

**THE ECONOMICS OF PHARMACEUTICAL DEVELOPMENT:
COSTS, RISKS, AND INCENTIVES**

by

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Abstract

This dissertation addresses three open questions related to the economics of pharmaceutical development. First, how much does it cost to conduct a clinical trial? Second, what effect has the model policy for incentivizing pharmaceutical development, the Orphan Drug Act, had on pharmaceutical availability? And third, how can the costs and risks of pharmaceutical development be used to model an optimal development portfolio? We estimate clinical trial costs by decomposing firms' publicly reported research and development expenses against clinical trial data. We obtain estimates that are broadly consistent with older estimates based on proprietary data. We also estimate the costs of clinical trial subjects. To our knowledge, such costs have not been estimated previously. We find that the costs of Phase I and Phase II clinical trial subjects are very high, supporting the adoption of adaptive trial designs to decrease trial length and size. We measure the effects of the Orphan Drug Act by estimating the size of a regression discontinuity in drug prescriptions as a function of disease prevalence. We find no significant discontinuity around the prevalence threshold that qualifies products to receive "orphan incentives" under the Act. We offer a novel theoretical explanation for the lack of an observed discontinuity: the Act has a perverse effect on drug availability due to price effects of the orphan incentives. Last, we estimate the costs of the U.S. Public Health Emergency Medical Countermeasure Enterprise (PHEMCE), based on a survey of product pipelines, and design an optimal portfolio for achieving fixed success probabilities. Our results support the President's budget request for PHEMCE but suggest that to achieve reasonable success probabilities, PHEMCE will need to prioritize some

products over others, or reduce costs by funding smaller trials. We formally model the tradeoff of cost for safety, and describe some policy implications of the tradeoff.

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*For those who have dedicated themselves to developing and distributing
affordable drugs and vaccines against infectious diseases.*

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INTRODUCTION

The delivery of drugs and vaccines ranks among the most cost-effective health interventions in both developed and developing countries. A number of public and private initiatives have been proposed to support the development of new pharmaceuticals, which are needed to address the remaining burden of diseases such as HIV, malaria, and tuberculosis, the potential burden of pandemic influenza and other emerging infectious diseases, and the prevention of several cancers. These initiatives include Advanced Market Commitments that guarantee markets for new products, expansions of Priority Review Vouchers that allow firms to transfer regulatory benefits to other products, and expansions of the Orphan Drug Act that provide market exclusivity to new pharmaceuticals.

Evaluations of these policy proposals have been handicapped by a dearth of economic analysis. While the costs of delivering existing pharmaceuticals to populations are well-documented, the costs of developing new pharmaceuticals, and the effectiveness of incentives to accelerate their development, have received scant attention from economists. As a result, we have little evidence to support budgets for pharmaceutical development, to support cost-effectiveness analysis of investments in pharmaceutical development, or to help design incentives intended to increase pharmaceutical availability.

In this three-manuscript dissertation, I address three open questions related to the economics of pharmaceutical development. First, how much does it cost to conduct a clinical trial? Second, what effect has the model policy for incentivizing pharmaceutical

development, the Orphan Drug Act, had on pharmaceutical availability? And third, how can the costs and risks of pharmaceutical development be used to model an optimal development portfolio?

In the first manuscript, I, along with co-author Brad Herring, estimate the costs of clinical trials. Clinical trials are the most costly aspect of pharmaceutical development, but just how costly remains a matter of sustained debate. Clinical trial costs are a trade secret for pharmaceutical companies, and there are no publicly available data on clinical trial costs for more than a few individual products. We impute the costs of clinical trials using FDA clinical trial data and data from pharmaceutical firms' reported annual research and development expenses. We estimate firm-level multivariate regression models with firms' total annual R&D expenses as the dependent variable and various indicators for the number and scale of clinical trials as explanatory variables. Using this approach, we estimate the costs of a clinical trial and the costs of a clinical trial subject. To our knowledge, our study represents the only empirical estimate of these costs using recent data, based on a sample of 189 firms and roughly 10,000 clinical trial-years.

In the second manuscript, I, along with co-author Brad Herring, estimate the effects of the Orphan Drug Act (ODA) on pharmaceutical availability. The ODA included a number of incentives to encourage the development of drugs against "orphan diseases" – diseases with a prevalence less than 200,000 cases in the U.S. These incentives have been viewed as a model for effective policy and have been widely imitated globally. But the empirical evidence for the ODA has remained equivocal. We adapt Salop's spatial market model to develop an economic model of drug prescriptions. We test our model using a regression discontinuity design and data from the U.S.

National Ambulatory Medical Care Survey. Our approach estimates the size of the discontinuity in prescription behavior that would be expected between diseases with prevalence less than 200,000 cases, and those with prevalence greater than 200,000 cases. Our design is the closest we can come, absent a controlled experiment, to an estimate of the causal effects of orphan drug incentives.

In the third manuscript, I, along with co-authors Michael Mair, Brad Smith, and Brad Herring, demonstrate a general approach for planning a portfolio of pharmaceutical development. As a case study, we consider the U.S. Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) -- the most detailed set of requirements for drugs and vaccines established by the U.S. government. We survey candidate products in development and estimate their future clinical development costs, based on historical costs and failure rates. We then design an optimal portfolio to ensure fixed probabilities of success. To our knowledge, this is the only empirical estimate of the PHEMCE's expected costs. In addition, we explore one strategy for reducing the costs of PHEMCE -- reducing the size of clinical trials. We estimate the economic advantages of decreasing clinical trial sizes and the effects on Type II errors for detecting adverse events.

Together, the three manuscripts provide new empirical evidence on three controversial topics -- the costs of clinical trials, the effects of orphan drug incentives, and the costs of the PHEMCE. The manuscripts also illustrate methods that can be applied more generally to open problems in pharmacoeconomics. In the conclusion of this dissertation, I discuss our results and their implications for policy -- from setting realistic budgets for publicly and privately funded pharmaceutical development programs, to setting appropriate sizes and structures for R&D incentives.

MANUSCRIPT 1

The Costs of Clinical Trials

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Abstract

Information about the costs incurred by the pharmaceutical industry to produce a new drug is relatively limited. We examine the costs of clinical trials using data from pharmaceutical firms' reported annual research and development expenses and FDA clinical trial data for years 2006 through 2010. We estimate firm-level multivariate regression models with total annual R&D expenses for the firm as the dependent variable and various indicators for the number and scale of Phase I through IV clinical trials as explanatory variables. We find that the annual cost is \$19.9 million for a Phase I trial, \$24.2 million for a Phase II trial, \$48.9 million for a Phase III trial, and \$35.2 million for a Phase IV trial. These results are consistent with previous estimates and yield an expected cost per approved pharmaceutical of \$600 million – or over \$1.2 billion when capitalized at 11% per year. Because the scale of these clinical trials varies considerably, we also decompose these average costs into the fixed costs of running a trial and the variable costs per human subject. We find that the annual cost for a clinical trial subject is \$489,900 for Phase I, \$303,100 for Phase II, \$12,400 for Phase III, and statistically insignificant for Phase IV. We believe that these estimates can help firms, policymakers, and foundations to set realistic budgets for pharmaceutical development, and to quantify the benefits of alternative trial designs that reduce trial size and length.

Introduction

To be approved for marketing by the U.S. Food and Drug Administration (FDA), a new pharmaceutical must undergo three phases of clinical trials, in which the safety and efficacy of a new product is demonstrated in tests involving human subjects. The clinical trial process is lengthy, costly, and risky. Four candidates enter clinical trials for every one approved by the FDA, and the transformation of a candidate into a marketable product typically takes more than 10 years (Davis et al., 2011).

Phase I trials are typically conducted with up to 100 healthy subjects to assess the safety of a previously untested product. Phase I trials are often conducted in inpatient clinics for full-time observation. Manufacturing costs can be high for Phase I trials, given the initial startup costs of producing a sufficient volume of the pharmaceutical at a precise dosage and purity. Because there are no prior human data on the product's safety, monitoring costs may be high, and subjects are exposed to a higher level of risk than in subsequent phases. Because the subjects are healthy, they do not receive any health benefit from participating in the trial. One study found that difficulties in recruiting healthy volunteers delayed US-based trials by more than one year, on average (Belforti, et al., 2010). Phase I trials last 2.4 years, on average, and of drug candidates that enter Phase I studies, 83% successfully complete them (Davis et al., 2011).

Phase II trials are typically conducted with up to 300 subjects who suffer from the target disease, and measure both safety and efficacy. The product has already been tested for safety, and these subjects may benefit from an effective drug. Monitoring is typically performed on an outpatient basis. Phase II trials last 3.4 years, on average, and of drug

candidates that enter Phase II studies, 56% successfully complete them (Davis et al., 2011).

Phase III trials are typically conducted with up to 3,000 subjects who suffer from the target disease, and measure safety and efficacy in a larger, more diverse population, with different dosages and product combinations. Phase III trials last 3.2 years, on average, and of drug candidates that enter Phase III studies, 65% successfully complete them (Davis et al., 2011).

Phase IV studies occur after the FDA has approved a drug for marketing, to gather additional information about a product's safety, efficacy, and optimal use in a patient population (FDA, 2012). Phase IV monitoring is typically performed on thousands of subjects on an outpatient basis, with less frequent data collection.

The cost of conducting a single clinical trial is generally believed to average in the tens of millions of dollars, but estimates of the actual amounts remains controversial. Clinical trial costs include manufacturing costs for the pharmaceuticals used during testing, laboratory costs, advertising and search costs for subject recruitment, and salaries and contract payments to study administrators (Wright, et al., 2005). Financial payments to clinical trial subjects are common (Grady, 2005; Ripley et al., 2010), as are payments to subjects' physicians, to compensate for the additional monitoring physicians are required to perform during a trial (Emanuel et al., 2003).

The costs associated with clinical trials are a trade secret for pharmaceutical companies, and to our knowledge, there are no publicly available data on clinical trial costs for more than just a few individual products. The most commonly cited estimate of drug development costs -- \$802 million (in year 2000 dollars) in capitalized costs per new

drug approved -- is based on a confidential survey of pharmaceutical firms by Tufts University's Center for the Study of Drug Development (CSDD), for the period 1980 to 1999 (DiMasi, Hansen, and Grabowski, 2003). More recent estimates of drug development costs have also used these CSDD data: Adams and Brantner (2006) estimated capitalized costs of \$868 million per approved drug (2000 dollars), while DiMasi and Grabowski (2007) estimated capitalized costs of \$1.3 billion (2005 dollars).

The CSDD data have several limitations. Most of the data are now more than two decades old. The sample included only 10 firms and 68 drugs. All of the firms are large multinational pharmaceutical firms, whose costs may be unrepresentative of small- and medium-sized firms. All firms self-selected into the study and all firms self-reported their costs. Costs are unverifiable, as there are no independent data to confirm the development costs of individual drugs. There is no evidence that pharmaceutical firms misreported their costs in the CSDD surveys. But critics have argued that firms may be motivated to collectively exaggerate their costs in order to support lobbying efforts for pharmaceutical subsidies and patent protection (Light and Warburton, 2005; Love, 2003).

To our knowledge, there is only one published empirical estimate of the cost of drug development that does not use these CSDD data. Adams and Brantner (2010) estimated drug development costs between 1989 and 2001 by decomposing the R&D expenditures of 183 publicly traded firms against clinical trial data for those firms. The study used annual R&D expenditure data reported in firms' audited public filings, and firm-level drug development data reported in Pharmaprojects, a proprietary database that summarizes industry press releases and direct correspondence with the firms. By regressing each firms' annual R&D expenditures on the number of drugs under

development, Adams and Brantner estimated the uncapitalized annual costs of clinical trials to be \$17 million for Phase I, \$34 million for Phase II, and \$27 million for Phase III (1999 dollars). Using phase durations and success probabilities estimated from Pharmaprojects data, Adams and Brantner estimated the capitalized costs at \$1.2 billion per approved drug, even higher than the CSDD estimate of \$802 million.

Adams and Brantner (2010) address many of the concerns with the CSDD results by using an independent, publicly verifiable source of expenditure data for a large number of firms. But the study still has a number of limitations. To match part of the time period of CSDD's data, they used data that are more than a decade old. This time period also prevented the use of official FDA data on clinical trials, as the FDA did not maintain such a database until 2005. They also excluded Phase IV costs. By necessity, Adams and Brantner obtained drug development data from a proprietary database, based on industry reports that may be incomplete -- particularly for smaller firms that do not issue press releases. Relatively few regressions were tested, none of which leveraged the panel structure of the data. Finally, some of their results simply lack face validity; for instance, their estimated Phase I costs are not significantly different from zero. Our study produces more up-to-date estimates of clinical trial costs and attempts to produce more accurate estimates by addressing many of the Adams and Brantner (2010) study's limitations, while adopting their general decomposition strategy.

We believe that our estimates can yield a number of benefits. Cost estimates help firms set realistic expectations for pharmaceutical R&D budgets. Estimates of the costs of clinical trials also help set appropriate budgets for government- and foundation-funded R&D initiatives, such as those of the National Institute of Allergy and Infectious Diseases

(NIAID), the Biomedical Advanced Research and Development Authority (BARDA), and the Malaria Vaccine Initiative (Matheny, Mair, and Smith, 2008). Estimates help multilaterals establish appropriate sizes and structures for R&D incentives, such as Advanced Market Commitments and Priority Review Vouchers (Berndt et al., 2007; Ridley, Grabowski, and Moe, 2006; Matheny et al., 2009). And reliable estimates of the costs of clinical trials can allow researchers to perform cost-effectiveness analysis of pharmaceutical R&D in priority-setting exercises, such as the Disease Control Priorities Project (Mahmoud et al., 2006). A recurring question in such exercises is whether the cost of pharmaceutical development is justified, given potentially cheaper public health interventions. But such judgments depend on having a reliable account of pharmaceutical development costs.

While there are few estimates of the costs of clinical trials, to our knowledge there are no estimates of the costs of a clinical trial subject, or how these costs vary by trial size and duration. Reliable estimates of clinical trial subject costs would have their own benefits. The regulatory process for drug approval is a difficult balancing act. Increasing the size of clinical trials increases statistical power and thus improves the inferences that regulatory bodies can make about a drug's estimated safety and efficacy. At the same time, increasing the size of clinical trials presumably increases their costs and increases the aggregate risks to human subjects who participate. A regulator trying to determine the optimal size (and length) of a clinical trial would require a careful accounting of the costs, benefits, and risks. At the same time, recent developments in clinical trial design could significantly affect the costs of recruiting and managing clinical trial subjects through all phases. In "adaptive" designs, preliminary trial results are used to adjust the

size, duration, and/or structure of a trial while it is active. Several studies have outlined the potential advantages of adaptive clinical trials in reducing clinical trial size and length, thus reducing subjects' exposure to risk (Chow and Corey, 2011; Kairalla, et al., 2012; Chow and Chang, 2008). Adaptive designs have been chosen to be a key part of FDA's Critical Path Initiative – a U.S. effort to improve the speed and efficiency of drug development. However, without estimates of clinical trial subject costs, no study appears to have quantified the potential economic benefits of adaptive designs – or even more conventional tradeoffs of trial size and risk.

Research Methods

We estimate the costs of clinical trials by decomposing firms' public annual R&D expenditures against FDA clinical trial data associated with those firms. This approach allows us to use only publicly available data and to draw upon both a large and comprehensive set of diverse firms and clinical trials. In the section below, we first describe the COMPUSTAT database for annual R&D expenditures and the FDA's ClinicalTrial.gov database for clinical trials. We then describe our empirical methods for decomposing these annual R&D expenditures.

Data

Although pharmaceutical firms do not release information on the costs of individual clinical trials, the U.S. Securities and Exchange Commission (SEC) requires publicly traded firms to submit public filings on their finances, including their sales and their R&D expenditures. These filings are subject to SEC audits and public review. We obtain

filings data from the COMPUSTAT Fundamentals Annual database. COMPUSTAT is a database of corporate financial data dating back to 1950, maintained by McGraw-Hill Companies. (In COMPUSTAT, pharmaceutical firms' annual R&D expenditures and sales are coded XRD and SALE, respectively.) We obtain all the available data for years 2006 through 2010 for firms with the industry code for pharmaceuticals (i.e., NAICS 325412). (We begin with year 2006 due to the availability of the clinical trials data we merge to these COMPUSTAT data.) Data for subsidiaries are merged with those of their parent companies. For example, "Abbott Diagnostics" and "Abbott Vascular" are merged under "Abbott." The financial data are adjusted to 2010 U.S. dollars using the Consumer Price Index (USBLS, 2012). (We discuss the limitations associated with using only publicly-traded companies in our conclusion section, though we note that the COMPUSTAT data are not limited to firms based in the U.S.)

We obtain clinical trial data from the FDA's ClinicalTrials.gov database. Registration of clinical trials in ClinicalTrials.gov has been required by the International Committee of Medical Journal Editors since September 2005 (Laine, Horton, DeAngelis, et al., 2007) and by the Food and Drug Administration Amendments Act (PL 110-95), since 2007. The database includes over 130,000 clinical trials registered since the year 2005. As of January 2013, ClinicalTrials.gov had over 19,000 citations in PubMed, and multiple studies have documented its accuracy, timeliness, and representativeness (Zarin, et al., 2011; Califf, et al., 2012).

We extract all of the clinical trial data from interventional studies by industry in Phase I, II, III, or IV, that were active at some point between January 1, 2006 and December 31, 2010. We obtain data on the sponsoring firm, intervention class

(categorized as drug, vaccine, or other), start date, primary completion date, phase, and number of subjects enrolled. We then aggregate these data by the firm-year for our subsequent merge with the COMPUSTAT data; for each firm-year, the number of trials and number of subjects are totaled by phase and by intervention class.

We then merge the COMPUSTAT data to the clinical trial data by firm name and year. Naming conventions vary across ClinicalTrials.gov and COMPUSTAT. For instance, ClinicalTrials.gov names “Pfizer” while COMPUSTAT names “Pfizer Inc”. Firm names are therefore fuzzy-matched to an 80% substring match.¹ The resulting candidates are then manually matched.

Methods

Our first set of empirical models examines the cost per clinical trial, while our second set of models examines the cost per clinical trial subject.

Cost per clinical trial

Clinical trial costs are estimated by regressing firms’ annual R&D expenditures against firms’ numbers of clinical trials. This approach estimates the average annual marginal cost of a clinical trial. Importantly, R&D expenditures include not only the costs of clinical trials, but also the preclinical R&D expenditures – drug discovery, *in vitro* studies, and (nonhuman) animal tests. Preclinical R&D spending is a source of unexplained heterogeneity in Adams and Brantner (2010). Assuming that annual

¹ Fuzzy matching, also known as approximate string matching, is a technique for matching expressions that are similar but not identical. In our case, we generated candidates for manual matching from cases where a substring in one database (e.g., “Pfizer” is a substring of “Pfizer Inc.”) had at least 80% of the same characters as a substring in another database.

preclinical spending varies across firms but does not vary significantly within firms across the five-year period, a fixed-effects model is appropriate. Assuming preclinical spending is uncorrelated with development spending, a random-effects model is appropriate. We test both assumptions using the Hausman specification test.

We estimate the following four main specifications using an ordinary least squares regression:

$$y_{jt} = \alpha + \beta n_{jt} + \varepsilon_{jt} \quad (\text{Model 1})$$

$$y_{jt} = \alpha + \sum_{c=1}^3 (\beta_c n_{cjt}) + \varepsilon_{jt} \quad (\text{Model 2})$$

$$y_{jt} = \alpha + \sum_{i=1}^4 (\beta_i n_{ijt}) + \varepsilon_{jt} \quad (\text{Model 3})$$

$$y_{jt} = \alpha + \sum_{c=1}^3 \sum_{i=1}^4 (\beta_{ci} n_{cijt}) + \varepsilon_{jt} \quad (\text{Model 4})$$

In these models, y_{jt} is the R&D expenditure of firm j in year t ; α is the intercept; β is the estimate of the annual marginal cost per trial, for intervention class c (if applicable) in phase i (if applicable); and n is the number of relevant trials in effect for a given firm in a given year. Compared to Model 1, Model 2 examines these three classes separately: drugs, vaccines, and other.² Compared to Models 1 and 2, Models 3 and 4 use separate counts of the Phase I, II, III, and IV trials. For each of these four models, we examine models replacing the intercept term with both firm-level random effects and fixed effects. We also examine models using the log of the number of relevant trials (restricted to firms with a non-zero number of trials).

Using the coefficients from these decomposition models, we then calculate the expected cost per clinical trial as:

² The “other” class includes non-vaccine biologics, medical devices, procedures, radiation therapy, behavior modification, and dietary supplements.

$$\hat{c}_i = \bar{t}_i \hat{\beta}_i \quad (\text{Eq. 1})$$

where \bar{t}_i is the mean phase length for phase i in years, and $\hat{\beta}$ is the coefficient estimating the annual phase cost. Standard errors for \hat{c} are calculated (assuming uncorrelated errors between t and β) as:

$$SE_{t,\beta} = \sqrt{\bar{t}^2 SE_{\beta}^2 + \hat{\beta}^2 SE_t^2} \quad (\text{Eq. 2})$$

The expected clinical development cost per approved product is calculated as:

$$\hat{C} = \frac{\sum_{i=1}^3 p_i \hat{c}_i}{p_a} \quad (\text{Eq. 3})$$

where p_i is a Phase $i-1$ candidate's probability of reaching phase i , and p_a is a Phase III candidate's probability of receiving FDA approval. Transition probabilities and mean phase lengths are obtained from Davis et al. (2011), based on a sample of 4,235 drugs and vaccines. Note that the cost of clinical development does not include Phase IV costs, which are post-development costs incurred after marketing.

Because drug development can take a decade or longer, the choice of discount rate affects the estimates of capitalized costs considerably. By funding drug development, a pharmaceutical firm ties up large amounts of capital over many years. The opportunity cost is the profit that could have been obtained by the firm, had it invested that capital in some other profitable activity, such as the stock market. The discount rate is thus assumed to equal the rate of return for investments of similar risk. The variance of pharmaceutical profits has historically corresponded to the variance observed in stocks with an 11% (real) rate of return (DiMasi and Grabowski, 2007). Here we also assume an 11% discount rate, consistent with past models (DiMasi, Hansen, and Grabowski, 2003;

Adams and Brantner, 2006), but we also produce results assuming a 5% discount rate.

The expected capitalized cost per approved product is calculated as:

$$\hat{C}^* = \frac{\sum_{i=1}^3 p_i \hat{c}_i e^{rt_i}}{p_a} \quad (\text{Eq. 4})$$

where r is the discount rate.

Cost per clinical trial subject

Because the FDA's ClinicalTrials.gov database provides detailed information on the number of human subject enrolled in each trial phase, we are also able to estimate the costs of clinical trials per subject.

We examine the four models described above, where Model 2 (relative to Model 1) again examines these three classes separately, and Models 3 and 4 (relative to Models 1 and 2) again use separate counts of the Phase I, II, III, and IV trials. As before, we estimate an OLS regression using the firms' annual R&D expenditures as the dependent variable, while we now use the firm-level data on the number of clinical trial subjects as the explanatory variables. This approach estimates the annual marginal cost of a clinical trial per subject. As before, we also estimate fixed-effects and random-effects models to see how preclinical spending varied across firms and test them using the Hausman specification test.

Due to the higher risk of an untested product in a Phase I trial, initial manufacturing startup costs, monitoring costs, and the impossibility of healthy subjects receiving a medical benefit, one would expect per-subject costs to be highest in Phase I. If costs decrease with the level of prior testing, and if there are diminishing marginal

costs in the number of subjects, one would expect costs to strictly decrease in each subsequent phase. We therefore test the hypothesis that per-subject annual costs strictly decrease from Phase I to Phase IV for Models 3 and 4:

$$H1_1: 0 > \beta_2 > \beta_3 > \beta_4 \quad (H1_0: 0 \leq \beta_2 \text{ or } \beta_2 \leq \beta_3 \text{ or } \beta_3 \leq \beta_4)$$

One would also expect economies of scale in study administration and recruitment. We therefore additionally examine the following fifth empirical model to test the hypothesis that firms have diminishing marginal costs in trial subjects:

$$y_{jt} = \alpha + \beta_1 \sum_{k=1}^{K_{jt}} n_{jkt} + \beta_2 \left(\sum_{k=1}^{K_{jt}} n_{jkt} \right)^2 + \varepsilon_{jt} \quad (\text{Model 5})$$

$$H2_1: \beta_1 > 0 \text{ and } \beta_2 < 0 \quad (H2_0: \beta_1 \leq 0 \text{ or } \beta_2 \geq 0)$$

Results

Data summary

Table 1 shows the number of firm-years, clinical trial-years and clinical subject-years, broken down across both the different classes (e.g., drug, vaccine, other) and the different Phases I through IV. The matched dataset includes 189 firms, 573 firm-years, 11,145 clinical trial-years, and 4,153,155 clinical subject-years. 312 firms are listed in COMPUSTAT as having industry code NAICS 325412. 123 of these firms could not be matched to entries in ClinicalTrials.gov during 2006-2010. These firms may not have conducted clinical trials during the period. Alternatively, they may have conducted clinical trials under a different legal name. The unmatched firms had average R&D spending of \$116 million (2010 dollars), and average sales of \$649 million (2010 dollars). In contrast, the matched firms had average R&D spending of \$716 million and

average sales of \$3.06 billion (2010 dollars). The unmatched firms are thus much smaller, on average, and may have included more biotechnology companies that perform only nonclinical research.

[Table 1 here]

Table 2 shows the distribution of firm-level annual R&D costs across the 573 firm-years. The sample of firms is diverse, ranging in size from small biotechnology companies with no sales and/or no R&D expenditures, to large multinational pharmaceutical companies with billions of dollars in sales and/or R&D expenditures.

[Table 2 here]

Cost per trial

Table 3 presents the results for the clinical trial cost regressions using the number of relevant clinical trials as the independent variable. A minimal OLS model regressing research costs on the number of clinical trial years yields an average trial-year cost of \$30.54 million (Model 1). Disaggregating product types improves the model's r-squared but yields coefficients not significantly different from zero (Models 2 and 4).

Disaggregating phases yields estimates for all phases significantly different from zero, with the mean annual marginal cost per Phase I trial at \$19.93 million, Phase II trial at \$24.23 million, Phase III at \$44.88 million, and Phase IV at \$35.18 million (Model 3).³

³ In results not shown, we used a variable for annual sales as an explanatory variable for R&D expenditures to examine whether these merged data produced results consistent with findings for R&D intensity from the

[Table 3 here]

A Hausman test indicates that a random-effects model is appropriate, due to the low correlation between the regressors and the firm-level effects. However, the random-effects models for Models 3 and 4 still yield insignificant and negative coefficients. Fixed effects also generates poor results (Appendix Table 1). Using the logarithm of trial-years does not improve estimates for any model, suggesting that there are not diminishing marginal costs in the number of trials that firms manage (Appendix Table 1).

Table 4 shows our estimates for the mean cost per clinical trial using the results from Model 3. The point estimate for the mean cost is calculated from Equation 1 above, while the standard error is calculated from Equation 2 above. The mean cost per Phase I trial (in 2010 dollars) is \$47.6 million; the mean cost per Phase II trial is \$81.9 million; and the mean cost per Phase III trial is \$141 million. All estimates are significantly different from zero at the 0.05 level.

[Table 4 here]

Per Equation 3, we obtain an estimate of \$600 million for the expected clinical development cost for one FDA-approved drug. Per Equation 4, applying a cost of capital at a real discount rate of 11%, the expected capitalized clinical cost of developing one

Congressional Budget Office (2006). Doing so improved the r-squared and produced a coefficient on sales of 0.1 which was statistically significant. This implies that every \$1 increase in sales is associated with a mean \$0.10 increase in R&D expenditures, which is consistent with the CBO's review of past research in the range of 8% to 10% (CBO, 2006).

approved drug is \$1.21 billion. Applying a cost of capital at a real discount rate of 5%, the expected capitalized cost of developing one approved drug is \$818 million.

Cost per clinical trial subject

Table 5 presents our results for clinical trial subject costs. A minimal OLS model regressing annual research expenditures on the number of clinical subject-years yields an annual marginal cost per subject of \$56,000 (i.e., Model 1). Disaggregating products (i.e., Model 2) improves the r-squared (relative to Model 1) and yields estimates for all classes significantly different from zero. We find that the annual marginal cost per subject is \$89,600 for drugs, \$9,500 for vaccines, and \$123,000 for other products.

Disaggregating phases (i.e., Model 3) improves the r-squared (relative to Model 1) and yields estimates for Phases I, II, and III significantly different from zero. Specifically, we find that the annual marginal cost per subject across all products is \$489,900 for Phase I, \$303,100 for Phase II, and \$12,400 for Phase III. Phase IV subject costs are not significantly different from zero. Disaggregating product classes and phases together (i.e., Model 4) yields some insignificant and negative coefficients. A Hausman test indicates that a random-effects model is justified, due to the low correlation between the regressors and the firm-level effects. However, neither the random effects model nor the fixed effects model improves fit.

We test $H1_0$ using a Wald test for the results from Model 3 and obtain $F(1,567)=8.03$, $p>F=0.0048$, rejecting the null. Costs appear to be strictly decreasing with each phase. We test $H2_0$ using a Wald test for the results from Model 5 and obtain $F(1,570)=754$, $p>F=0.000$, rejecting the null. Firms appear to experience diminishing marginal

costs with the number of subjects, but the cost savings are very small -- less than a 0.001% decrease in marginal costs for every 1% increase in trial size.

[Table 5 here]

Discussion

Our estimates for clinical trial costs are comparable to past estimates, shown in Table 6. The estimates from the Tufts University's CSDD data are that Phase I, Phase II, and Phase III clinical trial costs are \$15.2, \$23.5, and \$86.3 million in 2000 dollars, respectively (DiMasi, Hansen, and Grabowski, 2003). Adjusting their costs for inflation (USBLS, 2012), and dividing their phase costs by their phase lengths from the CSDD data (1.83, 2.17, and 2.17 years, respectively) yields clinical trial costs of \$10.5, \$13.8, and \$50.5 million per year in 2010 dollars. Adams and Brantner (2010) estimate these annual costs as \$16.8, \$33.6, and \$26.8 million in 1999 dollars; adjusting for inflation yields clinical trial costs of \$22.0, \$44.0, and \$35.1 million per year in 2010 dollars. Our estimates of \$19.9, \$24.2, and \$44.9 million per year are thus intermediate between CSDD and Adams and Brantner. Our study has potential advantages over both, including the use of more recent, official FDA data. But the broad conclusions are the same -- namely, that clinical trials are a highly costly undertaking.

[Table 6 here]

Our results do not include estimates of preclinical research. However, our model intercepts can be interpreted as the average annual fixed costs of preclinical research, plus the average annual fixed costs of supporting clinical trials. From our results for Model 3, these fixed costs are \$122 million per year per firm, on average, representing 18% of average annual R&D costs. In contrast, CSDD estimates preclinical research costs, alone, are 30% of annual R&D costs in their sample of firms (DiMasi, Hansen, and Grabowski, 2003).

To our knowledge, no previous study has estimated the cost per clinical trial subject, so we are unable to compare our results to others. However, our results are consistent with expectations: per-subject costs progressively decrease from Phase I to Phase IV, as the risks to subjects decrease, requirements for intensive monitoring decrease, and potential benefits to subjects increase. By Phase IV, marginal per-subject costs are not significantly different from zero. (Phase IV fixed costs are captured in the model intercept.) Our results also suggest that firms enjoy diminishing marginal costs in trial size, perhaps due to economies of scale in trial administration. We are unable to compare subject costs across product classes, though the descriptive statistics indicate that vaccine trials are significantly larger than other trials (Table 1).

Our results suggest that clinical trial costs could be significantly reduced by decreasing clinical trial size and/or length, particularly in Phases I and II. Our study makes no claims about whether these cost savings are worth the potential risks to the quality of trial results. Adaptive trial designs remain controversial, and the FDA's "Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics"

remains in draft form after three years. Nevertheless, our figures can help inform an accounting of the costs and benefits of trial designs.

Caveats

All of our estimates are based on a decomposition of firm-level R&D spending. While this allows us to use public data, the approach has a number of potential weaknesses. First, the start and end dates of clinical trials rarely coincide with the start and end dates of fiscal years used for financial reporting. This does not bias estimates as long as clinical trial dates are uniformly distributed; however, the misalignment of data reduces the precision of our estimates.

Second, much of the heterogeneity in R&D costs may be due to preclinical R&D. While pharmaceutical companies are required to submit data on clinical trials to a public FDA database, there is no comparable requirement or database for preclinical R&D activities. The poor results from our panel models suggest that, while there may be firm-level differences in preclinical R&D, those differences may not be systematic. Alternatively, the poor results may be due to the highly unbalanced panel dataset, which ranges from one to five COMPUSTAT observations per firm. An unbalanced panel is one in which observations are missing for some individuals for some time periods. If many observations are missing, this can reduce the precision of the firm-level intercept, as there are fewer data to explain variance. If missing observations are due to a nonrandom process, then the estimates can also be biased. In our case, there is no evidence of bias in COMPUSTAT – the missing years appear to be years in which the firm was not publicly traded.

A third limitation to our study is that our models rely on expenditure data from public filings that are required only for publicly traded firms. Our sample is thus likely to be biased toward larger, more established pharmaceutical firms. Table 2 indicates that our sample does include small firms – but they may still be unrepresentative of private companies, for which we have no expenditure data.

Fourth, our models do not account for joint ventures by multiple firms. As a result, the models may misattribute R&D effort from supporting firms to the single firm that took primary responsibility for managing a clinical trial. This should reduce the precision of our estimates rather than biasing them.

Despite these caveats, our clinical trial cost estimates are comparable to previous estimates by CSDD and Adams and Brantner. That three different estimates, each based on different data and modeling assumptions, produce similar clinical development costs lends credence to the results. Claims that the “\$802 million” figure is an exaggeration by pharmaceutical firms (Light and Warburton, 2005) appear increasingly unlikely. Clinical development is an extremely costly enterprise, and a realistic assessment of these costs is needed to set appropriate budgets for R&D investments, and to estimate their cost-effectiveness relative to other health interventions.

Future research

Future research could focus on estimating clinical trial costs by product type. A few studies have reported expert opinions on vaccine development costs (e.g., U.S. Department of Defense, 2001). But to our knowledge no study has empirically estimated these costs. Although the development of vaccines bears similarities to the development

of other pharmaceuticals, vaccines face unique technical and economic challenges due to pathogen evolution, a narrow preclinical research pipeline, and additional regulatory requirements, such as certification of vaccine manufacturing processes prior to clinical approval (Coleman et al. 2005; Offit 2005). As such, the costs of vaccine R&D may differ in important respects from those of drugs. Few pharmaceutical companies develop vaccines, and our dataset had insufficient observations to separately estimate the costs of vaccine development. Additional years of data, including financial data manually obtained from firms' annual reports, might allow estimation in the future.

Future research could also quantitatively compare the risks and benefits of smaller trials. For instance, the economic cost of achieving a particular statistical power in a clinical trial could be compared to the expected number of disability-adjusted life years averted, given a prior probability for adverse outcomes that would be detected in a larger trial. Such an analysis could help inform debates over clinical trial designs.

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Table 1: Matched observations by phase and product class

	Phase I	Phase II	Phase III	Phase IV	Total
<i>Trial-years by phase and product class</i>					
All	3,483	2,870	3,333	1,459	11,145
Drugs	3,207	2,430	2,717	1,248	9,602
Vaccines	95	272	394	74	835
Other	181	168	222	137	708
<i>Subject-years by phase and product class</i>					
All	166,616	560,588	2,651,898	774,053	4,153,155
Drugs	140,810	401,481	1,743,329	496,112	2,781,732
Vaccines	16,836	131,331	748,201	204,516	1,100,884
Other	8,970	27,776	160,368	73,425	270,539
<i>Mean annual number of trials per firm</i>					
All	3.69	3.04	3.53	1.54	11.79
Drugs	3.39	2.57	2.88	1.32	10.16
Vaccines	0.10	0.29	0.42	0.08	0.88
Other	0.19	0.18	0.23	0.14	0.75
<i>Mean number of subjects per trial</i>					
All	48	195	796	531	1,569
Drugs	44	165	642	398	1,248
Vaccines	177	483	1,899	2,764	5,323
Other	50	165	722	536	1,473

Table 2: Firm annual Research and Development (R&D) costs and sales (\$M, 2010)

	R&D costs	Sales
N	573	573
Mean	716	3,060
Standard deviation	1,897	10,697
Minimum	0	0
25 th percentile	15	0
Median	40	2
75 th percentile	161	134
Maximum	10,991	67,691

Table 3: Model results for estimated clinical trial costs per year (2010 \$M)

Model	1	2	3	4	3, with Random effects	4, with Random effects
All Trials	30.54** (0.94)					
All Drugs		20.67** (1.18)				
All Vaccines		-7.04 (4.87)				
All Other		6.62 (11.63)				
All Phase I			19.93** (3.48)		4.06* (2.07)	
All Phase II			24.23* (10.78)		29.35** (7.29)	
All Phase III			44.88** (9.38)		7.04 (5.65)	
All Phase IV			35.18** (13.56)		10.17 (8.57)	
Drug Phase I				14.02** (3.75)		3.93 (2.33)
Drug Phase II				68.53** (14.25)		25.00** (10.39)
Drug Phase III				45.92** (9.67)		12.15 (6.82)
Drug Phase IV				22.41 (14.35)		9.00 (10.18)
Vaccine Phase I				107.87 (79.15)		73.44 (44.31)
Vaccine Phase II				-18.28 (44.58)		33.49 (26.65)
Vaccine Phase III				-41.84 (28.40)		7.37 (18.24)
Vaccine Phase IV				66.83 (121.91)		-49.76 (69.59)
Other Phase I				53.65 (47.78)		-5.99 (28.43)
Other Phase II				95.39 (59.60)		74.17** (32.85)
Other Phase III				126.43** (42.61)		80.79** (30.56)
Other Phase IV				-101.93 (82.60)		-2.55 (52.58)
Constant	121.51* (50.80)	60.64 (34.02)	122.43* (50.60)	21.28 (50.45)	371.76** (87.97)	340.14** (85.68)
Observations	573	573	573	573	573	573
R ²	0.64	0.84	0.65	0.69	0.64	0.63

* Statistically different from zero at the 0.05 level; ** at the 0.01 level. Standard errors are in parentheses.

Table 4: Clinical trial costs, lengths, and success probabilities

	Cost per trial-year (2010 \$M)	Phase length (years)	Probability of succeeding in phase	Cost per trial (2010 \$M)
Phase I	19.9 (3.48)	2.39 (0.07)	0.83 (0.02)	47.6 (8.43)
Phase II	24.2 (10.8)	3.38 (0.07)	0.56 (0.02)	81.9 (36.5)
Phase III	44.9 (9.38)	3.15 (0.07)	0.65 (0.02)	141.0 (29.7)

Standard errors are in parentheses.

Table 5: Model results for estimated annual marginal cost per subject (2010 \$M)

Model	1	2	3	4	3 with Random Effects	4 with Random Effects	5
All Trials	0.0560** (0.0020)						.1252396** (.0045589)
All Trials^2							-4.73e-07** (2.88e-08)
All Drugs		0.0896** (0.0038)					
All Vaccines		0.0095* (0.0045)					
All Other		0.1230** (0.0188)					
All Phase I			0.4899** (0.0770)		0.1339** (0.0441)		
All Phase II			0.3031** (0.0348)		0.0855** (0.0182)		
All Phase III			0.0124* (0.0057)		0.0088** (0.0030)		
All Phase IV			0.0042 (0.0091)		0.0071 (0.0044)		
Drug Phase I				0.2586** (0.0840)		0.1185* (0.0554)	
Drug Phase II				0.5357** (0.0479)		0.1676** (0.0293)	
Drug Phase III				0.0249** (0.0083)		0.0107 (0.0057)	
Drug Phase IV				0.0159 (0.0147)		0.0186* (0.0088)	
Vaccine Phase I				0.9420* (0.392)		0.8402** (0.2307)	
Vaccine Phase II				0.0122 (0.0549)		0.0505 (0.0334)	
Vaccine Phase III				-0.0049 (0.0064)		0.0189** (0.0051)	
Vaccine Phase IV				-0.0190 (0.010)		-0.0078 (0.0061)	
Other Phase I				1.6831* (0.691)		0.3506 (0.4375)	
Other Phase II				-0.0368 (0.118)		-0.1809** (0.0680)	
Other Phase III				0.1167** (0.022)		0.0205 (0.0134)	
Other Phase IV				0.0960** (0.034)		0.0665** (0.0202)	
Constant	304.91** (56.49)	204.19** (51.58)	213.01** (52.67)	100.03* (46.56)	421.18** (89.49)	354.56** (79.22)	115.28** (47.99)
Observations	573	573	573	573	573	573	573
R ²	0.53	0.62	0.61	0.71	0.60	0.62	0.68

* Statistically different from zero at 0.05 level; ** at 0.01 level. Standard errors are in parentheses.

Table 6: Comparing annual clinical trial cost estimates (2010 \$M)

	CSDD (2003)	Adams and Brantner (2010)	Our estimates
Phase I	10.5	22.0	19.9
Phase II	13.8	44.0	24.2
Phase III	50.5	35.1	44.9
Phase IV	--	--	35.2

Table 7: Model results for estimated clinical trial costs per year (2010 \$M)

Model	3 with Fixed effects	4 with Fixed effects	1 with Log Number	2 with Log Number	3 with Log Number	3 with Log Number & Random effects	3 with Log Number & Fixed effects
All Trials			893.52** (39.42)				
All Drugs				2000.61** (326.11)			
All Vaccines				-133.74 (243.92)			
All Other				200.71 (367.33)			
All Phase I	-3.20 (1.78)				311.52* (145.20)	114.25 (114.15)	-135.10 (102.86)
All Phase II	-0.97 (6.49)				728.93* (293.56)	551.76* (263.18)	-174.08 (258.34)
All Phase III	-7.47 (4.79)				685.28** (252.26)	614.54** (225.19)	-205.54 (242.89)
All Phase IV	12.50 (7.22)				503.46* (213.95)	429.86* (197.08)	246.12 (193.45)
Drug Phase I		-1.93 (1.94)					
Drug Phase II		-7.78 (8.83)					
Drug Phase III		-0.78 (5.71)					
Drug Phase IV		9.00 (8.48)					
Vaccine Phase I		-2.06 (36.88)					
Vaccine Phase II		-12.66 (22.83)					
Vaccine Phase III		3.70 (15.35)					
Vaccine Phase IV		-110.73 (56.98)					
Other Phase I		-39.96 (23.19)					
Other Phase II		13.71 (26.84)					
Other Phase III		50.20 (25.50)					
Other Phase IV		-4.16 (44.11)					
Constant	751.46** (33.07)	751.77** (35.23)	- 652.77** (83.40)	-3415.65** (783.07)	-1861.56** (362.20)	-912.84 (468.79)	3908.85** (766.09)
Observations	573	573	573	573	573	111	111
R ²	0.43	0.26	0.47	0.47	0.71	0.71	0.46

* Statistically different from zero at 0.05 level; ** at 0.01 level. Standard errors are in parentheses.

MANUSCRIPT 2

**Determinants of Pharmaceutical Availability:
The Case of the Orphan Drug Act**

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Abstract

In 1983, the United States enacted the Orphan Drug Act (ODA) to encourage the development of drugs against “orphan diseases” – diseases with a prevalence less than 200,000 cases in the United States. The ODA is widely considered to be a success: in the United States from 1983 to 2010, the number of drugs with orphan indications increased from 38 to 353. However, the increase may have been due to causes other than the ODA, and may not have translated into an increase in orphan drug use. To illustrate the intended incentives from the ODA, we adapt Salop’s spatial market model to develop an economic model of drug prescriptions. We test our model’s predictions using a regression discontinuity design and data from the U.S. National Ambulatory Medical Care Surveys for the years 1985, 1996, and 2006. We do not find evidence of a significant discontinuity in drug prescriptions as the disease prevalence approaches 200,000 cases. One possible explanation for our empirical finding is a perverse effect of the ODA: it encourages firms to charge monopoly prices for existing products. A price increase could cause a sufficient decrease in prescriptions for existing orphan drugs, and that effect could negate any increase in prescriptions for new orphan drugs.

Introduction

A range of policies have aimed to increase the availability of pharmaceuticals in order to achieve public health objectives. These include the Orphan Drug Act (ODA), which provides incentives to firms that introduce products for rare diseases; FDA's Priority Review Program, which accelerates the review of new products deemed important to public health; and the Hatch-Waxman Act, which increases a product's patent life by recovering the time spent during FDA reviews. But there is little empirical evidence on the drivers of, and barriers to, pharmaceutical availability. Pharmaceutical availability may be influenced by a number of variables, including those related to target disease characteristics, product characteristics, regulatory factors, and firm characteristics (Figure 1). Below we describe these variables and the (generally scant) empirical literature on their effects.

[Figure 1 here]

Disease characteristics

Disease characteristics can influence both product characteristics and regulatory factors. They include disease prevalence, disease research, known targets, whether the disease is chronic or acute, and affected global regions. Prevalence may influence regulatory risk-benefit tolerance, FDA review type (e.g., Priority Review), market exclusivity (e.g., "orphan" designation), a product's expected market size, the market's willingness-to-pay, and clinical trial recruitment costs. Lichtenberg and Waldfogel (2003) found that disease prevalence was positively correlated with the number of drugs prescribed for that disease.

Prevalence may also affect the volume of published research on a disease, which can in turn affect the number of drug targets. Ward and Dranove (1995) and Toole (2000) found that NIH funding on diseases was positively correlated with private R&D spending.

Product characteristics

Product characteristics that may influence pharmaceutical availability, either directly or indirectly through regulatory factors, include drug class, drug targets, product novelty, market size, and willingness-to-pay. Pharmaceutical classes such as vaccines, antibacterials, and antivirals may vary in R&D costs due to distinct technical challenges, as well as differences in regulatory treatment; for instance, biologics undergo a different review process from small molecules, and because vaccines are given to healthy individuals, there may be less risk tolerance during their review. DiMasi et al. (1995), DiMasi, Grabowski, and Vernon (2004), and Adams and Brantner (2006) found that costs and risks varied significantly across classes and targets. Product novelty may affect both the level of technical challenge, as well as regulatory treatment. Reiffen and Ward (2005) found that the R&D costs of imitative generics are significantly lower than that of novel products.

Walker (2002) reported the reasons for terminating development of new products among 28 pharmaceutical manufacturers, estimating that 20% of terminations were due to clinical safety issues, 23% were due to disappointing clinical efficacy results, 16% were due to various other factors, and 22% were based on “portfolio considerations.”

Expected returns for a product can influence a firm’s level of R&D effort. Grabowski and Vernon (2000) and Vernon (2005) found that expected returns explained

much of the variation in pharmaceutical firms' R&D expenditures. Similarly, Scherer (2001) found that R&D investments were correlated with profitability, Giaccotto et al. (2003) found that at the industry level, R&D expenditures were associated with prices, while Acemoglu and Linn (2004), Lichtenberg (2005) and Civan and Maloney (2006) found that the likelihood of developing a pharmaceutical was positively associated with its expected market size.

Regulatory factors

Regulatory factors that may influence development success include patent and market exclusivity; review type; clinical trial size, duration, and location; FDA staffing; and whether efficacy is determined by testing against a competing therapy or against a placebo. The Prescription Drug User Fee Act requires that, with few exceptions, drug developers pay a fee to the federal government to help cover FDA's review costs. The Internal Revenue Code's Research and Experimentation Tax Credit provides a 50% subsidy for eligible preclinical Research and Development (R&D) costs; clinical trial costs are typically disallowed. Orphan designation confers to a developer tax credits for clinical trials, as well as seven-year market exclusivity on a licensed product. Evidence regarding the effects of orphan designation is described in detail below. Priority Review shortens the FDA review period by several months. Clinical trial size, duration, and location may be determined both by product and disease characteristics, and in turn influence R&D costs. FDA staffing levels can influence the duration of review, which affects discounted costs and the net present value of returns. A product proved effective

compared to a placebo can be more or less technically challenging to develop than a product proved effective compared to a competing therapy.

Firm characteristics

Firm characteristics that may affect pharmaceutical availability include firm size, R&D salaries, R&D management, funding sources, the cost of capital, and the R&D technologies the firm employs. Larger firms may have economies or diseconomies of scale in R&D. DiMasi, Grabowski, and Vernon (1995) and Henderson and Cockburn (1996) found that average R&D costs tended to correlate with firm size. R&D salaries can influence the level of funding available for product development. The type of R&D management employed (e.g. contract research or “virtual pharma”) may influence costs. Firms attracting public versus private funding may be more or less efficient. A firm’s cost of capital influences the rate of return it will tolerate in product development. Some technologies used in R&D, such as high-throughput screening, may affect R&D costs.

Product development partnerships (PDPs) may lower R&D costs by outsourcing R&D to the lowest-cost developers, without regard for potential intellectual property violations or trade secret piracy. However, PDPs may have higher failure rates if their managers face less incentive to terminate dead-end candidates (Munos, 2006; Grace, 2006).

The Congressional Budget Office (2006) hypothesized that the historical growth in pharmaceutical R&D costs could be due to increasing clinical trial sizes and durations, comparisons to existing treatments rather than placebos, R&D salaries, a shift from acute to chronic diseases, and FDA staffing. However, these potential associations were not

measured by CBO. The Government Accountability Office (GAO) (2006) found that industry experts cited several of these factors as important determinants of R&D costs.

The ODA represents a unique lens through which to examine the determinants of pharmaceutical R&D. Probably no policy has been more strongly focused on increasing the availability of a class of pharmaceuticals than the ODA, and no policy has influenced more determinants simultaneously – market exclusivity, FDA staffing, tax credits, PDUFA waivers, and R&D funding. Below we describe the history of the ODA and evidence regarding its effects on pharmaceutical availability.

The Orphan Drug Act

In 1983, the United States enacted the Orphan Drug Act (ODA) to encourage the development of drugs against “orphan diseases” – diseases for which there is “no reasonable expectation” that sales could support a drug’s development. The ODA was amended in 1984 to define “orphan diseases” as those with prevalence less than 200,000 cases in the United States. There are over 7,000 such diseases, and they represent a major health burden, affecting over 25 million people in North America, alone (Braun et al., 2010).

The ODA provides a number of benefits to sponsors that develop a drug for an orphan disease: a 50% tax credit on clinical trial expenses, a waiver of user fees charged under the Prescription Drug User Fee Act (PDUFA), development grants, counseling and guidance from the U.S. Food and Drug Administration (FDA), and a seven-year market exclusivity period for its drug if ultimately approved. The exclusivity period is potentially the most valuable to a firm: if a market competitor wishes to introduce a drug for the

same indication, the competitor must prove that its drug is therapeutically superior to the incumbent. While the ODA was intended to boost drug development, its benefits apply not only to new drugs, but also to drugs that have already been marketed, and even those whose patents have expired.

The FDA's Office of Orphan Products Development (OOPD) is responsible for reviewing requests for orphan designation. To qualify for designation, a sponsor must provide evidence that a product is "promising" for the treatment or prevention of a disease, and demonstrate that the prevalence of the disease is less than 200,000 in the United States. If a product meets these two criteria, the product is "designated" for the disease. At that point, the sponsor is qualified to receive the all of the benefits authorized by the ODA, with the exception of market exclusivity. Market exclusivity can be awarded only after a product has received FDA approval for marketing, following an FDA review of the product's safety and efficacy (Thorat et al., 2012).

The prevalence criterion is critical to orphan designation, and prevalence must be based on verifiable data. According to OOPD staff, "Sponsors do their due diligence to provide credible prevalence data in their application packages. This information is crucial to determining whether or not the disease of interest is a rare one. The sources of prevalence figures include authoritative references that may include published journal articles, government and patient support group Web sites, and so forth. . . . The prevalence estimate must also be current in relationship to the time of submission of the request for orphan drug designation. These are then verified by OOPD review staff" (Thorat et al., 2012).

The ODA is widely considered to be a success (Arno, Bonuck, and Davis, 1995; Grabowski 2005), and similar orphan legislation has been enacted in Singapore (1991), Japan (1993), Australia (1997), and the European Union (1999) (Braun et al., 2010). Empirical evidence for the effect of the ODA remains equivocal, however. Here we briefly review the evidence for and against the ODA's effects on drug research, development, introductions, and prescriptions.

Two studies estimated the effect of the ODA on orphan drug R&D. Heemstra et al. (2009) measured the number of medical publications on rare diseases over time. From the period 1976-1983 to the period 2000-2007, the average number of publications per rare disease increased from 330 to 1,319. However, this increase was not significantly different from the increase in medical publications, as a whole, over the same period. Heemstra et al. concluded that the ODA did not significantly affect research on orphan diseases – at least as measured in publication rates. In contrast, Yin (2008) found that following the ODA, the number of clinical trials for rare diseases was 69% greater than the number of clinical trials one would have expected, based on a set of matched clinical trials for control diseases with prevalence above 200,000. However, Yin's choice of control diseases was nonrandom and these diseases may have differed in important ways from rare diseases. For instance, diseases with higher prevalence may be more difficult targets for pharmaceuticals. (A Bayesian argument is that one should downwardly update the probability of success against prevalent diseases -- if prevalent diseases were easy to treat, they would not be prevalent.)

The evidence for the ODA's effects on drug introductions is more suggestive. In the United States from 1983 to 2010, the number of orphan drug introductions increased

from 38 to 353 (FDA, 2013). Improvements in drug discovery, clinical trial design, and drug review increased the introduction of new drugs, overall. However, even the share of orphan drugs increased. Orphan drug approvals increased as a fraction of all drug approvals, from 17% in 1984-1988, to 31% in 2004-2008 (Cote et al. 2010). Still, the ODA may not have been the only reason for the observed increase in orphan drug introductions.

Even if the ODA increased the introduction of orphan drugs, the ODA may not have affected the treatment of orphan diseases. Drugs that are already approved for non-orphan diseases can be prescribed “off-label” for orphan diseases. The effect of the ODA on prescriptions for orphan diseases could thus be muted by physicians’ judgments about existing treatment options. Indeed, after the ODA passed, many orphan designations simply “caught up” with existing treatment options: pharmaceutical companies obtained orphan indications for drugs that had already been approved and, in many cases, already prescribed for orphan diseases. Grabowski (2005) estimated that from 1983 to 2002, more than half of the drugs approved for orphan indications were already approved for other indications. Even new orphan drugs may not have affected prescription behavior if they were not perceived to be of sufficient quality or affordability.

The strongest evidence for a positive effect of the ODA on prescriptions comes from Lichtenberg and Waldfogel (2003). Using U.S. medical survey data from 1979 (pre-ODA) and 1998 (post-ODA), they regressed the differences between the two surveys in the rates of *any* drug prescriptions for a disease, on the differences in disease prevalence and the rates of *orphan drug* prescriptions. They concluded that the ODA increased the probability of having *any* drug prescribed from 5% to 6%. Although this difference-in-

difference model controls for unobserved heterogeneity that may have affected prescription rates at a single point in time, it assumes that the only relevant exogenous change between the two surveys was the introduction of the ODA. This is possible, but it is also quite plausible that other changes over the 19-year period may have affected the relationship between disease prevalence and drug prescriptions.

Whether the ODA has had positive effects, and whether these effects have been clinically significant, is a question that remains relevant today. The apparent success of the ODA has inspired efforts to amend the ODA to cover additional diseases (Villa, Compagni, and Reich, 2009). And even sustaining the ODA carries significant potential costs and risks. Because of the ODA's market exclusivity clause, orphan drugs face significantly less competition from generic products, causing higher prescription costs (Seoane-Vazquez et al., 2008). The ODA's tax credit and user fee waiver are a cause of lost federal income: the user fee waiver costs the FDA more than \$1 million per product (Braun et al., 2010), and ODA-related tax credits have cost over \$400 million per year (Yin, 2008). In addition, safety problems have disproportionately affected orphan drugs since the ODA passed, attributed to the favorable regulatory treatment and the small, nonrandomized trial designs commonly used after the ODA (Kesselheim, 2011). For example, alglucerase, a treatment for a rare congenital enzyme deficiency, was approved for orphan designation after a one-year trial with twelve patients (Kesselheim, 2011).

Therefore it remains important to evaluate the benefits of the ODA, and how these benefits might compare to its potential costs. In addition, the ODA is one of only a few U.S. policies that use supply-side subsidies to stimulate R&D (Yin, 2008). Tests of the ODA's effects may thus be of broader significance to policy efforts aimed at stimulating

innovation. In the remainder of this paper, we begin by outlining a simple economic model of pharmaceutical availability. We then test this model’s predictions using prescription data from clinical visits in the United States.

An economic model of pharmaceutical availability

We derive a model of pharmaceutical availability from Salop’s (1979) spatial market model. Like Yin (2008), we conceive of “locations” that are associated with the benefits obtained from a pharmaceutical. If we assume that physicians are responsible agents for their patients, a physician prescribes drug i to maximize the patient’s utility:

$$\max_i [U(l_i, l^*) - p_{it}] \geq s \quad (\text{Eq. 1})$$

where l_i is the actual “location” of a drug in pharmacokinetic space, l^* is the optimal “location” of the drug for treating the patient, p_i is the price of the drug i at time t , and s is the patient’s surplus. The distance between l_i and l^* is a measure of the efficacy and safety of the drug. At distance zero, the drug provides maximum benefit to the patient. At some maximum distance, the drug has no benefit for the patient, and will not be prescribed. Equation (1) can be rewritten as

$$\max_i [v - c|l_i - l^*| - p_{it}] \geq 0 \quad (\text{Eq. 2})$$

where c is the “transport cost” in using a drug that is not perfectly indicated for the patient and v is the resulting utility-based “willingness to pay” for the drug. This “transport cost” could be the cost of inefficacy and/or the cost of side effects. The maximum distance of a drug to a patient is

$$x = \max [l_i - l^*] \quad (\text{Eq. 3})$$

Physicians will not prescribe drugs that exceed x distance from l^* . If no drug exists within this distance, then no drug will be prescribed. Combining Equations (2) and (3) we get

$$x = \frac{v - p_{it}}{c} \quad (\text{Eq. 4})$$

The prevalence, θ , of a disease can be thought of as the “density” of patients in this pharmacokinetic space. Additionally, we use the terminology $i=0$ here and below to denote an instance when no drug exists (i.e., a drug company has not invested adequate R&D costs to produce the drug), and we use $i \neq 0$ to denote an instance when a drug does exist. When a drug exists, the total number of drug prescriptions, Q , for patients is then:

$$Q = \theta(|l^* - x| + |l^* + x|) = 2x\theta, \text{ for } i \neq 0 \quad (\text{Eq. 5})$$

Substituting Equation (4) into Equation (5), we get

$$Q = \frac{2\theta}{c}(v - p_{it}), \text{ for } i \neq 0 \quad (\text{Eq. 6})$$

Equation (6) therefore represents the quantity of drugs that will be prescribed *if* a drug exists within this pharmacokinetic space. This quantity is higher when the prevalence θ is higher, when the inefficacy and/or side effects are lower (i.e., c is smaller), when the “willingness to pay” v is higher, and when the price p_{it} is lower. If a drug does not exist within this space, then the quantity is simply zero.

For time periods t after a drug’s exclusivity has expired, the manufacturer will face the competitive price p_c , equaling marginal cost, m :

$$p_c = m \quad (\text{Eq. 7})$$

For time periods t prior to a drug’s exclusivity expiring, exclusivity allows a monopoly price p_m , equal to:

$$p_m = m/(1 + \eta) \quad (\text{Eq. 8})$$

where η is the inverse of the price elasticity of demand.

Let N equal the average effective period of exclusivity in the absence of orphan designation. (In the case of a typical New Chemical Entity, $N=5$.) Manufacturers of drugs with disease prevalence greater than or equal to 200,000 cases will therefore receive p_m for years $t=1$ through $t=N$ and then receive p_c for years $t=N+1$ onward. The ODA increases this period of exclusivity from N years to 7 years for manufacturers of drugs with disease prevalence less than 200,000 cases. As a result, these orphan drug manufacturers will receive p_m for years $t=1$ through $t=7$ and then receive p_c for year $t=8$ onward.

Substituting Equation (7) for the monopoly price and Equation (8) for the competitive price into Equation (6) gives the following expression for the total number of prescription drugs:

$$Q = \begin{cases} 0 & , \text{ for } i(\theta)=0 \quad (\text{Eq. 9}) \\ \sum_{t=1}^7 \delta^t \frac{2\theta}{c} (v - m/(1 + \eta)) + \sum_{t=8}^{\infty} \delta^t \frac{2\theta}{c} (v - m) & , \text{ for } i(\theta) \neq 0 \text{ and } \theta < 200,000 \\ \sum_{t=1}^N \delta^t \frac{2\theta}{c} (v - m/(1 + \eta)) + \sum_{t=N+1}^{\infty} \delta^t \frac{2\theta}{c} (v - m) & , \text{ for } i(\theta) \neq 0 \text{ and } \theta \geq 200,000 \end{cases}$$

where we have now altered the expression for whether a drug exists ($i \neq 0$) or does not exist ($i = 0$) to instead be $i(\theta)$ to clarify that the existence of the drug is determined by

whether the ODA is in effect and whether the prevalence θ is below or above the 200,000 prevalence threshold.

The number of prescriptions is thus generally increasing in prevalence, but with a potential discontinuity at $\theta=200,000$. Interestingly, though, whether the number of prescriptions Q increases or decreases as the prevalence crosses the 200,000 threshold is actually ambiguous.

For the “extensive” margin for whether a drug is developed (and thus able to be consumed), being just underneath the ODA’s 200,000 prevalence threshold has a positive effect on the quantity Q , as the increase in potential monopoly profits has an unambiguous effect on increasing the likelihood that a new drug is developed. Most advocates for the ODA seemingly focus on this extensive margin regarding drug development.

However, for the “intensive” margin for the number of prescriptions for existing drugs (which would have been developed in the absence of the ODA’s new incentives), being just underneath the ODA’s 200,000 prevalence threshold actually has a negative effect on the quantity Q . That is, the higher monopoly price for years $N+1$ through 7 (i.e., the price is p_m rather than p_c) implies a lower number of drug prescriptions during those years. Moreover, the magnitude of this marginal reduction in quantity depends on the extent to which the demand for the drug is elastic. (To our knowledge, this potentially perverse effect of the ODA does not appear to have been described elsewhere.)

Our theoretical model therefore predicts one of three possibilities. One is a positive discontinuity on quantity of prescription drugs as the prevalence passes below the 200,000 threshold; this would result from the consumption of newly-developed drugs

outweighing the reduced consumption of higher-priced existing drugs. The second is a negative discontinuity on quantity as the prevalence passes below the 200,000 threshold; this would result from reduced consumption of higher-priced existing drugs outweighing the consumption of newly-developed drugs. The third is no discontinuity at the 200,000 prevalence threshold; this would result from the consumption of newly-developed drugs equaling the reduced consumption of higher-priced existing drugs. Our empirical strategy is to therefore test for the presence (and, if applicable, the direction) of this discontinuity, which can in turn help us evaluate the overall effect of the ODA.

Research Methods

We test whether there is a discontinuity in drug prescriptions for conditions with prevalence above and below 200,000 cases. In particular, we measure how many drug prescriptions were made for each ICD9 per year, as a function of prevalence for that ICD9, and we test for the presence of a discontinuity at a prevalence of 200,000 cases. In contrast to prior research on the effect of the ODA, we employ a regression discontinuity design that approaches the unbiasedness of a true experiment. This design also allows us to infer whether the ODA increased the availability of drugs, as reflected in the prescription of drugs located an acceptable “distance” from the patient.

Data

We examine prescription patterns for the years 1985, 1996, and 2006 – a period that covers a time shortly after the ODA’s passage, to more than 10 years after its passage, to more than 20 years after its passage. Diagnosis codes and drug prescription codes were

obtained from the National Ambulatory Medical Care Surveys (NAMCS) for the years 1985, 1996, and 2006. The NAMCS collect data on patient visits to a national sample of office-based physicians. The sample includes office visits to non-federally employed physicians classified by the American Medical Association or the American Osteopathic Association as “office-based, patient care” from 112 Primary Sampling Units in the United States.

We used the following NAMCS records from each office visit: the physician’s diagnoses (classified by ICD9 codes), any drugs prescribed, and the sampling weight. For each ICD9 diagnosis, we estimated the U.S. disease prevalence by multiplying survey diagnosis counts by survey sampling weights. Likewise, for each prescription in the sample, we estimated U.S. drug prescription counts by multiplying survey drug counts by the survey sampling weight associated with the entry.

Methods

Equation (9) above suggests that the number of drug prescriptions for a disease is generally an increasing function of disease prevalence. Lichtenberg and Waldfogel (2003) found this assumption to hold true for drug prescriptions, as a whole. If the ODA has positively affected drug prescriptions for rare diseases, we should observe a larger-than-expected number of prescriptions as prevalence decreases just below the threshold of 200,000 cases. That is, the ODA should introduce a discontinuity in the relationship between disease prevalence and drug prescriptions (Figure 2).

[Figure 2 here]

The presence of such a discontinuity can be tested using a regression discontinuity design (RDD). RDD is an econometric technique used in cases where assignment to one of two groups is determined by position above or below a threshold on a single continuous variable -- in this case, disease prevalence. Two lines are fit to data within a small distance of both sides of the threshold, and the effect of assignment is the difference between the two lines' intercepts. Observations at small distances above or below the threshold are unlikely to be systematically different, except for their (exogenous) assignment to one of the two groups – in this case, orphan drug designation. Thus their assignment is effectively random, and RDD approaches the unbiasedness of a true experiment (Lee and Lemieux, 2010).

Following the RDD approach, the numbers of drug prescriptions were estimated in the non-parametric local linear regression:

$$Q = \alpha + \beta_1 1[\theta < 200] + \beta_2 (\theta - 200) + \beta_3 1[\theta < 200] * (\theta - 200) + \varepsilon \quad (\text{Eq. 10})$$

where $1[\theta < 200]$ is the indicator function for prevalence less than 200,000 cases, and where $200-h \leq \theta \leq 200+h$. The optimal bandwidth, h , was determined by the cross-validation criterion:

$$h = \arg \min_h \frac{1}{N_h} \sum_{a=1}^{N_h} (Q_a - \widehat{Q}(\theta)) \quad (\text{Eq. 11})$$

where \widehat{Q} is the estimated number of drug prescriptions as a function of prevalence for a given bandwidth, and N is the number of observations captured in that bandwidth (Imbens and Lemieux, 2008). For ease of implementing the RDD, we used a nonparametric regression rather than an alternative model of utilization counts using a

Poisson or negative binomial. All coding and analyses were performed in Stata 10. (The Stata .do file is available online at www.jgmatheny.org.)

Results

Data summary

Table 1 lists the sample size, number of unique diagnoses, and number of drug prescriptions observed in each NAMCS. The 1985 survey was three times the size of the 1996 and 2006 surveys. As a result, the diversity of diagnoses and prescriptions was substantially larger.

[Table 1 here]

Figure 3 plots the total annual number of drug prescriptions against disease prevalence. The top, middle, and bottom panels show results for 1985, 1996, and 2006, respectively. All plots show an increasing trend in prescriptions as a function of prevalence.

[Figure 3 here]

Regression discontinuity estimates

Table 2 lists the regression discontinuity estimates for prescriptions as a function of prevalence. The estimates represent the effects of orphan designation – the differences between the right- and left-hand vertical intercepts on the prevalence threshold of

200,000 cases. The table presents the estimates and standard errors for the effect of orphan designation on the number of drug prescriptions. The three columns show the results for the different years. In all three instances, the estimates are not significantly different from zero. That is, for all three years, there is no significant discontinuity in the number of drug prescriptions for a disease, as a function of prevalence. Moreover, the point estimates are relatively small in magnitude, suggesting that our insignificant results are mainly driven by small underlying magnitudes rather than by large estimated standard errors. For instance, in 1996, the point estimate for the effect of the discontinuity at the 200,000 prevalence threshold on the number of drug prescriptions is only 2,480, compared to a predicted value of 161,052 prescriptions for a prevalence of 200,000.

[Table 2 here]

Discussion

The absence of regression discontinuities in 1985, 1996, and 2006 suggests that the ODA did not affect the rates of drug prescriptions for rare diseases. This result is not inconsistent with most of the prior research we cited above. The strongest evidence for the ODA's effects has been the number of orphan drugs developed and marketed (Cote et al., 2010; Yin, 2008). But as we demonstrated in our theoretical model, an increase in the number of orphan drugs marketed does not necessarily imply an increase in the overall number of orphan drug prescriptions. Regardless, an increase in the number of orphan drugs prescribed over time could be due to causes other than the ODA.

Our results contradict only one study's findings – Lichtenberg and Waldfogel (2003). They found a statistically significant but small (one percentage point) effect of the ODA on orphan drug prescriptions. The differences in our results might be explained by the different assumptions in our empirical strategies. The weakest assumption in their strategy is that exogenous changes during the 19-year study period were due only to the ODA. Over such a long period, it seems likely that changes in income, treatment-seeking behavior, and clinical practice could have significantly affected the relationship between disease prevalence and drug prescriptions.

In contrast, the weakest assumption of our strategy is the relevance of prevalence estimates from NAMCS. This assumption is shared by Lichtenberg and Waldfogel, but our models may be more sensitive to the assumption. Like Lichtenberg and Waldfogel, we matched prevalence data with prescription data of the same year. It typically takes several years for a pharmaceutical to move from the beginning of clinical trials to marketing approval. Thus the prevalence data supporting a drug's orphan designation are typically several years older than the drug's prescription data. If disease prevalence changed significantly over this time, the time-lag would blur any threshold in our sample. However, Yin (2008) found that this was not the case in his study. In a sample of 1,177 diseases studied from 1981 to 1994, U.S. disease prevalence estimates changed significantly for only six diseases. This suggests that our contemporaneously matched data are unlikely to mask a threshold.

Another concern regarding our prevalence data is that they may not be representative of the data used in orphan-designation. Developers applying for orphan designation are responsible for providing FDA with evidence that the target disease has a

prevalence less than 200,000. Developers may thus be motivated to develop drugs for a disease with a prevalence marginally above 200,000 if they can find corroborating prevalence studies, however suspect or outdated. Such behavior would have the effect of increasing the right-side intercept on the RDD threshold, decreasing the apparent effect of the ODA. Without access to confidential orphan drug applications to FDA, this is difficult to test.

A possible explanation for our results is that market exclusivity has had a perverse effect on orphan drug price, quality, and consumption. One perverse effect was mentioned as a feature of our economic model above: the monopolist's increase in the price decreases the number of prescriptions for the drug, and the magnitude of this decrease in consumption depends on the price elasticity of demand for an orphan drug. Most drugs receiving orphan designation were actually already on the market (Grabowski, 2005). The introduction of monopoly prices for these existing products could have decreased consumption sufficiently to balance any increase in consumption resulting from the introduction of new orphan drugs. The dual effects of increasing the prices of existing products while increasing the number of new products could neutralize any impact of the ODA, positive or negative, on orphan drug prescriptions.

Another perverse effect of the ODA is deterrence of late entrants. While the ODA provisions reward early-entry firms for introducing new orphan drugs, they deter late-entry firms. Firms may be unable to prove the superiority of a product in a small clinical trial (as efficacy trials for rare diseases necessarily are), and the ODA provides no reward for reducing cost. As a result, the total number of drugs for a condition may rarely exceed one, and quality may be only marginally better than off-label drugs.

It is also possible that the ODA had clinically significant effects by increasing the quality, rather than the quantity, of prescribed drugs. Physicians may be motivated to prescribe an ineffective drug in the absence of an effective one. (In our model, such physicians would be prescribing drugs that exceed a distance of x from the patient.) The psychology of such a practice seems realistic -- physicians may feel compelled to do something rather than nothing, and patients may prefer the same. Such practice would tend to inflate prescription behavior for rare diseases, masking the effect of orphan-designation. The main effect of the ODA could have been a substitution of effective drugs for ineffective drugs. Further research could test this effect, by examining regression discontinuities in health outcomes for diseases by prevalence.

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Figure 1: Conceptual framework for pharmaceutical availability

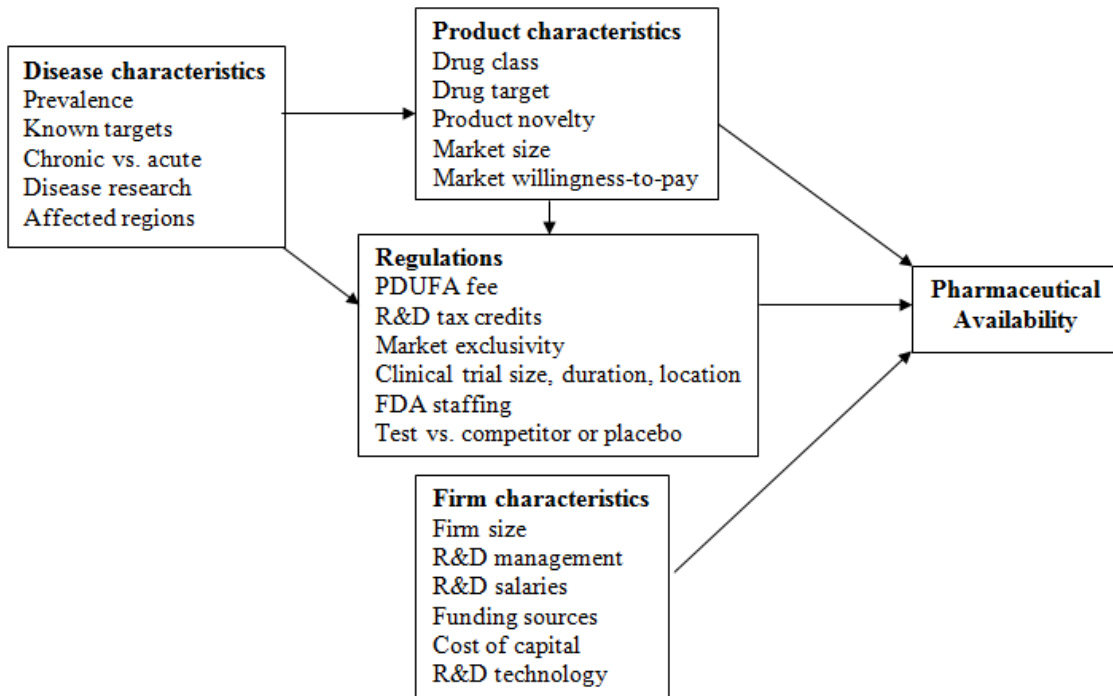


Figure 2. Hypothetical discontinuity in drug prescriptions (thousands per year) as a function of prevalence (thousands of cases per year)

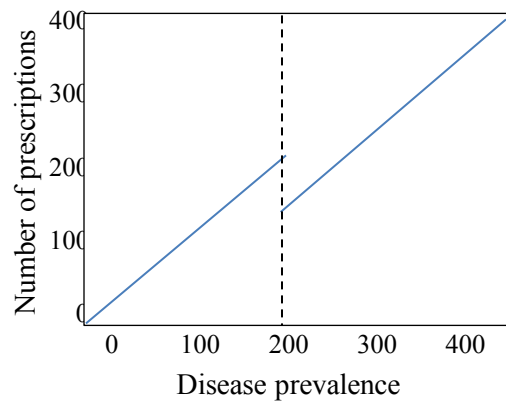
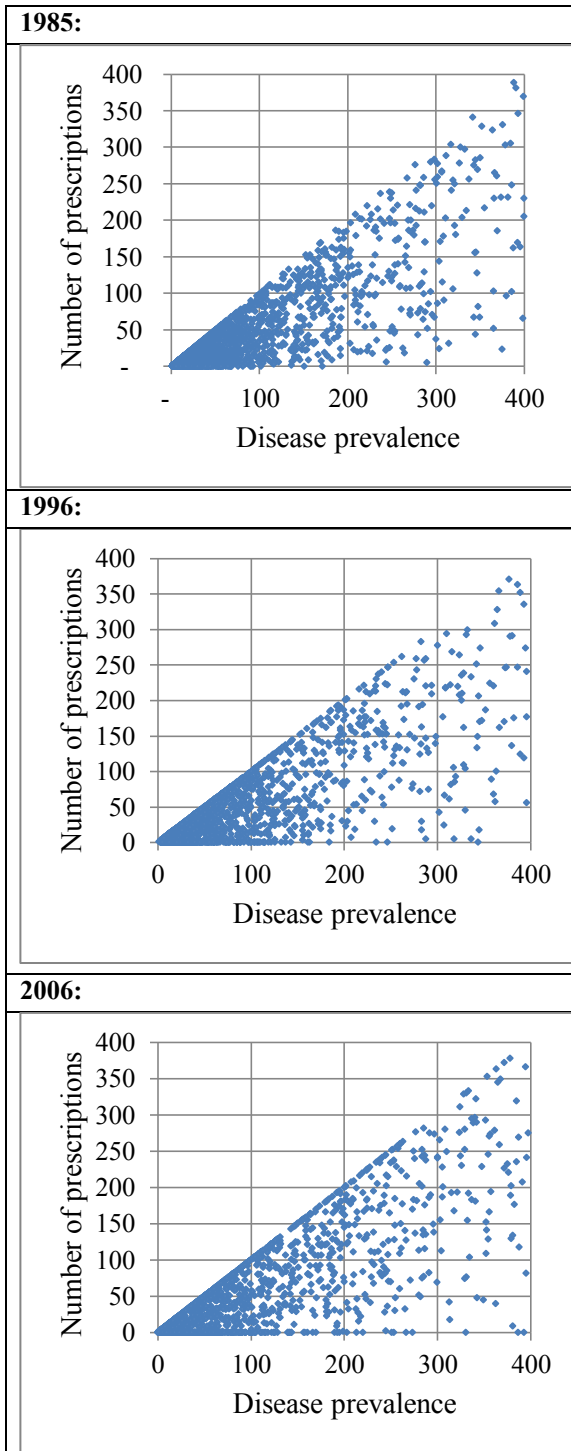


Figure 3. Scatter plots of numbers of drug prescriptions (thousands per year) by disease prevalence (thousands of cases per year).



Note: Based on diagnosis and prescription data in the National Ambulatory Medical Care Surveys (NAMCS) for the years 1985, 1996, and 2006. Prescription data and prevalence data were matched by ICD9 code. Every point represents a unique ICD9 code. For clarity, figures are centered on disease prevalence of 200,000 cases.

Table 1: Cases and numbers of unique diagnoses and prescribed drugs

	1985	1996	2006
Cases with a diagnosis	71,281	24,956	23,088
Unique ICD9 diagnosis codes	3,234	2,196	2,280
Unique Drug IDs	1,642	1,099	834

Note: Based on ICD9 case counts and drug prescriptions from the National Ambulatory Medical Care Surveys (NAMCS) for the years 1985, 1996, and 2006.

Table 2: Regression discontinuity estimates

	1985	1996	2006
Number of drug prescriptions			
RD point estimate	-15.43	2.48	27.71
RD standard error	22.40	31.66	25.75

Note: Point estimates in thousands. Estimates based on diagnosis and prescription data in the National Ambulatory Medical Care Surveys (NAMCS) for the years 1985, 1996, and 2006. Prescription data and prevalence data were matched by IC9 code. The numbers of matched observations were 3,234, 2,196, and 2,280 for the years 1985, 1996, and 2006, respectively.

MANUSCRIPT 3

**A Portfolio Model of the
Public Health Emergency Medical Countermeasure Enterprise**

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Abstract

The U.S. Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) has defined a set of requirements for drugs and vaccines to protect civilians against biological threats. We survey candidate PHEMCE products in development and estimate their future clinical development costs based on historical costs and failure rates. We estimate that the cost of supporting existing candidates through clinical development is likely to be \$428 million in fiscal year 2014 alone. Given the high failure rate of biopharmaceutical development, the probability of developing approved products from the existing pipeline is between 0% and 90% per requirement. To increase the probability to 90% for all requirements, a significantly expanded portfolio would be needed, with an expected clinical development cost of \$9.8 billion over ten years.

Introduction

In 2006, the Pandemic and All-Hazards Preparedness Act (PAHPA, PL 109-417) was signed into law, creating the Biomedical Advanced Research and Development Authority (BARDA) within the U.S. Department of Health and Human Services (HHS). One of BARDA's core missions, as defined by PAHPA, is to promote the clinical development of drugs and vaccines effective against chemical, biological, radiological, and nuclear (CBRN) threats to the United States. BARDA was intended to bridge the "valley of death" between National Institute of Allergy and Infectious Diseases (NIAID) funding for research and preclinical development, and federal procurement of developed products via the BioShield program that was established by law in 2004 (P.L. 108-276) (Figure 1).

[Figure 1 here]

In the April 2007 Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) Implementation Plan (USDHHS, 2007), HHS defined requirements for pharmaceuticals that address CBRN "Material Threats" – threats assessed by the US Department of Homeland Security to pose a significant risk to US citizens. Since 2007, pharmaceuticals addressing the PHEMCE requirements are eligible to receive funding from BARDA for clinical development. The President's fiscal year 2014 (FY14) budget includes \$415 million for BARDA. However, to our knowledge, no empirical analysis has been performed to determine whether this budget is sufficient to accomplish BARDA's mission.

To analyze BARDA's current budget's capabilities, we first survey the pipeline of candidates in or entering clinical development that could be responsive to the eight PHEMCE requirements addressing infectious diseases (Box 1), updating earlier surveys by Matheny, Mair, and Smith (2008, 2009). We then apply recent estimates of pharmaceutical development costs (Matheny and Herring, 2013) to calculate the level of funding needed to support this pipeline through clinical development. Using historical failure rates of pharmaceutical development, we estimate the size and cost of a portfolio that could yield a 70%, 80%, and 90% probability of at least one FDA-approved product per PHEMCE requirement.

We conclude by exploring one possible approach to reducing PHEMCE requirement costs: reducing the size and/or lengths of BARDA-funded clinical trials. The size and lengths of clinical trials are typically chosen to achieve a level of statistical power for assessing the safety and efficacy of candidate products. However, PHEMCE products are an unusual case, as they are intended to be used only during a public health emergency. During a declared emergency, the FDA has the authority to issue "Emergency Use Authorizations" (EUAs) to deploy products that have not met the usual requirements for regulatory review. P.L. 108-276 states: "the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by such agents, when there are no adequate, approved and available alternatives." While EUAs place the public at some risk, the public would arguably be at greater risk if they had no access to products during an emergency. The same argument could be used to justify smaller clinical trials, if it is a choice between products tested in

small trials, versus no products, whatsoever. We therefore explore the consequences of smaller trials for costs and statistical power.

Data and Methods

As noted above, our methodological approach is to first identify the set of candidates currently in clinical development that are likely to respond to the PHEMCE requirements for infectious diseases. We then calculate the level of funding needed to support this current pipeline through clinical development and estimate the probability that this current portfolio yields at least one FDA-approved product. We then calculate the level of funding needed to support alternative pipelines with higher probabilities of yielding at least one FDA-approved product. We conclude by also examining the consequences of reducing the number of clinical trial participants.

PHEMCE requirements are based on the PHEMCE Implementation Plan (USDHHS, 2007), reiterated in the 2012 PHEMCE Strategy (USDHHS, 2012). (See Box 1.) Our analysis includes only pharmaceutical requirements for infectious diseases, which form the majority of PHEMCE requirements, and excludes pharmaceuticals for radiological, nuclear, or chemical agents, as well as diagnostics and biodosimetry assays.

[Box 1 here]

There is no single database of pharmaceutical candidates that could meet PHEMCE requirements. We identify candidates by drawing upon five sources of information: (1) FDA's ClinicalTrials.gov database (FDA, 2012), using searches for the

appropriate targets (e.g., “smallpox”, “junin”); (2) HHS’ MedicalCountermeasures.gov contract database (HHS, 2012); (3) National Institute of Allergy and Infectious Diseases (NIAID) reports (NIAID, 2012); (4) pharmaceutical and biotechnology companies’ press releases and quarterly and/or annual reports; and (5) discussions with biopharmaceutical managers and HHS staff. The resulting list of pharmaceutical candidates we compile excludes products that are already under an HHS BioShield procurement contract, as these are ineligible for BARDA funding.

We base the clinical development costs on recent empirical estimates from public data for over 2,000 clinical trials during the years 2006 to 2010 (Matheny and Herring, 2013). These costs are assumed to remain constant at 2010 levels. Annual clinical trial costs are assumed to be equal across product classes (antibiotics, antivirals, vaccines, and antitoxins). Transition probabilities and durations are based on historical averages (Davis et al., 2011), separated into two classes: small molecule drugs (antibiotics and antivirals) and biologics (vaccines and antibodies).

We assume that our cost estimates from a wide range of product classes are comparable to those costs for drugs in the PHEMCE portfolio. Most PHEMCE requirements address infectious diseases that present a potential risk to human health but currently have a prevalence of zero. For instance, there are currently no human cases of smallpox. Without human patients already suffering from such diseases, and given the significant risks to subjects who might volunteer to be infected under experimental conditions, candidate products for PHEMCE requirements cannot be evaluated for efficacy on human patients. While a product’s safety is still assessed using human patients, its efficacy is evaluated using non-human animals. The FDA’s Animal Efficacy

Rule provides guidance for using animal models as replacements for traditional efficacy tests (Gronvall, Trent, Borio, et al., 2007). While one might expect this Rule to reduce clinical trials costs, typical Phase II and Phase III trials employ the same human patients for both safety and efficacy tests, so the removal of efficacy tests is unlikely to reduce trial size. In fact, BARDA-funded candidates currently in Phase II trials involve a larger than average number of human subjects. (There are no BARDA-funded candidates in Phase III trials.)

We also assume that candidate products are at the midpoint of their current phase of preclinical or clinical development. As each phase has a mean duration over two years, we assume that for FY14, all candidates would remain in their current phase for the remainder of the fiscal year.

FY14 costs of clinical development for existing candidates are calculated by multiplying the number of candidates in each clinical phase by the respective annual cost per FY14 phase. The cost of supporting clinical development for all existing candidates up to failure or approval is calculated as:

$$C = \sum_{i=0}^3 N_i \left(\prod_{j=i+1}^3 \Pr(j) c_j t_j + \frac{1}{2} c_i t_i \right) \quad (\text{Eq. 1})$$

where N_i is the number of candidates at phase i (“phase 0” is preclinical), $\Pr(j)$ is the probability of transitioning from phase $j-1$ to phase j , c_j is the annual cost per trial in phase j , and t_j is the duration of phase j in years. The probability of at least one approved product per PHEMCE requirement is calculated as:

$$\Pr(\text{Approval} \geq 1) = 1 - \prod_{i=0}^3 (1 - \Pr(\text{Approval} | i))^{N_i} \quad (\text{Eq. 2})$$

where $\Pr(\text{Approval} | i)$ is the conditional probability of a candidate at phase i receiving FDA approval.

In addition to reporting the cost and success probability of the current PHEMCE portfolio, we also use Equations (1) and (2) to analyze alternative portfolios. Specifically, we use Equation (2) to first estimate three alternative number of candidates N_i^* in order for $\Pr(\text{Approval} \geq I)^*$ to equal to 70%, 80%, and 90%. We then determine the corresponding costs C^* for each of these three alternative N_i^* values using Equation (1).

We conclude by analyzing the implications of reducing the number of participants in clinical trial sizes – specifically focusing on the reduction in overall costs of development and on the reduced likelihood of detecting adverse events. Regarding the costs of development, we estimate the cost savings of reducing clinical trial sizes by using an alternative specification for clinical trial costs based on the number of clinical trial subjects:

$$C = \sum_{i=0}^3 N_i \left(\prod_{j=i+1}^3 \Pr(j) (k_j + n_j c_j t_j) + \frac{1}{2} (k_i + n_i c_i t_i) \right) \quad (\text{Eq. 3})$$

where n_j is the number of subjects in phase j , c_j is now the marginal cost per subject, and k_j is the fixed cost of a clinical trial; each of these estimates are from Matheny and Herring (2013).

Regarding the reduced likelihood of detecting adverse events, we estimate how reductions in clinical trial size would affect inferences about a product's safety, given observations of a control group and an experimental group. In particular, we estimate the statistical power of a one-sided t-test for $\alpha=0.05$:

$$\pi = 1 - \Phi(1.64 - D\sqrt{n_i}\sigma) > 0.90 \quad (\text{Eq. 4})$$

where n_i is the number of subjects in phase i , D is the expected difference in the adverse event rates between the control and experimental groups, σ is the standard deviation of the observed number of adverse events, and Φ is the normal cumulative distribution function. For illustration, we focus on the statistical power of a Phase II drug trial and assume a difference of 0.1 in adverse event rates and a standard deviation of 0.2.

Results

Our survey identified 32 candidates that could fulfill PHEMCE requirements (Table 1). Of these 32 candidates, 12 are now in preclinical development, 13 are in Phase I trials, and 7 are in Phase II trials.

[Table 1 here]

Given the assumptions described above for expected costs, timelines, and success rates (Table 2), we estimate that the direct (out-of-pocket) costs for the clinical development of all 32 existing candidates up to failure or approval would total \$4.2 billion over 10 years, comprised of \$1.6 billion towards antivirals and antibiotics and \$2.6 billion towards vaccines and antitoxins (Table 3). Costs for FY14, alone, would total \$428 million, comprised of \$152 million towards antivirals and antibiotics and \$276 million towards vaccines and antitoxins.

[Table 2 here]

[Table 3 here]

The probability of at least one approved product per PHEMCE requirement within the existing pipeline is 90% for an anthrax vaccine, 83% for an anthrax antitoxin, 64% for a filovirus vaccine, 77% for a filovirus antiviral, 26% for a Junin virus antiviral, 67% for a smallpox antiviral, 61% for a Gram(-) antibiotic, and 0% for a Gram(+) antibiotic (Table 4).

[Table 4 here]

To yield at least a 70% probability of one approved product for each of the eight PHEMCE requirements, the portfolio of preclinical candidates would need to expand by a total of 19 candidates (Table 5). There is relatively wide variation in the number of additional candidates needed across the requirements, with a value of zero for three of the requirements, up to 8 for a gram(-) broad spectrum antibiotic. Supporting the clinical development of these additional candidates up to failure or approval would cost approximately \$5.8 billion over 10 years for the 70% threshold, compared to the current portfolio's cost of \$4.2 billion with 5 of the 8 requirements under 70%. While the costs increase linearly with the number of candidates, the probability of success increases only logarithmically, as illustrated in Figures 2 and 3. Adding those costs to the clinical development costs of existing candidates, the clinical development costs for a portfolio large enough to have a 80% probability of yielding at least one approved product per PHEMCE requirement would be \$7.2 billion over 10 years (for an additional 35 candidates relative to the current portfolio), and the clinical development costs for a

portfolio large enough to pass the 90% probability for each PHEMCE requirement would be \$9.8 billion over 10 years (for an additional 64 candidates relative to the current portfolio).

[Table 5 here]

[Figure 2 here]

[Figure 3 here]

Finally, reducing clinical trial size would result in significant cost savings. While costs increase linearly with trial size, statistical power increases as a function of the square root of trial size. For instance, a 25% decrease in the size of a Phase II drug trial would decrease costs by \$12 million, while decreasing the probability of detecting an adverse event by only 8 percentage points (Figure 4).

[Figure 4 here]

It should be noted that these results assume the use of classical inference in estimating the rates of adverse events. Alternative trial designs have been proposed that use Bayesian inference. Such designs could reduce the number of subject-years with minimal effect on the probability of Type II errors (Chow and Chang, 2008; Kairalla, et al., 2012). However, such designs are rarely used due to uncertainties about their regulatory treatment.

Four caveats should be noted about our analysis. First, because our analysis assumes that clinical development will be funded by the U.S. government under BARDA, our cost estimates include only out-of-pocket costs. Capitalized costs would be significantly higher. (For instance, at the 11% rate typically used for pharmaceutical companies, the capitalized cost of \$5.6 billion over ten years would be \$15.9 billion; even at a 5% rate, the capitalized cost would be \$9.1 billion.) Second, our analysis underestimates the total level of funding needed to support BARDA, whose requirements include the development of diagnostics and biodosimetry assays, as well as pharmaceuticals for chemical, radiological, and nuclear agents. (However, these additional requirements are a minority of PHEMCE requirements.) Third, our cost estimates are for clinical development and do not include the costs of basic research, preclinical development, large-scale manufacturing, or stockpiling in the Strategic National Stockpile (SNS), which are not part of BARDA's advanced development mission, as defined by law. Fourth, our cost projections assume constant clinical trial costs at 2010 levels. There is some historical evidence of clinical trial costs increasing faster than inflation (DiMasi, Hansen, and Grabowski, 2003), but we are not aware of recent evidence.

Discussion

Our survey identified 32 products currently in preclinical development or clinical trials that could satisfy the eight requirements set by HHS in its PHEMCE Implementation Plan. To support these candidates through clinical development, BARDA would need an estimated \$428 million in fiscal year 2014 and a total of \$4.2 billion over 10 years. The

\$415 million requested in the President's FY14 budget is thus almost sufficient to cover existing candidates. However, because of the high failure rates in drug and vaccine development, the existing pipeline of candidates has a low probability of ultimately satisfying all of the government's requirements. Without additional candidates, it is unlikely that products will be approved for most of the PHEMCE requirements.

Supporting an expanded portfolio of candidates to yield with 90% probability one approved product per PHEMCE requirement would cost more than \$9.8 billion over 10 years.

With historic funding rates, it is unlikely that BARDA could support such a pipeline. HHS has several alternatives. First, it could consider exercising its Emergency Use authorities to employ products that have been approved using smaller clinical trials. Our results suggest that reducing clinical trial sizes would significantly reduce costs with relatively small losses in statistical power. HHS could also consider focusing its limited funds on the one or two agents believed to present the greatest risk to public health. Congress could provide BARDA with the authority to employ incentives, such as priority review vouchers, to supplement funding shortfalls in pharmaceutical development grants and contracts (Matheny, Smith, Courtney, Mair, 2009). Lastly, the costs and benefits of achieving the PHEMCE requirements could be compared to those of achieving other public health objectives that may be more cost-effective.

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Box 1: PHEMCE requirements for infectious diseases

Anthrax antitoxin
Filovirus vaccine
Anthrax vaccine
Smallpox antiviral
Filovirus antiviral
Junin virus antiviral
Gram(+) broad-spectrum antibiotic
Gram(-) broad-spectrum antibiotic

Table 1. Candidates potentially eligible for BARDA funding in FY14

Category	Company	Candidate	Phase
Anthrax Vaccines	Fraunhofer USA	Plant-derived oral anthrax vaccine	Preclinical
	Pharmathene	Third-generation rPA	Preclinical
	DynPort	IM vaccine	Phase I
	Emergent Biosolutions	BioThrax AVA	Phase I
	Panacea Biotech	Recombinant anthrax vaccine	Phase I
	Vaxin	Adenovirus-vectored nasal anthrax vaccine	Phase I
	Emergent Biosolutions	rPA (formerly VaxGen)	Phase II
	Pharmathene	SparVax	Phase II
	Filovirus Vaccines	Alphavax	Marburg
Genphar		Pan-Filovirus	Preclinical
Integrated BioTherapeutics		Ebola/Marburg	Preclinical
Genphar		Marburg	Phase I
Genphar		Ebola	Phase I
Anthrax antitoxins	Cangene	Anthrax Immune Globulin	Phase I
	Elusys Therapeutics	Anthim monoclonal antibody	Phase I
	Emergent Biosolutions	AVP-21D9 monoclonal antibody	Phase I
	Emergent Biosolutions	Anthrax Immune Globulin	Phase II
	Pharmathene, Medarex	Valortim antibody	Phase II
Filovirus antivirals	Siga Technologies	ST-383	Preclinical
	UTMB, USAMRIID	LJ001 - Ebola	Preclinical
	Functional Genetics	FGI-101	Phase I
	Sarepta	AVI-7537 - Ebola	Phase I
	Sarepta	AVI-7288 - Marburg	Phase II
Junin Antivirals	Siga Technologies	ST193	Preclinical
	Siga Technologies	ST-294	Preclinical
Smallpox antivirals	Biofactura	Monoclonal antibody	Preclinical
	TSRL	Cyclic cidofovir	Preclinical
	Chimerix	CMX001	Phase I
	Siga Technologies	ST-246	Phase II
Broad spectrum antibiotics*	Nanotherapeutics	NanoGENT Gram(-)	Preclinical
	CUBRC, Tetrphase	TP-434 Gram(-)	Phase I
	GlaxoSmithKline	GSK2251052 Gram(-)	Phase II

* Only broad-spectrum antibiotics with PHEMCE indications were included.

Table 2. Underlying assumptions for clinical development costs, sizes, durations, and transition probabilities

	Antivirals and antibiotics	Vaccines and antitoxins
Preclinical development		
Transition probability	47%	48%
Phase I		
Annual cost per trial (\$M)	19.9	19.9
Annual cost per subject (\$K)	490	490
Number of subjects	44	177
Duration (years)	2.39	2.88
Transition probability	83%	74%
Phase II		
Annual cost per trial (\$M)	24.2	24.2
Annual cost per subject (\$K)	303	303
Number of subjects	165	483
Duration (years)	3.38	3.96
Transition probability	56%	58%
Phase III		
Annual cost per trial (\$M)	44.9	44.9
Annual cost per subject (\$K)	12.4	12.4
Number of subjects	642	1,900
Duration (years)	3.15	3.76
Transition probability	65%	61%

Notes: Costs and numbers of subjects from Matheny and Herring (2013) in 2010 dollars; durations and transition probabilities from Davis et al. (2011).

Table 3. R&D costs for clinical development of candidates

	Current number of candidates per phase				Expected clinical development costs (\$M)	
	Pre-clinical	Phase I	Phase II	Phase III	FY14	Total*
Antivirals and antibiotics	7	4	3	0	\$152	\$1,584
Vaccines and antitoxins	5	9	4	0	\$276	\$2,611
Total	12	13	7	0	\$428	\$4,195

* Total costs represent clinical development costs accrued until the success or failure of existing candidates (in 2010 dollars).

Table 4. Probability of satisfying PHEMCE requirements

PHEMCE requirement	Number of Candidates				Probability of Approval at Phase*				Probability of at least one approval
	Pre-clinical	Phase I	Phase II	Phase III	Pre-clinical	Phase I	Phase II	Phase III	
Anthrax vaccine	2	4	2	0	13%	26%	35%	61%	90%
Anthrax antitoxin	0	3	2	0	13%	26%	35%	61%	83%
Filovirus vaccine	3	2	0	0	13%	26%	35%	61%	64%
Filovirus antiviral	2	2	1	0	14%	30%	36%	65%	77%
Junin virus antiviral	2	0	0	0	14%	30%	36%	65%	26%
Smallpox antiviral	2	1	1	0	14%	30%	36%	65%	67%
BSA: Gram(-)**	1	1	1	0	14%	30%	36%	65%	61%
BSA: Gram(+)**	0	0	0	0	14%	30%	36%	65%	0%

* These estimates are based on historical, aggregate data, and do not reflect judgments of the merits of any specific product currently in development.

** BSA = Broad spectrum antibiotic

Table 5. Portfolios to satisfy PHEMCE requirements

PHEMCE requirement	Additional preclinical candidates needed for one approved product per requirement with probability:		
	70%	80%	90%
Anthrax vaccine	0	0	0
Anthrax antitoxin	0	0	4
Filovirus vaccine	2	5	9
Filovirus antiviral	0	1	6
Junin virus antiviral	6	9	13
Smallpox antiviral	1	4	8
Broad spectrum antibiotic: Gram(+)	2	5	9
Broad spectrum antibiotic: Gram(-)	8	11	15
Total	19	35	64
Total clinical development costs for existing pipeline plus additional candidates (\$M)	\$5,834	\$7,229	\$9,786

Figure 1. R&D and funding pathway for meeting PHEMCE requirements

Development Phase	Pre-clinical Research & Development	Clinical Development	Production
Activities	<ul style="list-style-type: none"> • Basic Research • Lead Discovery • Animal Testing • Small Scale Production 	<ul style="list-style-type: none"> • Clinical Testing • Animal Testing • Production Scale-up • FDA Approval 	<ul style="list-style-type: none"> • Large-scale Manufacturing • Procurement for Strategic National Stockpile
Funding	NIAID	BARDA	BioShield

Figure 2. Cost and success probabilities for at least one approved drug

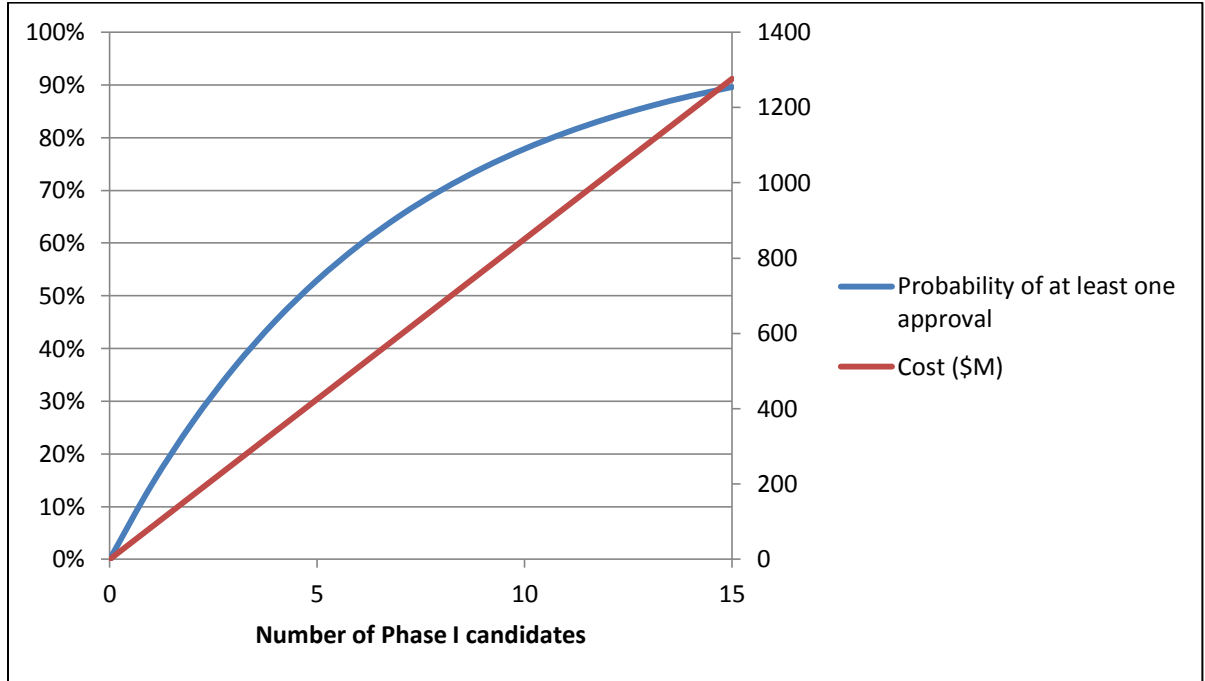


Figure 3. Cost and success probabilities for at least one approved vaccine or antitoxin

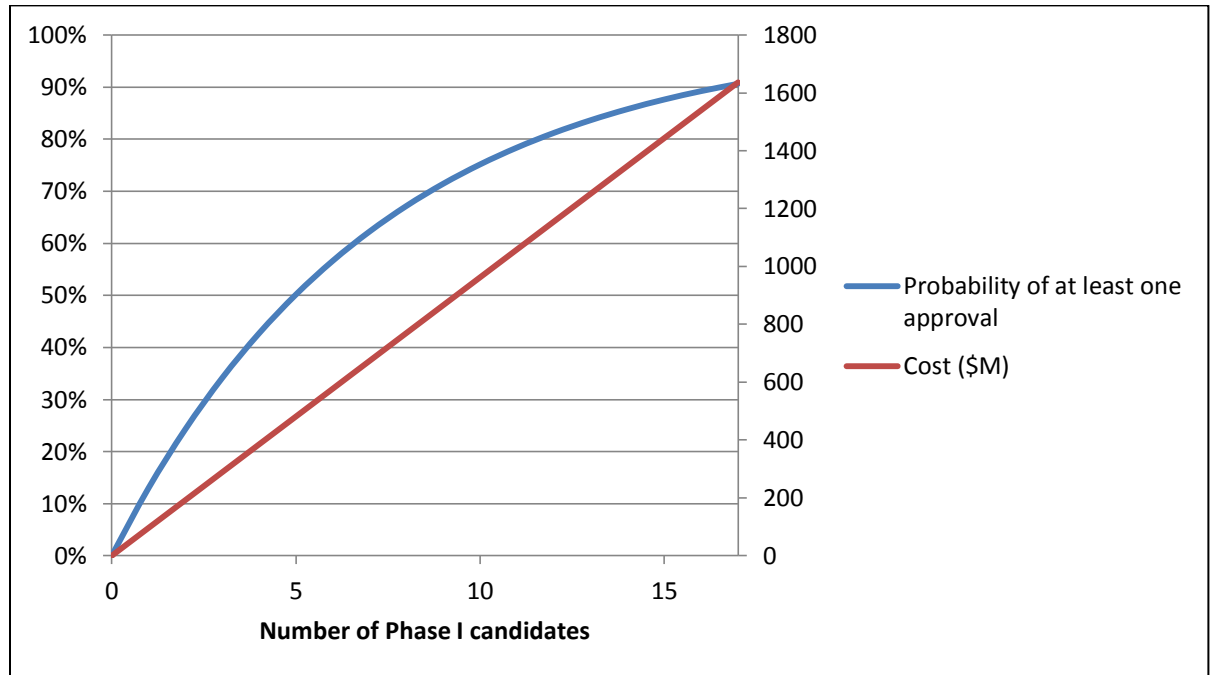
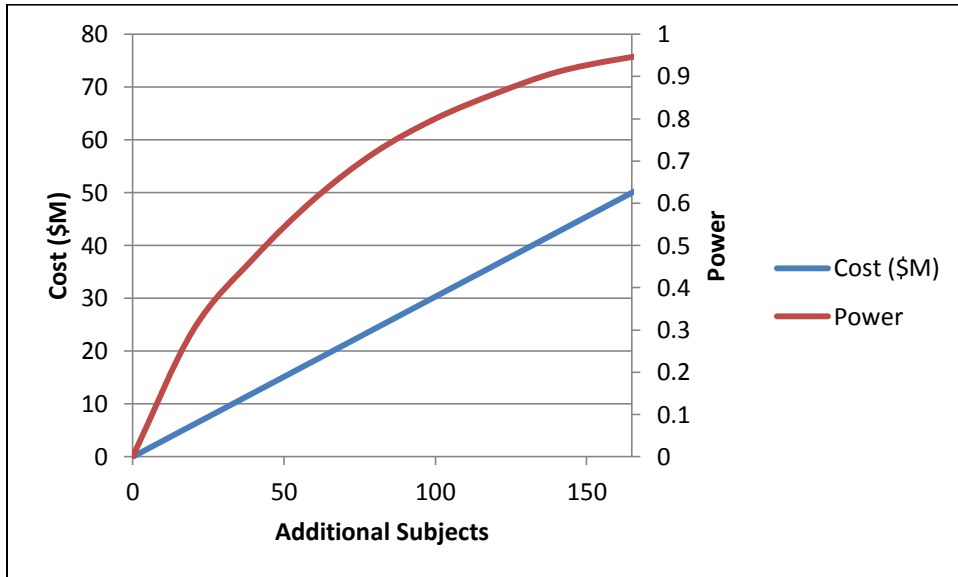


Figure 4. Phase II drug clinical trial size, cost, and statistical power



CONCLUSION

In this dissertation, I, along with co-authors, addressed three open questions related to the economics of pharmaceutical development. First, how much does it cost to conduct a clinical trial? Second, what effect has the model policy for incentivizing pharmaceutical development, the Orphan Drug Act, had on pharmaceutical availability? And third, how can the costs and risks of pharmaceutical development be used to model an optimal development portfolio?

Regarding the first question, we find that the annual cost of clinical trials is \$19.9 million for a Phase I trial, \$24.2 million for a Phase II trial, \$48.9 million for a Phase III trial, and \$35.2 million for a Phase IV trial. These results are consistent with previous estimates and yield an expected cost per approved pharmaceutical of \$600 million – or over \$1.2 billion when capitalized at 11% per year. Previous claims that pharmaceutical firms exaggerate their costs therefore appear to be unfounded. Pharmaceutical development is a very costly enterprise, and firms, policymakers, and foundations need a realistic accounting of these costs when planning pharmaceutical development efforts.

Because the scale of clinical trials varies considerably, we also decompose average costs into the fixed costs of running a trial and the variable costs per human subject. We find that the annual cost for a clinical trial subject is \$489,900 for Phase I, \$303,100 for Phase II, \$12,400 for Phase III, and statistically insignificant for Phase IV. Our results suggest that clinical trial costs could be significantly reduced by decreasing clinical trial size and/or length – particularly during the first two phases. Adaptive trial designs are one such approach to reducing the number of clinical trial subject-years, by

using early results to inform the design of subsequent experiments. FDA has been slow to provide guidance on adaptive trial designs. Our results suggest that much could be gained if FDA were to enable such designs.

Our second question was, what effect has the Orphan Drug Act (ODA), had on pharmaceutical availability? We do not find evidence of a significant discontinuity in drug prescriptions as prevalence approaches 200,000 cases. The absence of such a discontinuity suggests that the ODA did not significantly affect prescriptions for orphan diseases. One possible explanation for our result is a perverse effect of the ODA: it encourages firms to charge monopoly prices for existing products. A price increase could cause a sufficient decrease in prescriptions for existing orphan drugs, and that effect negates any increase in prescriptions for new orphan drugs. Given how costly the ODA is to maintain, more research on this question would be highly valuable. If confidential orphan drug applications to the FDA could be analyzed, this would help to clarify whether the prevalence estimates we used in our analysis are representative. A second research question is whether the main effect of the ODA could have been a substitution of effective drugs for ineffective drugs. Further research could test this effect, by examining regression discontinuities in health outcomes for diseases by prevalence.

Our third question was, how can the costs and risks of pharmaceutical development be used to model an optimal development portfolio? As a demonstration, we estimate the cost of the U.S. Public Health Emergency Medical Countermeasure Enterprise (PHEMCE) – the U.S. government’s most detailed set of pharmaceutical requirements for any class of diseases. We find that the cost of supporting existing PHEMCE candidates through clinical development is likely to be \$428 million in fiscal

year 2014 alone. This is close to the President's request of \$415 million in fiscal year 2014, suggesting that the request was informed by a similar model.

However, given the high failure rate of biopharmaceutical development, the probability of developing approved products from the existing pipeline is between 0% and 90% per requirement. To increase the probability to 90% for all requirements, a significantly expanded portfolio would be needed, with an expected clinical development cost of \$9.8 billion over ten years. At historic funding rates, building such a portfolio is unlikely. PHEMCE would need to identify a subset of products to receive priority funding. Alternatively, PHEMCE could significantly reduce the cost per product by funding smaller clinical trials. We find that the benefits from decreasing clinical trial sizes can be substantial. For instance, a 25% decrease in the size of a Phase II drug trial would decrease costs by \$12 million, while decreasing power by only 0.08. We note that the U.S. Department of Health and Human Services could exercise Emergency Use authorities to employ products that have been approved using small clinical trials. We could find no prior analysis of the tradeoffs between cost and safety in choosing clinical trial sizes – but formalizing this tradeoff, particularly when costs could mean there is no product at all, seems valuable.

This dissertation offers answers to three controversial questions in pharmacoeconomics. It also demonstrates technical approaches that can be applied more generally to set realistic budgets for pharmaceutical development, support policies tailored to accelerate pharmaceutical development, and inform cost-effectiveness analysis of pharmaceutical projects. More accurate data on the costs and risks of pharmaceutical R&D, as well as their determinants, would help to: set appropriate budgets for

government R&D initiatives, such as those of the National Institute of Allergy and Infectious Diseases (NIAID), the Biomedical Advanced Research and Development Authority (BARDA), and BioShield; set realistic expectations and funding levels for anti-infective R&D within the global health community, including NGO-led efforts to develop products for HIV, malaria, and tuberculosis; set targets for development pipelines needed to ensure at least one approval per target disease; establish appropriate sizes and structures for R&D incentives, such as Advanced Market Commitments and Priority Review Vouchers; support evaluation of Product Development Partnerships; and support cost-effectiveness analysis of pharmaceutical R&D in global health priority-setting exercises, such as the Disease Control Priorities Project, including comparisons with non-pharmaceutical measures to control infectious diseases.

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Degrees

M.P.H. Johns Hopkins University, Baltimore, Maryland
M.B.A. Duke University, Durham, North Carolina
B.A. University of Chicago, Chicago, Illinois

Employment

Intelligence Advanced Research Projects Activity (IARPA),
Office of the Director of National Intelligence, Washington, DC
Program Manager, 2009-
Oxford University, James Martin School, Oxford, United Kingdom
Visiting Scholar, 2008-2009
Applied Physics Laboratory, Johns Hopkins University, Laurel, MD
Consultant, 2008-2009
Center for Biosecurity, Baltimore, MD
Consultant, 2006-2009
World Bank, Health, Nutrition, and Population Group, Washington, DC
Consultant, 2002-2004, 2007
Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD
Consultant, 2004, 2006
Princeton University, Center for Human Values, Princeton, NJ
Research Associate, 2004-2005
Center for Global Development, Washington, DC
Consultant, 2004
India AIDS Initiative, Population Services International, New Delhi, India
Technical Specialist, 2003-2004
David and Lucile Packard Foundation, Population Program, Los Altos, CA
Research Associate, 2002
Family Health International, Research Triangle Park, NC
Research Intern, 2002
Seva Foundation, Berkeley, CA
Research Intern, 2000-2001
Public Education Network, San Francisco, CA
Director, Co-Founder, 1997-2001

Journal articles

Matheny, J.G., B. Smith, B. Courtney, M. Mair, "Developing drugs and vaccines for infectious diseases," *Clinical Pharmacology and Therapeutics* 85(6), 2009.

Smith, B.T., M. Mair, G.K. Gronvall, J.G. Matheny, "Developing medical countermeasures for biodefense," *Biosecurity and Bioterrorism* 17(1), 2009.

Matheny, J.G., M. Mair, B. Smith, "BARDA's budget," *Nature Biotechnology* 27(8), 2009.

Matheny, J.G., M. Mair, B. Smith, "Cost and success projections for U.S. medical countermeasure development," *Nature Biotechnology* 26(9), 2008.

Matheny, J.G., M. Cikovic, A. Sandberg, "How can we reduce the risk of human extinction?" *The Bulletin of the Atomic Scientists*, September 2008.

Abramovich, M., E. Toner, J.G. Matheny, "Panalysis: a tool for pandemic planning," *Biosecurity and Bioterrorism* 6(1), 2008.

Matheny, J.G., E. Toner, R.E. Waldhorn, "Costs and benefits of influenza pandemic preparedness," *Journal of Health Care Finance* 34(1), 2007.

Matheny, J.G., M. Mair, A. Mulcahy, B. Smith, "Incentives for biodefense countermeasure development," *Biosecurity and Bioterrorism* 5(3), 2007.

Gronvall, G.K., Matheny, J.G., Smith, B.T., et al., "Flexible Biodefense Roundtable Meeting: Promoting the Strategic Innovation of Medical Countermeasures," *Biosecurity and Bioterrorism* 5(3), 2007.

Matheny, J.G., "Reducing the risk of human extinction," *Risk Analysis* 27(5), 2007.

Gronvall, G.K., Smith, B.T., Matheny, J.G., et al., "Biomedical Advanced Research and Development Authority (BARDA) Roundtable," *Biosecurity and Bioterrorism* 5(2), 2007.

Matheny, J.G., C. Leahy, "Farm animal welfare, legislation, and global trade," *Law and Contemporary Problems* 70:325-57, 2007.

Matheny, J.G., K.M.A. Chan, "Human diets and animal welfare," *Journal of Agricultural and Environmental Ethics* 18 (6), 2005.

Edelman, P.E., D.C. McFarland, V.A. Mironov, J.G. Matheny, "In vitro meat production," *Tissue Engineering* 11 (5/6), 2005.

Matheny, J.G., "Family planning programs: getting the most for the money," *International Family Planning Perspectives* 30 (3), 2004.

Matheny, J.G., "Least harm," *Journal of Agricultural and Environmental Ethics*, 16 (5), 2003.

Matheny, J.G., "Expected utility and contributory causation," *Journal of Applied Philosophy*, 19 (3), 2002.

Book chapters

Matheny, J.G., "Alternatives to meat production," in Swabe (ed.) *Meat the Truth: Essays on Livestock Production, Sustainability and Climate Change*, forthcoming.

Fearing, J., J.G. Matheny, "The role of economics in achieving welfare gains for animals," in D. Salem and A. Rowan (eds.), *State of the Animals*, Humane Society of the United States, 2007.

Levine, R., A. Langer, N. Birdsall, J.G. Matheny, M. Wright, A. Bayer, "Contraception," in *Disease Control Priorities in Developing Countries*, 2nd ed., D.T. Jamison, et al. (eds.), New York: Oxford University Press, 2006.

Matheny, J.G. "Utilitarianism and animals," in Peter Singer, ed., *In Defense of Animals*, Blackwell, 2005.

Selected presentations

Various briefings to the Director of National Intelligence, the National Intelligence Council, the National Security Staff, the Joint Chiefs of Staff, the Office of Science and Technology Policy, the U.S. Senate Select Committee on Intelligence, and the U.S. House Permanent Select Committee on Intelligence, on topics related to national intelligence, 2009-2013.

"Evaluating geopolitical forecasts," International Studies Association, Presidential Symposium, San Francisco, CA, April, 2013.

"Forecasting humanitarian crises," Council on Foreign Relations, Washington DC, December, 2012.

"Human and machine forecasts," American Association for the Advancement of Artificial Intelligence, Washington, DC, November 2012.

"Evaluating technology forecasts," to the Office of Net Assessment, Department of Defense, Naval War College, July 2012.

“Automated machine learning,” National Science Foundation Symposium on Machine Learning, June 2012.

“Open source indicators of humanitarian crises,” to the National Academy of Science and the National Academy of Engineering, Washington, DC, December 2011.

“Global catastrophic risks” (Symposium Chair), Society for Risk Analysis, Boston, December 2008.

“Risks from emerging biotechnologies,” Oxford University, June 2008.

“*In vitro* and *in silico* modeling of biological systems,” Milan, Italy, May 2008.

“Large-scale tissue engineering approaches,” Norwegian University of Life Sciences, As, Norway, April 2008.

“Incentives for drug and vaccine development,” Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, September 2007.

“Disease control priorities,” World Bank, Washington, DC, July 2007.

“Disease control priorities,” U.S. Agency for International Development, Washington, DC, August 2006

“Economic evaluation and technology assessment,” Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, July 2006

Other professional and voluntary service

DARPA Source Selection Evaluation Boards, 2011-

DTRA Source Selection Evaluation Board, 2012

IARPA Source Selection Evaluation Boards, 2009-

Department of Defense, Office of Net Assessment, Summer Study Group, 2012

Reviewer for MIT Press, *Nature Biotechnology*, *Risk Analysis*, *Global Policy*, *Biosecurity and Bioterrorism*, 2007-

Working Group, Scientific and Technical Intelligence Committee, ODNI, 2009-

Catalyst Project, U.S. Joint Forces Command, 2009

Future Operational Environment and Red Franchise, TRADOC, U.S. Army, 2009

20XX, Office of Net Assessment, Department of Defense, 2008

Biometrics and Personnel Protection Study Group, U.S. Army, 2008

Associate Editor, *Biosecurity and Bioterrorism*, 2008-9

Member, Royal Economic Society, 2008-

Member, Society for Risk Analysis, 2008-

Science Advisor, National Public Radio, 2008-9

New Harvest, Founder, Board of Directors, 2004-

Awards, funding, and recognition

IARPA Program of the Year, 2012

Chosen to represent IARPA before US Congress at US TechExpo, US Capitol, 2012

Elected member of St. Cross College, Oxford University, 2008

Faculty Innovation Grant (with Brad Herring), Johns Hopkins University, 2008

Sommer Scholarship, Johns Hopkins University, 2007-2012 (accepted)

National Institutes of Health Fellowship, 2007 (declined)

National Institutes of Health Fellowship, 2004 (declined)

Faculty Prize for Outstanding Honors Thesis, University of Chicago, 1996

Press coverage

My work on agricultural biotechnologies was featured in *The New York Times*' annual "Ideas of the Year," *Discover Magazine*'s "Top Science Stories of the Year," *Scientific American*, an episode of *NOVA*, and over 100 other media outlets. My work on risk analysis was covered by *Nature*. My work on humanitarian intelligence was featured in *The Economist*, *Nature*, and *Wired*. My work to improve the accuracy of national intelligence estimates was featured on the front page of *The Los Angeles Times*, and in *The New York Times*, *The Washington Post*, *The Wall Street Journal*, NPR, *Discover*, and *Forbes*. *The University of Chicago Magazine* published a cover story on my efforts, since graduating college, to donate most of my income to cost-effective charities.