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Do Market Incentives Generate Innovation or Balkanization? Evidence from the Market for Rare Disease Drugs*

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Abstract

The 1983 Orphan Drug Act (ODA) established incentives for the development of drugs to treat rare diseases. I find that for most rare disease drug markets, the impact of the ODA was largely limited to an increase in the stock (not flow) of drugs; however, the magnitude and sustained intensity of the impact was greater for more prevalent rare diseases. I also find that the ODA generated an unintended impact: the development of drugs to treat "new" rare diseases defined by subdividing long-recognized diseases. Model predictions are tested to determine the extent to which subdividing represents improved drug targeting or artificial partitioning of disease markets to acquire ODA incentives—a behavior I call balkanization. I estimate that 25-percent of clinical trials generated by the ODA represent balkanization. This result suggests that there is waste associated with public policies that seek to stimulate innovative effort that is unobservable.

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1. Introduction

A widely-held view is that market failures lead to inefficient allocation of R&D investments (Hall 2002). 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—measures which are well-known to be associated with inefficiencies and agency problems (Arrow 1962; Hall 1993; Kremer 2001). It is clear that market incentives matter for innovation (Newell, Jaffee et al. 1999; Acemoglu and Linn 2004; Finkelstein 2004). However, little is known about how specific policy mechanisms affect innovative activity, and little empirical work has been devoted to identifying the source and extent of inefficiencies associated with the structure of the incentives.

In this paper, I consider the impact of the 1983 Orphan Drug Act (ODA) on pharmaceutical innovation. The ODA established tax incentives to stimulate innovation in drugs for rare diseases, defined as diseases with prevalence less than 200,000 Americans. The pharmaceutical industry is an ideal place to investigate the role of policy in R&D. It has been one of the most innovative industries in the economy over the past half century, and one whose medical innovations embody substantial technological progress (Lichtenberg and Virabhak 2002). The ODA is of particular interest because it is the most recent example of a clear policy initiative to stimulate innovative activity in the drug industry. Further, the structure of the ODA incentives is similar to that of other policies that seek to stimulate R&D activity in other industries, making the ODA an ideal setting to study both the impact of market incentives on innovation and the inefficiencies associated with the structure of those incentives.

Existing evidence indicates that firms do respond to incentives to increase innovative activity. For example, Finkelstein (2004) find that policy-induced increases in expected demand for drugs in certain pharmaceutical classes are associated with increases in clinical trials and final drug approvals. Studies of demand-side "pull" incentives follow earlier analyses that examine the

impact of R&D tax incentives and grants—examples of "push" incentive mechanisms.[1] Studies based on US data consistently estimate negative price elasticities of R&D expenditures as a response to the availability of R&D tax credits (Mansfield 1986; General Accounting Office 1989; McCutchen 1993). However, several important issues require further research. First, existing research has not studied inefficiencies that may arise due to the structure of incentives. The ODA, as with push-type R&D policies more generally, subsidizes unobserved effort. Agents may exploit the inability of an asymmetrically informed regulator to monitor R&D effort in order to claim the subsidy while directing actual effort towards more lucrative projects (Kremer 2001). To what extent this occurs, and its implications on efficiency, have not been explored. Related to this, little is known about whether the introduction of incentives results in truly innovative activity. Previous studies of tax incentives have focused on aggregate firm-level R&D expenditures—a gross measure of true innovation. R&D expenditure data obscure differences between true innovation and marginal manipulations, and between sustained innovative effort and short-run development of technologies that had been shelved due to lack of profitability.

This paper overcomes both of these limitations. First, 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. I exploit variation in rare disease status across diseases, as well as within diseases over time, in a difference-in-difference approach to estimate the impact of the ODA incentives.

I then turn my attention to an unintended consequence of the ODA: the creation of "new" rare diseases defined to be subdivisions of long-established diseases. The 1980s and 1990s saw a rise in the number of clinical trials for "new" diseases defined to be subdivisions of long-recognized disease with patient populations small enough to qualify for the ODA. (I refer to these diseases as "ODA-qualifying subdivisions".) An important issue is whether clinical trials for

[1] See Kremer (2001) for a discussion of various types of "pull" incentives that reward final-product development and "push" incentives that subsidize R&D effort.

subdivided diseases reflect effort to develop better targeting drugs, or reflect effort by drug companies to artificially subdivide a drug's non-rare disease market into narrowly defined patient subpopulations so as to qualify for ODA tax breaks—a behavior I call "balkanization."

I develop a model of drug development in the presence of FDA-created quality requirements, which is used to show how the introduction of the ODA affects innovative activity in diseases with small populations. The model implies that the ODA should have increased innovation on both extensive and intensive margins with respect to the size of a drug's market. I then extend this model to develop a theory of disease subdividing that generates several testable predictions to distinguish between better drug targeting and balkanization.

I find that the ODA had a significant impact on rare disease drug development. I estimate that on average the ODA led to a 68 percent increase in the annual flow of new clinical trials for drugs for "traditional" (i.e. non-subdivided) rare diseases. Innovation in the smallest of these disease markets is limited to the years immediately subsequent to the ODA's passage. This increase in the stock of drugs likely represents the development of existing technologies that had been shelved due to lack of profitability. The immediate and long-term impact on innovation for rare disease with higher prevalence was larger and sustained throughout all later periods, an indication of greater innovative intensity.

I also find that the ODA had a large and unintended impact on drugs developed for "new" rare diseases—that is, ODA-qualifying subdivisions of long-established diseases. I test predictions of the model to distinguish between better targeting and balkanization. The balkanization response can further be partitioned into marginal innovation of drugs that would *not* have been developed absent the ODA (yet should not receive ODA incentives), and pure re-labeling of drug indications from a non-rare disease to an ODA-qualifying subdivision of a non-rare disease for clinical trials that would have been undertaken absent the ODA.

Consistent with balkanization, I find that firms seldom subdivide rare diseases, yet engage in significantly more clinical trials for drugs to treat ODA-qualifying subdivisions of

diseases with prevalence (before subdividing) slightly above 200,000. I find similar results exploiting time series variation in orphan status of diseases whose prevalence grows and reaches a level that slightly exceeds 200,000 during the study period. The model also suggests that the incentive to balkanization a non-rare disease drug market should diminish in the total, pre-subdivided, market size of the drug—a response to the revenue losses associated with restrictions on marketing drugs for uses not formally approved by the FDA. I present several empirical findings consistent with this prediction. Finally, I present evidence using data on drug prescriptions to support the balkanization hypothesis. I find that drugs approved to treat ODA-qualifying subdivisions of non-rare diseases are prescribed much more frequently than would be expected given the size of the drugs' approved patient population, indicating that firms seek approval for narrow subdivisions, and then sell the drugs to their larger therapeutic markets.

Overall, my results are consistent with those of 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. However, the evidence of balkanization adds a cautionary note. Calculations I present at the end of the paper indicate that, of the new drug trials generated by the ODA, approximately 25-percent were for balkanized disease drugs. And 10-percent represents a lower bound estimate of the extent of the ODA impact due to re-labeling. R&D subsidies for these trials represent social waste. The opportunity to balkanize disease markets stems from the inability of the regulatory agency to observe a drug's true therapeutic market when orphan drug approval is sought. More generally, these findings suggest that concern over potential waste due to agency problems associated with push-type policies (Hall 1993; Office of Technological Assessment 1993; Kremer, 2001) may be well-founded.

This paper proceeds as follows. Section 2 briefly describes the Orphan Drug Act. Section 3 investigates the impact of the ODA on innovative activity for drugs used to treat a set of long-established rare diseases. Section 4 investigates the extent that the ODA has led to the creation of

new rare diseases. Section 5 concludes with calculations of how the effects of the ODA are divided between true innovation and balkanization.

2. Orphan Drug Act

The Orphan Drug Act, passed in 1983, established incentives for firms to develop drugs to treat rare diseases. The passage of the ODA was in large part due to the vigorous lobbying effort of patient groups and members of the medical community frustrated at the lack of drugs approved to treat rare diseases (Asbury 1986). Initial action taken by Congress was to sponsor a survey of drugs of limited commercial value. 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 one main incentive to develop orphan drugs: an income tax credit equal to 50-percent of clinical trial expenses.[2] The aim of the credit was to lower the cost of conducting clinical trials, now estimated to be $800 million for each marketed drug (DiMasi, Hansen et al. 2003). About two-thirds of this amount finances human clinical trials that establish adequate levels of drug efficacy and safety in order to gain marketing approval from the FDA.[3]

The ODA initially defined a rare disease to be an "orphan" indication if a drug marketed to treat it could be shown to be unprofitable. The difficulty and costs associated with establishing "unprofitability" were blamed for the negligible R&D response by firms after the ODA was

[2] Whereas tax deductions are write-offs against taxable income, tax credits count against tax liabilities. The ODA tax credit can be carried forward to subsequent years in instances when the credit exceeds taxes owed. Current federal executive budgetary projections forecast the ODA tax credit to amount to nearly $1Billion over the next 10 years.

[3] The ODA also included a seven-year marketing exclusivity clause, starting from the drug's approval date to prevent competitors from marketing the same drug for the approved rare disease indication. The protection offered by this provision is narrower than a patent, so it was of little benefit to patentable orphan drugs (the vast majority of orphan drugs), and will not be modeled in this study.

passed (Rohde, 2000). A 1984 amendment to the ODA addressed this difficulty 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 treats a condition with prevalence less than 200,000. The OOPD designates the drug an orphan if the evidence sufficiently and reliably supports this claim.[4] Firms acquire the tax credit upon their drug receiving orphan designation.

3. The Impact of the ODA on Long-Recognized Rare Diseases

Section 3 examines how the ODA affected drug development for rare diseases. For now, I restrict attention to "traditional" rare diseases that were recognized as such when the ODA was passed. I present a simple model of the effects of the ODA; then I discuss the data and empirical strategy used to estimate the impact of the ODA on drug innovation. Section 3.3 presents the results. The issue of balkanization and the proliferation of "new" rare diseases are taken up in Section 4.

3.1 Theory

I introduce a fixed cost of R&D that is a function of drug quality into a standard spatial model of product differentiation (Salop 1979; Riordan 1986).[5] The market for a particular disease is modeled as a unit circle, where disease prevalence, or potential market size, is characterized by the density of consumers, θ, that sit on the circle. Patients sharing a disease (those on the same circle) are uniformly distributed along 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, q; but they differ in their treatment response to a given drug. Heterogeneous drug response is modeled as a consumer's

[4] This is based on a conversation with John J. McCormick, MD, Deputy Director at the Office of Orphan Product Development.
[5] 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 experience heterogeneous drug responses to a given drug. Distance to an ideal location in a spatial model can be interpreted as the extent to which a particular drug is well-targeted for a disease sub-group.

distance, *x*, to the nearest drug. The ideally located patient receives the full therapeutic benefit of the drug, while patients situated further away have a less beneficial response. Consumers have a constant transport cost, *t*, which they must pay to reach the nearest drug. This cost is the reduction in utility from not receiving the full benefit of the nearest 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* away. A consumer situated between the two drugs, *x* units away from the representative firm's product, is indifferent between the two drugs when $h(q) - tx - P = h(q) - t(1/N - x) - P$. Therefore, a consumer at a distance $x(P, q; v) = (h(q) - P - v)/2t$ from the representative firm's drug is indifferent between the two drugs, where $v = h(q) - t/N - P$ is the utility from the nearest rival's drug for a consumer whose location is matched perfectly to the drug of the representative firm. The representative firm faces a demand of $Q = 2\theta \cdot x(P, q; v)$.

For a given disease market of size θ, the representative firm chooses Q and q to solve

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

The inequality refers to the constraint that drug quality must exceed a minimum safety and efficacy standard, $\underline{q}$.[6] $P = P(Q, q; v)$ is the inverse demand function, *m* is the marginal cost of production, and $F(q)$ is the fixed cost of drug development—including the cost of clinical trials—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 θ can be characterized by:

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

[6]The constraint reflects the 1962 Amendments to the Food Drug and Cosmetic Act, which enhanced the safety and efficacy of marketed drugs. It required drug sponsors to conduct clinical trials to document safety, and to establish clinical efficacy of new drugs to gain marketing approval. Prior to 1962, sponsors had only to show evidence of minimal drug safety to gain approval (Hilts 2003).

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

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

(6) $$Q = \frac{\theta}{N}$$

Equations (3) and (4) are the first order conditions which require firms to choose quantity and quality so that marginal revenue equals marginal cost. Free-entry requires that firms earn zero-profits in equilibrium; i.e. price equals average total cost as expressed in equation (5). Equation (6) requires that the market is covered.[7]

To solve for the equilibrium levels of N^e, Q^e, P^e, and q^e, I specify the functional form for consumer utility and fixed costs: $h(q) = q$, and $F(q) = c(1-q)^{\beta}$.[8] The parameter c is a constant coefficient on fixed costs. In equilibrium, drug quality and the number of drugs in the market are

(7) $$\left\{ \begin{array}{l} q^e = 1 - \left[\frac{c \cdot \gamma_1}{\theta} \right]^{\frac{1}{2-\beta}} \\ N^e = \left[\frac{\theta \cdot \gamma_2}{c} \right]^{\frac{1}{2-\beta}} \end{array} \right\} \text{for } \theta \geq \theta^{reg}$$

(8) $$\left\{ \begin{array}{l} q^e = \underline{q} \\ N^e = \left[\frac{t\theta}{c(1-\underline{q})^{\beta}} \right]^{\frac{1}{2}} \end{array} \right\} \text{for } \theta < \theta^{reg},$$

where the γ_i's are positive constant terms involving parameters t and β.[9] The equilibrium choice of drug quality monotonically increases with the size of the patient population in absence of the quality constraint. At $\theta^{reg} = ct\beta^2/(1-\underline{q})^{2-\beta}$, equilibrium level of quality equals $\underline{q}$. For

[7] 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 θ.

[8] *F(q)* has the desired properties that it is convex in q and has an asymptote at $q = 1$ when $\beta \leq -1$.

[9] $\gamma_1 = t \cdot \beta^2$ and $\gamma_2 = [t^{\beta-1}(-\beta)^{\beta}]^{-1}$. It is straightforward to solve for the equilibrium price and output level.

sufficiently large drug markets ($\theta > \theta^{reg}$), firms choose quality to exceed $\underline{q}$. The constraint binds for all markets where $\theta < \theta^{reg}$.

Quality regulation decreases the number of drugs sold in a drug market. Regarding entry, the market size at which all firms exit is now $\underline{\theta}^{reg} = c(1-\underline{q})^{\beta} / t$ (that is, where the market supports only one drug). This is greater than the no-entry threshold $\underline{\theta} = c / \gamma_1$ in absence of the quality regulation. For diseases with prevalence between $\underline{\theta}$ and $\underline{\theta}^{reg}$, potential revenues are too small to recoup the costs of developing drugs of quality $\underline{q}$. This unintended distortion of quality regulation motivates policy measures, such as the ODA, that subsidizes R&D for rare diseases.

To analyze the effects of the ODA, I assume that the quality regulation is sufficiently strict so that the quality constraint binds for all disease markets defined as rare by the ODA. The ODA tax credit is modeled as a decrease in the cost parameter *c*. It is straightforward to show that reductions in *c* increases product variety in along both the extensive margin ($\partial \underline{\theta}^{reg} / \partial c > 0$) and the intensive margin ($\partial N^e / \partial c < 0$ and $\partial^2 N^e / \partial c \partial \theta < 0$). In markets previously supporting positive entry, a decrease in development costs increases the level of entry in proportion to market size. Lower fixed costs also leads to lower drug prices. Because both average distance to the ideal drug and drug price decline in development cost, consumer welfare unambiguously increases. The effects of the ODA on social welfare (relative to the pre-ODA, regulated setting) are ambiguous, and depend directly on functional form assumptions of travel cost to drugs.[10]

The main results are summarized in Figure 1, which shows the levels of *N* and *q* as functions of the patient population θ. The line ABCD represents the number of drugs that will be developed as a function of the patient population without the ODA. The implementation of the

[10] Whether drug development in the pre-ODA equilibrium is lower or higher relative to socially optimal levels depends on two opposing effects: firms' inability to appropriate the social surplus (which leads to under-provision), and firms' ability to steal customers from rivals (which leads to an overprovision). In the standard Salop model, convex travel cost, *t*, implies that the business stealing effect dominates. Admittedly, a theoretical welfare analysis hinges on an arbitrary specification of cost. Therefore, analysis of the ODA is viewed in light of a policy objective to stimulate drug development in small markets made unprofitable due to earlier quality regulation. Empirical analysis of the innovative impact and potential waste associated with the ODA will be made relative to each other and to aggregate social cost.

ODA shifts this function to the A'B' and BCD lines. The ODA should not affect drug development for diseases with patient populations in excess of 200,000, and should increase the development of drugs for all but the smallest rare diseases. Among the rare diseases with the smallest populations, the ODA will have no effect on drug development, as entry remains unprofitable even with lower fixed costs. The empirical results that follow test these predictions.

3.2 Data and Empirical Strategy

Data

My 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 non-profit agency established in 1983 that engages in knowledge dissemination regarding uncommon diseases and conditions to medical and policy practitioners. They publish a database of 1,177 uncommon diseases which, since it was published shortly after the ODA was passed and has remained virtually unchanged[11], can be considered a list of traditional, long-recognized diseases. Most important for the results that follow, the NORD list does not contain the "new" subdivided diseases that may have been created in response to the ODA. Based on reviews of the epidemiological and medical reference literature, I partitioned the NORD list into three groups: (1) "Rare" diseases, defined as those with prevalence below the 200,000 threshold throughout the study period; (2) "Non-rare" diseases, defined as those always above the threshold; and (3) "Status-changers" which move from being rare to non-rare during the study period. The NORD list can be partioned into 1,023 Rare diseases, 148 Non-rare diseases, and 6 Status-changer diseases (Figure 2). Table 1 reports the year the OOPD last designated a drug to treat each of the Status-changer diseases.[12]

[11] This is based on a telephone conversation with Mary Dunkle, NORD, in September 2003.

[12] Prevalence estimates from the epidemiological literature often report a range of estimates (i.e. 1:10,000 to 1:5,000, or 25,000 to 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. For non-rare diseases, prevalence estimates are relatively more precise so that such an analysis is more appropriate.

My measure of innovation is *new* clinical drug trials for a given disease. 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.[13] The principle source of data on new clinical trials data come *The NDA Pipeline.*[14] This journal has been published since 1982 by F-D-C Reports, long-respected for its research of the drug industry.[15] 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-profit research institutions. For each firm, the journal reports on the clinical trials for all chemical entities known to the publisher. This includes 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, on non-US based firms, and on trials for larger indications.[16] This publication is used to clarify ambiguities in *The NDA Pipeline*, and in some cases to obtain information that is uniquely contained in *Pharmaprojects*. Appendix Table 1 describes in more detail the process by which new clinical trials are counted.

I assembled my dataset by searching through the volumes of these two publications, and recording when clinical trials began for drugs indicated for the diseases in the three groups. The final panel data set contains the number of new clinical trials for each of the 1,777 diseases in the NORD list, for every year in the study period.

The data on number of new clinical trials for rare and non-rare diseases are depicted in Figure 3. The lines represent the percentage increase in the number of new clinical trials over

[13] Also, since clinical trials often span more than 17 years (DiMasi, Hansen et al. 2003), measuring new clinical trials avoids the problem of capturing decisions based on past investment climates.
[14] Finkelstein (2004) uses this journal to gather data on clinical trials for vaccines.
[15] 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 published in *The NDA Pipeline*, and supplement information found in the main tables.
[16] This is based on a conversation with Ian Lloyd, Editor-in-Chief of *Pharmaprojects*, in November, 2003.

time, relative to the number of trials in the base year of 1981. There is a noticeable increase in the number of new trials for rare diseases starting in 1984. Descriptive statistics for the number of new clinical trials for diseases in each of the groups are shown in Table 2. The top panel shows statistics for counts of new clinical trials by group for 1983, the last year before the effective amendment of the ODA was passed, and the bottom panel shows data from 1990, which was chosen only because it dates in the middle of the post-ODA time series. The mass of the counts clearly lies at zero, and the data tend to be over-dispersed (variance greater than the mean). Further, the distribution of counts noticeably differs across the disease treatment groups. These characteristics motivate the choice of count regression models, discussed below.

Estimation Framework

To test the impact of the ODA on innovation, I begin with a difference-in-difference approach, which compares innovation across rare and non-rare diseases, before and after passage of the ODA. Although the ODA was passed in January of 1983, it was not until the 1984 amendment that the ODA established the current definition of a rare disease: any disease with an American prevalence of 200,000 or less. The relevance of the ODA is widely thought to have begun in 1984 (Rohde 2000). Therefore I use a balanced panel of "rare" and "non-rare" diseases from 1981 to 1994 to estimate equations of the following form:

$$(9)\quad NT_{it} = f(\alpha_0 + \sum_t \alpha_t Year_t + \beta_1 PostODA_t + \beta_2 RARE_i + \beta_3 (PostODA * RARE)_{it} + \varepsilon_{it}).$$

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. 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 β_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 β_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 those diseases on the NORD list (and not newly defined diseases defined in response to the ODA). 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.[17] Second, any prevailing change in the investment climate must have affected rare and non-rare diseases in the same manner. Although this assumption cannot be tested, the restriction of the control diseases to "non-rare" (yet still uncommon) diseases makes this assumption plausible. Third, passage of the ODA must not have shifted investments from drug treating uncommon diseases to those that treat rare diseases. This would bias the estimate of β_3 upward. Credit constraints would lead to substitution of this sort. Finally, to the extent that the passage of the ODA was endogenous to the stock of drugs shelved due to lack of profitability, the estimate of β_3 will be biased upward. Figure 3, 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 were not withholding clinical trials work for shelved drugs in anticipation of the passage of the ODA.

In the cross-sectional difference-in-difference approach outlined above, I am only able to use three years of data to establish the pre-ODA trend in the flow of new clinical trials. A short time-series diminishes the precision of the estimated impact of the ODA. This data limitation, in addition to the conditions required for consistent estimation above, motivates an alternative identification strategy. I exploit a second source of identification—estimating changes in flow of new clinical trials for status-changer diseases—diseases whose prevalence that grow from rare to

[17] More innovation is likely to increase the awareness of a disease and its symptoms, leading to an increase in prevalence estimates through increased diagnosis. Alternatively, drug innovation may lower the prevalence through treatment is possible only for diseases that are completely treatable (e.g. infectious diseases). These biases will be discussed below in the status-changer disease analysis.

"non-rare" levels during the study period. I proxy the date when prevalence of status-changers grew beyond the 200,000 prevalence threshold by the year the OOPD last designated an orphan drug for that disease.[18] I generate a list of six status-changer diseases. These diseases are described in Table 1. Here I can utilize at least 9 years of pre-event data (the earliest year of a status-change for any disease in the sample is 1990). I estimate:

$$(10) \qquad NT_{it} = f(\alpha_0 + \sum_t \alpha_t Year_t + \beta_1 StatusChanger_i + \beta_2 Changed\_from\_Rare_{it} + \varepsilon_{it}).$$

The variable of interest is *Changed_from_Rare*, an indicator which takes 1 when a status changer disease has changed to an "non-rare" disease from a rare disease. The estimate of β_2 represents the impact on the flow of new clinical trials from a disease losing its orphan status. Consistent estimation of β_2 requires that prevalence changes are exogenous to the outcome variable. This is likely to be the case since the changes in demographics and diagnostic techniques determining prevalence are likely to be orthogonal to clinical trials effort.[19] Also, the six diseases changed status at different points in time—a fact used to address a weakness of the previous identification strategy.

Figure 4 offers a visual interpretation of β_2. The equilibrium number of drugs is plotted against disease prevalence, where the top 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 β_2 actually capture the drop to C from point A. So I underestimate the magnitude of β_2. And to

[18] The decision of the OOPD to cease designating certain diseases as rare is based on epidemiological studies. Citations for specific epidemiological studies for diseases that moved from rare to non-rare were provided by John McCormick of the OOPD during a telephone conversation in October, 2003. These citations are listed in Table 1.

[19] It is possible that the availability of drugs allows for, or encourages, 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 the increase in the available stock of marketed drugs for a given disease, this endogeneity the will bias the estimate of β_3 towards zero (underestimate the ODA impact). Alternatively, new drugs may lower prevalence by eliminating the underlying disease. This would be the case for, say, bacterial diseases, where antibiotics may treat the disease completely. Of the six status-changer diseases, five are chronic diseases, and only AIDS is an 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.

the extent that a disease grows rapidly in prevalence (A to D, such as the case with AIDS), estimates of β_2 will be further underestimated in magnitude.

The functional form for equations (9) and (10) is chosen so as to account for the nature of the count data. Data on the yearly flow of new clinical trials is non-negative, integer-valued, and has mass at low counts. These characteristics motivate a count data regression model.[20] Popular count regression models include the Poisson and negative binomial models (Hausman, Hall et al. 1984) for panel data. Maximum likelihood estimation of the Poisson model has the advantage of being consistent even when the data generating process of the counts is misspecified. Estimates are consistent under the weaker assumption that the conditional mean is correctly specified. However, consistency of the standard error estimates requires that the count data be distributed as Poisson (Wooldridge 1997). This assumption can be relaxed by estimating the Poisson regression model using quasi-ML.[21] The negative binomial model is more restrictive in that consistency of parameter estimates requires that the data be distributed as negative binomial (Cameron and Trivedi 1998). Therefore the more robust Poisson model is preferred. Parameter estimates can be determined by maximizing the likelihood function (expressed here for the i^{th} observation):

(11a) $$L_i(\beta) = \exp(-\gamma_i \sum_t \lambda_{it}) \cdot \prod_t \alpha_i^{NT_{it}} \cdot \prod_t \lambda_i^{NT_{it}} / \prod_t NT_{it}!$$

(11b) $$\lambda_{it} = \exp(x_{it}'\beta)$$

The parameter γ_i is the disease-specific random or fixed effect. Equations (9) and (10) correspond to equation (11b). Maximum likelihood estimation is consistent if the conditional mean, $E[NT_{it} \mid x_{it}] = \gamma_i \lambda_{it}$, is correctly specified as linear exponential.

[20] 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 is in the exponential form of typical count regression models.

[21] The multiplicative fixed or random effects allows 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 (Wooldridge 1999, Wooldridge 1997). This is equivalent to reporting ML coefficient estimates with standard errors taken from the robust variance-covariance matrix estimate. This study reports quasi-ML estimates.

3.5 Empirical Results

Table 3 reports the results from estimation of equation (9). I first report results from estimating the conditional Poisson regression model. The specification in column (1) assumes a random effects structure of the individual heterogeneity in the Poisson model. Using the entire sample of rare and control diseases in the NORD list, the coefficient estimate on the interaction term of interest is 0.52, suggesting that the ODA led to a 68 percent 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.[22] Estimates from the fixed effects specification are necessarily identical to those of the random effects model in this regression.[23]

In columns (3)-(4), I report the results from the negative binomial regressions. The results are similar to Poisson parameter estimates, indicating that estimates are robust to functional form assumptions. Quasi-ML estimation of the Poisson model is consistent under weaker assumptions, so I henceforth report results from only conditional fixed effects Poisson specifications.

The model developed in the section 3 implies that by excluding smaller rare diseases from the sample specification estimates of β_3 should increase. In column (2), I restrict the sample of rare diseases to those with prevalence above 100,000. I restrict the relevant comparison to those non-rare diseases with prevalence between 200,000 and 500,000. I estimate that the ODA led to an 83-percent $(=[\exp(1.04)-1]*100)$ increase in the rate of new clinical trials for rare diseases relative to control diseases. The impact on the extensive margin is clear as well. Whereas only 61 rare diseases had any new clinical drug trial during the three pre-ODA years, 111 (226) rare diseases had at least one new drug trial in the three (eleven) years after the ODA was passed.

[22] 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 express estimates as incident rate ratios, defined as $E[y \mid x_i = 1] / E[y \mid x_i = 0] = \exp(\beta_i)$. An estimate of β_i can be interpreted as an $(\exp(\beta_i)-1)*100$ percent change in y, given a change of 0 to 1 in the independent variable. The 68% increase is calculated as exp(0.52)-1=0.68.

[23] The covariates are indicators for prevalence category and data occurring after the passage of the ODA. As such, they are necessarily orthogonal to any disease-specific effects. The common form of the negative binomial used here 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.

The narrower disease prevalence sample specification also lends itself to OLS estimation. Diseases in this narrower range are more similar in prevalence, so that OLS impact estimates are less subject to misinterpretation due to absolute differences in pre-ODA levels of clinical trials. Column (6) estimates the ODA impact using OLS for diseases in this narrower range. The predicted level of clinical trials for the sample of rare diseases in the last pre-ODA year is 0.240, making an impact of 0.527 equivalent to a 119-percent increase in the flow of new clinical trials.

Linearity of the year dummies is rejected, largely an outcome of kinks in the time series occurring after 1990 observed in Figure 3. 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*.[24] Year dummies account for such idiosyncratic differences across years. One threat to identification is the possibility that R&D investment climate changed differentially for rare and non-rare diseases during the study period. Finkelstein (2004) finds that policy changes (occurring in the post-ODA period) that affected expected returns on vaccines led to significant increases in pharmaceutical R&D to treat relevant infectious diseases. To check for robustness, I re-estimate equation (9) dropping all rare and non-rare diseases classified by NORD as an infectious disease.[25] The estimated impact of the ODA increases in all specifications, albeit insignificantly.

Timing of the Investment Response

It is not clear from the analysis estimated above whether the ODA led firms to generate new innovations, to merely hastening 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, and include their interactions with the *RARE* indicator variable. This

[24] 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 Figure 3, could be the outcome of diminished R&D growth in the drug industry. Likewise, it could represent changes in the scope of the data journal itself. There is no evidence that year to year changes in the *NDA Pipeline* differentially affected counts of rare diseases relative to non-rare diseases.

[25] This specification drops 31 diseases in the Poisson fixed-effects regression—23 rare diseases and 8 non-rare diseases.

allows for the effect of the ODA to be estimated more flexibly than in equation (9). Using a Poisson fixed-effects model, I estimate:

$$NT_{it} = \gamma_i \exp(\alpha_0 + \sum_t \alpha_t Year_t + \beta_1 PostODA_{(1-3),t} + \beta_2 PostODA_{(4-6),t} + \beta_3 PostODA_{(7\,plus),t} + \beta_4 (PostODA_{(1-3)} * RARE)_{it} + \beta_5 (PostODA_{(4-6)} * RARE)_{it} + \beta_6 (PostODA_{(7\,plus)} * RARE)_{it} + \varepsilon_{it}). \quad (12)$$

The three *PostODA(t, t')* variables are indicators for whether a clinical trial began for disease *i* in the immediate three years following, in the three-to-six year window following, or in the period from seven years and 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. Equation (12) 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-percent $(= \exp(1.038) - 1 * 100)$ increase in the flow of new clinical trials for rare diseases in the three years immediately after the ODA was passed. The impact is more than halved in later periods.

I can formally test the prediction that the average impact of the ODA is smaller for diseases with the lowest prevalence. I create indicator variables for a rare disease having prevalence below and above 100,000 (*Rare(<100k)* and *Rare(100k, 200k)*), and interact these with the *PostODA(t, t')* variables. For the smallest rare disease, I find that the ODA led to an initial doubling of the yearly flow of new clinical drug trials in the years immediately subsequent to the ODA's passage. In later years, the impact declines significantly. For the larger rare diseases, the initial impact of the ODA on the flow of new clinical trials is bigger than for smaller rare diseases. These diseases see a drop-off in clinical trials effort of only about 30 percent. The

impact of the ODA is still large and sustained throughout all periods after the ODA was passed.[26] Despite these differences, joint pair-wise equality of the coefficients on the *Rare(<100k) x* and *Rare(100k, 200k) x PostODA(t, t')* interaction terms cannot be rejected.

The results suggest that, for the smallest rare diseases, the ODA led to an increase in the stock of drugs, suggestion that firms engaged in clinical trials to bring existing stock of shelved technologies to market. For rare diseases with larger prevalence, the impact of the ODA is largest immediately after the passage of the ODA; yet the innovative response is sustained throughout all periods. This differential response is consistent with the ODA incentives acting to counter low drug development in small product markets that face fixed costs of development.

Time Series Variation in Orphan Status of Diseases

Estimating equation (10) allows for a second identification strategy to estimate the intended impact of the ODA. The coefficient of interest is parameter on the variable *Changed_from_Rare.* The coefficient estimate can be interpreted as the relative *decrease* in expected rate of new clinical trials for a disease after it loses its status as rare.

Results from estimating equation (10) are reported in Table 5.[27] Columns (1) and (2) restrict the sample to only the six status-changer diseases. The parameters are identified because each of the diseases change status in different years, and the timing of the change is exogenous to the number of clinical trials sponsored by firms. The results indicate a drop in the number of new clinical trials for the status-changer diseases in the years after they grow beyond 200,000 in prevalence. Columns (3) and (4) include different comparison groups to control for drug investment in rare diseases. The estimates in column (4) are likely to be the best estimates of the impact of losing ODA incentives since it uses, as a comparison, diseases with prevalence similar to that of status-changer diseases. The effect on innovative activity of losing orphan status is a

[26]Here, too, a threat to identification is the possibility that other policy changes differentially affected non-rare and rare diseases drug development—e.g. policies affecting returns to vaccine development (Finkelstein, 2004). The results do not change significantly when infectious diseases are dropped from the sample specification.

[27] Due to small sample sizes, estimation of 1-year dummy variables becomes problematic. 2-year dummy variables are used instead. Appendix Table 2 repeats this analysis using a linear specification for year effects. The qualitative results do not change, and the magnitude of the impacts increase in each specification.

reduction of 30-percent in the flow of new drug trials to treat that disease—an effect similar to that which was similar to the doubling effect of estimated in the cross-sectional analysis. As expected, removing AIDS from the sample decreases the coefficient estimate (increases the negative impact) associated with losing ODA eligibility (columns (2) and (5)).

4. Impact of ODA on the Creation of New Diseases and New Disease Drugs

In section 3, I examined the impact of the ODA on drug development for "traditional" rare diseases. Yet the ODA generated innovation in an unintended dimension: the development of drugs indicated for "new" rare diseases, defined by subdividing patient populations of long-recognized diseases. These drugs may embody better drug targeting technology, or may be the outcome of rent-seeking behavior (balkanization). In this section I present a model of balkanization in which firms seek drug approval for an artificially defined subdivision of a large disease in order to gain ODA tax credits. I then discuss the data and empirical strategy used to distinguish between better drug targeting and balkanization by firms. Finally I present the results and calculations for the extent of balkanization.

4.1 Balkanization

Of the 1228 drugs designated as orphan drugs by the OOPD, only 60 percent are indicated for a disease in the NORD list (Figure 5).[28] Drugs to treat "new" rare diseases comprise the remaining 40 percent, and appear to embody a significant innovative response to the ODA. These innovations potentially represent an enhanced ability to target diseases based on the age or sex of the patient, the genetic subtype, severity, or the status of the disease as chronic or acute.

Anecdotal evidence suggests another possibility. Examples of abuse of the ODA have been the subjects of a few widely publicized studies. These studies brought to public attention a number of instances where orphan drugs were first approved to treat a rare disease and then were found to have therapeutic benefit to patients with larger diseases (Rin-Laures and Janofsky 1991;

[28] This refers to data on orphan designation as of June 2003.

Senate Subcommittee Hearings s2060 1992; Maeder 2003). What may be considered "good fortune" for firms in a few well-publicized examples of off-label uses (uses not approved by the FDA for marketing but for which physicians may still prescribe the drug) may be indicative of more widespread rent-seeking behavior.

For illustration, the FDA granted the Titan Pharmaceuticals drug Spheramine orphan status for the treatment of late stage type 4 or 5 Parkinson's disease. While Parkinson's disease is not rare, there are fewer than 200,000 patient with late-stage type 4 or 5 Parkinson's disease. Titan may have had knowledge that Spheramine would be effective for the entire patient population with Parkinson's disease—knowledge not shared by the FDA. But to acquire the ODA incentives, Titan may have pursued clinical trials for only an ODA-qualifying subdivision, with intentions to sell Spheramine off-label in the event it received marketing approval. I call this behavior balkanization.

To model balkanization, I modify the previous model to allow firms to choose the size of the disease for which it seeks marketing approval. This was exogenously given, previously. The firm now explicitly chooses an "*on*-label" market—defined as the disease for which the firms seeks FDA marketing approval; and it chooses its "*off*-label" market—defined to be all potential consumers of the drug who do not have the disease specified on the approved drug label.[29] The predictions of the model are intuitive. For diseases that are already rare, firms have no rent-seeking incentive to balkanize these patient markets; they can obtain tax credits without artificially subdividing these markets. Drugs developed to treat subdivisions of long-established rare diseases must embody advancements in disease targeting technology—not balkanization. For drugs with potential markets that are not rare, firms have an incentive to balkanize these markets into ODA-qualifying subdivisions to obtain the ODA tax credit. Firms are also able to sell approved orphan drugs off-label to the broader patient market. Marketing drugs for off-label uses

[29] The FDA prohibits firms from advertising off-label uses for a drug. However, physicians have the prerogative to prescribe drugs off-label. Such prescriptions are common, and are often based on informal clinical evidence accumulated in the scientific community over an extended period of time. Insurance coverage of off-label use is discretionary.

comes with a cost: FDA restrictions on advertising off-label drug uses tie the hands of firms, forcing them to depend on knowledge of off-label uses to diffuse through the medical community. For drugs that benefit very large disease populations, the costs associated with restrictions on off-label marketing outweigh the benefit of the orphan tax credit. This disincentivizes balkanization of large disease drug markets.

Balkanization Equilibrium

I distinguish between "subdividing" and "balkanizing" a traditional disease in the following way. "Subdividing" characterizes the partitioning any traditional, long-established disease in the NORD list (whether rare or non-rare) into a rare, ODA-qualifying patient sub-populations. It makes no reference to the scientific or medical legitimacy behind the partitioning of a NORD disease. "Balkanization" involves artificially subdividing a drug's potential therapeutic market of 200,000 or greater and identifying a sub-population of the larger market with prevalence under 200,000. Rent-seeking motives underpin the incentive to balkanize.

Balkanization is modeled by extending the theory in Section 3. The post-ODA competitive economy assumes that profits are zero in equilibrium. Firms choose to balkanize its drug label if doing so results in positive profits. Formally, firms balkanize the drug market when

$$\pi(Q) = P^e \cdot \overline{Q} + \lambda P^e \cdot (Q^e - \overline{Q}) - mQ^e - F(\underline{q}, c_2) > 0 \quad (13)$$

Here, $\overline{Q}$ is the on-label market and $Q - \overline{Q}$ is the off-label market. The superscript *e* denotes equilibrium values under the no-balkanization equilibrium in Section 3; c_2 denotes the fixed cost parameter under the ODA. The first term of the profit equation is the revenue from selling the drug on-label to patients with the subdivided disease on the drug label at the existing equilibrium price. When balkanizing a disease, firms will choose a sub-population of that disease with prevalence equal to the rare disease threshold: $\overline{Q} = 200{,}000.$[30] The second term represents the revenue from selling drugs off-label, where $\lambda \in (0,1)$ denotes the loss in revenue due to

[30] Artificially choosing a label with smaller prevalence would be less profitable as the on-label market size would be made smaller.

restrictions on advertising off-label uses. The fixed cost term uses the cost parameter associated with the ODA: $c_2 = (1/2)c_1$. After inserting the equilibrium values for price and quantity and solving for θ, it is straightforward to show that there exists some θ^{Balk} such that for all $\theta \in (200{,}000, \theta^{Balk})$ profits will be positive. Within this range, firms will find it profitable to balkanize drug indications to gain the ODA tax credits.

For drug markets where balkanization of drug indications is profitable, firms settle into a new competitive, zero-profit, equilibrium. Firms choose the profit-maximizing level of quantity, *Q*, equal to the size of the on- and off-label markets. Both the quality, $\underline{q}$, and the size of the market corresponding to the drug's label, $\overline{Q}$, are given.. Equations (14) and (15) show the equilibrium values of N^{Balk} and Q^{Balk}, having imposed the zero-profit and covered market constraints, written in terms of the no-balkanization equilibrium values:

(14) $$N^{Balk} = \frac{\phi_1 + (\phi_1^{\,2} + 4\phi_2)^{1/2}}{2\phi_2^{\,1/2}} N^e$$

(15) $$Q^{Balk} = \frac{2\phi_2^{\,1/2}}{\phi_1 + (\phi_1^{\,2} + 4\phi_2)^{1/2}} Q^e .$$[31]

Figure 6 depicts the equilibrium under balkanization. As λ approaches 1, the number of drugs sold to non-rare markets of size 200,000 to θ^{Balk} increases, and drug prices decline. If $\lambda = 1$ (i.e. there is no cost to marketing off-label drug uses) then θ^{Balk} approaches infinity, suggesting that the ODA subsidizes clinical trials for drugs treating *any* disease.[32]

The model has several testable predictions with regards to subdividing which are consistent with balkanization, but not drug targeting. First, there is no rent-seeking incentive to subdivide a traditional disease that is already rare, but there is an incentive to balkanize a disease

[31] The ϕ parameters are used for notational simplicity, where $\phi_1 = \frac{(1-\lambda)}{\lambda} m$, and $\phi_2 = \frac{tF(\underline{q}, c_2)}{\theta}$.

[32] When $\lambda = 1$, equation (13) becomes $\pi = (c_2 / c_1) F(\underline{q}, c_2)$. Firms find it profitable to balkanize all large disease and earn profit equal to the amount of the ODA tax credit.

with prevalence just above the 200,000 prevalence threshold. Second, the incentive to balkanize decreases with the market size of the disease. Third, balkanization implies that orphan drugs treating ODA-qualifying subdivisions of non-rare diseases will be systematically prescribed more often than other orphan drugs, stemming from their value to the broader unbalkanized disease market for which approval was not sought. Drugs approved for an ODA-qualifying subdivision of non-rare disease should have a larger market size than that of an orphan drug approved for a traditional rare disease, conditional on the prevalence of its approved market.

Also, note that the increase in drugs arising from balkanization (Figure 6) can take the form of marginal new innovation for non-rare disease drugs (albeit characterized as an ODA-qualifying subdivision), or re-labeling of drug trials for non-rare diseases that would have occurred in absence of the ODA. Empirical tests are employed to gauge the relative magnitudes of marginally new balkanization and substitution.

4.2 Empirical Model and Results

Previously, I counted the number of new clinical trials for diseases in the NORD list from *The NDA Pipeline*. Here, I count the number of new trials explicitly indicated for ODA-qualifying subdivisions of diseases in the list, and strictly follow the typology of subdivisions outlined in Table 6. The data is a balanced panel of 1,177 diseases over the 1981-1994 study period.

Table 7 shows summary statistics for these data. As before, the data on clinical trials counts has mass at zero, and is distributed differently across the disease groups. The entire time series of the counts of new clinical trials for ODA-qualifying subdivisions of NORD diseases is shown in Figure 7. There is a large percentage increase in the number of new clinical trials for non-rare diseases beginning in 1984. The number of new drug trials for subdivisions of traditional rare diseases increases after 1990.

Incentive to Balkanize

To test whether subdividing non-rare diseases represents better drug targeting or balkanization, I examine the impact of ODA incentives on the flow of clinical trials for subdivided diseases. To

do this, I re-estimate equation (10) using the new outcome variable, *NST*—the number of new trials for an ODA-qualifying subdivision. The coefficient on *Changed_from_Rare* represents the proportional change in flow of new trials for ODA-qualifying subdivisions that occurs as a result of moving from a rare disease to a non-rare disease, controlling for changes in the flow of subdividing for control group diseases.[33]

The results are reported in Table 8. The coefficient estimate is 2.40 when the full sample of rare diseases is included as controls in column (1). Column (3) is the preferred sample specification as it controls for diseases most similar in prevalence to the status-changer diseases. The flow of clinical trials for ODA-qualifying subdivisions of a disease increase by 285-percent $(= (\exp(1.3457) - 1) * 100)$ in the years after status-changer diseases lose orphan status.[34] Note that this increase occurs simultaneously as the decline in the flows of new trials for *un*-subdivided status-changer diseases (i.e. the results from Table 5). This is clear evidence of substitution away from new clinical trials devoted status-changer diseases towards their ODA-qualifying subdivisions in the years immediately following the loss orphan disease status.

The differences-in-differences approach comparing ODA-qualifying subdivisions of rare and non-rare diseases is reported in Table 9. Column (1) shows a positive but insignificant increase in the flow of trials for ODA-qualifying subdivisions of non-rare diseases. Limiting the sample to diseases with prevalence close to the 200,000 threshold yields a larger, but still insignificant (p=0.73), impact on disease subdividing in clinical trials (column (2)).

No Incentive to Balkanize Large Diseases

Note that while there is no incentive to balkanize already rare diseases, there is a large incentive to balkanize diseases with prevalence just greater than 200,000; further, the incentive to balkanize

[33] Again, as in Table 5, small sample size makes single year dummy variables difficult to estimate. Instead, 2-year dummy variables are used in this analysis, reported in Table 8. Similar results are obtained using a linear year effects specification, reported in Panel B of Appendix Table 2.

[34] An increase in the number of identifiable subdivisions may be a natural outcome of an increase in disease prevalence. For the coefficient on *Changed_from_Rare* to capture this effect, distinct subdivisions would have to be identified, then firms would have to identify potentially effective chemical entities to bring to clinical trials, in sharp response to when the OOPD last designated a drug for the disease. There is no compelling reason to believe this to be the case.

declines with prevalence. If subdividing is motivated by an incentive to balkanize, then we should find an inverted-U relationship between the fraction of clinical trials devoted to ODA-qualifying subdivisions and the prevalence of the *un*-subdivided disease. I test this prediction in two ways.

First, I construct a new variable representing the fraction of all new clinical trials for a given disease devoted to an ODA-qualifying subdivision over the entire post-ODA period (1984-1994). Figure 8 shows the predicted values of a non-parametric regression of the fraction of clinical trials devoted to ODA-qualifying subdivisions over the entire post-ODA period, on the prevalence of the disease.[35] I restrict the analysis to disease with prevalence greater than 100,000, dropping the status-changer diseases. Clearly an inverted-U shape relationship is observed. Around the 200,000 threshold, there is clear and dramatic positive relationship between the fraction of clinical trials devoted to ODA-qualifying subdivisions of diseases and the prevalence of the disease. The steady negative relationship seen for disease with prevalence greater than 500,000 is consistent with balkanization being a substantial explanation for the prevalence of disease subdividing.[36]

Second, I quantify the extent of balkanization by testing whether firms subdivide smaller non-rare diseases disproportionately more often than larger non-rare diseases. I employ a differences-in-differences strategy to estimate the investment response for non-rare diseases with prevalence between 200,000 and 500,000, compared to diseases with prevalence exceeding 500,000. The sharp turning point in Figure 8 suggests a prevalence of 500,000 to be a natural cut-off above which costs associated with marketing restrictions outweigh the balkanization incentive. Clearly, subdividing diseases into ODA-qualifying subdivisions still occurs for

[35] I use the most recent prevalence estimates available for each disease in the analysis. Many estimates are reported with confidence intervals. The uncertainty of these estimates motivates the differences-in-differences analysis to follow comparing non-rare diseases with prevalence above and below 500,000, rather than directly estimating the coefficient on a continuous prevalence variable.

[36] One seminar participant noted that the negative relationship may be due to naturally forming subdivisions constituting a fixed fraction of all patients with a given disease. If 20% of people with a given disease form a natural subdivision, then diseases with prevalence fewer than 1,000,000 form a rare disease. Other diseases may form subdivisions at 10%, 15%, etc. A mix of these will generate a downward relationship between the *fraction of patients* with a rare disease and the prevalence of the larger disease. However, the size of rare disease subpopulations should increase in the prevalence of the broader disease, generating a positive relationship between the *fraction of clinical drug trials* devoted to rare subpopulations and prevalence of the larger disease. Further, as disease become more prevalent, it becomes easier it is to identify rare subdivisions. This, too, would suggest a positive relationship, not a negative one as is observed.

diseases with prevalence larger that 500,000. Therefore, I expect that a control group based on the 500,000 prevalence threshold will generate conservative estimates for the extent of balkanization.

I estimate a fixed-effect Poisson regression where the outcome variable is the number of new clinical trials for ODA-qualifying subdivisions. I restrict the sample of disease to those that are not rare, and include a dummy variable for a disease being a *Non-Rare(200k, 500k)* diseases (prevalence between 200,000 and 500,000). The omitted category corresponds to *Non-Rare(>500k)* diseases (those with prevalence greater than 500,000). Column (3) of Table 9 reports the results. Non-rare diseases with prevalence under 500,000 see a relative increase of 462-percent $(= \exp(1.726) - 1) * 100)$ in the number of clinical trials devoted to ODA-qualifying subdivisions after the ODA is passed, over and beyond increase for larger non-rare diseases. The disproportionate effort devoted to subdividing non-rare diseases with smaller prevalence suggests that firms respond to the incentive to balkanize.

Balkanized Disease Drugs Have Larger Prescription Drug Markets

The central motivation for balkanization is the ability of a firm to market an orphan drug to a larger, off-label, patient population. The analysis in the previous subsection suggests that balkanization does occur. This balkanization result, if correct, should bear out in the drug prescription data. Drugs approved to treat ODA-qualifying subdivisions of non-rare diseases should have a larger off-label market than other approved orphan drugs, conditional on the prevalence of the disease indication for which was approved. To test this, I estimate:

$$(16)\quad TotalRx_i = \exp(\alpha + \beta_1 SubNonRare_i + \beta_2 \log(OnLabelPop_i) + \beta_3 ApprovalYr_i + \varepsilon_i).$$

The variable *Total Rx* represents the number of prescriptions written for a given orphan drug, *i*. *ApprovalYr* denotes the year the drug was approved for commercial marketing, and controls for the time elapsed since knowledge its uses first diffused through the medical community. Data on the number of prescriptions in the US for each approved orphan drug are obtained from the 2002 National Ambulatory Medical Care Survey (NAMCS) survey. It provides data on the number of

times approved orphan drugs were prescribed, and records the illness associated with the prescription. Nationally representative estimates are available on the NAMCS website.[37] Data for *OnLabelPop*—the prevalence corresponding to only the approved indication of all 245 orphan drugs—was obtained from the FDA. A positive coefficient on *SubNonRare*—an binary variable that takes one when the drug is approved to treat an ODA-qualifying subdivision of a non-rare disease—would suggest that subdivided disease drugs have larger prescription markets than traditional rare disease drugs, conditional on market size for which it was approved.[38]

Results of this analysis are presented in Table 10. Estimation of the log equation is identical to quasi-ML estimation of a Poisson model. Column (1) reports the results from quasi-ML estimates, reported as incident rate ratios (IRR—the ratio of the predicted prescription count given a unit change in the independent variable). The IRR estimate on *SubNonRare* suggets that, on average, drugs approved for a subdivided non-rare disease were prescribed 319-percent more often than drugs approved for a traditional rare disease, conditional on the disease prevalence for which they were approved. Similar results are found estimating equation (16) with OLS.[39]

I also construct new binary outcome variables for drug prescriptions—whether a drug appear in the 2002 NAMCS survey, and whether a drug appears in *any* previous NAMCS survey. Aggregating all NAMCS surveys increases the likelihood that any given drug appears at least once. Column (3) reports probit regression estimates of the probability that a given orphan drug appears in the survey. An orphan drug that is indicated to treat a subdivision of a non-rare disease is 36 percent more likely to have been mentioned at least once, and is 26 percent more likely to have been mentioned in any prior survey. Note the significance of the coefficient associated with

[37] See the http://www2.cdc.gov/drugs/ website. For a list of approved orphan drugs, see http://www.fda.gov/orphan/.
[38] Ideally, I would regress the number of off-label prescriptions against the *SubNonRare* variable. This directly captures the additional extent of off-label market power associated with a subdivided disease drug. However, the NAMCS is often not specific enough in the categorizing of the disease. Therefore, the number of on- and off-label prescriptions cannot be determined. *Total* prescriptions for a given drug, conditional on the market size of the approved indication, is used as a proxy for off-label prescriptions.
[39] OLS is used to estimate the logged version of equation (18). I use the log of 1 in instances where prescription counts are zero. This is the case for 142 of the 240 drugs in the sample.

the year of approval. It is negative, which implies that newer drugs are less likely to have penetrated the market, and that diffusion of knowledge of drug use is not immediate.[40]

Are Balkanized Disease Drugs are Less Innovative?

The model makes no predictions as to the degree of innovation associated with balkanization. It is possible that balkanized disease drug trials are as innovative as other drug trials, except that rent-seeking firms respond to an incentive to balkanize non-rare disease drug markets. Alternatively, effort devoted to balkanization may crowd-out effort to further develop a truly novel drug, in which case balkanization signals lower innovative intensity. Yet another possibility is that balkanized disease drugs represent R&D effort into "me-too" drugs—marginal manipulation of existing drug technologies marketed to treat subpopulations of a larger disease market. Such behavior could represent development of drugs to treat small subsets of individuals who are refractory to (or who incur dangerous side effects from) an existing drug. If so, drugs to treat ODA-qualifying subdivisions would appear to be less innovative, yet their development would not represent balkanization but better drug-targeting.[41] "Me-too" drug development may also reflect a desire to extend the *de facto* patent-length of an existing drug. Firms may develop marginal changes to an existing drug to treat an ODA-qualifying subdivision as a low-cost way to replace an existing drug. To distinguish among these possibilities, I estimate:

$$\Pr(NME_i = 1) = f(\beta_1 SubNonRare_i + \beta_2 SubRare_i + \beta_3 \log(OnLabelPop_i) + \beta_4 ApprovalYr_i + \varepsilon_i) \quad (17)$$

where *NME* is an indicator for whether an orphan drug was a new molecular entity when approved, *SubRare* is an indicator for whether a drug was approved for a subdivision of a *rare* disease. Finding that $\beta_1 < 0$ would suggest that drugs approved for a subdivision of a non-rare disease embody less innovative technologies. I also estimate this equation with a second

[40] Drugs mentions in the NAMCS survey are listed by both its generic name and its trade name. One generic compound may be associated with multiple drug trade names, often corresponding to different formulations, delivery mechanisms, or dosage levels. To control for differences in formulations, I restrict the analysis to the number of mentions of a given orphan drug's trade name. I have repeated the analysis using generic names of orphan drugs. The magnitudes of the coefficient estimates are even larger.

[41] I thank Will Manning for this comment.

dependent variable, *Priority*. It is an indicator for whether the application for marketing approval was given a priority review by the FDA. A priority review is given when the FDA considers a drug to have potential therapeutic benefit markedly exceeding that of existing drugs indicated for the same disease—a measure generally uncorrelated with the novelty of a drug's mechanism (as measured by *NME*). [42] This difference helps to distinguish between "me-too" drugs motivated by treating refractory patients, and "me-too" drugs developed largely in order to extend drug patents.

Results are reported in Table 11. I find that drugs indicated for an ODA-qualifying subdivision of a non-rare disease is 32 percent less likely to be a new molecular entity; and 24 percent less likely to be given a priority review by the FDA. I also find that orphan drugs indicated for subdivisions of traditional rare diseases are just as likely to represent novel technologies as are drugs approved for traditional rare diseases. This is consistent with the prediction that there is no incentive to balkanize disease markets of traditional rare diseases; such drugs represent an effort to create drugs that therapeutically target a select patient subpopulation.

Drugs approved to treat ODA-qualifying subdivisions of non-rare diseases may reflect efforts to develop better targeting drugs by modifying existing technologies. Indeed, these orphan drugs would appear to be less innovative as measured by *NME*. If better targeting explained most instances of subdividing, then we should see no effect of *SubNonRare* on the priority review status of a drug. However, I find that drugs approved for ODA-qualifying subdivision of a non-rare disease are 22 percent less likely to have been given a priority review. The decline in the coefficient on *SubNonRare* from column (1) to (2) of Table 11 suggests that a portion of the total extent of subdividing represents development of better targeting drugs. More generally, the idea that disease subdividing represents "me-too" drugs that better target small disease subtypes is inconsistent with the balkanization predictions in the previous subsection, and the results reported in Tables 8 and 9.

[42] Data on new molecular entities and priority review was provided by Frank Lichtenberg, and has previously been used by (Lichtenberg and Lleras-Muney 2002), (Lichtenberg and Virabhak 2002), and (Acemoglu and Linn 2004).

5. Interpreting the Extent of Balkanization

I characterize the extent of balkanization by estimating the fraction of new clinical trials generated by the ODA that can be attributed to balkanization. Table 12 (Panel A) is an account of all new clinical trials induced as a result of the ODA, including the impact on traditional rare diseases (Panel A1), and on newly defined ODA-qualifying subdivisions of traditional diseases (Panel A2). The predicted number of trials induced by the ODA is calculated simply as:

$$(18) \qquad \#\,NewTrials = \sum_i \{\exp(\hat{\beta}_i) - 1\} * Base\ Level\ Flow_i * No.\ Diseases_i * Duration_i\ .$$

Given an estimated impact of the ODA, β_i, from regression parameters associated with a specific disease subset *i* over a specific period of time corresponding to a *PostODA(t-t')* indicator variable, the predicted number of trials induced by the ODA is the product of the estimated IRR, the predicted flow of new clinical trials per disease in the base year (the most recent year preceding the start of the relevant time period), the number of diseases in the disease subset, and the number of periods associated with the relevant sample time frame. Panel A1 reports the number of ODA-induced drug trials for traditional rare diseases, which are based on the differences-in-differences Poisson fixed-effects estimates reported in Table 4 column (2). The number of trials for ODA-qualifying subdivisions (reported in Panel A2) can be calculated by summing over 1) the impact on subdividing rare and non-rare diseases with prevalence less than 500,000 (based on column (3) of Table 9)[43]; and 2) the impact on subdividing status-changer diseases into ODA-qualifying subdivisions (based on column (3) of Table 8).

The balkanization response is reported in Table 12 (Panel B). The estimate of the number of balkanized disease drug trials is based on the estimated impact on ODA-qualifying subdivisions of status-changer diseases (column (3) of Table 8), and the estimated impact on non-

[43] Non-rare diseases with prevalence above 500,000 serve as the set of control diseases. This differences-in-differences approach was preferred over simply estimating break in trends separately for rare and for (all) non-rare diseases as use of some control was deemed indispensable; further, the balkanization incentive is theorized to be small for the largest diseases.

rare diseases with prevalence under 500,000, relative to non-rare diseases with larger prevalence (column (3) Table 9).

The balkanization response can further be partitioned into marginal drug innovation of drugs to treat balkanized subdivisions of non-rare diseases (which would not have occurred absent the ODA but should not receive ODA incentives), and pure re-labeling of drug indications from a non-rare disease to an ODA-qualifying subdivision that would have been undertaken absent the ODA. Panel C of Table 12 quantifies the two types of balkanization. For status-changer diseases, I compare the loss in the accumulated flow of new clinical trials (column (4) Table 5) to the increase in the accumulated flow of new trials for ODA-qualifying subdivisions stemming from the change in rare disease status (column (3) Table 8). The minimum of these two predicted values captures the extent of substitution. The same analysis is done for balkanization of non-rare diseases. I compare the loss in the accumulated flow of new clinical trials for less prevalent non-rare disease (column (4) Table 9) to the increase in the accumulated flow of new trials for ODA-qualifying subdivisions induced by the ODA passage (column (2) Table 9). There is no measurable loss in trials for *un*-subdivided non-rare disease trials associated with the ODA. I therefore estimate the extent of substitution to be zero. Note, however, that in using non-rare diseases with prevalence greater than 500,000 as a control group, I bias up the estimate in column (4) of Table 9 (against finding a loss of new trials for *un*-subdivided indications), and bias down the estimate in column (3) of Table 9 (against finding balkanization). Therefore, the zero-substitution estimate for non-rare diseases implies the estimate for the total extent of substitution will be a lower bound estimate.

Taken together, line-items in Table 12 suggest that at least 25-percent of all trials induced by the ODA represent balkanization. And 10-percent represents a lower bound estimate of the extent of the ODA impact due to re-labeling. R&D subsidies for these trials represent pure waste. The remaining 15-percent of balkanized trials represent marginal innovations, which, due to their large drug markets, should not receive ODA subsidization.

6. Conclusion

For a set of long-established diseases known to exist at the time the ODA was passed, I find that the ODA largely encouraged final development of existing drugs that had been previously shelved due to lack of profitability. Notably, the ODA impact on innovation is larger and more sustained as the rare disease drug market size increases—an indication that the ODA operates to counter the small market-fixed cost problem that renders rare disease drugs largely unprofitable.

The profusion of drugs to treat newly defined diseases (subdivisions of long-recognized disease) appears to be an unintended impact of the ODA. It may represent the development of better targeting drug. Alternatively, it may represent effort by firms to seek marketing approval for only a small, artificially defined subset of a larger market for which the drug is beneficial—i.e. balkanization. Balkanization to gain the ODA tax credits stems from the government's inability to observe the true market size of the drug when orphan designation is sought. Asymmetric information between regulator and firm gives rise to opportunities for firms to exploit R&D incentives, a response that theory predicts will be prevalent in push-type R&D policies more generally.

This paper brings empirical evidence to bear on this prediction. I find that 25-percent of all clinical trials induced by the ODA represent balkanization. Central to the incentive to balkanize is the prospect gaining revenue from off-label drug sales. While limiting off-label drug use may be impractical, reducing balkanization by imposing a fee when an orphan drug reaches a trigger level of off-label sales may be viable. Extending the moral hazard analogy, the fee or tax repayment can serve as a "co-payment" to reduce the incentives to balkanize. At the same time, co-payments also create a disincentive for firms to develop drugs for previously unconsidered alternative uses (true R&D externalities). More creative solutions may be able to limit social waste without extensive cost to innovative activity.

The design of the ODA incentives is qualitatively similar to the structure of tax incentives in other forums. The Research and Experimentation (R&E) Tax credit, for example, is expected

to cost taxpayers over $60 billion over the next 10 years. It uses a simple rule to define its subsidy: 20 percent tax credit on qualified research expenditures. The R&E tax credit is similar to the ODA in that the very behavior the government wishes to subsidize is not observable. Neither the level of effort nor the type of innovative activity can be monitored. Indeed, there has been concern that firms exploit the R&E tax credit by misrepresented R&D expenditures (Office of Technological Assessment 1993).

The implications of this study on health policy are also notable, in light of the impact of ODA incentives for newly defined diseases. The development of niche drugs that treat narrowly defined subpopulations of broader diseases (e.g. phenotypic variations of a large disease) is often argued to be a promising area for future pharmaceutical innovations (Haffner, Whitley et al. 2002). This study is relevant to understanding how incentives can be used to encourage drug development in small niche disease markets. In total, the ODA led to 240 new orphan drugs. By extrapolating the results in Table 12, I estimate that 60 drugs on the market (25-percent) can be attributed to balkanization. Yet, this extrapolation suggests that another 60 approved orphan drugs represent better targeting drugs that were developed to treat a rare subpopulation of patients within a non-rare or rare disease. This calculation is consistent with Figure 7. Trials for ODA-qualifying subdivisions of non-rare disease respond immediately to the ODA passage. While the incentives to develop drugs for subdivisions of rare diseases occur at the same time, it is not until the early 1990's that innovation begins for these diseases. This likely represents the cumulative time lag associated with identifying genuine disease subtypes and developing drugs to treat them.

The results suggest that the ODA was able to generate new drugs to treat conditions of specific disease subpopulations (specific genetic subtypes, or that treat patients who are refractory to existing drugs). With modification, the ODA incentives can be a model for how policy can use market incentives to encourage innovation of effective therapeutic technologies for small patient markets while limiting the extent of social waste.

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Figure 1: The Orphan Drug Act Tax Credit

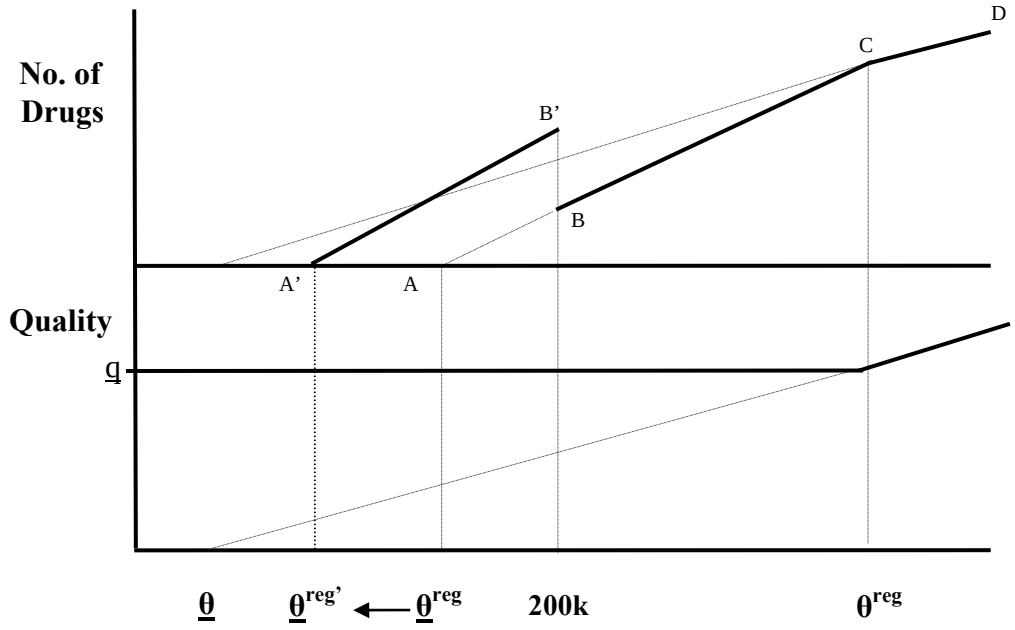
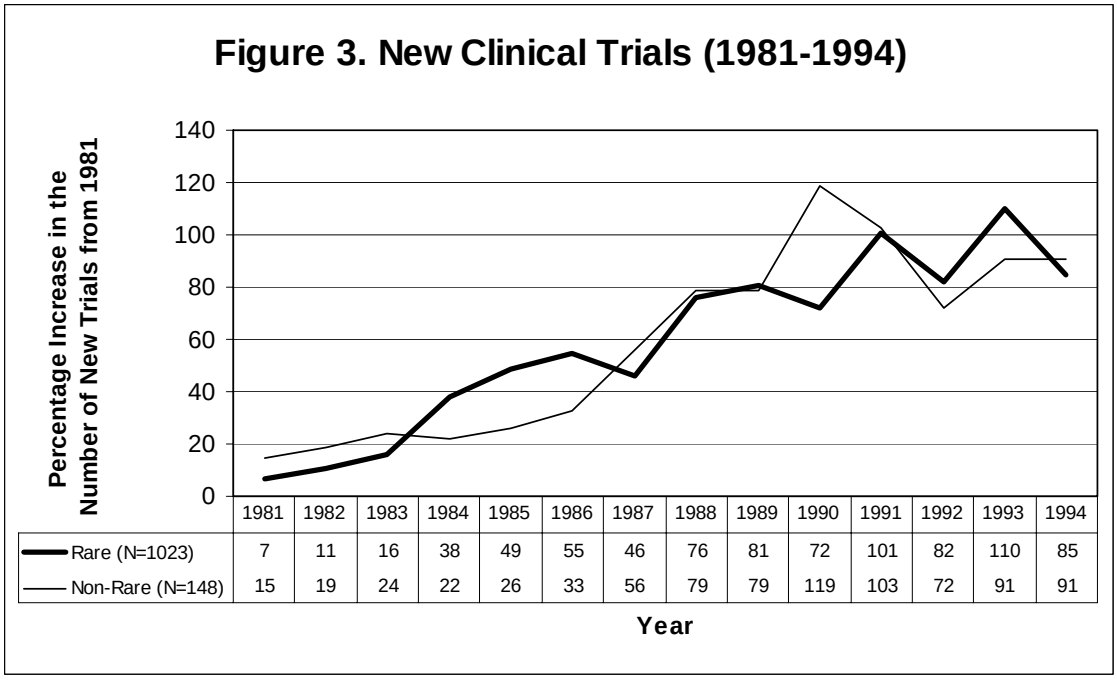


Figure 2: Categorization of Diseases in the NORD List

NORD List 1177 Diseases				
Rare (Prevalence < 200k) 1023 Diseases		**Status Changer** 6 Diseases	**Non-Rare** (Prevalence > 200k) 148 Diseases	
Prevalence < 100k 1014 Diseases	Prevalence 100k-200k 9 Diseases		Prevalence 200k-500k 50 Diseases	Prevalence > 500k 98 Diseases



	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994
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

*Table shows the counts of new clinical trials, by treatment group, by year (1981-1994).

Figure 4: Effect of Losing the ODA Tax Credit

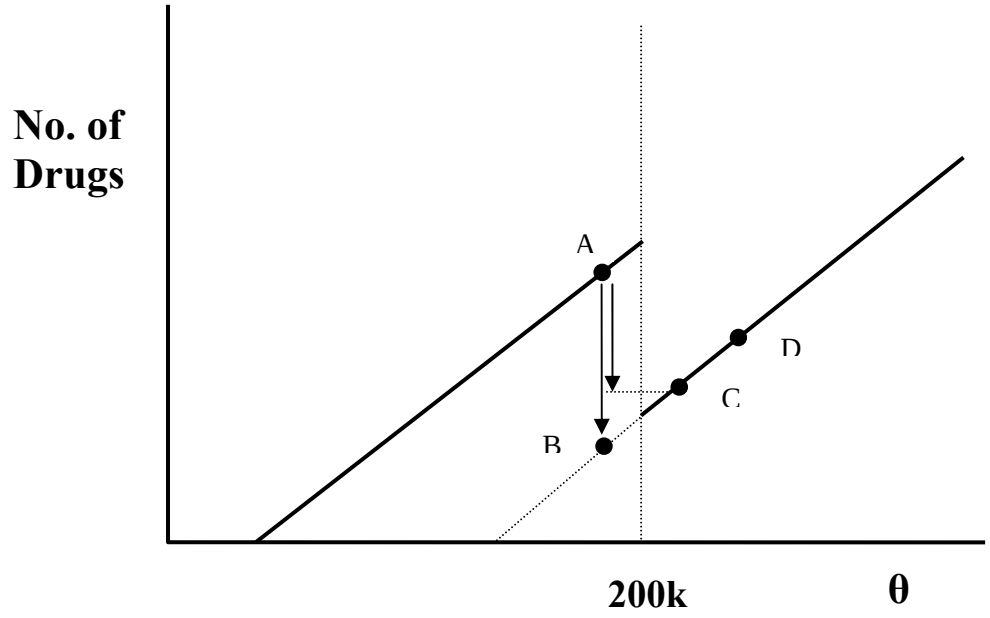
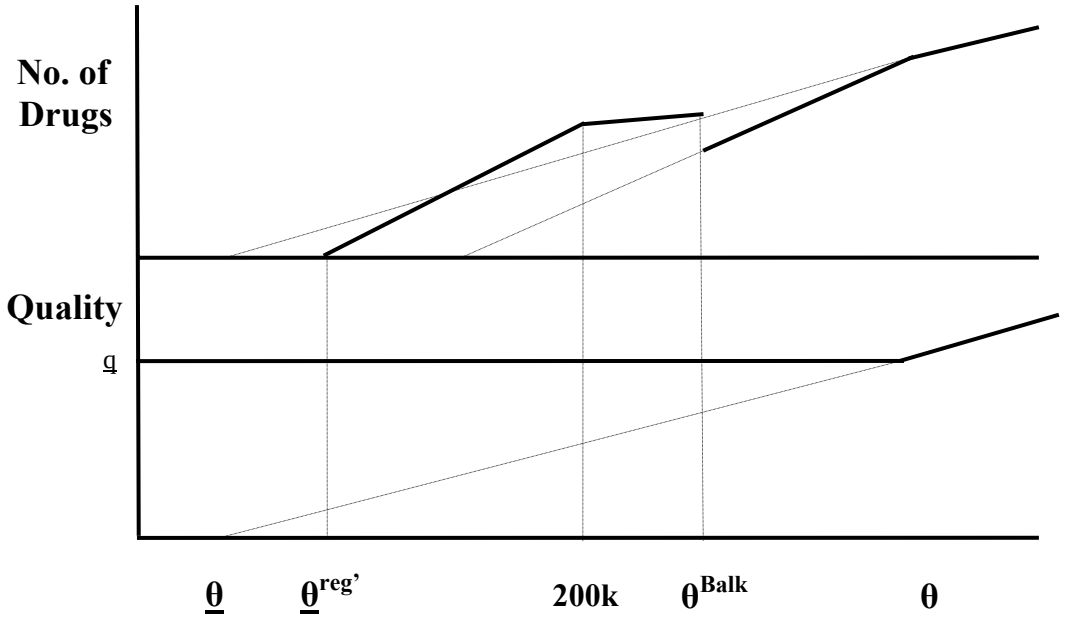


Figure 5: Types of Drugs Designated as Orphan by the OOPD

<table>
<tr><td colspan="4">Total Orphan Designations
1228</td></tr>
<tr><td colspan="2">Indication in NORD List
732</td><td colspan="2">Subdivided Disease Indication
496</td></tr>
<tr><td>Rare
668</td><td>Status Changer
68</td><td>Subdivision of a Rare Disease
210</td><td>Subdivision of a Non-Rare Disease
286</td></tr>
</table>

Figure 6: Equilibrium Drug Variety under Balkanization



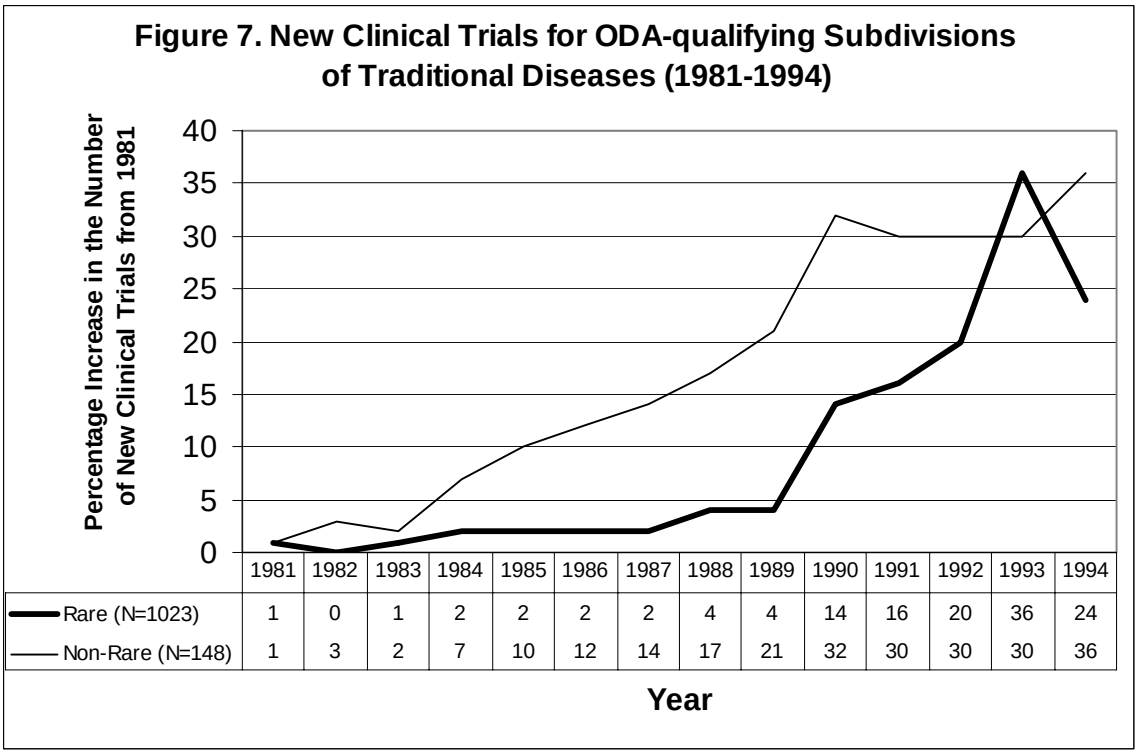


*Table shows the counts of new clinical trials for rare subdivisions of traditional disease, by treatment group, by year (1981-1994).

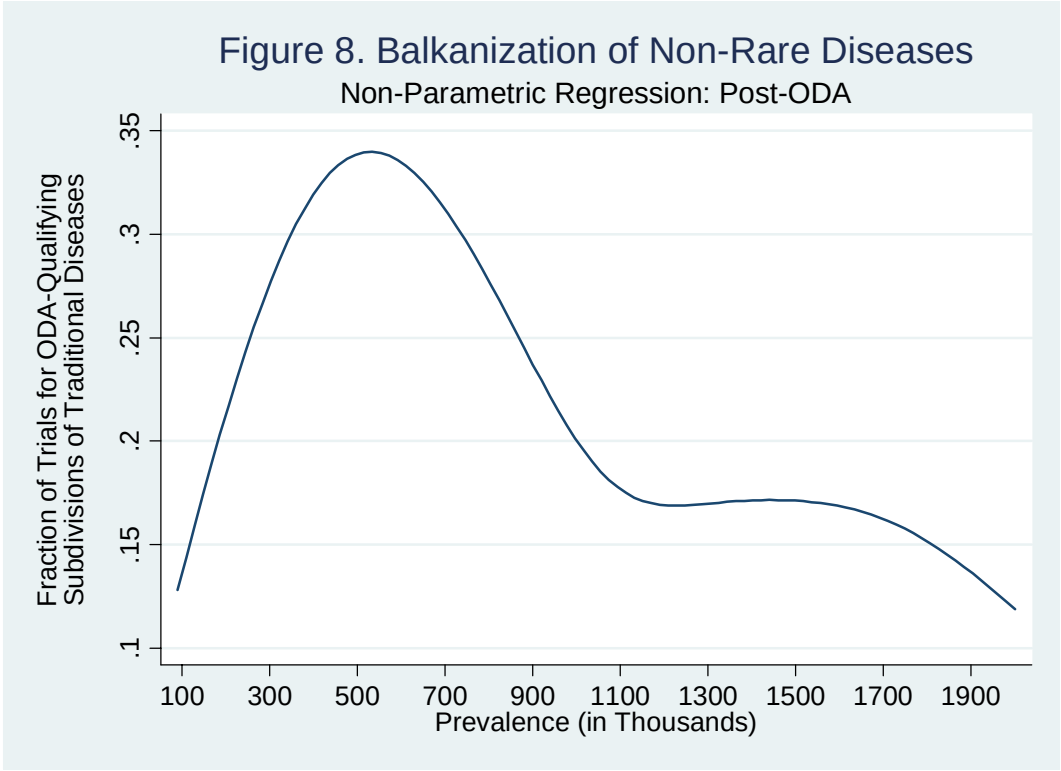


Table 1. Status Changers

Disease	Year Drug Last Designated to Treat Disease	Current Prevalence Estimate
Crohn's Disease[1]	1999	400,000
Systemic Lupus Erythematosus[2]	1999	400,000
Multiple Sclerosis[3,4,5]	1991	350,000
Sjogren Syndrome[4,5,6]	1992	2,000,000
HIV/AIDS[7]	1991	496,000
End Stage Renal Disease[8,9]	1990	350,000
Interstitial Cystitis[10,11]	1991	500,000
Paget's Disease of the Bone[12]	1990	2,000,000

[1] Loftus, EV, P. Schoenfeld and WJ Sandborn. "The epidemiology and natural history of Crohn's disease in population-based patient cohorts from North America: a systematic review." Aliment Pharmacol Ther. 2002 Jan;16(1):51-60. (Medline 11856078)

[2] Hochberg, MC, *et al*. "Prevalence of self-reported physician-diagnosed systemic lupus erythematosus in the USA." Lupus. 1995 Dec;4(6):454-6. (Medline 8749567)

[3] Anderson, DW, *et al*. "Revised estimate of the prevalence of multiple sclerosis in the United States." Ann Neurol. 1992 Mar;31(3):333-6. (Medline 1637140)

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

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

[8] Trivedi HS, MM Pang, A. Campbell and P. Saab. "Slowing the progression of chronic renal failure: economic benefits and patients' perspectives." Am J Kidney Dis. 2002 Apr;39(4):721-9 (Medline #11920337).

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

[12] Altman RD, DA Bloch, MC Hochberg and WA Murphy. "Prevalence of pelvic Paget's disease of bone in the United States." J Bone Miner Res. 2000 Mar;15(3):461-5. (Medline 10750560).

Table 2. Summary Statistics for the Counts of New Clinical Trials for Traditional Diseases

		Group			
		Rare	Status Changer	Status Changer (No AIDS)	Non-Rare
1983	New Clinical Trials	0.017	0.333	0.2	0.162
		(0.135)	(0.516)	(.447)	(0.535)
		[.018]	[.267]	[.200]	[.286]
	75-percentile	0	1	0	0
	90-percentile	0	1	1	1
	95-percentile	0	1	1	1
	99-percentile	1	1	1	3
	Max	2	1	1	3
	N	1023	6	5	148

		Group			
		Rare	Status Changer	Status Changer (No AIDS)	Non-Rare
1990	New Clinical Trials	0.07	5.333	1.4	0.804
		(0.374)	(9.688)	(1.140)	(2.036)
		[.140]	[93.867]	[1.300]	[4.145]
	75-percentile	0	3	2	0
	90-percentile	0	25	3	4
	95-percentile	0	25	3	5
	99-percentile	2	25	3	11
	Max	4	25	3	12
	N	1023	6	5	148

Row one of each panel shows the mean number of new clinical trials for traditional diseases (diseases in the NORD list) grouped by treatment group. The variance is shown in square brackets. The number of new clinical trials counts at the 75th, 90th, 95th, and 99th percentile of the distribution are shown below. The maximum number of counts are also reported by treatment group.

Table 3. D-in-D Estimates of Impact on New Drug Development of the ODA
Dependent Variable: Number of New Clinical Trials

	Model	Poisson		Negative Binomial		Poisson	OLS
		Random Effects	Fixed Effects	Random Effects	Fixed Effects	Fixed Effects	Fixed Effects
	Rare Sample	All	All	All	All	Above 100k	Above 100k
	Control Sample	All	All	All	All	Below 500k	Below 500k
		(1)	(2)	(3)	(4)	(5)	(6)
Rare		-2.427***		-2.159***			
		(0.374)		(0.363)			
PostODA		1.760***	1.760***	1.761***	1.826***	2.052***	1.004***
		(0.233)	(0.358)	(0.255)	(0.275)	(0.457)	(0.251)
Rare*PostODA		**0.524****	**0.524****	**0.411***	**0.338**	**1.040****	**0.527***
		(0.217)	**(0.257)**	**(0.227)**	**(0.234)**	**(0.359)**	**(0.315)**
Constant		-2.295***		1.381***	0.050		0.136
		(0.363)		(0.454)	(0.354)		(0.174)
Year Dummies		Yes	Yes	Yes	Yes	Yes	Yes
R-Squared							0.13
No. of Rare Diseases		1023	168	1023	168	7	9
No. of Control Diseases		148	56	148	56	28	50
No. of Diseases		1171	224	1171	224	35	59
Observations		16394	3136	16394	3136	490	826

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 1981-1994, for all 1171 (= 1777-6) non-statuschanger 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. The variables *RARE* , *PostODA* , and *RARE*PostODA* are indicator variable. 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%.

Table 4. Timing of New Drug Development
Dependent Variable: Number of New Clinical Trials

	Poisson Fixed Effects	
Disease Sample	All	All
	(1)	(2)
Postoda_13	0.774***	0.774***
	(0.295)	(0.259)
Postoda_46	1.706***	1.706***
	(0.264)	(0.238)
Postoda_7plus	1.802***	1.802***
	(0.234)	(0.234)
Rare x PostODA_13	1.038***	
	(0.253)	
Rare x PostODA_46	0.442*	
	(0.233)	
Rare x PostODA_7plus	0.440**	
	(0.221)	
Rare(<100k) x PostODA_13		**0.982*** **
		(0.260)
Rare(<100k) x PostODA_46		**0.346**
		(0.240)
Rare(<100k) x PostODA_7plus		**0.338**
		(0.228)
Rare(100k, 200k) x PostODA_13		**1.505** **
		(0.644)
Rare(100k, 200k) x PostODA_46		**1.135***
		(0.620)
Rare(100k, 200k) x 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

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 1981-1994, for all 1171 (= 1777-6) non-statuschanger diseases in the study. Fixed-effects models drop all disease for which there are no counts in the time series. The variables *RARE* , *PostODA* , and *RARE*PostODA* are indicator variable. 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%.

Table 5. Impact on New Drug Development: Status Changer Diseases
Dependent Variable: Number of New Clinical Trials

			Poisson FE		
Status Changer Sample	Status Changers	Status Changers (NO AIDS)	Status Changers	Status Changers	Status Changers (NO AIDS)
"Control" Sample	None	None	All Rare	Rare Diseases Above 100k	Rare Diseases Above 100k
	(1)	(2)	(3)	(4)	(5)
Changed from Rare	**-0.285**	**-1.227****	**-0.046**	**-0.331****	**-0.666****
	(0.251)	**(0.576)**	**(0.120)**	**(0.166)**	**(0.303)**
2-Year Dummies	Yes	Yes	Yes	Yes	Yes
No. of Statuschanger 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

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 1981-1994. The fixed effects model drops all disease for which there are no counts in the time series. Column headers note which statuschanger 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%.

Table 6. Typology of Diseases Subdivisions

	Typology	Example(s)	Coding of Example
No Subdivision	Disease X	Infant Respiratory Distress Syndrome	**Indication:** Infant Respiratory Distress Syndrome **Subpopulation:** None
	Symptom of Disease Y	Muscle contracture in cerebral palsy	**Indication:** Cerebral Palsy **Subpopulation:** None
Subdivision	Disease X associated with Disease Y	Pneumocystis Carinii infection associated with AIDS	**Indication:** Pneumocystis Carinii infection **Subpopulation:** for patients with AIDS
	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
		Neutropenia where neotrophil counts are below 500/mm3	**Indication:** Neutropenia **Subpopulation:** for patients with neotrophil counts below 500/mm3
	Advanced case of Disease X	Stage III-IV Malignant Melanoma	**Indication:** Malignant Melonoma **Subpopulation:** patients with stage III or IV melanoma
	Disease X, subtype Y	Gaucher's Disease, Type I	**Indication:** Gaucher's Disease **Subpopulation:** patients with type I
		Relapsing and Remitting Multiple Sclerosis	**Indication:** Multiple Sclerosis **Subpopulation:** patients with relapsing and remitting type

Table 6 lists the types of drug indications found in the *NDA Pipeline.* Within sample, at least, the 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.

Table 7. Summary Statistics for Counts of New Clinical Trials for ODA-Qualifying Subdivisions of Traditional Diseases

		Group			
		Rare	Status Changer	Status Changer (No AIDS)	Non-Rare
1983	New Clinical Trials	0.001	0	0	0.014
		(0.031)	.	.	(0.116)
		[.001]	.	.	[.013]
	75-percentile	0	0	0	0
	90-percentile	0	0	0	0
	95-percentile	0	0	0	0
	99-percentile	0	0	0	1
	Max	1	0	0	1
	N	1023	6	5	148

		Group			
		Rare	Status Changer	Status Changer (No AIDS)	Non-Rare
1990	New Clinical Trials	0.014	0.667	0.2	0.216
		(0.132)	(1.211)	(0.447)	(1.243)
		[.017]	[1.467]	[.200]	[1.545]
	75-percentile	0	1	0	0
	90-percentile	0	3	1	0
	95-percentile	0	3	1	1
	99-percentile	1	3	1	4
	Max	2	3	1	14
	N	1023	6	5	148

Row one of each panel shows the mean number of new clinical trials for ODA-qualifying subdivisions of traditional diseases (diseases in the NORD list) grouped by disease treatment group. The variance is shown in square brackets. The number of new clinical trials counts at the 75th, 90th, 95th, and 99th percentile of the distribution are shown below. The maximum number of counts are also reported by treatment group.

Table 8. The Impact of the ODA on Subdivided Disease Clinical Trials: Time Series Variation in Rare Status
Dependent Variable: Number of New Trials for Rare Subdivided Indications

	Poisson Regression Fixed Effect			
Status Changer Sample "Control" Sample	Status Changers None	Status Changers All Rare	Status Changers Rare Diseases Above 100k	Status Changers (NO AIDS) Rare Diseases Above 100k
	(1)	(2)	(3)	(4)
Changed from Rare	**2.400****	**0.825****	**1.347*****	**1.310***
	(1.042)	**(0.348)**	**(0.406)**	**(0.706)**
2-Year Dummies	Yes	Yes	Yes	Yes
No. of Status Changers	3	3	3	2
No. Of Control Diseases	0	42	6	6
No. of Diseases	3	45	9	8
Observations	42	630	126	112

Table reports the parameter estimates of the fixed effects Poisson regression. The dependent variable is the number of new clinical trials for ODA-qualifying subdivisions of a given disease, in a given year from 1981-1994. The fixed effects model drops all disease for which there are no counts in the time series. Column headers note which statuschanger diseases, and which diseases are included in the sample specification as controls. 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 in poisson fixed effects models are estimated by quasi-MLE (Wooldridge, 1999). * significant at 10%; ** significant at 5%; *** significant at 1%.

Table 9. Extent of Balkanization Among Non-Rare Diseases

Dependent Variable:	No. Trials for ODA-Qualifying Subdivisions	No. Trials for ODA-Qualifying Subdivisions	No. Trials for ODA-Qualifying Subdivisions	No. Trials for Traditional Diseases
Rare Sample	All	Above 100k	None	None
Non-Rare Sample	All	Below 500k	All	All
	(1)	(2)	(3)	(4)
PostODA_13	1.681	-0.189	1.545	0.454
	(1.036)	(1.372)	(1.184)	(0.368)
PostODA_46	2.154**	2.397*	2.697**	1.365***
	(0.998)	(1.231)	(1.118)	(0.322)
PostODA_7plus	3.897***	3.174***	1.922*	1.515***
	(0.947)	(1.137)	(1.120)	(0.312)
NonRare x PostODA_13	0.575	1.504		
	(0.930)	(1.368)		
NonRare x PostODA_46	0.606	0.930		
	(0.886)	(1.249)		
NonRare x PostODA_7plus	-0.736	0.532		
	(0.826)	(1.173)		
NonRare(200k, 500k) x PostODA_13			1.686*	0.452
			(0.951)	(0.348)
NonRare(200k, 500k) x PostODA_46			0.804	0.393
			(0.867)	(0.297)
NonRare(200k, 500k) x PostODA_7plus			2.255***	0.379
			(0.860)	(0.278)
Year Dummies	Yes	Yes	Yes	Yes
No. Rare Diseases(<100k)	36	---	---	---
No. Rare Diseases(100k, 200k)	6	6	---	---
No. of NonRare(200, 500k) Diseases	22	22	22	26
No. of NonRare(>500k) Diseases	14	---	14	28
Number of Diseases	78	28	36	54
Observations	1092	504	504	756

Table reports the parameter estimates of the Poisson fixed effects model. The dependent variable is the number of new clinical trials for ODA-qualifying subdivisions of a given disease, in a given year from 1981-1994, for all 1171 (= 1777-6) non-statuschanger diseases in the study. The fixed effects model drops all disease for which there are no counts in the time series. The variable *PostODA* is an indicator variable for observations in years after the ODA passage. The variable Nonrare(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%.

Table 10. Prescription Use of Orphan Drugs

	Drug Mentions (Trade Name)			
	Poisson IRR	OLS	Probit	Probit
Dependent Variable	No. of Drug Mentions in 2002	Log No. of Drug Mentions in 2002	Drug Appears in 2002: Yes-No	Drug Appears in Prior Survey: Yes-No
	(1)	(2)	(3)	(4)
Subdivided Nonrare	**3.190*** **	**3.989*** **	**0.361*** **	**0.264*** **
	(1.551)	**(0.745)**	**(0.073)**	**(0.065)**
log(On-Label Population)	1.065	0.360**	0.040*	0.044**
	(.136)	(0.172)	(0.020)	(0.018)
Approval Year	.982	-0.129**	-0.014**	-0.032***
	(.042)	(0.062)	(0.007)	(0.007)
Constant		256.913**		
		(123.898)		
Observations	240	240	240	240
R-squared		0.15		

Column (1) reports incident rate ratios from a Poisson regression, where the outcome variable is the number of prescriptions for a given drug. Paremter and (robust) standard error estimates are consistent under distribution-free assumptions. Column (2) reports the parameter estimates from an OLS regression. The dependent variable is the log of 1 plus the number of prescriptions for a given FDA approved orphan drug in the US in 2002. Prescription counts come from nationally representative NAMCS survey on physician visits. The variable *Subdivided_NonRare* is an indicator that takes 1 when a drug is approved to treat an ODA-qualifying subdividion of a non-rare disease. The variable *Prevalence* corresponds to the prevalence of the disease for which an approved given drug is indicated. Columns (3)-(4) report probit regression estimates. The dependent variable in column (3) is an indicator which takes 1 if a given orphan drug appeared in the 2002 NAMCS survey; in column (4), it is an indicator for whether the drug appeared in any NAMCS survey. Standard errors in parentheses. * significant at 10%; ** significant at 5%; *** significant at 1%.

Table 11. Extent of Innovation of Orphan Drugs

	Probit	
Dependent Variable	Drug is a New Molecular Entity: Yes-No	Drug had Priority Review: Yes-No
	(1)	(2)
Subdivided Rare	**0.001**	**0.029**
	(0.089)	**(0.093)**
Subdivided Nonrare	**-0.327*** **	**-0.224** **
	(0.086)	**(0.103)**
log(On-Label Population)	0.022	-0.015
	(0.023)	(0.025)
Approval Year	-0.022***	-0.014
	(0.009)	(0.009)
Observations	179	161

The dependent variable in column (1) is an indicator which takes 1 if the orphan drug was designated a new molecular entity by the FDA when approved; in column (2) the dependent variable is an indictor for whether the drug was given a priority review for marketing approval. Cells report marginal probability estimates from a probit regression. The variable *Subdivided_ NonRare* is an indicator that takes 1 when a drug is approved to treat an ODA-qualifying subdividion of a non-rare disease. The variable *Subdivided_Rare* is an indicator that takes 1 when a drug is approved to treat a subdividion of an already rare disease. The omitted variable corresponds to orphan drugs indicated for traditional rare diseases in the NORD list. The variable *Prevalence* corresponds to the prevalence of the disease for which a given drug is approved by the FDA. Standard errors in parentheses. * significant at 10%; ** significant at 5%; *** significant at 1%.

Table 12. Estimates for the Extent of Balkanization

Panel A. Number of New Clinical Trials Induced by ODA	Parameter Estimate (Poisson FE) (1)	Predicted Average No. of Clinical Trials (Base Year) (2)	No. of Periods (3)	No. of Diseases (4)	New Drug Trial Counts (5)
1. Trials for Traditional Rare Diseases					
i Traditional Rare Diseases(<100k) PostODA(1-3)	0.98	0.0140	3	1014	70.89
ii Traditional Rare Diseases(<100k) PostODA(4-6)	0.35	0.0140	3	1014	17.85
iii Traditional Rare Diseases(<100k) PostODA(7plus)	0.34	0.0140	5	1014	28.74
iv Traditional Rare Diseases(100k, 200k) PostODA(1-3)	1.51	0.1439	3	9	13.70
v Traditional Rare Diseases(100k, 200k) PostODA(4-6)	1.14	0.1439	3	9	8.26
vi Traditional Rare Diseases(100k, 200k) PostODA(7plus)	1.17	0.1439	5	9	14.39
2. Trials for ODA-Qualifying Subdivisions of Traditional Rare Diseases					
i Traditional Diseases PostODA(1-3)	0.59	0.0009	3	1023	2.21
ii Traditional Diseases PostODA(4-6)	-0.13	0.0009	3	1023	0.00
iii Traditional Diseases PostODA(7plus)	2.40	0.0009	5	1023	46.04
iv Traditional NonRare(200k, 500k) Diseases PostODA(1-3)	1.69	0.0130	3	50	8.58
v Traditional NonRare(200k, 500k) Diseases PostODA(4-6)	0.80	0.0130	3	50	2.41
vi Traditional NonRare(200k, 500k) Diseases PostODA(7plus)	2.26	0.0130	5	50	27.74
vii StatusChanger Diseases (Base year = 1990)	1.35	0.4099	4	6	28.00
Panel A Totals					**268.80**

Table reports the predicted number of new clinical trials induced by the ODA. Estimates are based the product of the estimated impact of the ODA for a given diseases, the predicted base level flow of clinical trials for those diseases, and the duration of years associated with the impact estimate (see section 5 of the paper). Panel A1 reports the predicted number of new clinical trials induced by the ODA for traditional rare diseases, based on coefficient estimates in column (2) of Table 4. Panel A2 reports the predicted number of new trials for ODA-qualifying subdivisions of tradtional non-rare diseases, based on coefficient estimates in column (2) of Table 9 (for traditional diseases) and column (3) of Table 8 (for status-changer diseases).

Table 12 (continued). Estimates for the Extent of Balkanization

Panel B. Number of New Clinical Trials due to Balkanization	Parameter Estimate (Poisson FE) (1)	Predicted Average No. of Clinical Trials (Base Year) (2)	No. of Periods (3)	No. of Diseases (4)	Drug Trial Counts (5)
i Non-Rare(200k, 500k) Diseases PostODA(1-3)	1.69	0.0130	3	50	8.58
ii Non-Rare(200k, 500k) Diseases PostODA(4-3)	0.80	0.0130	3	50	2.41
iii Non-Rare(200k, 500k) Diseases PostODA(7plus)	2.26	0.0130	5	50	27.74
iv StatusChanger Diseases (Base Year = 1990)	1.35	0.4099	4	6	28.00
Panel B Totals					66.72
Fraction of Trials due to Balkanization					**0.25**

Panel C. Number of Balkanized Trials due to Substitution	(1)	(2)	(3)	(4)	(5)
1. Substitution Away from NonRare Disease Drug Trials					
i Non-Rare(200k, 500k) Diseases PostODA(1-3) (from B.*i*)	1.69	0.0130	3	50	8.58
ii Non-Rare(200k, 500k) Diseases PostODA(4-3) (from B.*ii*)	0.80	0.0130	3	50	2.41
iii Non-Rare(200k, 500k) Diseases PostODA(7plus) (from B.*iii*)	2.26	0.0130	5	50	27.74
iv New Trials for NonRare Diseases *lost* due to ODA	---	---	---	---	0
Minimum(sum{C.1.*i-iii*}, C.1.*iv*)					0
2. Substitution Away from Status Changer Disease Drug Trials					
i StatusChanger Diseases (Base Year = 1990) (from B.*iv*)	1.35	0.4099	4	6	28.00
ii New Trials for Status Changer Diseases *lost* due to ODA	0.330	3.2	4	6	30.03
Minimum(C.2.*i*, C.2.*ii*)					28.00
Fraction of Trials due to Substitution					**0.10**

Panel B1 reports the total predicted number of new clinical trials that represent balkanization. Estimates are based the product of the estimated impact of the ODA for a given diseases, the predicted base level flow of clinical trials for those diseases, and the duration of years associated with the impact estimate (see section 5 of the paper). Balkanization of non-rare diseases are based on coefficient estimates in column (3) of Table 9, while balkanization of status-changer diseases are based on coefficient estimates in column (3) of Table 8. Panel C, the balkanization is partitioned into marginal drug innovation of drugs to treat balkanized subdivisions of non-rare diseases, and pure re-labeling of drug indications from a non-rare disease to an ODA-qualifying subdivision that would have been undertaken absent the ODA. For status-changer diseases, I compare the loss in the accumulated flow of new clinical trials (based on column (4) of Table 5) to the increase in the accumulated flow of new trials for ODA-qualifying subdivisions stemming from the change in rare disease status (column (3) of Table 8). The minimum of these two predicted values captures the extent of substitution. For non-rare diseases, I compare the loss in the accumulated flow of new clinical trials for less prevalent non-rare diseases (column (4) of Table 9) to the increase in the accumulated flow of new trials for ODA-qualifying subdivisions induced by the ODA passage (column (3) of Table 9).

Appendix Table 1: Counting of Clinical Trials

				NDA Pipeline Data			Coding		
Line			Drug	Generic Name	Indication	Trial Phase	New Trial	NORD#	Orphan Subdivision
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	1987	Johnson & Johnson		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			
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	1988	Johnson & Johnson		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

Appendix Table 1 shows a portion of a typical data table from the *NDA Pipeline* , sampled from years 1987 and 1988 for Johnson & Johnson, and how data is eventually coded to be used in the panel data set. 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 determmined 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 Johnson & Johnson 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 volume of the NDA Pipeline. C) Sibelium is listed in 1987 to treat alternating hemiplegia (Line 11). The *Trial Phase* cell is blank, which usually represents that a firm has self-reported plans to begin trials for a given indication. In 1988 (Line 27) Johnson & Johnson has begun trials for Sibelium to treat alternating hemiplegia; so I record the start year for this trial 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.

Appendix Table 2. Impact on New Drug Development: Status Changer Diseases

Panel A: Dependent Variable: Number of New Clinical Trials

			Poisson FE		
	Status Changer Sample	Status Changers	Status Changers (NO AIDS)	Status Changers	Status Changers (NO AIDS)
	"Control" Sample	None	None	All Rare	Rare Diseases Above 100k	Rare Diseases Above 100k
		(1)	(2)	(3)	(4)	(5)
Changed from Rare		**-1.062*** **	**-1.333*** **	**-0.312** **	**-0.732*** **	**-0.745** **
		(0.173)	**(0.408)**	**(0.128)**	**(0.151)**	**(0.306)**
Year		**0.297*** **	**0.299*** **	**0.151*** **	**0.230*** **	**0.185*** **
		(0.027)	**(0.061)**	**(0.009)**	**(0.018)**	**(0.023)**
No. of Statuschanger 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

Panel A: Dependent Variable: Number of New Clinical Trials for ODA-Qualifying Subdivisions

		Poisson FE			
	Status Changer Sample	Status Changers	Status Changers	Status Changers	Status Changers (NO AIDS)
	"Control" Sample	None	All Rare	Rare Diseases Above 100k	Rare Diseases Above 100k
		(1)	(2)	(3)	(4)
Changed from Rare		**0.937***	**0.702** **	**0.978** **	**1.052**
		(0.547)	**(0.345)**	**(0.391)**	**(0.697)**
Year		0.267***	0.317***	0.259***	0.265***
		(0.092)	(0.031)	(0.047)	(0.053)
No. of Status Changers		3	3	3	2
No. Of Control Diseases		0	42	6	6
No. of Diseases		3	45	9	8
Observations		42	630	126	112

Panel A (Panel B) reports the parameter estimates of the fixed effects Poisson regression from Table 5 (Table 8) a linear year effect is used in place of 2-year dummy variables. The dependent variable in Panel A (Panel B) is the number of new clinical trials (new clinical trials for ODA-qualifying subdivisions) 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 statuschanger 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. 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%.