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CENTER FOR LIFE SCIENCES INNOVATION

Evidence-Based Biopharmaceutical Policymaking: Symposium Report

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There is a need for more rigorous evidence and more recent, high-quality data to inform biopharmaceutical policymaking by shedding light on the relationship between pharmaceutical firms' expectations of financial returns from new drugs and their ability to invest in further R&D to discover future generations of drugs.

OVERVIEW

The Information Technology and Innovation Foundation (ITIF) convened an expert symposium on October 10, 2024, to discuss the evidence that is currently available to assess financial returns from clinical development of biopharmaceuticals, and to consider related questions such as how investors measure financial returns, how drug development has evolved in the past 10 years, what kind of information is most useful in guiding biopharmaceutical policy, and what factors drive further innovation after drugs are initially launched. This symposium report summarizes the key elements of the discussion.

Although there are many observational studies on the relationship between investment in clinical study and expected financial reward from drug development, the data is outdated, as ITIF has documented.[1] So, to support the development of better evidence, ITIF is sponsoring a grant program and a special issue of *Health Affairs Scholar*.[2] ITIF will award three grants under the program, each worth $50,000, and the winners will be invited to submit their research to be considered for publication in the special issue of *Health Affairs Scholar*. Further details, including proposal guidelines and due dates, are available from ITIF's Center for Life Sciences Innovation.[3]

SYMPOSIUM REPORT

ITIF's October 10 symposium featured two presentations on the evolution of drug development and the current state of evidence related to financial return and clinical development, and how it informs policy for biopharmaceuticals. The symposium also featured three expert panel discussions on what kind of data and information is useful to guide policy, how investors consider financial returns on drug research and development (R&D), and how decisions are made to pursue additional indications of a drug. See the attached agenda.[4]

The Current State of the Evidence Related to Financial Return and Clinical Development for Medicines

Research based on 19 expert interviews indicates that the elasticity of innovation—how responsive innovation activity is to changes in various economic or market conditions—varies by the size of the market shock, the firm size and type, and the therapeutic area.[5] Respondents asserted the assumptions of the Congressional Budget Office's (CBO's) current model do not adequately reflect the impacts of investors' decision-making. The ecosystem is diverse, capital is mobile, "big bets require big returns," and R&D is more expensive today than in the past. The Inflation Reduction Act (IRA)—which established a program to control drug prices by empowering the Secretary of Health and Human Services to negotiate prices for a list of drugs through Medicare Part D—is already having an impact on investor behavior, particularly in reducing interest in small molecule, orphan drugs, and extending drugs to additional indications.[6] Moreover, investors' risk tolerance decreases throughout the drug development pathway.

How Investors Consider Financial Return When Making Investments

This panel discussion considered approaches to analyzing the impact of a change in policy on investor behavior, particularly in early-stage research. The panel asserted that the IRA is having a sizeable impact on small-molecule investments, particularly in early-stage companies, with later-stage investments less affected.

Mobility of capital is an issue for investors. Biopharmaceutical companies compete with private equity, leveraged buyouts, real estate, artificial intelligence (AI), and other industries for funding. Venture managers are typically evaluated on an internal rate of return (IRR) tracked on a quarterly basis compared to other industries.[7] The needed return on investment (ROI) for biopharmaceuticals is high (15 percent to 35 percent) because it usually takes 10 to 15 years to return capital to investors and there is a lot of failure in clinical drug development. Investing partners will shift out of biotechnology funds that have a lower IRR if their portfolios become less valuable due to a policy change like the IRA.

While venture funding has not necessarily decreased in total, that does not mean the IRA is not changing investment patterns in early drug development. Already, investors are reconsidering small molecules if the drugs in question have one orphan indication or if they are for the Medicare population. Investors are not putting funds into the development of secondary indications because they are not likely to produce a return in a price-controlled environment. Most successful orphan drugs resulted from multiple indications. It remains to be seen how this impact can be measured, but it is a topic of discussion and affects investor actions.

For small biotechnology ventures, speed to market and capital efficiency are essential because they have less money and resources. Small biotech companies usually launch in small markets, and it takes a long time to develop and eventually launch drugs in larger indications. The IRA disincentivizes launching in small indications first because companies only have nine years before price controls are (possibly) imposed. Companies are being incentivized to launch in bigger indications such as front-line breast or prostate cancer, and small biotech companies cannot afford such clinical trials. While the government invests in early drug development, the costs of R&D are large enough that private capital is needed even in early stages. National

Institutes of Health (NIH) funding is not sufficient to make up for the loss of expected investment as a result of the IRA.

Many biotech companies are in an arms race to manufacture better versions of blockbuster drugs. Competition drives down net pricing and expands therapeutic options. For selected drugs in Medicare, the revenue window is now only five to seven years, which is not worth it, especially for follow-on investors.

An important consideration for a biopharmaceutical policy's implications would be whether it would harm the United States relative to other countries. Strong science, safety regulations, venture capital, and intellectual property (IP) protections are needed to develop a drug successfully. The United States provides all of those, which is why it is leading the world in this industry. The IRA is antithetical to innovation and dangerous from a national security point of view, and a policy to expand price setting or shorten the time period for market-based pricing would harm investment in drug development. The panel also discussed how to connect the process of investor decision-making to the impact investments have on patients when engaging with policymakers to make the issue more salient.

The Evolution of Drug Development and How It Affects Investment and Risk

There are several areas that have meaningfully changed in drug development over the last decade.[8] These include investment flows in biopharma, the role that emerging biopharma companies play in R&D ecosystems, the geographic mix of companies sponsoring clinical trials, global approvals and launches of new drugs, clinical development success rates, the complexity of trials as a proxy for cost, timelines for clinical development, and how trials are designed and executed. This presentation reflected data from IQVIA Global Trends in R&D 2024.[9]

R&D spending for the 15 largest pharmaceutical companies in 2014 was $87 billion, and in 2023 it doubled to $163 billion. Most companies have shared assets and businesses that are not core to biopharma innovation. Venture capital flows grew from $14.3 billion in 2014 to $54 billion in 2021 and $30.6 billion in 2023. The number of clinical trials peaked in 2021, and there has been a 22 percent decline since then in clinical trial starts, but this cannot be attributed to the IRA impact due to confounding factors like the impact of COVID-19 on reducing trial starts and a pullback by larger companies because of interest rate issues. Most clinical trial starts are funded by small and emerging biopharma companies that have taken over the innovation space. Emerging biopharma companies are holding onto their assets longer and then selling to large firms.

The geographic mix of companies sponsoring trials has shifted as China-headquartered companies have expanded their presence. Europe has lost out in terms of being a center for companies to originate and start trials. Clinical development focus has shifted toward oncology, rare diseases, and novel modalities over the past decade. The characteristics of the Novel Active Substances (NASs) launched in the Unites States have trended toward specialty, biologics, orphan drugs, and first-in-class.

Phase and composite success rates have generally decreased over the past decade, with some uptick in 2023. Clinical trial complexity has increased with more eligibility criteria, subjects, and endpoints in the past 10 years. Enrollment is taking longer across all phases of development, increasing by 56 percent over this period. Trial durations have declined, while the "white space"

before starting a subsequent clinical trial phase has increased. White space time is spent on decision-making and the commercial opportunity of these trials. Most approvals are on an expedited regulatory pathway with a median overall development duration of one to two years faster.

Kinds of Data and Information That Are Useful in Guiding Policy

This panel discussion noted that CBO is charged with evaluating the effects of legislation on the federal budget. Much of the data is not created by CBO and comes from external experts. Congress acts on specific estimates, not on ranges or uncertainty. CBO is always looking for more information, and often has to buy private data. Congress recently passed legislation that gave CBO more federal data access.

It is difficult for academics to understand, gain access to, and use, federal data.[10] Academics quantify drug R&D through measures such as clinical trials and new molecular entities and use countries and disease burdens as proxies for market size. Different studies use different metrics and therapeutic classes, yielding different results. The cost of R&D has also been increasing over the years.

CBO's assumptions are only as good as the existing literature, so new evidence is needed. The IRA will negatively affect revenue and certainty, but it is unclear how much and what the effects will be on shortages, prices, and R&D investment. An investment looks at lifetime revenues, so it is essential to consider dynamic efficiency and the elasticity of innovation. CBO and researchers in other organizations have grappled with measuring the value of drug R&D output.

80 to 90 percent of healthcare spending in the United States is on chronic diseases, but it is difficult to attribute cost savings to drugs alone because of limited evidence. Innovation in this field must go beyond health-sector costs. There is a misalignment between politicians' incentives and patients' best interests.

The panel discussion also emphasized the importance of having good data on R&D structure. A big part of the cost of R&D is failure, and researchers and the public need to know those costs.

Post-Market Development Decisions

This panel discussion included a recent paper examining 155 drugs initially approved in oncology indications in the United States between 2000 and 2021. Of the highlighted findings, there is a substantial amount of post-approval investment in innovation. For example, for new drug indications, roughly half of the drugs had at least one post-approval indication; 90 percent of drugs had at least one post-approval trial; and about half of the drugs in oncology are in new disease areas for that drug.[11] While this analysis is not a forecast, it provides a useful baseline for further analysis. Half of the drugs had new indications, and those generally need trials that take up to six or seven years. One researcher found that post-approval indications are essential and reflect a 40 percent share increase of prescriptions compared to initial indications. The market learns from small indication trials, which takes time, and this scientific ecosystem drives medical innovation. The IRA impacts clinical research on small patient populations.

Biopharmaceutical companies have certain expectations for the profitability of the whole lifecycle of a drug. It is risky to invest in clinical research, but it is necessary, so the more the risk can be mitigated, the more it will benefit clinical development. A critical question that companies ask

themselves when deciding whether to pursue the development of a drug is: What is the potential of the drug in 10 years? The more certainty in the regulatory environment, the better for investment. Further, investors can only buy small biotechnology companies if they expect to earn a return. One of the panelists noted that companies are probably not getting better at identifying successful assets early on, which is why they should continue to invest in costly and risky R&D. New technologies such as AI might help with identifying successful leads early on, but health care and the human body are complicated, and it can be quite challenging to explain why one drug works in one person and not in another.

More in This Series

Other publications in this series are available through ITIF's Center for Life Sciences Innovation. To read the whole series, search #BiopharmaPolicyEvidence on itif.org.

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About ITIF

The Information Technology and Innovation Foundation (ITIF) is an independent 501(c)(3) nonprofit, nonpartisan research and educational institute that has been recognized repeatedly as the world's leading think tank for science and technology policy. Its mission is to formulate, evaluate, and promote policy solutions that accelerate innovation and boost productivity to spur growth, opportunity, and progress. For more information, visit itif.org/about.

ENDNOTES

1. Kirsten Axelsen and Sandra Barbosu, "The Relationship Between Biopharma R&D Investment and Expected Returns: Improving Evidence to Inform Policy" (ITIF, May 2024), https://itif.org/publications/2024/05/06/relationship-between-biopharma-rd-investment-expected-returns/.
2. Sandra Barbosu, Kirsten Axelsen, and Stephen Ezell, "Evidence to Inform Biopharmaceutical Policy: Call for Research on the Impact of Public Policies on Investment in Drug Development," *Health Affairs Scholar*, October 10, 2024, https://doi.org/10.1093/haschl/qxae129.
3. See: ITIF Center for Life Sciences Innovation, "Call for Grant Proposals on Evidence-Based Biopharmaceutical Policy," at: https://itif.org/publications/2024/10/03/drug-development-proposals/.
4. ITIF Center for Life Sciences Innovation, "Investment in Clinical Trials and the Expectation of a Financial Return: Developing Better Evidence to Inform Biopharmaceutical Policy and Regulation," October 10, 2024, https://www2.itif.org/2024-biopharma-evidence-agenda.pdf.
5. Graham Cookson presentation to ITIF's symposium on evidence-based biopharmaceutical policymaking, "Current State of the Evidence Related to Financial Return and Clinical Development," October 10, 2024, available at: https://www2.itif.org/2024-cookson-drug-return-evidence.pdf.
6. Inflation Reduction Act of 2022, H.R. 5376, 117th Congress (2022), https://www.congress.gov/bill/117th-congress/house-bill/5376/text; Stephen Ezell, "Senate Reconciliation Legislation Fails to Reconcile the Interests of Biomedical Innovation and Drug Price Affordability," ITIF *Innovation Files* commentary, August 5, 2022, https://itif.org/publications/2022/08/05/senate-reconciliation-legislation-fails-to-reconcile-the-interests-of-biomedical-innovation-and-drug-price-affordability/.
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8. Murray Aitken presentation to ITIF's symposium on evidence-based biopharmaceutical policymaking, "Evolution of drug development: What has changed in the last 10 years?" October 10, 2024, available at: https://www2.itif.org/2024-aitken-drug-development-evolution.pdf.
9. IQVIA, "Global Trends in R&D 2024: Activity, productivity, and enablers," February 22, 2024, https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-trends-in-r-and-d-2024-activity-productivity-and-enablers.
10. Panelist Kosali Simon of Indiana University has worked on efforts to expand access to federal data, https://oneill.indiana.edu/faculty-research/directory/profiles/faculty/full-time/simon-kosali.html.
11. Henry Grabowski, Joseph A. DiMasi, and Genia Long, "Post approval Innovation For Oncology Drugs And The Inflation Reduction Act," *Health Affairs*, Vol. 43, No. 10, https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2024.00202.