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The Relationship Between Biopharma R&D Investment and Expected Returns: Improving Evidence to Inform Policy

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Better evidence is needed to evaluate the impact of policy changes on new drug development. Greater availability of government data should support more rigorous evaluations to inform evidence-based policymaking.

KEY TAKEAWAYS

- There exists a clear link between the expected financial return from a drug and investment in drug research and development (R&D) in the biopharma industry.
- Government actions aimed at reducing drug costs, including price controls or reduced intellectual property (IP) protection, decrease the expected financial returns from drugs, leading to less R&D.
- However, the exact extent of this trade-off remains poorly understood due to the age, data quality, and data analysis limitations of existing studies.
- U.S. government agencies such as the Congressional Budget Office (CBO) use these studies to estimate the impact of policy changes, despite their limitations.
- The CBO acknowledges the need for better data and more rigorous studies to inform evidence-based policymaking, and has called for new research to assess the trade-off between cost savings and future health benefits from biopharma clinical development.

INTRODUCTION

A significant body of evidence suggests there is a positive relationship between the expectation of financial return from an approved medicine and biopharmaceutical firms' investments in research and development. Economists widely recognize that government actions targeted at reducing drug costs, such as price controls for drugs or reducing IP protection, also reduce expected financial returns from a medicine, and therefore carry a trade-off of less investment in R&D. The result is fewer clinical studies, new medicines, and new indications. However, the scope and magnitude of this trade-off are poorly understood.

All existing studies estimating this trade-off have a significant degree of error and uncertainty, and many are outdated or irrelevant to the current biopharmaceutical R&D process. Nevertheless, U.S. government organizations, including the Congressional Budget Office (CBO), rely on these studies to estimate the impact of major changes in federal policy. Moreover, due in large part to the lack of relevant and reliable data, models that the CBO has developed to simulate firm decision-making do not reflect the mobility of capital or the full spectrum of investment decisions inherent in today's R&D ecosystem.[1] Recognizing the need for better data, the CBO issued a call for "Research in New Drug Development."[2] This call addresses some, but not all, of the evidence needed to enable a more adequate assessment of the trade-off between cost savings for biopharmaceuticals today and the health benefits from clinical development in the future.

This whitepaper summarizes the state of the evidence relating expected biopharmaceutical financial returns to investment in R&D and provides specific suggestions for generating new evidence and improving methodological rigor. In the absence of better quality and more accurate, rigorous studies about the impacts of biopharmaceutical policy changes, policymakers considering enacting or expanding policies such as price setting remain poorly informed about their consequences. This poses a risk to medicine development, global health and longevity, and future U.S. health spending trends. We conclude with a call to action for better evidence.

A Call to Action

- Better evidence is needed to evaluate the impact of policy changes on new drug development.
- Without reliable evaluations of policy impacts, policies should not be expanded.
- Policy impact models should be reformed to address limitations and incorporate feedback from stakeholders with relevant expertise.
- Government data should be more easily accessible.
- Policy impact assessments should be transparent, replicable, and independently verified, and should clearly represent uncertainty.

BACKGROUND: NEED FOR NEW EVIDENCE RELATING EXPECTED FINANCIAL RETURN FOR DRUGS TO R&D

The amount of money and effort invested in biopharmaceutical R&D is influenced by two key factors: first, by the likelihood that the science being investigated will be successful in modifying a disease or symptom safely, and second, that there will be a financial reward from an approved treatment to allow organizations to recoup R&D costs and invest in future drug development. Most clinical investigations do not result in new drugs, so investors place bets on several drug candidates. Capital comes from biopharmaceutical companies and venture and institutional investors. Each source of capital is deployed toward therapeutic investigations deemed to be most likely to succeed considering both science and financial outcomes. Public and private data sources offer a limited view into these decisions, particularly for the foregone investments.

The United States comprises more than 40 percent of the world's biopharmaceutical market.[3] At this size, U.S. policy, including reimbursement and IP policy, has a particularly strong influence on the expected financial returns for biopharmaceuticals. Changes in U.S. policy, including government price setting in Medicare or weakened IP protection, will have a disproportionate effect on incentives for global drug development. These policies do not just affect biopharmaceutical profits, but also investment in academic institutions, clinical trial centers, and novel scientific methods. Policy changes will have a poorly understood impact on R&D for new and existing medicines, human health and longevity globally, and longer-term consequences in spending.

Often cited estimates of the strength of the response in R&D investment to a change in expected financial returns include Dubois (2015), Blume-Kohout and Sood (2013), and Acemoglu and Lin (2004).[4] These studies consider the effect of changes in market size on the development of new chemical entities from 1997 to 2007 in 14 countries compared to their population by age and mortality rates from certain diseases (Dubois); the effect of the passage of Medicare Part D on the number of drugs entering each stage of clinical development from 1998 to 2010 (Blume-Kohout and Sood); and the relationship between the number of new drugs approved from 1970 to 2000 and population aging as a proxy for anticipated demand for certain therapeutics (Acemoglu and Linn). These studies all add significantly to the body of evidence on the magnitude of the relationship between biopharmaceutical R&D investment and the expectation of financial return. Yet the studies are not a complete representation of how a policy that changes the profitability or revenue of an approved medicine more broadly affects R&D or clinical development programs for medicines and vaccines.

Limitations of Existing Studies

- Explicitly consider how expected financial returns may affect development of post-market advances from advances for existing medicines.
- Address to a meaningful degree how success or failure in an R&D program contributes to the development of future therapies or combinations of therapeutics.
- Examine the relationship between R&D and expected financial returns in recent years, when the types of drugs being developed have become more complex and the trials more expensive.

Another challenge in estimating the association between biopharmaceutical financial returns and R&D is that the amount of capital required, and the associated risk of investment, are variable throughout the development lifecycle for a drug, with distinct entities involved. Each of these entities has a different ability to tolerate financial risk and deploy capital. However, the information about their risk tolerance and alternative ways to deploy capital is not well documented. A representative firm model intended to capture the impact of policies that affect the biopharmaceutical market should reflect the risk tolerance, access to capital, and alternative uses of capital in the distinct phases of development. Yet there are limited data or models to inform how these decisions are made by the different actors, and in particular why some drug candidates are not pursued even if the expected return is positive.[5]

Figure 1: Stages of R&D and sources of capital and investors

ADDRESSING GAPS IN THE EVIDENCE TO INFORM DRUG POLICY DECISIONS

Before the passage of the Inflation Reduction Act (IRA) in 2022, government price setting did not exist in Medicare for drugs. Medicare accounts for 32 percent of the American biopharmaceuticals market.[6] With no analogs, it is difficult to estimate the impact of a change of this magnitude on R&D, which is likely a motivation for the CBO call for information. Moreover, there are other important evidence gaps. Recent forecasts of the impact of U.S. government price setting, including those previously undertaken by the CBO, have often focused on how much the policy would affect expected pharmaceutical revenue and then relate that to a change in the number of "new" drugs developed.[7]

The CBO asks for more evidence of the impact on "new" drugs, but a policy that affects the expected financial return from an approved medicine, particularly later in the lifecycle of drug development, also has an impact on investment in R&D for existing drugs. This includes the development of new indications such as for different conditions or for pediatric and other special populations. Furthermore, government price setting in Medicare for a branded medicine near the end of its lifecycle also affects the continued development of competitors in the therapeutic class, as well as post-patent competition by generic or biosimilar drugs. The impacts of price setting on these market dynamics—which have historically broadened access to clinical data for medicines, expanded treatment options, and reduced costs—have not been well studied.

The uncertainty in the existing methodology is evident, as other models considering the impact of the IRA on new drug development have projected a wide range of estimates much larger than the CBO's. For example, one estimated that 135 new drugs would not be developed by 2039 and

another estimated that 139 drugs would not be developed from 2026 to 2035.[8] These estimates may also underappreciate the full impact as they do not explicitly model additional indications not developed post-market, such as pediatric studies. Moreover, the magnitude of the government-established price declines is still unknown and not accounted for in any of the existing models.

IMPROVEMENTS IN DECISION SIMULATION MODEL: REPRESENT EFFECT ON CAPITAL ALLOCATION FOR R&D

Need for Better Evidence to Estimate R&D to Market Size Relationship

- **Post-market development:** Focusing on new drug development disregards the effects of late in lifecycle price setting on investment in R&D for existing medicines. This type of investment supports new indications, combination therapy development for conditions like oncology or HIV, or for special populations like children or people with co-morbid conditions.
- **Dated analogs:** Even the leading estimates of the relationship between investment in R&D and biopharmaceutical market size are outdated; both the risk and cost of R&D has changed over time as drugs are increasingly specialized with more complex development protocols. Existing evidence of the cost and risk are not necessarily reflective of today's investment decisions.
- **Disparate impact on certain disease states:** Because the relationship of R&D to market size is variable based on therapeutic class, a more accurate representation of therapeutic dynamics would serve to better inform forecasts.
- **Variable ability to tolerate risk to capital:** The approach of simulating the decisions of a representative firm is informed by a limited dataset and does not include information about the decisions not to invest in certain drugs, nor does it reflect the differing risk profiles. Furthermore, simulation models should reflect the mobility of capital throughout the stages of drug development and how decisions are made across a portfolio of investments.
- **Effect on prices of other drugs in class:** Government price setting would also impact revenue of competitor drugs, which would likely also reduce their net prices in response to this policy. It is still unknown to what degree that will happen and its effect.
- **Competitive market for generics and biosimilars:** Updated evidence is needed to assess the impact of lower expected returns for a branded drug due to government price setting on the number of generic or biosimilar entrants in Medicare and their associated prices.
- **Focus on cost over health or equity:** Existing models do not adequately consider the health or health equity effects that would come from reducing new drugs or R&D on existing drugs.

Building a well-defined model of a representative firm's investment decision-making, as the CBO aims to do, also requires more information than is available today about how capital is allocated between multiple potentially profitable projects, and an adjustment in the assumptions regarding the risk profile of decision-makers at each phase of development. Better information is needed about how investors respond to changes in risk, even when it is believed the project may still return a positive investment. In particular, evidence is needed to better understand the implications of reducing revenue toward the end of the drug lifecycle as occurs with the government price setting elements of the IRA.

Firm Decision Simulation Models Lack Evidence

- **Reasons drugs are not developed:** The only data currently available is for drug candidates that are being advanced through the development pipeline. There is a lack of available information about the characteristics of the candidates not developed to inform what projects may be dropped due to profitability or science.
- **Capital mobility:** Assumptions may not reflect the mobility of capital. For example, the CBO assumes that all candidates with a non-zero expected return will receive R&D investment. In reality, firms allocate their investment to the highest return and make trade-offs between investments, including outside of biopharmaceuticals for venture capital.

CALL TO ACTION: IMPROVING THE ASSESSMENT OF POLICY IMPACTS ON DRUG DEVELOPMENT

The CBO recognized the limitations in the existing evidence by announcing "A Call for New Research in the Area of New Drug Development," including a request for more specific information about how changes in the expected financial return, or market size, for differing therapeutic areas or modalities like small vs. large molecules affect investment decisions.[9] In addition, the call recognizes that there is a need to better understand the holistic impact of the policy, such as how investment in drugs affects health outcomes or post-market indications. Other important effects are not known such as the potential impact on formulary access or therapeutic competitors for drugs selected for government price setting, which could further impact incentives to invest in R&D for affected classes.[10]

We also suggest that the methods and assumptions in these models should more accurately reflect firm decision-making and the mobility of capital. Generating this evidence is not solely the responsibility of government agencies such as the CBO but of institutions and researchers as well. Government however can support the proliferation of analysis and evidence that would enable the CBO to build better models by providing greater access to data about drug utilization and clinical trials and showing receptivity to integrating new evidence as the CBO has in their call for information.

In light of the limited evidence to describe how these biopharmaceutical policies will affect health, U.S. competitiveness, and institutions, there is a need to refine the models that estimate their impact. Furthermore, the U.S. federal government owns a trove of data that can inform the impact of policy and can make that information more accessible to independent researchers who may use it to investigate the impact of policy change. Without such information, it is not sensible to expand such policies further. Doing so puts at risk an industry that has dramatically reduced mortality from cardiovascular disease, cancer, HIV, and infectious pandemics.

Policymakers also lack evidence of how such policies are expected to impact health, well-being, and longevity. Equity is not currently a central consideration, such as whether drugs not developed, or the post-market studies foregone, are likely to affect a particular race, ethnicity, age, or disease state. Moreover, the dynamic effect is not estimated, meaning there has been no assessment of whether the short-term budgetary savings from a policy funded by government price setting outweigh the loss of health from less clinical development or spending on future healthcare services for which drugs may be a substitute.

Policy assessment is not just the domain of federal agencies. Researchers in academia, think tanks, and private organizations have historically contributed to the body of evidence that informs policy. Given the complexity of R&D investment decision-making and the lack of available evidence on its relationship to the expected financial return from an approved medicine, it is not clear that having organizations like the CBO (or the CBO alone) assess policy impacts is necessarily in the best interest of health and wellbeing. Analysis of policy impact should be held to the same standard as academic research—it should be rigorous, replicable, reproducible, and independently verified. Moreover, it should represent the magnitude of uncertainty in the estimates.

More estimates of the impact, each considering the relevant aspects of major policy change such as on new drug development, access to medicines for all populations including people who are often underserved by the health system, and the health effects of price setting or other policy that affects the expected financial return from an approved medicine, will lead to more informed and better decision-making. There is a wide degree of variation in the approach to and estimates of this type of policy change, indicating that there is still a lot to be studied. Policymakers need to demand better and more accurate evidence of the impact of policy change of this magnitude.

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