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R&D policy, agency costs and innovation in personalized medicine☆

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ABSTRACT

The Orphan Drug Act (ODA) was designed to spur the development of drugs for rare diseases. In principle, its design also incentivizes pharmaceutical firms to develop drugs for "rare" subdivisions of more prevalent diseases. I find that in response to this incentive, firms develop drugs for ODA-qualifying subdivisions of non-rare diseases. The impact in these tailored drug markets represents half of the total R&D response to the ODA. I also find that 10-percent of the innovation in subdivided disease drugs induced by the ODA would have been conducted without the policy. While modest in size, this inefficiency suggests that agency problems should be considered when designing innovation policy.

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1. Introduction

A widely held view is that market failures lead to inefficient allocation of R&D investments. If so, there is scope for the development of welfare-improving policies to alter firms' R&D activities. When it is impractical to implement optimal corrective measures, incentive mechanisms are chosen from the set of available "second-best" policies. These policies are designed to stimulate private R&D investments; at the same time, they are thought to be associated with inefficiencies (Arrow, 1962; Lazear, 1996; Hall, 2002). Despite its importance for innovation policy, little empirical work has been devoted to studying how specific policy mechanisms affect private innovation, or to identifying empirically the source and extent of inefficiencies related to the design of incentives.

In this paper, I study these issues in the context of pharmaceutical innovation. The pharmaceutical industry has been one of the most innovative industries over the past half century, and one whose innovations embody substantial technological progress (Lichtenberg and Virabhak, 2002). Specifically, I study the private R&D investment response to incentives created by the Orphan Drug Act (ODA). Passed in 1983, the ODA established supply and revenue-side incentives to stimulate drug development for rare diseases, defined as diseases with prevalence less than 200,000 Americans. Passage of the ODA provides an ideal setting in which to test whether tools at the disposal of policy-makers are able to stimulate innovation in areas where private R&D is deemed inadequate.

Previous studies of the ODA estimate a significant private R&D response to incentives created by the ODA (Lichtenberg and Waldfogel, 2003; Yin, 2008). Yin (2008) finds a significant increase in the flow of new clinical trials for drugs treating rare diseases immediately after the ODA was passed relative to the flow of new drug trials for a set of control diseases—uncommon disease but with prevalence slightly above the ODA threshold. The set of diseases comprises nearly twelve hundred low-prevalence diseases known to exist at the time the ODA was passed. As such, these diseases represent a set of the most widely recognized, long-established, rare diseases that lawmakers hoped would be affected by the ODA.

Notably, these studies focus only on traditionally defined rare diseases, and do not study the impact of the ODA on innovation in more prevalent, non-rare disease drug markets. While the ODA was created to spur the development of drugs for traditionally defined rare diseases, its design may also have encouraged firms to define and then to develop drugs tailored to treat distinct subsets of patients within traditionally defined disease populations. Under the ODA, subdivisions of traditionally defined diseases qualify as rare in and of themselves so long as the patients carved out by

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firms for clinical drug trials number fewer than the ODA prevalence threshold. This holds even if the prevalence of the unsubdivided traditionally defined disease exceeds 200,000. (Henceforth, I refer to these disease subdivisions as “ODA-qualifying subdivisions.”) Consistent with these ODA incentives, the post-ODA period is witness to a profusion of clinical trials for drugs indicated for newly defined diseases that distinguish patients according to their heterogeneous drug response, co-morbidities, or disease severity, each of which alter the risk–benefit profile of drug utilization.[1] The potential impact of the ODA on greater “personalization” in pharmaceutical treatment has significant clinical implications. Indeed, the use of genetic and genetic-environmental markers to distinguish patients who share the same traditionally defined disease phenotype by their drug response is widely thought to be a potential basis of future drug innovation (Collins et al., 2003; Couzin, 2005; Aspinall and Hamermesh, 2007). Yet to date, little attention has been paid to the economic principles underpinning innovation in these markets. The ODA offers a unique opportunity to study how innovation policy can affect pharmaceutical R&D, particularly in the emergent and clinically important market for more personalized drugs.[2]

In this study, I use the passage of the ODA to test whether firms respond to innovation incentives. In particular, I investigate whether the ODA spurred innovation in drugs that treat ODA-qualifying subdivisions of non-rare diseases—a behavior I call “indication-subdividing.” To estimate the impact of the ODA on indication-subdividing, I construct a unique dataset of new clinical drug trials conducted in the US. I then estimate the extent to which firms conduct new drug trials for ODA-qualifying subdivisions of a set of long-established, traditionally defined, diseases.

One challenge in conducting this analysis is to designate control diseases to capture secular trends in pharmaceutical R&D unrelated to the passage of the ODA. Simply estimating the change in the extent of indication-subdividing around the passage of the ODA captures both the response of interest as well as changes in pharmaceutical market coinciding with the ODA. At first glance, it would seem that the ODA created incentives for firms to subdivide *any* traditionally defined disease, leaving no obvious set of diseases to function as a control. However, I show that firms have an incentive to subdivide only those diseases with prevalence slightly higher than 200,000, i.e. “uncommon non-rare diseases.” Diseases that firms have no incentive to subdivide in response to the ODA are used as controls. I interpret increases in the flow of R&D for ODA-qualifying subdivisions of uncommon non-rare diseases, netting out observed subdividing for control diseases, as an estimate for the predicted behavior.

The intuition guiding this prediction is straightforward. Conventionally, a firm conducts clinical trials to test a drug on patients it believes the drug will benefit. Once the drug is approved by the FDA, the firm can market the drug for the purpose indicated on its drug label—i.e. treatment of the disease population on which the drug was tested and for which it was approved. The ODA subsidizes the development costs for drugs that treat patient populations with prevalence under 200,000, making it profitable for firms to carve out an ODA-qualifying subdivision of non-rare disease populations for clinical drug trials. However, indication-subdividing comes at a cost to the firm. By law, firms are prohibited from marketing their drugs for off-label uses (i.e. for patients with diseases not explicitly indicated on the approved drug label). For drugs with a large potential market, indication-subdividing leads to lost revenues from diminished sales to patients comprising its off-label market. If the off-label market is sufficiently large, then revenues lost will outweigh the benefits of the ODA incentives, making indication-subdividing an unprofitable strategy. Similarly, firms have little incentive to subdivide drug markets which, unsubdivided, already qualify as rare (traditional diseases with prevalence below 200,000). Firms thus have the greatest incentive to subdivide diseases with prevalence just above the ODA threshold—i.e. uncommon non-rare diseases.

I use a difference-in-differences strategy to estimate the extent of indication-subdividing (as measured by the flow of new clinical drug trials for ODA-qualifying subdivisions of traditionally defined disease) for a sample of uncommon non-rare diseases. Otherwise similar diseases with slightly lower or higher prevalence are used as controls. I estimate a substantial increase in the flow of new clinical drug trials for ODA-qualifying subdivisions of uncommon non-rare diseases relative to control diseases after the ODA was passed. As an alternative identification strategy, I exploit time series variation in rare-disease status for a small set of “status-changer” diseases—diseases that are rare at the start of the study period but grow in estimated prevalence to a level slightly above the 200,000 threshold at some point during the study period. Consistent with the predicted impact of the ODA, I estimate a significant and immediate increase in the flow of new clinical trials indicated for ODA-qualifying subdivisions following the loss of rare-disease status.

Note that subdividing may not necessarily represent *new* innovation. New clinical trials for ODA-qualifying subdivisions may represent R&D by firms which strategically redefine indications for drugs that would have been developed in the absence of the ODA. Thus, one challenge in interpreting the evidence is to quantify the extent to which new clinical trials for newly defined subdivided disease indications represent R&D that would have been conducted in the absence of the ODA. In drug markets where indication-subdividing occurs, some firms can earn rents in exchange for generating little new innovation.

Inefficient use of the ODA in this way is an empirical example of a principal-agent problem that can arise in any policy setting that subsidizes unobservable R&D. In these settings, firms can exploit the inability of asymmetrically informed regulators (in this case, the FDA or the tax authorities) to monitor pharmaceutical R&D effort; doing so allows firms to claim the subsidy while directing actual effort towards more lucrative projects, or towards projects that would have been undertaken in absence of the subsidy (Kremer, 2001; Hall, 2002). These principal-agent problems may also arise in more general settings. They may appear in both the basic research and the private R&D settings, and have motivated an extensive theoretical literature on optimal subsidy and compensation contracts.[3] Yet it is not clear to what extent information asymmetries lead to inefficiencies, particularly in the public R&D policy setting. The R&D data collected for this study capture the timing of new clinical trials, and identify the specific disease for which drugs under development are being tested. The disaggregated nature of the data

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[1] Patients with the same disease phenotype may differ in their etiology or clinical response to therapy. These differences give firms an incentive to develop differentiated drugs to capture a subset of patients for which the drug is clinically most appropriate. Examples of subdivided diseases include late-stage type-IV Parkinson’s disease and relapsing and remitting multiple sclerosis (MS). Note that while Parkinson’s disease and MS have estimated prevalence that exceed 200,000, late-stage type IV Parkinson’s disease and relapsing and remitting MS have estimated prevalence below 200,000, and are considered rare diseases for purposes of the ODA.

[2] Emphasis on personalized drugs has increased with a better understanding of how differences in genetic or genetic-environmental interactions lead to heterogeneous drug responses. Partitioning diseases according to “genotype drug response phenotype” necessarily segments existing markets into small component markets—a fact widely recognized as an economic impediment to innovation in personalized medicine (Garrison and Austin, 2006).

[3] See Lazear (1996) and Hall (2002) for reviews of this literature.

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