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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.

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

[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.

provides traction to study how agency problems associated with supply side R&D incentives leads to inefficiencies.

In an attempt quantify this type of inefficiency in the ODA, I estimate to what extent new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases are offset by simultaneous declines in new clinical drug trials for the corresponding *unsubdivided* traditionally defined disease indications. Calculations I present at the end of this paper indicate that roughly 10-percent of the estimated impact of the ODA on indication-subdividing would have been conducted in the absence of the policy. These results suggest that the ODA generates new R&D, particularly (and arguably unintentionally) in the direction of more personalized drugs with the potential to better-tailor drug therapies to patients. However, the evidence on inefficiencies adds a cautionary note, suggesting that concerns over agency costs associated with policies that subsidize unobservable effort may be well-founded.

This paper proceeds as follows. Section 2 describes the Orphan Drug Act and discusses the theoretical predictions of the ODA on the behavior of firms. Section 3 outlines the empirical strategy to test those predictions. Section 4 reports results of empirical analyses. Section 5 quantifies the extent of indication-subdividing and agency-related inefficiencies. Section 6 concludes.

2. Orphan drug act

2.1. ODA incentives

Between 1973 and 1983, only 10 drugs were marketed for rare-disease indications; and only 36 drugs had *ever* been approved for a rare disease by 1982 (HRSR, 1982). Pharmaceutical firms, however, frequently possessed drugs with potential benefits to rare diseases. Yet because these drugs were either not patentable or too costly to take through clinical trials (particularly in comparison to their low commercial demand) these drugs were "orphaned." These facts motivated passage of orphan drug legislation.

The 1983 Orphan Drug Act established two main incentives for firms to develop rare-disease drugs: an income tax credit equal to 50-percent of clinical trial expenses, and a marketing exclusivity provision.[4] The aim of the credit was to lower the cost of conducting human clinical trials. Clinical trials are conducted to test for safety and efficacy in order to gain marketing approval by the Food and Drug Administration (FDA), and account for approximately two-thirds of the total expenditures associated with drug development (DiMasi et al., 2003).

The original ODA was amended in 1984 to define orphan drugs to be those that treat diseases with prevalence below 200,000 Americans.[5] Sponsors of clinical trials submit applications to the FDA's Office of Orphan Product Development (OOPD) with epidemiological evidence that the drug treats a condition that has prevalence less than 200,000. The OOPD designates the drug an orphan if the evidence sufficiently and reliably supports that claim. Firms acquire the tax credit after their drug receives orphan designation.

2.2. Predicted impact of the ODA drug development

Consider all patients afflicted with a given traditionally defined disease. While these patients exhibit the same disease phenotype, they may differ in their clinical response to a given drug. A circular address model following Salop (1979) captures this heterogeneity, where patients with a given traditionally defined disease are uniformly distributed on a circle. Drugs are positioned at a finite number of locations on the circle. The clinical benefit of a given drug to a given patient is represented by the distance between them. On the production side, drug development has two cost components: a fixed cost of R&D and a marginal cost of drug production. For a given disease (and hence, a given drug market size θ), firms compete in a free-entry environment to develop drugs for patients on the disease circle.

Firms enter until revenues just offset the fixed costs of development. The equilibrium number of evenly spaced drugs, N^o, depends on several parameters: the fixed cost of drug development, the market size (which can also be interpreted as disease prevalence or expected revenue per patient), and the intensity with which distance to drugs affects utility. In equilibrium, the levels of R&D increase in market size. For very low-prevalence diseases, there is no entry because revenues are unable to offset the fixed cost of development. The ODA incentives are modeled as a decrease in the fixed cost of drug development.[6] This leads to higher levels of innovation, N^{ODA}, in drug markets that qualify as rare under the ODA ($\theta < 200{,}000$); and leads to a decrease in the no-entry market size. These predictions are formally modeled and investigated empirically by Yin (2008).

The present study examines the potential impact of the ODA on innovation in *non-rare* disease drug markets ($\theta > 200{,}000$). Under the ODA, subsets of these patients also qualify as having a "rare" disease so long as the distinct patient populations carved out by firms for clinical trials number less than 200,000. Consequently, firms have an incentive to first identify, and then to develop drugs tailored to, ODA-qualifying subdivisions of non-rare disease populations.

In the baseline model described above, firms choose the quantity of drugs to produce, Q, and price, P, to maximize profits. Further, a free-entry and a covered-market condition (so that every patient has unit consumption: $Q = \theta/N^o$) must hold in equilibrium. Now, I allow firms to partition a traditionally defined disease indication into (1) an on-label drug market Q_1 (the ODA-qualifying patient population for which it is tested and FDA approval is sought); and (2) an off-label market, $Q - Q_1$ (i.e. all other patients with the traditionally defined disease but who do not share the same treatment response profile of the patients carved out in Q_1). By redefining a drug's indication to an ODA-qualifying on-label population, the N^o firms obtain the ODA tax subsidy on clinical trials costs. These N^o firms earn positive profits, thereby encouraging entry of *additional* drugs. Entry generates a new zero-profit "subdividing" equilibrium,

[4] The ODA market exclusivity provision lasts seven-years starting from the drug's FDA approval date, and prevents competitors from marketing the same drug for the *same* approved rare disease. A competitor can still market the same drug for any other disease. While the market exclusivity provision is substantially narrower than a patent, it is beneficial for the development of drugs with little to no patent protection (e.g. naturally occurring compounds, drugs whose benefit and structure have been publicly disclosed, or drugs whose remaining patent life is short). A clinical superiority provision was added in 1991 to prevent competitors from making cosmetic changes to a drug and marketing it for the same rare disease. The 1991 amendment applies only when contested drugs share the same macromolecule; a competing firm may still seek approval for a distinct drug to treat the same disease, irrespective of the drug's clinical superiority.

[5] The 1983 ODA initially defined drugs that "lack commercial value" due to a small patient market to be orphan drugs. The difficulty associated with establishing unprofitability was blamed for the negligible R&D response by firms after the ODA was passed in January 1983. The relevance of the ODA is widely thought to have begun after the 1984 ODA amendment (Rohde, 2000).

[6] The effect of the ODA necessarily includes the impact of both the tax incentive and the market exclusivity provision. For simplicity, I model only the tax incentive. The market exclusivity provision could be modeled as some proportional increase in effective market size or revenue, $c\theta$, for $c > 1$. Note that the tax credit and the market exclusivity provision affect innovation in the same direction, and both affect innovation discontinuously at the 200,000 prevalence threshold. Thus, it is sufficient to show that one of the incentives leads to the subdividing behavior at the focus of this study.

N^{Sub}, characterized by a larger number of drugs relative to the no-ODA equilibrium, N^o. In the new equilibrium, average distance between patients and their nearest drug decreases. It is in this sense that the ODA fosters greater personalization in drug markets. This increase in subdividing can be tested empirically.

Note that in reality, each of the N^{Sub} drugs will be indicated for a subdivided disease. However, only $(N^{Sub} - N^o)$ drugs represent *new* innovation; N^o drugs would have been introduced in the absence of the ODA, and do not represent new innovation. Neither the FDA nor the tax authority can observe which drugs would have been developed in the absence of the ODA. Consequently, all N^{Sub} firms obtain the ODA incentives. The subsidy for N^o drugs (which would have been conducted in absence of the ODA, and which, in the subdividing equilibrium, are indicated for ODA-qualifying subdivisions of non-rare diseases) represents an agency-related inefficiency of the policy.

An important prediction of the model is that the subdividing equilibrium obtains in only certain markets. This fact guides the specification of treatment and comparison diseases when estimating the extent of indication-subdividing in response to the ODA. Intuitively, firms have little incentive to subdivide a traditional disease that is already rare; they can obtain tax credits without subdividing these patient populations. Likewise, firms have little incentive to subdivide diseases with high prevalence. While physicians are legally permitted to prescribe drugs off-label, firms are prohibited from advertising off-label uses of drugs to either patients or to physicians. Sales of drugs for off-label uses depend on knowledge of these non-approved uses diffusing through the medical community, a process which may be slow. For drugs that benefit very large patient populations, the loss in revenues associated with restrictions on off-label marketing outweighs the immediate benefit of the ODA tax credit. Indeed, beyond some threshold market size, θ^{Sub}, it is unprofitable for firms to engage in indication-subdividing.

More formally, note that the subdividing equilibrium will obtain only if the N^o firms in the prevailing equilibrium find it profitable to deviate by engaging in indication-subdividing. For the present purpose, it is not important to solve for the new equilibrium; it suffices to solve for θ^{Sub}, the market size at which the firms no longer earn positive profits by subdividing drug indications. This allows me to evaluate revenues at the prevailing equilibrium price without solving explicitly for the new zero-profit equilibrium under subdividing.[7]

In the prevailing no-subdividing equilibrium, total market revenue (of all symmetric, evenly spaced, firms) for a given disease's drug market of size θ is simply $R^{NoSub} = \theta p$, where p is the equilibrium unit price of the drug in the no-subdividing, no-ODA regime. The revenue can also be rewritten as $R^{NoSub} = k\theta_1 p$, where k is the constant multiple of the ODA-qualifying subdivision,θ_1, that defines the total size of the unsubdivided disease's drug market, θ. (Clearly, firms choose θ_1 to be 200,000, the ODA's maximum prevalence for a rare disease.)

The incentive for firms to subdivide drug indications stems from the ODA incentives for low-prevalence diseases, which I model as a tax subsidy on clinical trials costs. ODA-qualifying drugs have costs $F^{ODA} = \alpha F$, where $0 < \alpha < 1$ Firms will earn positive profits by deviating from the prevailing equilibrium by subdividing diseases with prevalence slightly higher than 200,000. Indication-subdividing will remain profitable for firms for all θ until revenues in the subdividing equilibrium $R^{Sub} = \alpha R^{NoSub}$.[8] (For larger drug markets, firms gain the ODA subsidy, but lose more revenue in the conversion of their drug's potential market to off-label status.) Collectively, the firms in a given market θ earn $R^{Sub} = \theta_1 p + \lambda \cdot p(\theta - \theta_1)$, where λ parameterizes the fraction of revenues from off-label sales that the firm is able to earn despite marketing restrictions. Tighter restrictions implies λ is closer to zero. θ^{Sub} can roughly be found by solving for the k that satisfies $(R^{Sub}/R^{NoSub}) \approx \alpha$. This yields $k \approx (1-\lambda)/(\alpha - \lambda)$. Consistent with the intuition of the descriptive model, θ^{Sub} depends on the degree to which marketing restrictions limit revenue from off-label sales. Tighter restrictions imply a smaller value for θ^{Sub}.

In summary, the model predicts a sharp discontinuity at 200,000 in prevalence in the incentive to subdivide disease markets; it also predicts a sharp decline in the incentive to subdivide diseases that have prevalence higher than θ^{Sub}. Specification of θ^{Sub} for the empirical analysis is discussed in the Section 3.

3. Empirical strategy

3.1. Control diseases

The empirical analysis relies on a comparison between uncommon non-rare diseases (for which I predict the ODA will have had an impact on indication-subdividing) and control diseases (diseases with prevalence slightly below 200,000 or those with prevalence above θ^{Sub}). A rough calibration of the model guides the choice of θ^{Sub} for the empirical analysis. The ODA subsidizes 50-percent of human clinical trials costs. Studies suggest that human clinical trials account for roughly two-thirds of all development costs (DiMasi et al., 2003). Therefore, the ODA lowers total development costs for ODA-qualifying drugs by roughly one-third ($\alpha = 2/3$). To determine a value for θ^{Sub}, I solve for the k that satisfies $(R_{NoSub}/R_{Sub}) = 2/3$. This yields $k = (1-\lambda)/(2/3 - \lambda)$. Complete loss of off-label revenue ($\lambda = 0$) suggests that the cut-off prevalence, θ^{Sub}, is $(3/2)\cdot\theta_1 = 300{,}000$. Perhaps a more reasonable calibration suggests that one-quarter to one-half of potential revenue is lost due to off-label restrictions. This implies the cut-off prevalence of roughly $(5/2)\cdot\theta_1$ to $3\cdot\theta_1$ (or roughly 500,000 to 600,000). Therefore, I define uncommon non-rare diseases to be diseases with prevalence between 200,000 and 500,000.

3.2. Data

The sample of diseases I use in this study come from a list diseases published by the National Organization for Rare Disorders (NORD), a not-for-profit agency established in 1983 to serve as a clearinghouse for information on uncommon and rare diseases. They publish a database of 1177 low-prevalence diseases known to exist at the time the ODA was passed. As such, these represent a large set of widely recognized, long-established, rare diseases that lawmakers hoped would be affected by the ODA. Given that the ODA (somewhat arbitrarily) set 200,000 as the rare-disease prevalence threshold, not all the diseases in the NORD list are rare. Indeed, a review of the epidemiological and medical reference literature allowed me to partition the NORD list into three groups: (1) 1023 rare diseases, defined as those with prevalence below the 200,000 threshold throughout the study period (nine of which have an

[7] There is no closed-form solution to the number of competing drugs in subdividing equilibrium, N^{Sub}; however it is straightforward to show that N^{Sub} exceeds the number of drugs in the prevailing no-ODA, no subdividing equilibrium, N^o, in markets where the subdividing equilibrium obtains.

[8] Technically, incumbents will cease to subdivide indications when $Cost^{Sub}/Cost^{NoSub} = \gamma = R^{Sub}/R^{NoSub}$, where $Cost^{Sub}/Cost^{NoSub} = (F^{ODA} + Qm)/(F^{ODA}/\alpha + Qm)$, and m is the marginal cost of drug production. When Qm is small relative to F (as is roughly the case with most drugs), then $\gamma \approx \alpha$. Note that as Qm increases relative to F, θ^{Sub} increases.

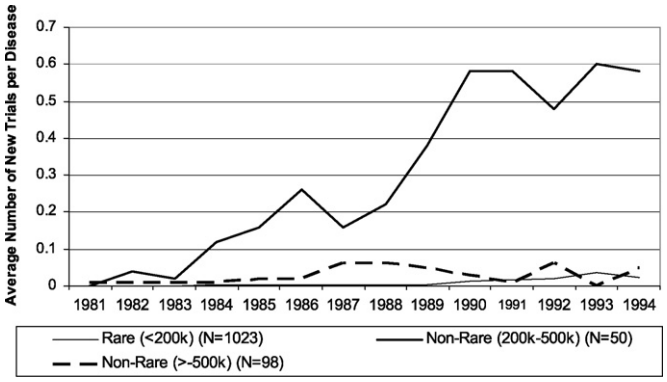

Fig. 1. New clinical drug trials for ODA-qualifying subdivisions of NORD diseases.

estimated prevalence between 100,000 and 200,000); (2) 148 non-rare diseases (of which 50 have prevalence between 200,000 and 500,000, and 98 have prevalence exceeding 500,000); and (3) six "status-changers" which move from being rare to non-rare during the study period.

I collect data on the number of *new* clinical drug trials for a given disease in a given year. New clinical trials (as opposed to new drugs brought to market, or the stock of clinical trials) have the advantage of reflecting investment decisions based on current market conditions.[9] The principal sources of data on new clinical trials data are two trade journals, *The NDA Pipeline* and *Pharmaprojects*, which closely track clinical trials conducted by all major pharmaceutical and biotechnology firms, as well as many small manufacturers and non-profit research institutions. The journals report on the clinical trials for all chemical entities known to the publisher, and include information on the indications for which a drug is being tested, the phase of its development, and whether the product has been previously marketed. This information is used to identify when a drug first appears in the pipeline for a specific disease indication. The *NDA Pipeline* is also the principal source of data used in other studies of pharmaceutical R&D (Finkelstein, 2004).

I assemble my dataset by recording when new clinical drug trials for diseases in the NORD list are first reported in these publications. The final panel dataset lists the number of new clinical trials indicated for each of the 1177 (unsubdivided) diseases in the NORD list, by year. Appendix Table A1 describes in more detail the process by which new clinical trials are counted. I construct a second panel dataset listing new trials indicated explicitly for ODA-qualifying subdivisions of NORD diseases. For example, a new clinical trial for late-stage type-IV Parkinson's disease appears as a new clinical trial in the second panel data set under Parkinson's disease. To track ODA-qualifying subdivisions, I strictly follow the typology of subdivisions outlined in Appendix Table A2. The final data are two balanced panels of clinical trial counts for the NORD diseases from 1981 through 1994.

The total number of new clinical trials for ODA-qualifying subdivisions of NORD diseases, grouped by the disease prevalence category over time is shown in Fig. 1. There is a noticeable increase in the relative number of new trials for ODA-qualifying subdivisions of uncommon non-rare diseases (those with prevalence between 200,000 and 500,000) starting in 1984. Summary statistics for the number of new clinical trials for ODA-qualifying subdivisions of traditional NORD diseases for 2 representative years are shown in Table 1 Panel A. The mean and distribution of counts by treatment group are shown for 1983 and 1985, the year before and after the critical 1984 amendment to the ODA was passed. Uncommon non-rare diseases experience the largest relative increase in R&D, a pattern consistent with Fig. 1. Note that the mass of the counts clearly lies at zero, and the data tend to be over-dispersed. Further, the distribution of counts differs by group. These characteristics motivate the use of count regression models. Table 1 Panel B shows the summary statistics of the clinical trials for the drugs indicated for (unsubdivided) traditionally defined NORD diseases.

3.3. Estimation framework

The empirical analysis relies on a comparison of uncommon non-rare diseases to control diseases. I interpret additional change in the flow of ODA-qualifying subdivisions of uncommon non-rare diseases to be an estimate for the extent of indication-subdividing.

3.3.1. Prediction 1: incentive to subdivide around 200,000

To estimate the extent of subdividing for non-rare diseases, I use a difference-in-differences (DD) approach that compares the number of clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases to those of rare diseases, before and after the passage of the ODA. I estimate the following equation for the sample of uncommon non-rare and rare diseases:

$$NST_{it} = f\left(\alpha_0 + \sum_t \alpha_t Year_t + \beta_1 PostODA_t + \beta_2 Uncommon\_NonRare_i + \beta_3 (PostODA * Uncommon\_NonRare)_{it}\right) + \varepsilon_{it}. \quad (1)$$

The outcome variable, NST_{it}, is the number of new clinical trials for an ODA-qualifying subdivision of a NORD disease i in year t. The variable *Uncommon_NonRare* is an indicator for whether the (unsubdivided NORD) disease i has prevalence between 200,000 and 500,000.[10] The variable *PostODA* is an indicator for the 1984–1994 post-ODA period. Single-year indicator variables are included to capture trends in clinical trials for all diseases in the sample. The coefficient of primary interest is β_3, which measures the increase in the yearly flow of new clinical trials for uncommon non-rare diseases after the passage of the ODA, beyond that which is observed for control diseases. In specifications that include disease-specific fixed effects, the time-invariant effect of *Uncommon_NonRare* is necessarily excluded.

In estimating Eq. (1), I am only able to use 3 years of data to establish the pre-ODA trend in the flow of new clinical trials. This motivates an alternative identification strategy: estimating changes in flow of new clinical trials for the six status-changer diseases whose prevalence grew to slightly above 200,000 during the study period. As a proxy for the date when the estimated prevalence of status-changer diseases grew past 200,000, I use the year the OOPD last designated an orphan drug for that disease (Table 2). To isolate the impact of a change in rare-disease status, I estimate the

[9] Clinical trials often span more than 17 years (DiMasi et al., 2003), so measuring flow of new clinical trials avoids the problem of capturing decisions based on past investment climates.

[10] Prevalence estimates for rare diseases found in the epidemiological literature often report a range of estimates (i.e. 1:10,000 to 1:5000, or 25,000 to 50,000). Other references explicitly report point estimates with confidence intervals. Thus there is some degree of imprecision in prevalence point estimates. For this reason, it is more appropriate to compare sets of control diseases by prevalence categories, rather than directly regressing R&D effort on a continuous measure of disease prevalence.

Table 1
Distribution of new clinical trial counts, by disease prevalence, for two representative years.

	Rare	Status changer	Non-rare (200k–500k)	Non-rare (>500k)
Panel A: number of new trials for ODA-qualifying subdivisions of NORD diseases				
1983				
	0.001 (0.031)	0	0.020 (0.141)	0.010 (0.101)
75-percentile	0	0	0	0
90-percentile	0	0	0	0
95-percentile	0	0	0	0
99-percentile	0	0	1	1
Max	1	0	1	1
N	1023	6	50	98
1985				
	0.002 (0.044)	0	0.160 (0.468)	0.020 (0.142)
75-percentile	0	0	0	0
90-percentile	0	0	1	0
95-percentile	0	0	1	0
99-percentile	0	0	2	1
Max	1	0	2	1
N	1023	6	50	98
Panel B: number of new clinical trials for unsubdivided NORD diseases				
1983				
	0.017 (0.135)	0.333 (0.516)	0.240 (0.591)	0.122 (0.503)
75-percentile	0	1	0	0
90-percentile	0	1	1	0
95-percentile	0	1	1	1
99-percentile	1	1	3	3
Max	2	1	3	3
N	1023	6	50	98
1985				
	0.048 (0.274)	1.000 (2.000)	0.380 (0.901)	0.082 (0.398)
75-percentile	0	1	0	0
90-percentile	0	5	2	0
95-percentile	0	5	3	1
99-percentile	1	5	4	3
Max	4	5	4	3
N	1023	6	50	98

In Panel A, the first row reports the mean number of new clinical trials in 1983 for ODA-qualifying subdivisions of NORD diseases. Means are reported by disease prevalence group (standard deviations are reported in parentheses). The number of new clinical trials counts at the 75th, 90th, 95th, and 99th percentile of the distribution are shown below. The summary table is repeated for 1985. Panel B shows the mean and distribution of new clinical trials for unsubdivided, traditionally defined, diseases in the NORD list for 1983 and 1985.

following equation for only the 1984–1994 post-ODA:

$$NST_{it} = f\left(\alpha_0 + \sum_t \alpha_t Year_t + \beta_1 StatusChanger_i + \beta_2 Changed\_from\_Rare_{it}\right) + \varepsilon_{it}. \quad (2)$$

The variable of interest is *Changed_from_Rare*, an indicator for when a status-changer disease loses its status as rare. The estimate of β_2 represents the impact on the flow of new clinical trials for ODA-qualifying subdivisions of status-changer diseases due to losing rare status. The model predicts β_2 will be positive. Consistent estimation of β_2 requires that changes in disease prevalence are exogenous to the outcome variable. This is likely to be the case since the changes in demographics and diagnostic techniques that determine prevalence are likely to be orthogonal to clinical trials effort.[11]

The functional form for Eqs. (1) and (2) is chosen to account for the nature of the data. The flow of new clinical trials is non-negative, integer-valued, and has density at low values. This motivates use of panel count regression models.[12] Unlike the frequently employed negative binomial (NB) models, which for consistent parameter estimation requires that the data be distributed as NB (Hausman et al., 1984), the Poisson panel model has the advantage of being consistent even when the data-generating process is misspecified (Cameron and Trivedi, 1998). The Poisson model is consistent under the weaker assumption that the conditional mean is correctly specified as linear-exponential. Further, the requirement that counts be distributed as Poisson for consistent estimation of standard errors is relaxed by estimating robust quasi-ML standard errors following Wooldridge (1997,1999).

[11] It is possible that innovation in drugs is associated with an improved ability to diagnose a disease. Likewise, omitted variables, such as campaigns by drug manufacturers to raise awareness of diseases, would be associated with both greater R&D levels and estimated prevalence (and loss of rare-disease status). These possibilities bias the estimate of β_2 away from zero and over-estimate the ODA impact on subdividing. These endogeneity issues are unlikely to be significant in this setting given that our measure of innovation is a new clinical trial. Unlike outcomes such as newly approved drugs, new clinical trials (which may precede a drug approval by a decade) are unlikely to influence awareness of a disease within the medical community. It may be that firms initiate disease awareness campaigns before drugs are approved. However, this is more likely for prevalent diseases with large markets and potentially large profit potential.

[12] The flow of new clinical trials for rare disease is smaller than for non-rare diseases. The impact of the ODA on the flow of new trials for rare diseases may be small in *absolute* magnitude; but relative to the pre-ODA flow of new trials, the post-ODA flow may be large. The proportional impact is not captured in a linear model, but it is captured in the exponential form of typical count models.

Table 2
Status changers.

Disease	Year drug last designated to treat disease	Current prevalence estimate
Crohn's disease[a]	1999	400,000
Systemic lupus erythematosus[b]	1999	400,000
Multiple sclerosis[c,d,e]	1991	350,000
Sjogren syndrome[d,e,f]	1992	2,000,000
HIV/AIDS[g]	1991	496,000
End stage renal disease[h,i]	1990	350,000
Interstitial cystitis[j,k]	1991	500,000
Paget's disease of the bone[l]	1990	2,000,000

Lists eight status-changer disease. Only six of the diseases experienced a change in rare disease status during the period studied in this paper (1981–1994). The first column lists the year the OOPD last designated a drug for that specific disease indication. Citations for specific epidemiological studies for diseases that lost rare-disease status were provided by John McCormick of the OOPD, and are listed in the footnotes to this table.

[a] Loftus, E.V., Schoenfeld, P., Sandborn, W.J., 2002. The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review. Aliment Pharmacol. Ther. 16 (January (1)), 51–60 (Medline 11856078).

[b] Hochberg, M.C., et al., 1995. Prevalence of self-reported physician-diagnosed systemic lupus erythematosus in the USA. Lupus 4 (December (6)), 454–456 (Medline 8749567).

[c] Anderson, D.W., et al., 1992. Revised estimate of the prevalence of multiple sclerosis in the United States. Ann. Neurol. 31 (March (3)), 333–336 (Medline 1637140).

[d] http://www3.niaid.nih.gov/.

[e] http://www.niams.nih.gov.

[f] Division of Oral Medicine, University of Minnesota, 1999. Sjogren's Syndrome. Quintessence Int. 30 (October (10)), 689–699 (Medline 10765853).

[g] http://www.cdc.gov.

[h] Trivedi, H.S., Pang, M.M., Campbell, A., Saab, P., 2002. Slowing the progression of chronic renal failure: economic benefits and patients' perspectives. Am. J. Kidney Dis. 39 (April (4)), 721–729 (Medline 11920337).

[i] Xue, J.L., Ma, J.Z., Louis, T.A., Collins, A.J., 2001. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J. Am. Soc. Nephrol. 12 (December (12)), 2753–2758 (Medline 11729245).

[j] Curhan, G.C., et al., 1999. Epidemiology of interstitial cystitis: a population based study. J. Urol. 161 (February (2)), 549–552 (Medline 9915446).

[k] http://www.niddk.nih.gov/.

[l] Altman, R.D., Bloch, D.A., Hochberg, M.C., Murphy, W.A., 2000. Prevalence of pelvic Paget's disease of bone in the United States. J. Bone Miner. Res. 15 (March (3)), 461–465 (Medline 10750560).

3.3.2. Prediction 2: diminishing incentive to subdivide more prevalent diseases

I estimate changes in the flow of new clinical trials for ODA-qualifying subdivisions for uncommon non-rare diseases relative to diseases with slightly higher prevalence. To do this, I partition the 148 non-rare diseases in the NORD list into 50 "uncommon non-rare" diseases that have prevalence between 200,000 and θ^{Sub}, and 98 NORD diseases with prevalence exceeding θ^{Sub}. Simple model calibrations performed in Section 3.1 suggest 500,000 as an estimate for θ^{Sub}. I then estimate Eq. (1) comparing these two sets of diseases. I interpret new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases – in excess of that which is observed for more prevalent non-rare diseases in the NORD list – to be evidence of indication-subdividing in response to the ODA.

4. Empirical results

The model presented in Section 2 suggests that there should be a significantly greater incentive to subdivide uncommon non-rare diseases relative to control diseases that have slightly lower or slightly higher prevalence. As an informal test of these predictions, I construct a variable that represents the fraction of all new clinical trials for a given NORD disease devoted to an ODA-qualifying subdivision over the entire post-ODA period (1984–1994). Fig. 2 shows the predicted values of a non-parametric regression of the fraction of clinical trials devoted to ODA-qualifying subdivisions over this period against the prevalence of the unsubdivided diseases. I restrict the sample to diseases with prevalence higher than 100,000, and omit status-changer diseases. Fig. 2 clearly depicts an inverted-U shape relationship. Around the 200,000 threshold, there is a clear and dramatic positive relationship between the fraction of new trials devoted to ODA-qualifying subdivisions of diseases and the prevalence of the unsubdivided diseases. The regression also exhibits a clear negative relationship for diseases with prevalence that exceeds 500,000.

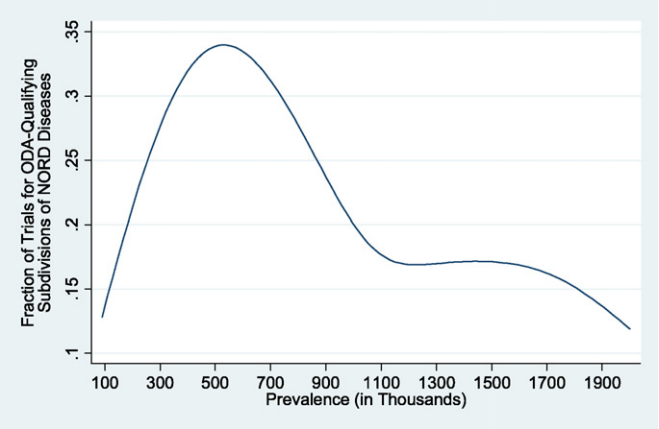

Fig. 2. Indication-subdividing among NORD diseases.

I compare uncommon non-rare diseases to more prevalent non-rare diseases in the NORD list to test the predictions of the model more formally. Note that back-of-the-envelope calculation for the cut-off prevalence that defines uncommon non-rare diseases, θ^{Sub} = 500,000, is consistent with the point where the non-parametric regression in Fig. 1 turns sharply downward.

Section 4.1 through 4.2 formally quantify the extent to which firms respond to the ODA by subdividing drug indications into ODA-qualifying subdivisions of non-rare diseases. Whether this response reflects new innovation is addressed in Section 5.

4.1. Incentive to subdivide disease indications

Eq. (1) specifies a DD approach to compare ODA-qualifying subdivisions of rare and non-rare diseases. Results of this estimation are reported in Table 3. Column 1 compares uncommon-rare diseases to more prevalent diseases in the NORD list. The results indicate a positive and significant increase in the flow of trials for ODA-qualifying subdivisions among all diseases associated with the passage of the ODA. The flow of new trials for ODA-qualifying subdivisions of uncommon non-rare diseases is significantly larger than that of the more-prevalent control diseases. The coefficient on the interaction term implies that the ODA led to a 460-percent (=[exp(1.727) − 1] × 100) increase in the flow of new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases relative to new trials for comparison diseases.

As in Finkelstein (2004) and Yin (2008), I also estimate Eq. (1) including period-interaction terms. I include three $PostODA(t,\ t)_i$ variables that indicate whether a clinical trial for disease i began in the first 3, 3–6, or 7 or more years after the ODA was passed. The variable $NonRare(200k, 500k) \times PostODA(t, t')$ is the interaction term between the prevalence category indicator and a *PostODA* indicator. Results of this analysis are reported in column 2. Firms appear to respond immediately to incentives to subdivide uncommon non-rare diseases; they also appear to respond to the ODA with greater intensity towards the end of the study period. Subdividing of uncommon non-rare diseases was somewhat diminished

Table 3
Subdividing uncommon non-rare diseases.

Dependent variable: No. of new clinical trials for ODA-qualifying subdivisions of NORD diseases						
Treatment disease	"Uncommon" non-rare diseases (200k–500k)					
Control disease	Rare diseases (100k–200k)		Non-rare diseases (>500k)		Diseases (100k–200k) and diseases (>500k)	
	(1)	(2)	(3)	(4)	(5)	(6)
PostODA	2.386** (1.261)		2.758*** (1.019)		2.939*** (1.183)	
NonRare(200k, 500k) × PostODA	1.727** (0.877)		0.684 (0.798)		1.349* (0.781)	
PostODA_13		1.545 (1.341)		0.693 (0.681)		1.812 (1.238)
PostODA_46		2.697** (1.304)		1.609 (0.662)		2.852*** (1.207)
PostODA_7plus		1.922 (1.229)		2.886*** (0.613)		2.833*** (1.183)
NonRare(200k, 500k) × PostODA_13		1.686* (0.972)		1.504** (0.683)		1.638* (0.852)
NonRare(200k, 500k) × PostODA_46		0.804 (0.901)		0.930 (0.711)		0.834 (0.809)
NonRare(200k, 500k) × PostODA_7plus		2.255*** (0.865)		0.532 (0.847)		1.489* (0.794)
Year dummies	Y	Y	Y	Y	Y	Y
No. Rare Diseases(100k, 200k)	6	6	–	–	6	6
No. of NonRare(200, 500k) diseases	22	22	22	22	22	22
No. of NonRare(>500k) diseases	–	–	14	14	14	14
Number of diseases	28	28	36	36	42	42
Observations	392	392	504	504	588	588

Reports the parameter estimates of the Poisson conditional fixed-effects regression. The dependent variable is the number of new clinical trials for an ODA-qualifying subdivision of a disease in the NORD list in a given year. The fixed effects model drops all disease for which there are no counts in the time series. The variable *NonRare*(*200k*, *500k*) is an indicator that takes 1 for diseases that have prevalence between 200,00 and 500,00. The variable PostODA is an indicator variable for observations in years after the ODA passage. The *PostODA_*(*t1*, *t2*) variables are indicators for observations between years (t1, t2) after the ODA passage. Column headers note which diseases are included in the sample specification. Regressions are estimated using single-year dummy variables. Quasi-ML estimation of standard errors were calculated following Wooldridge (1997, 1999) and are reported in parentheses.

* Significant at 10%.
** Significant at 5%.
*** Significant at 1%.

in the middle period. This is a result of greater subdividing of control diseases over this middle sub-period.

I repeat these analyses using diseases with prevalence higher than $\theta^{Sub} = 500{,}000$ as a control. The results of this analysis are reported in columns 3 and 4. Here, again, the results show that firms responded immediately to the incentives to conduct new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases. Declines in the intensity of indication-subdividing over the study period are driven largely by increases in the flow of clinical trials for ODA-qualifying subdivisions of the control diseases. Qualitatively similar results are reported in columns 5 and 6 where the sample includes both sets of control diseases.

Coefficient estimates on the uninteracted *PostODA*(*t*, *t*) terms suggest that the ODA is associated with substantial indication-subdividing among control diseases. Thus, there may be reasons for indication-subdividing in response to the ODA that are not modeled in Section 2. For example, if heterogeneous patients incur search costs (financial and clinical costs of inappropriate drug use) of finding the best drug on the market for a given disease, then firms have an incentive to make patients aware of the specific patient subpopulation for whom their drug is most beneficial. This may give rise to incentives to subdivide any disease, even those with prevalence below 200,000 or above θ^{Sub}. Another possibility is that the ODA broadly reduces the risk of conducting expensive clinical drug trials. A subsidized clinical trial for an ODA-qualifying subdivision of a drug's potential market can be used to inform the firm of its drug's safety and efficacy for a larger indication, thereby reducing the risk associated with larger and more expensive clinical trials. These mechanisms would lead to observed subdividing among the more prevalent control diseases in response to the ODA. However, they do not predict that firms have a *greater* incentive to subdivide uncommon non-rare diseases, as is observed empirically.

4.2. Time series variation in the incentives to subdivide

Status-changer diseases are not included in the estimation of Eq. (1). I measure the impact of losing rare-disease status on indication-subdividing among status-changer diseases by estimating Eq. (2). Results are reported in Table 4. The columns report the coefficient estimate on *Changed_from_Rare* under several specifications for comparison diseases. The coefficient estimates across the three columns are fairly stable, suggesting that the loss of rare-disease status led to a 350-percent (=[exp(1.5) − 1] × 100) increase in the flow of clinical trials for ODA-qualifying subdivisions of the status-changer diseases.

4.3. Secondary predictions

The model presented in Section 3 assumes that firms seek off-label sales for drugs whose on-label market they strategically reduce in order to qualify for the ODA-subsidy.[13] I test whether this assumption is consistent with the data on drug prescriptions and off-label sales. I compare off-label sales of drugs approved for an ODA-qualifying subdivision of a non-rare disease to those of other approved orphan drugs, conditional on the prevalence of the disease indication for which it was approved. Greater off-label sales for drugs indicated for a subdivision of a non-rare disease would be consistent with these drugs having larger potential markets than the indications sought by firms. I estimate the following equation on the sample of approved orphan drugs, *i*:

$$Total\ Rx_i = \exp(\alpha + \beta_1 SubNonRare_i + \beta_2 SubRare_i + \beta_3 \log(OnLabelPop_i) + \beta_4 ApprovalYr_i) + \varepsilon_i. \quad (4)$$

The variable *Total Rx* represents the number of prescriptions written for a given orphan drug, *i* in a given year, for the treatment

[13] Consistent with this prediction, there have been several instances of abuse of the ODA brought to the public's attention (Rin-Laures and Janofsky, 1991; Senate Sub-committee Hearings S.2060 1992; Maeder, 2003). In these cases, orphan drugs were first approved to treat a rare disease and then were found to benefit patients with much more prevalent diseases.

Table 4
Indication-subdividing of status-changer diseases.

Dependent variable: number of new clinical trials for ODA-qualifying subdivisions of NORD diseases			
Treatment disease	Status-changer diseases		
Control disease	Rare diseases (100k–200k)	Non-rare diseases (200k–500k)	Diseases (100k–200k) and diseases (200k–500k)
	(1)	(2)	(3)
Changed from rare	1.306*** (0.204)	1.572*** (0.228)	1.524*** (0.213)
Single-year dummies	Y	Y	Y
No. of diseases	9	25	31
Observations	99	275	341

Reports the parameter estimates of the Poisson conditional fixed-effects regression. The dependent variable is the number of new clinical trials for an ODA-qualifying subdivision of a disease in the NORD list in a given year. The fixed effects model drops all disease for which there are no counts in the time series. Column headers note which diseases are included in the sample specification. The variable *Changed_from_Rare* is an indicator that takes 1 when a disease is not rare, and 0 when a disease is rare. All regressions include single-year dummy variables. Quasi-ML estimation of standard errors were calculated following Wooldridge (1997, 1999) and are reported in parentheses.
*Significant at 10%.
**significant at 5%.
*** Significant at 1%.

of any disease. The independent variables of interest are *SubNonRare* and *SubRare*, indicators for whether the approved orphan drug is indicated to treat an ODA-qualifying subdivision of a non-rare or rare disease, respectively, in the NORD list. (The omitted category comprises orphan drugs approved for an unsubdivided rare disease.) *ApprovalYr* denotes the year the drug was approved for marketing, and captures the time elapsed since the knowledge of its uses first diffused through the market. Data on the number of prescriptions in the US for each approved orphan drug are obtained from the 2002 National Ambulatory Medical Care Survey. It provides data on the number of times drugs are prescribed in the US, and the International Classification of Diseases (ICD) code associated with the prescription. Data for *OnLabelPop*, the prevalence of the approved indication for each orphan drug, was obtained from the FDA. A positive coefficient on *SubNonRare* would be consistent with incentives underlying the model. Similarly, I expect the coefficient on *SubRare* to be insignificant.[14] I estimate Eq. (4) on the sample of 245 orphan drugs, where the outcome variable is the number of prescriptions for the brand name drug. I find:

$$Total\,Rx_i = \exp(\underset{(84.5)}{53.9} + \underset{(0.53)}{0.991} \cdot SubNonRare_i - \underset{(0.65)}{0.640} \cdot SubRare_i + \underset{(0.12)}{0.055} \cdot \log(OnLabelPop_i) - \underset{(0.04)}{0.022} \cdot ApprovalYr_i). \quad (5)$$

The estimate on *SubNonRare* suggests that on average orphan drugs approved for a subdivision of a non-rare disease were prescribed 170-percent more often than drugs approved for a traditional rare disease, conditional on the disease prevalence for which they were approved. The coefficient on *SubRare* is not significantly different from zero, consistent with the notion that such drugs were not developed as a strategic response to restrict the on-label population (and to sell extensively off-label) in order to acquire the ODA incentives.[15]

5. Quantifying the impact of the ODA on subdividing net of inefficiencies

The response to the ODA reported in Section 4 does not necessarily represent *new* innovation. As modeled in Section 2, some of the observed response may represent R&D that would have been conducted in the absence of the ODA. Neither the FDA nor the tax authorities are able to identify which trials are conducted on the margin in response to the ODA. Consequently, the ODA subsidizes every drug trial indicated for ODA-qualifying subdivisions, even if the R&D would have been conducted without the policy. In an attempt to quantify this inefficiency, I estimate the extent to which new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases are offset by simultaneous declines in new clinical drug trials for the corresponding *unsubdivided* traditionally defined disease indications. Data on new clinical trials for drugs indicated for traditionally defined disease are summarized in Table 1 Panel B.

I re-estimate Eq. (1), however now I use counts of new clinical trials for unsubdivided NORD diseases as the outcome. I test whether the ODA is also associated with declines in the flow of new trials for unsubdivided indications of uncommon non-rare diseases. I use NORD diseases with prevalence exceeding 500,000 as a control (drug development for these diseases – subdivided or otherwise – should be unaffected by the ODA). I interpret declines in R&D for unsubdivided uncommon non-rare diseases after the ODA passage, relative to larger non-rare NORD diseases, as evidence of redefining indications for drugs that would have been developed in the absence of the ODA.

Status-changer diseases offer a second setting in which inefficiencies can occur. I re-estimate Eq. (2) using new clinical trials for *unsubdivided* status-changer diseases as the dependent variable. I look for evidence of declines in the flow of new trials for the unsubdivided disease indications as evidence of indication-subdividing for these diseases.

Results of this analysis are reported in Table 5. Columns 1 and 2 report the results of estimating Eq. (1), using new trials for ODA-qualifying subdivisions of sample diseases and for the unsubdivided diseases, respectively. (Column 1 reports results from Table 3 column 2.) I find that the ODA was not associated with declines in new clinical trials for unsubdivided uncommon non-rare diseases. In fact, the flow of new trials for these diseases moves

[14] Ideally, I would use off-label prescriptions as the outcome variable. However, the NAMCS is sufficiently specific in coding disease diagnosis, making determination of off-label prescriptions unclear. Instead, I use *Total* prescriptions for a given drug, conditional on the market size of the approved indication. In theory, this should yield identical point estimates, assuming diseases in the sample are similar in their mapping from prevalence to market size.

[15] I also construct two binary outcome variables for drug prescriptions—whether a drug appears in the 2002 NAMCS survey, and whether a drug appears in *any* previous NAMCS survey. Aggregating all NAMCS surveys increases the likelihood that a given drug is mentioned. I estimate Eq. (4) in a probit framework, and find that orphan drugs indicated to treat a subdivision of a non-rare disease are 36-percent more likely to have been mentioned at least once in 2002, and 26-percent more likely to have been mentioned in any prior survey. The coefficient on *SubRare* is insignificant in both regressions. In these regressions, the coefficient on the year of approval is negative and precisely estimated, suggesting that market penetration and diffusion of knowledge about the use of drugs is not immediate.

Table 5
Substitution towards ODA-qualifying subdivisions of NORD diseases.

Treatment disease	Non-rare diseases (200k–500k)		Status-changer diseases	
Control disease	Non-rare diseases (>500k)		Rare diseases (100k–200k)	
Dependant variable: no. of new clinical trials	ODA-qualifying subdivisions	Unsubdivided indications	ODA-qualifying subdivisions	Unsubdivided indications
	(1)	(2)	(3)	(4)
PostODA_13	1.545 (1.341)	0.454 (0.554)		
PostODA_46	2.697** (1.304)	1.365** (0.561)		
PostODA_7plus	1.922* (1.123)	1.515*** (0.563)		
NonRare(200k, 500k) × PostODA_13	1.686* (0.972)	0.452 (0.454)		
NonRare(200k, 500k) × PostODA_46	0.804 (0.901)	0.393 (0.468)		
NonRare(200k, 500k) × PostODA_7plus	2.255*** (0.865)	0.379 (0.441)		
Changed from rare			1.306*** (0.204)	−0.287** (0.105)
Single year dummies	Y	Y	Y	Y
No. of diseases	36	54	9	15
Observations	504	756	99	165

Reports the parameter estimates of the Poisson conditional fixed-effects regression. This table compares the extent to which new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases offset clinical trials for drugs indicated for the unsubdivided disease indication that would have been developed in absence of the ODA. The dependent variable in column (1) is the number of new clinical trials for an ODA-qualifying subdivision of a disease in the NORD. The dependent variable in column (2) is the number of new clinical trials for an unsubdivided NORD disease in a year from 1981 to 1994. A similar comparison can be made for the flow of new clinical trials for status-changer diseases in columns (3) and (4) for the 1984–1994 post-ODA period. Note that columns (1) and (3) are preferred specifications taken from Tables 3 and 4. The fixed effects model drops all disease for which there are no counts in the time series. The variable *NonRare*(*200k*, *500k*) is an indicator that takes 1 for diseases that have prevalence between 200,000 and 500,000. The variable PostODA is an indicator variable for observations in years after the ODA passage. The PostODA_(t1, t2) variables are indicators for observations between years (t1, t2) after the ODA passage. The variable *Changed_from_Rare* is an indicator that takes 1 when a disease is not rare, and 0 when a disease is rare. All regressions included single-year dummy variables. Quasi-ML estimation of standard errors were calculated following Wooldridge (1997, 1999) and are reported in parentheses.

* Significant at 10%.
** Significant at 5%.
*** Significant at 1%.

in lock-step with the more prevalent NORD diseases. The analysis of status-changer diseases provides evidence of inefficiencies. The 269-percent increase in the flow of new trials for ODA-qualifying subdivisions of status-changer diseases (column 3) is offset by a simultaneous 25-percent decline in the flow of new trials for unsubdivided status-changer diseases when these diseases lose rare-disease status (column 4).

These percentage impacts are estimated off of different base flow rates. To quantify the inefficiencies in levels, I calculate the predicted increase in the aggregate number of new clinical trials attributed to the ODA. This accounting exercise suggests that the ODA led to 29 new clinical trials for subdivided indications of status-changer diseases over this period (based on Table 5 column 3), and to a simultaneous decline of 18 new clinical trials for unsubdivided status-changer disease indications (based on Table 5 column 4).

The total impact of the ODA on new clinical trials for ODA-qualifying subdivisions of uncommon non-rare diseases can be measured in the same way. Results reported in Table 3 column 2 for uncommon non-rare diseases (also reported in Table 5 column 1) suggest that the ODA led to approximately 156 new clinical trials. Thus, in total the ODA led to 185 new clinical trials for ODA-qualifying subdivisions of uncommon non-rare NORD diseases. This impact is similar in magnitude to the effect of the ODA on innovation in traditional rare-disease drugs that was estimated in Yin (2008). The evidence of simultaneous declines in R&D of drugs for unsubdivided NORD diseases suggests that at least 18 new trials – or roughly 10-percent – represent trials that would have been conducted in the absence of the ODA but are nevertheless subsidized.

6. Conclusion

This paper studies how innovation policy impacts private pharmaceutical innovation. Specifically, I examine the ODA, which created supply and demand-side incentives for the development of rare-disease drugs. While prior studies of the ODA have focused innovation in traditionally defined rare-disease drug markets, this study examines innovation in *non-rare* disease drugs. In theory, the policy's definition of a rare disease (any disease with US prevalence below 200,000) gives firms an incentive to carve out new ODA-qualifying diseases from patient populations with traditionally defined diseases.

Evidence reported in this paper bears out these predictions. I find robust evidence that the ODA encourages firms to develop drugs for ODA-qualifying subdivisions of non-rare diseases. Further, the impact on drugs that treat ODA-qualifying subdivisions of non-rare diseases is equal in magnitude to the impact measured on traditional rare-disease drug development estimated in earlier work (Yin, 2008). Commonly observed subdivisions in the raw clinical trials data include subpopulations that are refractory to existing therapies, have a severe or progressed form of a disease, or have key co-morbidities or other characteristics that differentiate patients according to their risk–benefit profile of drug utilization. To the extent that the observed differentiation leads to more tailored and personalized drug therapies (i.e. to a lower average "distance" between patients and the nearest drug on the disease circle), subsidizing drug innovation for small disease populations may increase average clinical benefits experienced by patients. Indeed, the development of personalized drugs that treat narrowly defined subsets of patients within broadly defined disease populations is widely thought to be a promising direction for future drug research (Haffner et al., 2002; Collins et al., 2003; Couzin, 2005).

This paper also shows that there are modest trade-offs associated with this innovation policy. Policies that subsidize unobserved effort may finance effort that is privately lucrative to agents, but not in line with the objectives of the principal (Lazear, 1996). Subsidizing innovation that would have been conducted in the absence of the policy is one example of how subsidizing R&D may yields little new innovation (Kremer, 2001; Hall, 2002). Calculations in Section 5 suggest that roughly 10-percent of new clinical trials for ODA-qualifying subdivisions of non-rare diseases represent R&D that

would have been conducted in the absence of the policy, but are nevertheless subsidized. Relative to all the new clinical trials that were conducted in response to the ODA, this inefficiency accounts for roughly 5-percent of the total response to the policy. While modest in size, it suggests that reducing agency-related inefficiencies should be considered when designing innovation policy.

The nature of information asymmetries make it impossible for regulators to identify which clinical trials would have been conducted without ODA incentives. At best, regulators could limit indication-subdividing in general. A number of actions could be triggered when an approved orphan drug is found to generate large off-label revenues. For example, revenues in excess of a predetermined return on investment could be taxed. A more extreme measure would combine an excess revenue tax with an ODA tax credit repayment penalty. Whether a policy placed greater weight on the repayment penalty or the excess off-label revenue tax would ideally depend on the extent to which taxes are expected to be passed on to consumers.[16] In principle, measures such as these would not affect R&D that would be conducted in absence of ODA incentives. The burden of inefficiency would be reduced as a consequence. However, these measures would also disincentivize R&D effort in disease subdividing which, in absence of the ODA, would not be conducted. Hence, the effectiveness of the proposed measures would depend on the benefit of reducing inefficiencies relative to the value of forgone innovation.

Similar (imperfect) attempts at limiting agency-related inefficiencies in R&D policies are found in the context of national R&D tax policies. To avoid subsidizing innovation that would occur in the absence of R&D tax incentives, many OECD countries subsidize *incremental* R&D only, where incremental is defined as current R&D expenditures less a firm's baseline level of R&D spending (Hall and Van Reenen, 2000). In these contexts, regulators are unable to determine the true baseline R&D levels (the firms' choice of R&D expenditures absent the tax incentive), and instead measure it as some moving average of R&D expenditures from previous years. In cases where the observed baseline is higher (lower) than the true unobserved baseline, the incremental tax discourages (encourages) additional innovation on the margin. As in the ODA context, provisions that attempt to limit agency-related inefficiencies may also weaken the main innovation incentives on the margin.

Finally, note that indication-subdividing may confer some benefits to patients, even for drugs that would have been developed without the ODA policy. Narrower labels help to identify subsets of patients for whom the drug may be especially beneficial. This information may reduce the cost of searching for the most appropriate drug. Search costs can be either financial or health-related in nature. Suboptimal drug consumption may be associated with longer duration of illness, worsening health, or simply a longer duration of unnecessary side-effects. Existence of costly search motivates innovation in diagnostic technologies, which may offer a second promising direction for growth in personalized medicine (Aspinall and Hamermesh, 2007).

Appendix A.

Tables A1 and A2.

[16] In cases where an orphan drug is found to generate excessive revenues for its indicated *on-label* population, regulators could also limit or revoke the market exclusivity provision. For example, the FDA could grant granting marketing approval for the same drug for the same rare disease to a competitor. Such a provision was included in the 1990 amendment to the ODA. Under the amendment, a firm earning excessive revenues would have to share its marketing exclusivity with a competitor in cases where the competitor applied for marketing approval for the same drug and indication, but was beaten out by the first firm. The President vetoed the amendment on the grounds that it weakened a key incentive of the ODA (Rin-Laures and Janofsky, 1991).

Table A1
Counting of clinical trials.

NDA pipeline data						Coding	
Line	Drug	Generic name	Indication	Trial phase	New trial	NORD#	Orphan subdivision
			Johnson & Johnson (1987)				
1		Epidermal growth factor, biosynthetic	Severe burn	IND			
2	Motilium	Thymoxamine HCl	Phenylephrine-induced mydriasis				
3		Domperidone	Parkinson's	Clinicals			
4		Gonadorelin acetate	Ovulation induction	NDA Pend.			
5		Histrelin	Precocious puberty	Clinicals			
6		Tepoxalin	Psoriasis	Clinicals			
7	Retin-A	Tretinoin	Psoriasis	Clinicals			
8	Immunox	Thymopentin (TP-5)	AIDS	Clinicals			
9		Vaccine	Hepatitis B	Clinicals			
10	Sibelium	Flunarizine	Epilepsy	II			
11	Sibelium	Flunarizine	Alternating hemiplegia				
12	Sporanox	Itraconzanole	Anti-fungal	Clinicals			
			Johnson & Johnson (1988)				
13		Epidermal growth factor, biosynthetic	Severe burn	Preclinicals			
14		Thymoxamine HCl	Phenylephrine-induced mydriasis				
15		Histrelin	Precocious puberty	Clinicals			
16		Gonadorelin acetate	Ovulation induction	NDA Pend.			
17	Eprex	Erythropoietin (EPO)	AIDS	Clinicals	1	5	0
18	Eprex	Erythropoietin (EPO)	Anemia	Clinicals	1	1178	0
19	Eprex	Erythropoietin (EPO)	Anemia of prematurity (orphan)	Clinicals	1	1178	1
20	Eprex	Erythropoietin (EPO)	Severe anemia assoc. w/AZT in AIDS (orphan)	Clinicals	1	1178	1
21		Tepoxalin	Psoriasis	Clinicals			
22		Tepoxalin	Atopic dermatitis	Clinicals	1	815	0
23	Immunox	Thymopentin (TP-5)	AIDS	Clinicals			
24		Vaccine	Hepatitis B	Clinicals			
25	Motilium	Domperidone	Parkinson's	III			
26	Sibelium	Flunarizine	Epilepsy	II			
27	Sibelium	Flunarizine	Alternating hemiplegia	Clinicals	1	623	0
28	Sporanox	Itraconzanole	Cryptoccocal meningitis	II	1	807	0

The table shows a portion of a typical data table from the *NDA Pipeline*, sampled from years 1987 and 1988 for Johnson & Johnson. Since the analysis uses *new* clinical trials as the main outcome variable, 1987 and 1988 data are used to generate data on new clinical trials for 1988. The methodology used to code the raw data is described below. Step 1: Identify new human clinical drug trials in 1988 that do not appear in 1987. (Identified as "1" in the column *New Trial*.) Several decisions were made for consistency. (A) The year associated with the start of a new trial for a disease in the NORD list was determined to be the first year the trial was explicitly indicated for that disease. For example, trials for Sporonox (line 12) had begun by 1987, but only in 1988 did the *NDA Pipeline* record that it was in trials to treat cryptoccocal meningitis (CM) (line 28). Therefore, the trial for CM is coded to have begun in 1988. Note that by 1988, the trial is in phase II. 1988 was chosen (rather than predating the trial for CM to the year Sporanox first appears in the journal) because it is very possible that J&J conducted phase I trials without having decided that Sporanox was best suited to treat MC, specifically, among other types of bacterial infections until phase II trials. (B) Likewise, had Eprex appeared in 1987 to treat anemia and AIDS, then among Eprex trials in 1988, only the trials for anemia of prematurity and for severe anemia for AIDS patients taking AZT (lines 19, 20) would be considered *new* trials. The trials for AIDS and anemia would be considered unique trials, as they are listed as separate trials in subsequent volumes of the *NDA Pipeline*. (C) Sibelium is listed in 1987 for alternating hemiplegia (line 11). The *Trial Phase* cell is blank, suggesting that a firm has self-reported plans to begin trials for an indication. In 1988 (line 27) Sibelium is first recorded to be in a specific stage of trials for alternating hemiplegia; so I record the trial start year to be 1988. Step 2: Record the NORD disease identifying number, which I previously assigned to every diseases in the NORD list. Identifying the NORD identifying number allows for mapping back to other disease characteristics when later merged with the main data tables. Step 3: Determine if the drug indication is an ODA-qualifying subdivision. Often, the *NDA Pipeline* will report whether the drug indication is an orphan indication (as it does in lines19 and 20). Identifying a trial as an orphan is often based on firms having already sought orphan designation from the OOPD. Other times, it is based on orphan status of a previous trial for the same indication. Subdivisions of an already rare disease were *ipso facto* recorded as an orphan indication.

Table A2
Typology of diseases indications.

Drug indication	Example(s)	Coding of example(s)	Coding: subdivided or unsubdivided indication
Disease X	Infant respiratory distress syndrome	*Indication*: infant respiratory distress syndrome *Subpopulation*: none	Unsubdivided
Symptom of disease Y	Muscle contracture in cerebral palsy	*Indication*: cerebral palsy *Subpopulation*: none	Unsubdivided
Disease X associated with disease Y	Pneumocystis Carinii infection associated with AIDS	*Indication*: pneumocystis Carinii infection *Subpopulation*: for patients with AIDS	Subdivided

Table A2 (*Continued*)

Drug indication	Example(s)	Coding of example(s)	Coding: subdivided or unsubdivided indication
Disease X, for patients of type Y	Crohn's disease refractory to conventional therapy	*Indication*: Crohn's disease *Subpopulation*: for patients refractory to conventional therapy	Subdivided
	Neutropenia where neotrophil counts are below 500 mm^{-3}	*Indication*: neutropenia *Subpopulation*: for patients with neotrophil counts below 500 mm^{-3}	Subdivided
Advanced case of disease X	Stage III–IV malignant melanoma	*Indication*: malignant melanoma *Subpopulation*: patients with stage III or IV melanoma	Subdivided
Disease X, specific subtype Xi	Gaucher's disease, type I	*Indication*: Gaucher's disease *Subpopulation*: patients with type I	Subdivided
	Relapsing and remitting multiple sclerosis	*Indication*: multiple sclerosis *Subpopulation*: patients with relapsing and remitting type	Subdivided

Lists the types of drug indications found in the *NDA Pipeline* and how determinations were made regarding whether an indication was coded as a subdivision of a NORD disease. Within sample, this typology provides an exhaustive list of every type of NORD disease subdivision encountered in the data collection. Examples of each typological subdivision is provided, as well as how such a clinical trial was coded.

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