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# Market incentives and pharmaceutical innovation

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**Abstract**

I study the impact of the Orphan Drug Act (ODA), which established tax incentives for rare disease drug development. I examine the flow of new clinical drug trials for a large set of rare diseases. Among more prevalent rare diseases, the ODA led to a significant and sustained increase in new trials. The impact for less prevalent rare diseases was limited to an increase in the stock of drugs. Tax credits can stimulate R&D; yet because they leave revenue margins unaffected, tax credits appear to have a more limited impact on private innovation in markets with smaller revenue potential.


*JEL classification:* I18; O3; H21

*Keywords:* Pharmaceutical innovation; Technological change; Health policy

## 1. Introduction

This paper studies the impact of public policy on private innovation. Policy intervention is normatively justified when market failures lead to inefficient allocation of R&D investments. Whether public policies can improve welfare in these cases depends in large part on whether they are able to stimulate innovation. While innovation in R&D-intensive industries has been shown to respond to market incentives (Newell et al., 1999; Acemoglu and Linn, 2004; Finkelstein, 2004), the ability of public policy to stimulate innovation is less clear. In this paper, I study the impact of the 1983 Orphan Drug Act (ODA) on pharmaceutical innovation. The ODA is interesting for several reasons. First, it established supply-side tax incentives to stimulate drug development for rare diseases, defined as diseases with prevalence less than 200,000 Americans. Aside from the economy-wide Research and Experimentation Tax credit, the ODA is the only other significant US policy designed to stimulate private R&D through supply-side subsidization. Passage of the ODA therefore provides an ideal setting in which to test whether supply-side tools at the disposal of policy-makers are able to stimulate innovation in areas where private R&D is deemed inadequate.[1]

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[1] While levels of rare disease drug development were considered inadequate from a political perspective, it is unclear whether there are market failures that justified the ODA on economic efficiency grounds. It has been argued that externalities to rare disease drug R&D may be larger than those arising from other types of pharmaceutical R&D (Kaspar, 2005). Incomplete insurance markets may be another source of market failure. Private insurance contracts are unable to pool risks of acquiring a rare disease, and then produce a drug to treat that disease when the policy is triggered. The ODA can be viewed as a measure to partially correct this market failure: tax credits function as a collective insurance premium paid out of general revenues—revenues which fund (albeit uncertain) development of rare disease drugs. Ultimately, the economic justification of the

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The ODA also has broad relevance to innovation policy in other health sectors. The design of R&D policy for small-market drugs and vaccines to treat infectious diseases has become a focal point of development policies (Kremer, 2001a,b). Similarly, pharmacological therapy is increasingly being viewed through the lens of genetics (Haffner et al., 2002). "Personalized" drug markets – i.e. genetics-based subdivisions of traditional diseases defined by heterogeneous treatment response to drugs – are thought to be the potential basis of future drug innovation (Collins et al., 2003; Couzin, 2005; Aspinall and Hamermesh, 2007).[2] In each of these contexts, the ODA has frequently been discussed as a potential model of public policy to encourage innovation. Yet neither the aggregate impact of the ODA, nor the margins along which the ODA impacts private R&D behaviour, have been rigorously investigated.

In this study, I estimate the impact of the ODA on drug innovation. I examine whether the ODA resulted in increased innovative activity – in the form of new clinical trials – for a group of long-established rare diseases that lobbyists and lawmakers hoped would be affected by the ODA. To estimate the response by firms to the ODA incentives, I construct a unique dataset on new clinical drug trials conducted in the US. I then employ a difference-in-differences (DD) strategy which exploits variation in rare disease status across diseases, as well as within diseases over time. I use a set of uncommon diseases with prevalence slightly greater than 200,000 as a control.

The impact of supply-side incentives – i.e. grants and tax credits – have long been the focus of research in innovation policy and public finance. Using US and international data, these studies consistently estimate a negative price elasticity of R&D expenditures in response to R&D tax credits (Mansfield, 1986; General Accounting Office, 1989; McCutchen, 1993; Hall, 1993; Office of Technological Assessment, 1993; Hall and Van Reenen, 2000). However, these studies offer less insight as to whether the policy incentives results in truly innovative activity. With the exception of Finkelstein (2004) and Lichtenberg and Waldfogel (2003), previous studies of pharmaceutical innovation policy have focused on the aggregate extensive margins of innovation.[3] Analyses using only drug approval or aggregate R&D expenditure data obscure differences between true innovation and marginal manipulations, and between sustained innovation and final development of existing technologies.

In estimating the impact of the ODA, this paper overcomes these limitations. Data on new clinical drug trials collected for this study allow me to identify timing of new clinical drug trials by disease indication. These disaggregated data allow me to distinguish between contemporaneous and long-run impacts on innovation, and allow for analyses according to disease characteristics (e.g. disease classification, disease prevalence). Together, these analyses allow me to better infer the financial margins along which the ODA affects private R&D.

I find that the ODA had a significant impact on rare disease drug development. I estimate that on average the ODA led to a 69% increase in the annual flow of new clinical trials for drugs for "traditional" long-established rare diseases. Innovation in the smallest markets was limited to an increase in the stock of drugs in the years immediately subsequent to the ODA's passage. This response likely represents final development of existing technologies. The impact on R&D for drugs treating rare diseases with higher prevalence was substantially larger in magnitude and sustained throughout the study period—an indication of greater innovative effort to develop novel technologies in response to the incentives.

Overall, my results are consistent with Finkelstein (2004), who finds that policy-induced increases in expected demand for drugs in certain pharmaceutical classes were associated with increases in later stage clinical trials and final drug approvals. They are also consistent with Lichtenberg and Waldfogel (2003), who find that, after the ODA, the increase in the variety of drugs was higher for rare diseases than for non-rare diseases. Results from the present study suggest that the ODA was able to increase both the stock and flow of R&D activity. However, the differential impact of the ODA according to disease prevalence suggests that the effectiveness of tax credits on pharmaceutical R&D depends in part on revenue potential. Stimulating R&D in smaller markets may require larger tax credits or use of multiple incentives that affect investments on both cost and revenue margins.

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ODA is unclear. Accordingly, this study abstracts from welfare analyses and focuses on measuring the nature and extent of the impact of the ODA incentives on pharmaceutical innovation.

[2] Emphasis on personalized pharmacogenomic drugs has increased with better understanding of how differences in genetic or genetic-environmental interactions lead to heterogeneous drug responses. Partitioning diseases according to "genotype drug response phenotypes" 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] For example, Mansfield (1986), General Accounting Office (1989), McCutchen (1993), Hall (1993), Hall and Van Reenen (2000) look at aggregate firm level R&D expenditures—a gross measure of true innovation. On the other hand, Finkelstein (2004) examines flows of clinical trials and timing of R&D investments to make inferences about R&D intensity.

This paper proceeds as follows. Section 2 briefly describes the Orphan Drug Act. Section 3 establishes the theoretical and empirical framework to study the impact of the ODA on innovative activity. Results of the empirical analysis are presented in Section 4. Section 5 concludes with a discussion of the implications of the ODA for innovation policy.

## 2. Orphan Drug Act

The Orphan Drug Act was passed in 1983 and created incentives for firms to develop drugs to treat rare diseases. The passage of the ODA was in large part due to the lobbying effort of patient groups frustrated at the lack of drugs approved to treat rare diseases (Asbury, 1986). The evidence was clear: during the decade prior to 1983, only 10 drugs were marketed for rare disease indications; and only 36 drugs had *ever* been approved for a rare disease indication by 1982 (House of Representatives Subcommittee Report, 1982). Furthermore, it was found that firms at times possessed drugs with potential benefits to rare disease populations; yet because these drugs were not patentable, or because the costs to conduct clinical trials were too high relative to commercial demand, these drugs were "orphaned" (Rohde, 2000). This evidence motivated lobbying effort of patient groups to pass orphan drug legislation.

The ODA established two main incentives to develop orphan drugs: an income tax credit equal to 50% of clinical trial expenses, and a 7-year market exclusivity provision. The tax credit lowers the cost of conducting human clinical trials. Human clinical trials are conducted to test the efficacy and safety of drugs for FDA approval, and account for approximately two-thirds total expenditures for drug development (DiMasi et al., 2003). To date, the tax credit has cost nearly $2B, and is projected to cost $1.9B between 2008 and 2012 (Office of Management and Budget, 2007). The market exclusivity provision is intended to address the limited revenue potential of rare disease drugs. Note, however, that the provision is significantly weaker than a patent (Rohde, 2000).[4] Therefore, while the impact of the ODA is necessarily the combined impact of the two incentives, I refer mainly to the supply-side tax credit when discussing the impact of the ODA incentives.

Under the original ODA legislation, firms had to substantiate that a rare disease drug was of "limited commercial value" due to its small patient market in order to receive "orphan drug" status. The ambiguity and difficulty associated with establishing "limited commercial value" were immediately identified as the reason for the negligible response by firms the year ODA was passed (Rohde, 2000). A 1984 amendment to the ODA addressed this issue by defining orphan drugs to be those that treat diseases with prevalence below 200,000 Americans. Sponsors of clinical trials submit applications to the FDA's Office of Orphan Product Development (OOPD) with epidemiological evidence that the drug satisfies the prevalence threshold. The OOPD designates the drug an orphan if the evidence sufficiently and reliably supports this claim.[5] Firms acquire the tax credit upon their drug receiving orphan designation.

## 3. The impact of the ODA on rare diseases

This section examines how the ODA affects drug development for rare diseases. In Section 3.1, I present a simple model of drug innovation. As discussed in the previous section, the model will focus on the supply-side incentives of the ODA. The model generates predictions for the impact of the ODA which motivate the empirical analysis. Sections 3.2 and 3.3 discuss the data and empirical strategy used to estimate the ODA impact on R&D. Results are presented in Section 4.

[4] The marketing exclusivity provision is narrower than a patent in that it prevents competitors from marketing the same drug for the *same* approved rare disease. A competitor can market the same drug for any other disease. Hence, it primarily protects drugs that are not fully protected under conventional patents (e.g. naturally occurring compounds). Such cases comprise a small fraction of ODA approved drugs. Further, the clinical superiority provision added in 1991 only applies when contested drugs share the same macromolecule (to prevent competitors from making cosmetic changes to a drug, then marketing it for the same rare disease). A competing firm can market a different drug to treat the same rare disease, irrespective of clinical superiority. And without patent protection, a competing firm can market the same macromolecule (with cosmetic changes) to treat a second disease.

[5] This is based on a conversation with John J. McCormick, MD, Deputy Director at the Office of Orphan Product Development.

### 3.1. Predicted impact of the ODA

I introduce a fixed cost of R&D that is a function of drug quality into a spatial model of product differentiation (Salop, 1979; Riordan, 1986).[6] The market for a given drug is modeled as a unit circle, where disease prevalence, or potential market size, is characterized by the density of consumers, $\theta$, that sit on the circle. Patients sharing a disease (those on the same circle) are uniformly distributed on the circle, and consume one unit of the nearest drug. Consumers buy the drug if utility to consumption is positive—that is, when

$$u = h(q) - tx - P > 0. \tag{1}$$

Consumers derive utility, $h(q)$, from consumption of a drug of quality level $q$. But consumers differ in their treatment response to a given drug. Heterogeneous drug response is modeled as a consumer's distance, $x$, to the nearest drug. The ideally located patient receives the full therapeutic benefit of the drug, while patients at other locales experience a reduction in benefit according to a linear transport cost, $tx$. $P$ represents the unit price of the drug.

Consider a representative firm in a competitive market which produces one drug located at point zero on the circle. Its nearest rival produces to the right at a distance of $1/N$, where $N$ represents the total number of drugs in that market. A consumer situated between the two drugs, but a distance $x$ from the representative firm's drug, is indifferent between the two drugs when $h(q) - tx - P = h(q) - t(1/N - x) - P$. Let $v \equiv h(q) - t/N - P$ be the utility from the nearest rival's drug for a consumer located at the representative firm's drug locale. A consumer situated $x(P,q;v) = (h(q) - P - v)/2t$ away from the representative firm's drug is indifferent between the two drugs. Accordingly, the representative firm faces a demand of $Q = 2\theta\, x(P,q;v)$.

For a given disease market of size $\theta$, the representative firm chooses $Q$ and $q$ to solve:

$$\max \pi(Q, q) = (P - m) \cdot Q - F(q), \quad \text{subject to } q \geq \underline{q}. \tag{2}$$

The inequality reflects an FDA drug safety and efficacy standard, $\underline{q}$.[7] $P = P(Q,q;v)$ is the inverse demand function, $m$ is marginal cost of production, and $F(q)$ is the fixed cost of drug development which is a function of drug quality. I assume that the cost of drug development is increasing and convex in quality, and approaches infinity as $q$ approaches 1. This reflects the idea that it is not possible to create a drug that is safe and efficacious with perfect certainty. The equilibrium for a given drug market, $\theta$, can be characterized by

$$\frac{\partial \Pi}{\partial q} = h'(q^e) \cdot Q^e - F'(q^e) = 0 \tag{3}$$

$$\frac{\partial \Pi}{\partial Q} = (P - m) + Q^e \cdot \frac{\partial P}{\partial Q} = 0 \tag{4}$$

$$P = \frac{F(q^e)}{Q^e} + m \tag{5}$$

$$Q = \frac{\theta}{N} \tag{6}$$

Eqs. (3) and (4) are the first order conditions which require firms to equate marginal revenue to marginal cost. Free-entry requires firms to earn zero-profits in equilibrium—i.e. price equals average total cost (Eq. (5)). Eq. (6) requires that the market is covered.[8]

[6] The product variety literature has dealt with the consumer symmetry in opposite ways. Symmetric models feature a representative consumer who consumes all products and values variety (Chamberlain, 1931; Spence, 1976; Dixit and Stiglitz, 1977); while address models stress consumer heterogeneity (Hotelling, 1929; Salop, 1979). Address models conveniently capture the fact that individuals afflicted with the same phenotypic disease may experience heterogeneous drug responses to a given drug.

[7] The constraint reflects the 1962 Amendments to the Food Drug and Cosmetic Act that required drug sponsors to conduct clinical trials to prove safety and efficacy of drugs for marketing approval (Hilts, 2003).

[8] In a covered market, every consumer chooses to consume one unit of the nearest drug. This assumption avoids the monopoly and kinked equilibriums studied in Salop (1979), and forces equilibrium quality and variety to be monotonically increasing in $\theta$.

To solve for the equilibrium, I specify functional forms for consumer utility and fixed costs: $h(q) = q$ and $F(q) = c/(1-q)^{\beta}$.[9] The parameter $c$ is a constant coefficient on fixed costs. Under the quality constraint, the equilibrium number of drugs and the level of drug quality are

$$q^e = \underline{q}$$
$$N^e = \left[\frac{t\theta(1-\underline{q})^{\beta}}{c}\right]^{1/2}. \tag{7}$$

Denser patient markets intuitively should support a greater number of drugs. This intuition is reflected in the way $\theta$ enters monotonically in Eq. (7). As the transportation cost increases, willingness to pay for more closely positioned drugs increases, resulting in a greater equilibrium number of drugs. Note that below $\underline{\theta} \equiv c/t(1-\underline{q})^{\beta}$, patient markets are too small to support entry.

I model the ODA tax credit as a decrease in the fixed cost parameter $c$. To analyze the effects of the ODA, I assume that the quality constraint is sufficiently strict so that it binds for all rare diseases. This model leads to three intuitive predictions for the impact of the ODA. First, for diseases with prevalence below 200,000, the ODA should clearly lead to increased levels of R&D (i.e. $\partial N^e/\partial c < 0$). Estimating the magnitude of this partial derivative in practice is a central part of the empirical analysis to follow. Second, the intensive impact of the ODA should increase in the disease market size ($\partial^2 N^e/\partial c \partial \theta < 0$). This is intuitive as profits earned after realizing the flat-rate tax credit will be larger for drugs with larger markets. It remains to be tested whether the ODA incentives impact larger markets more than smaller markets *relative* to baseline pre-ODA R&D levels. Finally, while the disease market size at which no firms engage in R&D should decrease ($\partial\underline{\theta}/\partial c > 0$), the ODA should not effect drug development for the least prevalent diseases as entry remains unprofitable even when fixed costs of drug development are subsidized.

### 3.2. Data

The empirical analysis relies on a comparison of rare diseases – which qualify for the ODA – and diseases that are uncommon but not rare enough to qualify. The list of diseases I use comes from the National Organization for Rare Disorders (NORD), a not-for-profit agency established in 1983 to serve as a clearinghouse to medical, policy and patient groups for information on uncommon diseases and conditions. They publish a database of 1177 uncommon diseases. The database has been virtually unchanged since it was first published when the ODA was passed, and can be considered a list of traditional, long-recognized diseases.[10] Based on an extensive review of the epidemiological and clinical reference literature, I 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; (2) 148 "Non-rare" diseases, defined as those with prevalence above the threshold (of which 50 have prevalence between 200,000 and 500,000); and (3) six "Status-changers" whose estimated prevalence at the start of the study period is below 200,000, but whose prevalence increases to a level slightly above the threshold during the study period.[11] Table 1 reports the year the OOPD last designated a drug to treat each of the status-changer diseases.

The key measure of innovation is the count 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.[12] The principle source of data on new clinical trials data is *The NDA Pipeline*. This journal has been published since 1982 by F-D-C Reports, long-respected for its research of the drug industry.[13] The annual volumes of *The NDA Pipeline* contain information on clinical trials of all major pharmaceutical firms, and most small but active drug manufacturers, biotechnology firms, and non-

[9] The functional form of $F(q)$ has the desired properties that it is convex in $q$ and has an asymptote at $q = 1$ when $\beta \geq 1$.

[10] This is based on a telephone conversation with Mary Dunkle, at NORD.

[11] Prevalence estimates from the epidemiological literature often report a range of estimates (i.e. 1:10,000–1:5,000, or 25,000–50,000). This uncertainty is the main reason the analysis relies on comparing a sets of control diseases to treatment diseases, rather than directly regressing R&D effort on disease prevalence, and measuring the discontinuity at 200,000.

[12] Clinical trials often span more than 17 years (DiMasi et al., 2003). Therefore, using the number of *new* clinical trials as a measure of R&D avoids the problem of capturing decisions based on past investment climates.

[13] This is based on a conversation with Peg Hewitt at the Center for the Study of Drug Development at Tufts University. F-D-C Reports also publishes *Pink Sheets* weekly since 1939, and provides detailed information about clinical trials and financial news. Excerpts from *Pink Sheets* are

Table 1
Status-changer diseases

| 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 |

The table lists the eight diseases that lose rare disease status since the ODA was passed. Six of the diseases experienced a change in rare disease status during the period studied in this paper (1981–1994). Orphan drug designations appeared in the data for each of the diseases listed in table. The first column lists the year the OOPD last designated a drug for that specific disease indication. The second column shows current disease prevalence estimates. 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 et al. (2002).
[b] Hochberg et al. (1995).
[c] Anderson et al. (1992).
[d] http://www3.niaid.nih.gov/.
[e] http://www.niams.nih.gov.
[f] Division of Oral Medicine (1999).
[g] http://www.cdc.gov.
[h] Trivedi et al. (2002).
[i] Xue et al. (2001).
[j] Curhan et al. (1999).
[k] http://www.niddk.nih.gov/.
[l] Altman et al. (2000).

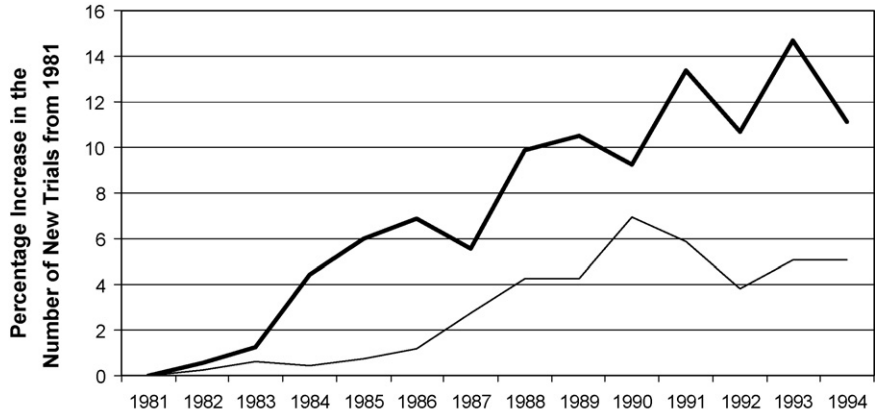
profit research institutions. For each firm, the journal reports on the clinical trials for all chemical entities known to the publisher. Typically, the journal includes information about the indications for which drug is being tested, the phase of development, and whether the product has been previously marketed. I use this information to identify when a drug first appears in the pipeline for a specific disease indication. *The NDA Pipeline* was supplemented with information from *Pharmaprojects*, which has been published since 1980. Relative to *The NDA Pipeline*, *Pharmaprojects* focuses more heavily on products in preclinical phases, and on non-US-based firms.[14] This publication is used to clarify ambiguities in *The NDA Pipeline*, and in some cases to obtain information that is uniquely contained in *Pharmaprojects*.

I assembled my dataset by recording when unique clinical drug trials indicated for the diseases in the NORD list first appear in these publications. The final panel dataset lists the number of new clinical trials for each of the 1177 NORD diseases, for each year between 1981 and 1994. Appendix Table 1A describes in greater detail the process by which new clinical trials are counted.

The total number of new clinical trials, grouped by rare and non-rare diseases, over time is shown in Fig. 1. Graphed values represent percentage increase over the number of new clinical trials in base year 1981; cells values at the bottom of the figure report raw counts. There is a noticeable increase in the relative number of new trials for rare diseases starting in 1984. Summary statistics for the number of new clinical trials for traditional rare diseases are shown in Table 2. Mean and distribution of counts by treatment group are shown for 1983, the last year before the effective amendment of the ODA was passed, and for 1985, the first full year after the relevant amendment was passed. The mass of the counts clearly lies at zero, and the data tend to be over-dispersed (variance exceeds mean). Further, the distribution of counts differs by group. These characteristics help to motivate the choice of count regression model.

published in *The NDA Pipeline*, and supplement information found in the main tables. Finkelstein (2004) uses the *NDA Pipeline* to gather data on clinical trials for vaccines.

[14] This is based on a conversation with Ian Lloyd, Editor-in-Chief of *Pharmaprojects*.




| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rare (n=1023) | 7 | 11 | 16 | 38 | 49 | 55 | 46 | 76 | 81 | 72 | 101 | 82 | 110 | 85 |
| Non-Rare (n=148) | 15 | 19 | 24 | 22 | 26 | 33 | 56 | 79 | 79 | 119 | 103 | 72 | 91 | 91 |

Fig. 1. Figure shows the percentage change in number of new clinical trials (base year = 1981). Counts of new clinical drug trials, by disease prevalence group, by year (1981–1994) are shown in the cells below the figure.

### *3.3. Estimation framework*

To estimate the average impact of the ODA on R&D effort, I use a difference-in-differences approach, which compares clinical trials for rare disease drugs to non-rare disease drugs, before and after passage of the ODA. I use the clinical trials panel data to estimate:

$$\mathrm{NT}_{it} = f(\alpha_0 + \sum_t \alpha_t \mathrm{Year}_t + \beta_1 \mathrm{PostODA}_t + \beta_2 \mathrm{Rare}_i + \beta_3 (\mathrm{PostODA} \times \mathrm{Rare})_{it} + \varepsilon_{it}). \quad (8)$$

Table 2
Summary statistics for the counts of new clinical trials

| | | Group | | |
|---|---|---|---|---|
| | | Rare | Status-changer | Non-rare |
| Panel A: counts of new clinical trials in 1983 | | | | |
| 1983 | New clinical trials | 0.017 (0.135) [.018] | 0.333 (0.516) [.267] | 0.162 (0.535) [.286] |
| | 75-Percentile | 0 | 1 | 0 |
| | 90-Percentile | 0 | 1 | 1 |
| | 95-Percentile | 0 | 1 | 1 |
| | 99-Percentile | 1 | 1 | 3 |
| | Max | 2 | 1 | 3 |
| | *N* | 1023 | 6 | 148 |
| Panel B: counts of new clinical trials in 1985 | | | | |
| 1985 | New clinical trials | 0.048 (0.274) [.075] | 1.000 (2.000) [4.000] | 0.182 (0.629) [0.395] |
| | 75-Percentile | 0 | 1 | 0 |
| | 90-Percentile | 0 | 5 | 1 |
| | 95-Percentile | 0 | 5 | 1 |
| | 99-Percentile | 1 | 5 | 2 |
| | Max | 4 | 5 | 4 |
| | *N* | 1023 | 6 | 148 |

The first row of Panels A and B show the mean number of new clinical drug trials for diseases in the NORD list for 1983 and 1985, respectively. Columns report statistics separately for each disease prevalence group. Variance of counts of new trials per disease within prevalence group is shown in square brackets. The number of new clinical trials counts at the 75th, 90th, 95th, 99th percentile, and the maximum of the distribution are shown in the rows below. The maximum number of counts for a disease in each group is also reported.

The outcome variable, $NT_{it}$, is the number of new clinical trials for disease $i$ in year $t$. PostODA is an indicator equal to 1 in the 1984–1994 time period, and the variable Rare is an indicator for whether disease $i$ is rare.[15] The model includes a set of year dummy variables to capture differences in R&D effort across years that are the same for rare and non-rare diseases. The coefficient of primary interest is $\beta_3$, which measures the increase in the yearly flow of new clinical trials for rare diseases after the passage of the ODA beyond that which is observed for non-rare diseases. In specifications that include disease-specific fixed-effects, the time-invariant effect of Rare is necessarily excluded.

A number of conditions must be met for the consistent estimation of $\beta_3$. First, the definitions of rare and non-rare diseases must be exogenous, i.e. not subject to firm manipulation. For this reason, I consider only drugs for the fixed set of diseases on the NORD list. This condition also demands that the six status-changer disease not be included in this analysis: drug development may affect disease prevalence, and therefore the rare status of a disease. Second, any prevailing change in the investment climate must affect rare and non-rare diseases in the same manner. Although this assumption cannot be tested, the restriction of the control diseases to similarly uncommon, low prevalence, diseases (but not "rare") makes this assumption plausible. Third, passage of the ODA must not have shifted investments from drugs treating uncommon diseases to those that treat rare diseases. This would bias the estimate of $\beta_3$ upward. Borrowing or capacity constraints would lead to substitution of this sort. Finally, to the extent that anticipation of the ODA led firms to withhold clinical trials that would have otherwise taken place, the estimate of $\beta_3$ will be biased upward. Fig. 1, however, shows a relatively steep and upward trend in the flow of new clinical trials for rare diseases *prior* to the passage of the ODA. This suggests that the firms did not withhold clinical trials for potentially profitable rare disease drugs in anticipation of the ODA legislation.[16]

In the cross-sectional DD approach outlined above, I am only able to use 3 years of data to establish the pre-ODA trend in the flow of new clinical trials. This data limitation, in addition to the conditions required for consistent estimation above, motivates an alternative identification strategy: estimating changes in flow of new clinical trials for six status-changer diseases—diseases whose prevalence grew to slightly above 200,000 during the study period. I proxy the date when prevalence of status-changers grew to above 200,000 by the year the OOPD last designated an orphan drug for that disease (Table 1). The earliest year for any status-change is 1990, resulting in at least 9 years of pre-event data. I estimate:

$$NT_{it} = f(\alpha_0 + \sum_t \alpha_t \text{Year}_t + \beta_1 \text{StatusChanger}_i + \beta_2 \text{Changed\_from\_Rare}_{it} + \varepsilon_{it}). \quad (9)$$

The variable of interest is Changed_from_Rare, an indicator for when a status-changer disease changes to a "non-rare" disease from a rare disease. The estimate of $\beta_2$ represents the impact on the flow of new clinical trials due to "losing" rare status. Consistent estimation of $\beta_2$ requires that prevalence changes are exogenous to the outcome variable. This assumption may fail to hold in reality, as the availability of drugs may be associated with an improved ability to diagnose a disease. Hence, more drugs may induce higher prevalence, causing a disease to lose rare status. To the extent that increases in the number of new clinical trials capture increases in the available stock of marketed drugs for a given disease, this endogeneity the will bias the estimate of $\beta_3$ towards zero (underestimate the ODA impact).[17] Also, the six diseases changed status at different points in time—a fact used to address a weakness of the previous identification strategy.

Fig. 2 offers a visual interpretation of $\beta_2$. The equilibrium number of drug trials conducted by firms to treat a given disease is plotted against disease prevalence (a proxy for market size in this figure), where the bold line represents the post-ODA equilibrium. Ideally, I would like to estimate the decrease in the number of new clinical trials associated with a move from point A to B. Because the status-changer diseases grow slightly in prevalence, estimates of $\beta_2$

[15] The first year of the PostODA period is set to 1984. Although the ODA was passed in January of 1983, it was not until the 1984 amendment that the 200,000 prevalence threshold for a rare disease was established. The relevance of the ODA is widely thought to have begun in 1984 (Rohde, 2000). Section 2 describes the passage of the ODA in greater detail.

[16] Strategic delaying of clinical trials of profitable rare disease drugs (which would be conducted in absence of the ODA) should be distinguished from shelving drugs due to limited commercial. Delaying trials of profitable drugs in anticipation of the ODA would lead to an upward bias of the estimates of the ODA impact. In contrast, final development of previously shelved drugs is one type of response this study seeks to measure. Indeed, development of shelved technologies was one of the goals of the ODA legislation.

[17] Alternatively, new drugs may lower prevalence by eliminating the underlying disease. This would be the case for, say, bacterial diseases, where antibiotics may reduce prevalence of infection. Of the six status-changer diseases, five are chronic diseases, and only AIDS is an (viral) infectious disease. No drug to date successfully reduces AIDS prevalence. Nevertheless, the status-changer disease analyses are done with and without AIDS in sample specifications below.

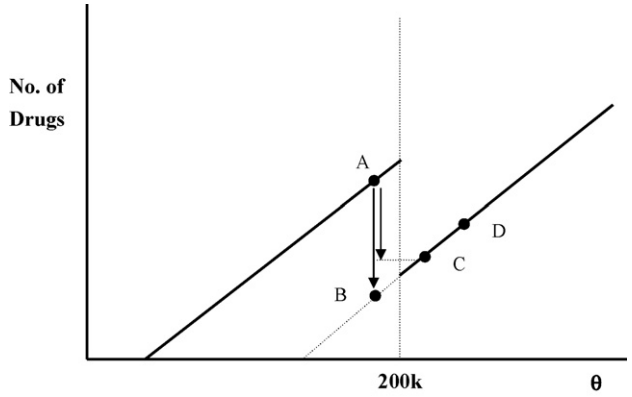



Fig. 2. Effect of losing the ODA tax credit.

actually capture the drop to C from point A. So I underestimate the magnitude of $\beta_2$. To the extent that a disease grows rapidly in prevalence (A to D, such as the case with AIDS), estimates of $\beta_2$ will further underestimate the true magnitude.

The functional form for Eqs. (8) and (9) is chosen so as to account for the nature of the data. Flow of new clinical trials is non-negative, integer-valued, and has density at low values. This motivates count regression models.[18] Commonly used count models for panel data include the Poisson and negative binomial (NB) models (Hausman et al., 1984). Unlike the NB models, which for consistent parameter estimation require that the data be distributed as NB, the Poisson model has the advantage of being consistent even when the data generating process is misspecified (Cameron and Trivedi, 1998). Poisson estimates are 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 the model using quasi-ML (Wooldridge, 1997, 1999).[19]

## 4. Empirical results

Table 3 reports the results from estimation of Eq. (8). I first report results from estimating the conditional Poisson regression model. Specifications in Table 3 assume a fixed-effects structure of disease heterogeneity in the Poisson model. The coefficient estimate on the interaction term of interest is 0.52, suggesting that the ODA led to a 69% increase in the rate of new clinical trials for rare diseases, net of any increases in the rate of new clinical trials for control diseases.[20] For Poisson specification in this setting, estimates from the fixed-effects model are necessarily identical to those of the random effects model, and are thus not reported.[21]

The model discussed in Section 3 suggests that the impact of the ODA should increase in the drug market size. In column (2), I restrict the sample of rare diseases to those with prevalence above 100,000, and include all non-rare

[18] 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.

[19] The multiplicative fixed or random effects allow for both distributional heterogeneity across diseases, and for over-dispersion. While ML estimates for standard errors in this setting are not *a priori* expected to be (over-) underestimates in the face of (under-) overdispersion (Cameron and Trivedi, 1998), consistency requires that the distribution be correctly specified. Poisson FE parameters can be estimated under distribution-free assumptions by quasi-ML according to Wooldridge (1997, 1999).

[20] Coefficients of a Poisson regression represent relative changes in the marginal effect of the outcome variable. Since the regressors of interest are binary, it is more intuitive to report estimates as incident rate ratios, defined as $E[y|x_i = 1]/E[y|x_i = 0] = \exp(\beta_i)$. An estimate of $\beta_i$ can be interpreted as an $(\exp(\beta_i) - 1) \times 100\%$ change in $y$, given a change of 0–1 in the independent variable.

[21] The covariates are indicators for prevalence category and time period, and are necessarily orthogonal to any disease-specific effects. Hence, coefficient estimates for the fixed and random effects models will be identical (with the exception of a negative and significant coefficient on RARE that appears in the random effects model). The common form of the negative binomial used in columns (3) and (4) imposes a heteroskedastic variance structure so that disease-specific effects are necessarily correlated with the regressors (Cameron and Trivedi, 1998). I reject random effects for the negative binomial regression model. I also reject random effects for later analysis that include status-changer diseases, suggesting that unobserved effects may be correlated with rare disease status.

Table 3
Impact of the ODA on new clinical drug trials (dependent variable: number of new clinical trials)

| | Model | | | | | |
|---|---|---|---|---|---|---|
| | Poisson FE | | Negative binomial FE | | Poisson FE | Linear FE |
| | All rare diseases[a] (all non-rare diseases[b]) (1) | Above 100k[a] (all non-rare diseases[b]) (2) | All rare diseases[a] (all non-rare diseases[b]) (3) | Above 100k[a] (all non-rare diseases[b]) (4) | Above 100k[a] (below 500k[b]) (5) | Above 100k[a] (below 500k[b]) (6) |
| PostODA | 1.760*** (0.358) | 1.775*** (0.270) | 1.826*** (0.275) | 1.827*** (0.321) | 2.052*** (0.457) | 1.004*** (0.251) |
| Rare × PostODA | 0.524** (0.257) | 1.200** (0.595) | 0.338 (0.234) | 1.185** (0.610) | 1.040** (0.359) | 0.527* (0.315) |
| Constant | | | 0.050 (0.354) | 0.668 (0.517) | | 0.136 (0.174) |
| Year dummies | Yes | Yes | Yes | Yes | Yes | Yes |
| *R*-Squared | | | | | | 0.13 |
| No. of rare diseases | 168 | 9 | 168 | 9 | 9 | 9 |
| No. of control diseases | 56 | 56 | 56 | 56 | 28 | 50 |
| No. of diseases | 224 | 224 | 224 | 224 | 35 | 59 |
| Observations | 3136 | 3136 | 3136 | 3136 | 490 | 826 |

The table reports the parameter estimates from Poisson, negative binomial and OLS models. The dependent variable is the number of new clinical trials for a given disease in the NORD list in a given year from 1981 to 1994, for all 1171 (=1777 − 6) non-status-changer diseases in the study. Fixed-effects models drop diseases for which there are no counts in the time series. The diseases sample specifications are noted in the column headers. PostODA, and Rare × PostODA are indicator variables. All regresions are estimated with year dummy variable. Standard errors are in parentheses. Standard errors in poisson fixed-effects models are estimated by quasi-MLE (Wooldridge, 1999). *Significant at 10%; **significant at 5%; ***significant at 1%.

[a] Treatment sample.

[b] Control sample.

diseases in the NORD sample as controls. I estimate that the ODA led to a 232% (=[exp (1.200) − 1] × 100) increase in the rate of new clinical trials for more prevalent rare diseases relative to control diseases.

In columns (3) and (4), I report the results from the NB model, using sample specifications in columns (1) and (2), respectively. The results are similar to Poisson parameter estimates, indicating that estimates are robust to functional form assumptions. Quasi-ML Poisson estimates are consistent under weaker assumptions, so I henceforth report results from only conditional fixed-effects Poisson specifications.

A narrower disease prevalence sample specification also lends itself to linear estimation. Diseases in this sample are more similar in prevalence, so linear estimates are less subject to misinterpretation due to level-differences in pre-ODA clinical trials. Columns (5) and (6) report estimated impacts by Poisson and linear fixed-effects models when the sample is restricted to rare disease with prevalence greater than 100,000 and control diseases between 200,000 and 500,000. The predicted level of clinical trials for the sample of rare diseases in the last pre-ODA year is 0.240, making the estimate of 0.527 in column (6) equivalent to a 120% increase in the flow of new drug trials—an impact similar to the 182% increase estimated in column (5).

Linearity of the year dummies is rejected, largely an outcome of kinks in the time series occurring after 1990 observed in Fig. 1. This may be due to idiosyncratic year-to-year differences in industry-wide R&D effort, or in the level of detail of the *NDA Pipeline*.[22] Year dummies account for such idiosyncratic differences across years. One threat to identification is the possibility that the R&D investment climate changed differentially for rare and non-rare diseases during the study period. Finkelstein (2004) finds that during the post-ODA period, several policies impacted expected returns on vaccines and led to significant increases in R&D for vaccines that treat relevant infectious diseases. To check for robustness, I re-estimate Eq. (8) dropping all rare and non-rare diseases classified by NORD as an infectious disease. The estimated impact of the ODA increases in all specifications, albeit insignificantly.[23]

The impact on the extensive margin is also fairly clear. Whereas only 61 rare diseases had at least one new clinical drug trial during the three pre-ODA years, 111 (226) rare diseases had at least one new drug trial in the 3 (11) years after the ODA was passed.

### 4.1. Timing of the investment response

It is not clear from the analysis estimated above whether the ODA leads firms to undertake development of new technologies, to hasten the development of future orphan drugs, or to market existing technologies that had previously been shelved due to limited commercial value. To distinguish among these scenarios, I follow Finkelstein (2004) and include indicators for time periods after the ODA. This allows for the effect of the ODA to be estimated more flexibly than in Eq. (8). Using a Poisson fixed-effects model, I estimate:

$$\begin{aligned} \mathrm{NT}_{it} = f(\alpha_0 + \sum_t \alpha_t \mathrm{Year}_t + \beta_1 \mathrm{PostODA}_{(1-3),t} + \beta_2 \mathrm{PostODA}_{(4-6),t} + \quad \beta_3 \mathrm{PostODA}_{(7\mathrm{plus}),t} \\ + \beta_4 (\mathrm{PostODA}_{(1-3)} \times \mathrm{Rare})_{it} + \beta_5 (\mathrm{PostODA}_{(4-6)} \times \mathrm{Rare})_{it} + \beta_6 (\mathrm{PostODA}_{(7\mathrm{plus})} \times \mathrm{Rare})_{it} + \varepsilon_{it}). \end{aligned} \tag{10}$$

The three PostODA($t$, $t'$) variables are indicators for whether a clinical trial began for disease $i$ in the immediate three, three-to-six, and 7 years or beyond the passage of the ODA. The variable Rare × PostODA($t$, $t'$) is the interaction term between status as a rare disease and the PostODA indicator variables. Eq. (10) allows for a test of $\beta_4 = \beta_5 = \beta_6$. If the three coefficients are equal and positive, then we can conclude that there was no drop-off in new clinical work for rare diseases in the years subsequent to the initial passage of the ODA.

The results are reported in Table 4. Column (1) reports the results using the entire sample of diseases. The ODA is associated with a 182% (=exp (1.038) − 1 × 100) increase in the flow of new clinical trials for rare diseases in the 3 years immediately after the ODA was passed. The impact is more than halved in later periods.

[22] The number of pages of yearly volumes of the *NDA Pipeline* increases every year until 1991, after which it levels off. This leveling off, evident in Fig. 1, could be the outcome of diminished growth in the drug industry. It could also represent changes in the scope of the journal itself. There is no evidence that changes in the journal differentially affected counts of rare or non-rare diseases.

[23] This specification drops 31 diseases in the Poisson fixed-effects regression—23 rare diseases and 8 non-rare diseases. Results of this specification are available upon request.

Table 4
Timing of new clinical trials (dependent variable: number of new clinical trials)

| | Poisson fixed-effects | |
|---|---|---|
| | (1) | (2) |
| Postoda_13 | 0.774*** (0.295) | 0.774*** (0.259) |
| Postoda_13 | 0.774*** (0.295) | 0.774*** (0.259) |
| Postoda_46 | 1.706*** (0.264) | 1.706*** (0.238) |
| Postoda_7plus | 1.802*** (0.234) | 1.802*** (0.234) |
| Rare × PostODA_13 | 1.038*** (0.253) | |
| Rare × PostODA_46 | 0.442* (0.233) | |
| Rare × PostODA_7plus | 0.440** (0.221) | |
| Rare (<100k) × PostODA_13 | | 0.982*** (0.260) |
| Rare (<100k) × PostODA_46 | | 0.346 (0.240) |
| Rare (<100k) × PostODA_7plus | | 0.338 (0.228) |
| Rare (100k, 200k) × PostODA_13 | | 1.505** (0.644) |
| Rare (100k, 200k) × PostODA_46 | | 1.135* (0.620) |
| Rare (100k, 200k) × PostODA_7plus | | 1.166* (0.604) |
| Year dummies | Yes | Yes |
| Joint *F*-test for equality of interactions | | 0.418 |
| No. of rare (<100k) diseases | 161 | 161 |
| No. of rare (100k, 200k) diseases | 7 | 7 |
| No. control diseases | 56 | 56 |
| No. of diseases | 224 | 224 |
| Observations | 3136 | 3136 |

The table reports the parameter estimates of the Poisson fixed-effects regression. The dependent variable is the number of new clinical trials for a given disease in the NORD list in a given year from 1981 to 1994, for all 1171 (=1777 − 6) non-status-changer diseases in the study. Fixed-effects models drop all disease for which there are no counts in the time series. PostODA, and Rare × PostODA are indicator variables. The variables PostODA_$t$, $t'$ denotes the indicator variable that takes the value 1 in years $t - t'$ after the passage of the ODA. The variable Rare($a$, $b$) is an indicator that takes 1 for diseases that have prevalence between $a$ and $b$. All regresions are estimated with year dummy variables. Standard errors are in parentheses. Standard errors in Poisson fixed-effects models are estimated by quasi-MLE (Wooldridge, 1999). *Significant at 10%; **significant at 5%; ***significant at 1%.

I formally test the prediction that the average impact of the ODA should be larger for diseases with the higher prevalence. I create indicator variables for rare disease in the NORD sample having prevalence below and above 100,000 (Rare(<100k) and RARE(100k, 200k)), and interact them with the PostODA($t$, $t'$) variables. For the least prevalent rare diseases, I find that the ODA leads to an initial doubling of the flow of new clinical trials in the years immediately subsequent to the ODA's passage. The impact declines and is no longer significant later in the study period. For more prevalent diseases rare diseases, the initial impact of the ODA on the flow of new clinical trials is significantly larger than for smaller diseases. And while the impact declines about 30% in later periods, joint pair-wise equality of the coefficients on the period-interaction terms cannot be rejected.[24]

### 4.2. Time series variation in orphan status of diseases

A second identification strategy is implemented by making use of status-changer diseases. Results from estimating Eq. (9) are reported in Table 5. Columns (1) and (2) restrict the sample to only the status-changer diseases. The results indicate a significant drop in the number of new clinical trials in the years after the diseases in the sample first lose rare disease status.[25] Columns (3) through (5) use various rare diseases from the NORD list as a comparison group. Column (4) uses rare diseases with prevalence above 100,000 are used as the comparison group. They are most similar to status-

[24] Here, too, a threat to identification is the possibility that other policy changes differentially affect non-rare and rare diseases drug development (e.g. policies that affect returns to vaccine development studied in Finkelstein (2004)). The results do not change significantly when infectious diseases are dropped from the sample specification. Results are available upon request.

[25] Due to small sample sizes, estimation of 1-year dummy variables becomes problematic. 2-year dummy variables are used instead. All analyses were repeated using a linear specification for year effects; results of these analyses are available upon request. The qualitative results do not change, and estimated impacts estimated in Tables 3–5 generally increase in magnitude.

Table 5
Impact on new drug development: status-changer diseases (dependent variable: number of new clinical trials)

| | Poisson FE | | | | |
|---|---|---|---|---|---|
| | Status-changers[a] (none[b]) (1) | Status-changers (NO AIDS)[a] (none[b]) (2) | Status-changers[a] (all rare[b]) (3) | Status-changers[a] (rare diseases above 100k[b]) (4) | Status-changers (NO AIDS)[a] (rare diseases above 100k[b]) (5) |
| Changed from rare | −0.285 (0.251) | −1.227** (0.576) | −0.046 (0.120) | −0.331** (0.166) | −0.666** (0.303) |
| 2-Year dummies | Yes | Yes | Yes | Yes | Yes |
| No. of status-changer diseases | 6 | 5 | 6 | 6 | 5 |
| No. of control diseases | 0 | 0 | 170 | 9 | 9 |
| No. of diseases | 6 | 5 | 176 | 15 | 14 |
| Observations | 84 | 70 | 2464 | 210 | 196 |

The table reports the parameter estimates of the fixed-effects Poisson regression. The dependent variable is the number of new clinical trials for a given disease, in a given year from 1981 to 1994. The fixed-effects model drops all disease for which there are no counts in the time series. Column headers note which status-changer diseases, and which control 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 included 2-year dummy variables. Standard errors are in parentheses. Standard errors are in parentheses. Standard errors in Poisson fixed-effects models are estimated by quasi-MLE (Wooldridge, 1999). *Significant at 10%; **significant at 5%; ***significant at 1%.

[a] Status-Changer Sample.

[b] Control Sample.

changer diseases in terms of prevalence, making column (4) the preferred specification. The result suggests that losing rare disease status is associated with a 30% reduction in the flow of new clinical drug trials to treat that disease. This impact is similar in magnitude to the doubling effect attributed to the ODA incentives for rare diseases with prevalence greater than 100,000 estimated in the cross-sectional analysis. As expected, removing AIDS from the sample decreases the coefficient estimates (increases the negative impact) associated with losing ODA eligibility (columns (2) and (5)).

## 5. Conclusion

Passed by Congress in 1983, the ODA was designed to stimulate innovation in rare disease drugs. Since then, the ODA has often been discussed as a model for how public policy can be designed to stimulate R&D in other health markets where technologies generate small private returns, and where R&D investments are upfront, high, and uncertain (Kremer, 2001a,b; Haffner et al., 2002; Grabowski, 2005).

Kremer (2001a,b), in particular, outlines the theoretical costs and benefits of various strategies for stimulating development of infectious diseases vaccines. While revenue-side policies such as purchase commitments and prizes have several key benefits (for example, they directly impact revenue margins), they suffer from time-inconsistency. Dominant purchasers of vaccines such as governments or aid agencies may renege on prize or purchase price commitments once the vaccine is developed. Given that upfront R&D costs tend to swamp marginal costs of drug or vaccine production, this uncertainty may deter firms from investing in R&D. For these reasons, supply-side incentives that occur contemporaneously with R&D expenditures are thought to be an effective tool for stimulating innovation.

In the US, two policies have been passed that allow for study of the impact of supply-side incentives. The first policy is the Research and Experimentation Tax Credit, an economy-wide subsidy on incremental expenditures for experimental operations relative to a firm's baseline level of expenditure. The ODA is the second and more recent policy, and has the empirical advantage of targeting a specific, well identified market. In this study, I examined the impact of the ODA on pharmaceutical R&D. I use of data on new clinical trials over time by disease to study the impact of the legislation. The disaggregated nature of the data allows me to infer the financial margins along which the ODA affects private drug R&D, analyses which firm-level R&D expenditure data do not permit.

I find that the ODA had a significant impact on rare disease drug development. I estimate that on average the ODA led to a 69% increase in the annual flow of new clinical trials for drugs for "traditional" long-established rare diseases. Innovation in the smallest of these disease markets was limited to the years immediately subsequent to the ODA's passage. This increase in the stock of drugs likely represents final development of existing technologies. The impact on innovation for rare disease with higher prevalence was larger and sustained throughout the study period—an indication that the ODA not only generated greater levels of R&D, but also spurred innovation in novel drug technologies.

The analysis of the ODA reveals several things about the potential impact of tax credits on innovation. First, tax credits are able to generate R&D through their direct impact on development cost margins. In the case of rare disease, the ODA tax credit led to increases in the stock and flow of R&D for rare disease drugs. Yet tax credits have key limitations. Most notably, they leave revenue margins unaffected. Consequently, policies structured as (flat-rate) tax credit may be relatively ineffective at stimulating innovation in markets with small revenue potential. Firms that do not posses revenue-generating products may be particularly unresponsive to tax credits, which obtain value only when firms earn taxable profits. And the ability to carry credits forward in time may be less effective for firms with relatively high costs of capital. More generally, even high levels of supply-side subsidization will not stimulate R&D in markets where revenue potential is too low. Small revenues simply cannot justify large capital investments (even if fully subsidized) from an opportunity cost perspective. For these markets, innovation policy must also operate on revenue margins.

In theory, the size of tax credits on R&D expenditures could correspond to profit potential, not just to cost. Such a policy would need to balance the variable nature of the credit with feasibility. Indeed, the original ODA legislation linked the flat-rate tax credit to profit potential; the ODA applied to any rare disease drug with "limited commercial value". In practice, firms found it impractical to establish that a drug had limited commercial value so early in development, and few firms responded to this incentive (Rohde, 2000). In its place, legislators developed a simple rule-of-thumb to define a rare disease—the discrete prevalence threshold of 200,000 Americans. Likewise, policies designed to stimulate drug innovation across markets of varying revenue potential could make use of rules-of-thumb. Step-wise tax credits pegged

to several disease incidence or prevalence markers could be employed. A more sophisticated combination of supply and revenue-side incentives might also be considered. For example, the chronic nature of the indicated disease could proxy for profit potential while maintaining feasibility.

The results of this paper are directly relevant to the development of personalized drugs, which are thought to hold great promise as a model for future drug innovation (Aspinall and Hamermesh, 2007). Personalized drug markets are by definition small, each consisting of patients within a traditionally defined disease phenotype who, based on their genotypes, exhibit similar clinical responses to drugs. In principle, a movement to greater personalization can offer greater therapeutic benefits and better side-effect profiles for the targeted subset of patients.

Personalized drug technologies can be interpreted within the framework developed in Section 3. Given a phenotypic disease's drug market, greater "personalization" can be viewed simply as an increase in the number of differentiated drug locales in a given drug market. The market can be defined as the circular city of all patients sharing the same traditionally defined phenotypic disease. The addition of one drug decreases the distance patients have to travel to the nearest drug locale (i.e. better pharmacogenomic drug targeting). Consumption utility of the nearest drug is consequently higher with greater personalization. However, note that Eq. (7) in Section 3 solves for the equilibrium number (and spacing) of drugs given the size of the phenotypic disease market. Small patient markets simply cannot support levels of drug development greater than that which is derived in Eq. (7). An increase in the number of drugs relative to equilibrium levels leads to greater utility from consumption of a closer drug; however, gains to consumption utility are factored into the price of the drug. This price offset, combined with the development costs of additional drugs, more than counteracts the increase in consumption utility from greater personalization.[26] A model of pharmaceutical innovation founded on personalized therapeutic technologies, greater product differentiation, and smaller local drug markets, simply cannot be supported given the underlying cost parameters of drug innovation.

A more viable model of "personalized" medicine would emphasize diagnostic technologies more so than therapeutic technologies. (See Aspinall and Hamermesh, 2007) for a brief discussion of "blockbuster" and personalized drug development models.) Improved diagnostics, in theory, can help physicians identify a patient's specific genotype within a more broadly defined disease phenotype. Accordingly, physicians can optimally prescribe drugs, thereby reducing "search costs" associated with inappropriate drug consumption (drug expenditures, duration of untreated illness, duration and intensity of side-effects)—costs that are not explicitly modeled in Section 3.

In theory, development of some personalized diagnostic technologies can be financed endogenously from unmet patient demand for technologies that reduce drug search costs. Still, diagnostic technologies whose benefits apply to few people (e.g. patients afflicted with a traditionally defined low-prevalence disease phenotype) offer less private incentives for firms to innovate. The economic principle dictating that private investments should follow expected market returns is as binding here as it is in the rare disease drug and vaccine contexts.

Ultimately, the only way to increase innovation in personalized drugs (i.e. to decrease the spacing between drug locales within phenotypic disease markets), or to generate innovation in personalized diagnostic technologies, is to affect the underlying parameters of the development model. By lowering fixed costs of drug development, the ODA is able to increase the level of R&D in drug development for a given disease market. In general, tax credits can increase equilibrium levels of R&D in each market, thereby increasing product differentiation and improving pharmacogenomic drug targeting. Note that for the same reasons here as in the rare disease drug context, flat-rate tax credits are likely to have a smaller impact on R&D of personalized technologies with smaller market potential. Here, too, combining supply-side incentives with incentives that impact revenue margins may be effective at stimulating innovation.

In fact, there is some direct evidence that the ODA generated new innovation in personalized drugs, and in the identification of new and distinct disease types. In the years following the passage of the ODA, there was a profusion of drugs to treat "new" rare diseases—diseases defined as partitions of traditionally defined and long-recognized disease. This response appears to be an unintended yet significant impact of the ODA, and suggest that the ODA may have encouraged greater research in pharmacogenomic drugs simply by subsidizing R&D in specific

[26] The cost attributable to heterogeneous treatment response in Section 3 can be re-parameterized to place greater weight on the distance (e.g. costs could reflect the square of distance). This would capture a higher marginal benefit for an additional drug in smaller markets where equilibrium levels of drugs is low—an arguably more realistic assumption. In equilibrium, smaller markets would support more drugs than when transportation costs are linear in distance. However, this would not affect the general point that greater personalization in drugs therapies cannot be funded endogenously without additional changes to the underlying development cost model.

markets. This response is consistent with the model in Section 3, and suggests that extending tax incentives to all drug markets (not only to diseases with prevalence less than 200,000) can help finance the movement to greater personalization.

Alternatively, this response may represent effort by firms to strategically re-label drug indications as a response to the ODA. Drugs which would have been developed in absence of the ODA may have received subsidization due to re-labeling of indications to artificially defined, ODA-qualifying, subsets of larger markets for which the drug is actually beneficial. Rent-seeking to gain the ODA tax credits stems from the regulator's inability to observe the true market size of the drug; and from its inability to monitor whether subsidized R&D is being devoted to large-market drug research. More generally, asymmetric information between a regulator and firms (or between any principal and agent) gives rise to opportunities for firms to exploit supply-side R&D incentives, a response that thought to be prevalent in policy settings in which the costs of unobserved R&D effort is subsidized (Kremer, 2001a; Hall, 2002).

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## Appendix A

See Table 1A.

Table 1A
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 | | Thymoxamine HCl | Phenylephrine-induced mydriasis | | | | |
| 3 | Motilium | Domperidone | Parkinsons | 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 |

Table 1A (*Continued*)

| NDA Pipeline Data | | | | | Coding | | |
|---|---|---|---|---|---|---|---|
| Line | Drug | Generic name | Indication | Trial phase | New trial | NORD# | Orphan subdivision |
| 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 | Cryptococcoal 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 cryptococcoal 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 Lines 19 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.

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