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Abstract

Essays on Government Policy and Pharmaceutical Innovation

Margaret E. Blume-Kohout

New drug therapies may deliver many social and economic benefits, but current levels of innovation across diseases may not be socially optimal. This dissertation investigates two mechanisms by which governments may influence pharmaceutical research and development (R&D) priorities: (1) public funding for life sciences research; and (2) prescription drug insurance, as in Medicare Part D. The author finds federal funding for life sciences research spurs non-federal investment in academic R&D as well as downstream drug development. Likewise, introduction of Medicare Part D increased both the number of drugs entering clinical trials and firm R&D expenditures for higher-Medicare-share drugs.

Executive Summary

Essays on Government Policy and Pharmaceutical Innovation

Margaret E. Blume-Kohout

U.S. pharmaceutical and biotech industry research and development (R&D) expenditures have grown exponentially over the past three decades. The number of new drugs approved, however, has decreased in recent years, prompting some observers to argue that this industry is in a state of innovative crisis.

While in general public mechanisms for influencing private sector innovation have yielded mixed results, a select few policy levers in the pharmaceutical and biotech industries have proven more effective. For example, publicly-funded life sciences research at universities, while yielding relatively few new drugs compared to R&D at private pharmaceutical and biotech firms, has instead prompted molecule discovery and process innovations that in turn have contributed significantly to industry R&D projects.

Federal funding for biomedical research may therefore act as a cost-reducing subsidy to the pharmaceutical industry, through its production of basic scientific knowledge and training of the biomedical labor force. As such, increases in federal funding for research on particular diseases has potential to influence private firms' R&D priorities. On the other hand, economic theory suggests that increases in federal funding for R&D may discourage non-federal investment, thereby reducing the effectiveness of federal funding in achieving public aims.

In addition to this supply-side «push» mechanism, there is also evidence suggesting demand-side «pull» mechanisms may encourage greater pharmaceutical innovation. For example, recent evidence suggests that Medicare Part D has increased prescription drug use among the elderly, and earlier studies have indicated that increasing market size induces pharmaceutical innovation. Thus, one might expect the pull of increased revenues under Medicare Part D to have influenced firms' R&D portfolios.

This dissertation examines the impact of federal funding for life sciences R&D on non-federal investment in academic life sciences R&D and downstream drug development, and the impact of the introduction of Medicare Part D prescription drug coverage on pharmaceutical industry R&D. Our results imply that demand-side interventions that increase market size and revenues for pharmaceutical firms will have greater impact on pharmaceutical R&D per federal dollar spent than supply-side funding increases for disease-specific research.

University Life Sciences R&D Funding

This chapter investigates the effect of federal funding on non-federal funding for university life sciences R&D at U.S. universities, to determine whether federal funding for university life sciences R&D spurs funding from non-federal sources. Economic theory suggests that federal funding for R&D could "crowd out" investment by fully-informed non-federal funders, thereby reducing its effectiveness. Federal funding for R&D could also make universities less inclined to pursue other funding sources. For any

of these reasons, a dollar increase in federal funding could yield less than a dollar increase in total R&D.

Our results indicate that a dollar increase in federal funding leads to $0.33 in additional non-federal funding at U.S. universities. In addition, receipt of federal funding may provide useful information to non-federal funders the quality of the program in question; non-PhD-granting universities, lower-ranked universities, and universities which historically have received less funding from all sources are among those who experience greater increases in non-federal funding for each federal dollar that they receive. This suggests that successful applications for federal funding may be interpreted by non-federal funders as a signal of university quality.

This paper examines for the first time the particular case of federal life sciences funding (mainly originating from the NIH), highlighting the varying effects across universities with differing characteristics, and extending earlier work with more current data from a variety of sources. We construct a new instrument that allows us to infer causality despite the presence of unobserved variables that may impact both federal and non-federal funding at a given university over time.

Data for this chapter is derived from the NSF Survey of Research and Development Expenditures at Universities and Colleges, and administrative records maintained by the Office of Extramural Research at NIH. Within the NSF survey we look at universities' total and federally-funded R&D expenditures by year and field for 1998 through 2006.

We use a fixed effects instrumental variable (IV) approach to infer causality despite unobserved variables that may contribute to both federal and non-federal funding at universities. For example, university fixed effects combined with our IV model allow us to control for bias stemming from both university-specific characteristics such as size of the faculty, and time-varying university-specific characteristics such as a university's decision to diversify funding sources. Through a series of investigations, we also show that our constructed variable, predicted NIH funding, is a useful instrument for the total federal life sciences R&D funding a university receives, and allows us to attribute causality to federal life sciences and NIH funding.

By enabling universities to attract more private resources, federal life sciences R&D funding may also influence the eventual commercialization of university research. However, to understand the mechanisms by which federal funding results in commercial products such as life-saving drugs, it would be necessary to look at broader outcomes such as university patenting and licensing behavior, and alliances between universities and the private sector.

Impact of NIH funding on Biopharmaceutical Industry R&D

Chapter III explores the impact of NIH funding on biopharmaceutical industry R&D. The NIH is the world's largest single institution supporting life sciences research; however, very few studies have investigated the relationship between these federal expenditures

and industrial innovation. In part, NIH funding subsidizes pharmaceutical firms by producing scientific knowledge and by training the biomedical labor force. This chapter explores the impact of federal funding for particular diseases on pharmaceutical and biotech firms' R&D priorities.

Our study finds that a 10% increase in NIH funding yields a 3-6% increase in drugs entering Phase I trials, reflecting the impact of NIH funding on truly novel drugs. We also find that changes in aggregate NIH funding levels by disease have no impact on the number of drugs entering later-stage Phase II and Phase III trials. The more significant effect we find for Phase I trials may indicate that NIH biomedical research funding has its greatest impact on development of novel molecules, but relatively little effect on success of those molecules in clinical testing and/or investigation of supplemental indications for an already-marketed product.

Prior research estimated that a permanent 10% increase in NIH research funding led to a 6% increase in approved new molecular entities (NMEs), or early-stage potential drugs. In our work, we disaggregate both NIH research funding and drug development to the level of individual diseases, or groups of similar diseases treated by similar drugs. We are therefore able to obtain more precise estimates while controlling for differences in drug development across diseases.

Data regarding the funding itself was obtained from the NIH's database of federally funded biomedical research projects. A catalog of the drugs in clinical trials was obtained

from a commercial database, Pharmaprojects, which collects data on the R&D activities of pharmaceutical and biotechnology companies. The potential market size of a particular drug or class of drugs was derived from data from the Medical Expenditure Panel Survey.

Almost a third of pharmaceutical R&D expenditures are for post-approval R&D, such as new uses for existing products, or new indications for existing drugs or combination therapies, rather than for new drugs altogether. Because these new indications may be just as socially useful as the new drugs themselves, our work investigates all clinical trial activity, regardless of the novelty of the drug molecule itself.

We first apply an ontology-enriched document classification algorithm to assign NIH grant abstracts to one or more specific diseases. Then, using time-series data on drugs entering clinical development from 1998-2007, we evaluate the impact of changes in lagged funding levels for each disease on industry R&D. We also control for products' potential market size at the expected time of product launch.

While our work confirms a positive impact of NIH funding on novel drugs entering clinical development, further research is needed to determine whether existing levels of industry R&D by disease are socially efficient, and whether the current mix of NIH funding mechanisms provides the best support for efficient development of new treatments and prevention of disease.

Medicare Part D

We investigate the implications of the introduction of Medicare Part D prescription drug coverage on pharmaceutical R&D. Medicare Part D, which went into effect in 2006, increased prescription drug use among the elderly. By increasing overall market size and expected revenues from the dual-eligible population, Medicare Part D should be expected to result in increased pharmaceutical R&D. Our work confirms that the increased outpatient prescription drug coverage provided through Medicare Part D has had substantial short-run impact on pharmaceutical R&D, both in terms of drugs entering clinical development and R&D expenditures for firms with higher Medicare market share

Firstly, our research shows that after the passage of Part D, there is a significant connection between changes in the number of drugs entering Phase I, Phase II, and all clinical trials, and the share of prescriptions in that drug class that were filled by Medicare beneficiaries. For the average Medicare market share class, we estimated 31% increase in Phase I trials, a 44% increase in Phase II trials, a 60% increase in Phase III trials, and a 40% increase in all clinical trials versus expected trends.

Furthermore, prior to the passage of Medicare Part D, certain drugs were already covered under Part B. Because many of these did not experience a significant shift in insurance coverage with the passage of Part D, we would expect relatively lower effects of Part D on R&D spending for these classes. Our research confirms this assumption.

We also consider possible dynamic effects of Medicare Part D over the course of Part D's legislative life: when it was under debate in Congress, when it had been passed, and finally, after its implementation. Our research reveals that in the uncertain, pre-signing climate of 2003, the pharmaceutical industry appears to have cut back the most expensive, late-stage trials, but predominantly for classes with lower Medicare share. Between 2004-2005 and 2006-2007, however, the number of Medicare Part D drugs entering all three trials is significantly higher than would have been expected based on prior trends. But because the *total* number of drugs entering clinical trials post-2003 did not increase significantly, the shift toward clinical trials for drugs with high Medicare market share may have come at the expense of new drugs for diseases which predominantly affect younger people. So while Medicare Part D is associated with dramatic increases in R&D for high-Medicare-share classes, this effect is being tempered either by contemporaneous decreases in overall R&D productivity, or by targeted substitution away from low-Medicare-share classes. Furthermore, the relatively rapid increase in number of Phase III clinical trials following Part D may be for drugs that were "on the shelf" and responsive at the margin to the increase of net present value presented by Part D, or were already marketed, and/or combination therapies that had already been tested in humans.

Finally, we expected that firms with more exposure to changes in the Medicare market would have greater percentage increases in R&D expenditures after the passage of Part D. To test this hypothesis, we investigate whether firms that already had higher average Medicare market share R&D portfolios prior to Medicare Part D also had greater

percentage changes in R&D investment after passage of the legislation. Even after controlling for year-to-year variations in overall R&D expenditures, we find that changes in firms' R&D expenditures after passage of Part D are not only positively correlated with their portfolio Medicare share, but that Medicare share becomes more important as a determinant of R&D expenditures over time.

For these investigations, time-series data on the number of drugs by therapeutic class at each stage of the pipeline is derived from the Pharmaprojects trend data "snapshot" published each year between 1998 and 2007. We estimate the total share of prescriptions filled by Medicare-covered individuals for each therapeutic class using data from a 2004 Medical Expenditure Panel Survey (MEPS) of US civilian non-institutionalized individuals. We then match Pharmaprojects therapeutic classes to those from the MEPS prescription data, to estimate Medicare market share for each drug class.

A list of publicly-traded pharmaceutical firms was generated using Compustat, for which we then calculate the weighted average Medicare share of the firm's baseline clinical portfolio, as the sum of the MEPS-estimated Medicare share for each drug in the firm's clinical portfolio from 1998-2002, divided by the total number of drugs in the portfolio. After inflating the firms' R&D expenditures to 2006 dollars, we examine spending over time. We find that real R&D expenditure growth overall slowed after 2003, and increased again in 2006.

Despite these significant short-run results, we cannot yet determine whether Medicare Part D will result in more or better drugs entering the market, both due to the relatively short time-series of data available for this research post 2003, and because R&D is an imperfect predictor of the number and quality of new drugs ultimately developed.

Conclusions and Future Research

Based on this work, we conclude that demand-side interventions that increase market size and revenues for pharmaceutical firms will have greater impact on pharmaceutical R&D per federal dollar spent than supply-side aggregate funding increases for disease-specific research. For example, a 1% increase in expected revenues due to increased market size is associated with a 3% increase in drugs entering Phase I trials, while in contrast, a sustained 1% increase in aggregate NIH funding for a given disease is associated with only a 0.3%-0.6% increase in drugs entering Phase I trials.

More research is needed to determine the relative efficacy of specific research funding mechanisms, the role of university and firm alliances and university intellectual property protection, and the more general effects of NIH funding, for example through training of the scientific workforce, in promoting downstream drug development.