the Patient Protection and Affordable Care Act in the U.S.). However, this limitation supports our finding that there are significant challenges in using past studies on the elasticity of innovation to forecast the future impact of price regulation policies that could substantially impact the largest biopharmaceutical market in the world.

Appendix B

FLOW DIAGRAM OF TARGETED LITERATURE REVIEW



* Dubois P, de Mouzon O, Scott-Morton F, and Seabright P. *Market Size and Pharmaceutical Innovation*. RAND Journal of Economics, 46(4): 844–71.; Blume-Kohout ME, Sood N. *Market Size and Innovation: Effects of Medicare Part D on Pharmaceutical Research and Development*. J Public Econ. 2013 Jan;97:327-336.; Acemoglu, D, and Lin, J. *Market Size in Innovation: Theory and Evidence From the Pharmaceutical Industry*. Quarterly J of Econ, 119(3): 1049-1090.

Appendix C

SUMMARY OF THE LITERATURE

Twelve of the 19 studies in our review examine the effects of factors associated with increased innovation including new drug development or increases in R&D spending. These factors, or determinants of innovation, include increases in expected market expansion or economic opportunity for drugmakers (n=10)[8-10,13,14,17,19,20,23,26] as well as demand-side public policies (n=2)[18,27] such as government-led pro-vaccination efforts. Two studies that examined market expansion as a determinant of innovation focus explicitly on Medicare Part D implementation,[9,17] and three analyze the benefits of free pricing against potential disincentives associated with price control policies.[19,20,26]

The two analyses that examined the market expansion effects of the Medicare Modernization Act (2003) found that the program increased pharmaceutical development as more drugs entered preclinical and Phase I-III clinical trials. This effect was highest for therapeutic areas with a higher Medicare market share.[9] One of the two studies examined the scientific novelty associated with increased R&D activity. It found little evidence that the program prompted firms to undertake scientifically novel R&D activity, but some evidence that firms invested in products involving novel combinations of scientific approaches.[17]

In all instances, innovative output or investment in R&D increased in response to positive incentives associated with these determinants of innovation; however, the magnitude of the increase varied across the studies.

Seven of the 19 studies included in our review examined how price control regulations affect innovation outputs (i.e., the number of new drugs approved).[15,16,21,22,24,25,28] These studies found that public policies that constrain biopharmaceutical prices, profits, and revenue lead to reductions in new biopharmaceutical innovation. However, the magnitude of the effect varied by study.

Given the nature of the free-pricing environment in the U.S., few studies examined the actual effect of drug pricing regulation in the U.S. and only one examined a U.S. policy that directly impacted net price. In an empirical analysis of the Medicaid rebate program, the authors examined how the program's implementation influenced future innovative output and found that the program led to a reduction in biopharmaceutical innovation (e.g., as many as four fewer NDAs were approved per year, a decline of 1.5%).[24]

All other studies of U.S.-specific price control policies included in our review relied on theoretical model simulations to estimate the impact of hypothetical price control regulations on innovative output. These analyses found that the implementation of price controls would adversely affect R&D spending, but to varying extents.[19,22,25] For example, one analysis explored how price limits in the U.S. would influence R&D spending. It found that if drug price increases were constrained by general consumer price index (CPI) growth from 1980-2001, the capitalized value of pharmaceutical R&D spending would have been about 30 percent lower.[19] This reduction would have resulted in 330-365 fewer new drugs during the assessed period of 1980-2001, amounting to over one-third of all actual new global drug launches during that period.

Another study similarly concluded that price regulations in the U.S. (i.e., setting gross margins equal to those in other industries) could shrink R&D spending between 23.4% and 32.7%.[25] However, the authors noted that the welfare effects of such a policy are unclear as losses in long-run innovation may offset short-term cost savings.

Because the U.S. has limited experience with the implementation of federal price regulation policy, a few studies in our review examined how price control policies implemented in ex-US countries could inform U.S. policy changes. For example, strict therapeutic reference pricing policies in New Zealand have been found to reduce reimbursement and limit availability of new drugs compared with Germany and the Netherlands, where the effect of reference pricing on innovation was muted due to multiple drug exemptions and high reference prices.[15] The authors also hypothesize that because the U.S. has a more competitive generic market and a much larger share of global pharmaceutical sales, international reference pricing policies implemented in the U.S. would likely negatively affect the prices of off-patent products.

In addition, a study that examined how price regulation affects the launch of new treatments found that countries with lower launch prices or smaller expected market size due to pricing regulations experience longer delays in new drug access.[16]

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1717 Pennsylvania Avenue, NW | Suite 800 | Washington, DC 20006

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